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Efalizumab and Etanercept for the Treatment of Psoriasis

Produced by CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination / Centre for Health Economics), University of York

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CRD/CHE Technology Assessment Group

The Technology Assessment Review team at the University of York is drawn from two specialist centres: the Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE).

CRD undertakes reviews of research about the effects of interventions used in health and social care (www.york.ac.uk/inst/crd). The centre maintains various databases, provides an enquiry service and disseminates results of research to NHS decision makers.

CHE undertakes research and training in all areas of health economics (www.york.ac.uk/inst/che). The bulk of the input into the TARs comes from the programme for economic evaluation and health technology assessment which

specialises in decision analysis and Bayesian methods in economic evaluations (see <http://www.york.ac.uk/inst/che/teehta.htm>).

Recent TAR's undertaken by CRD/CHE at York relate to topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer; methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder; and clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events.

Conflicts of interest

None of the authors have conflicts of interest.

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The views expressed in this report are those of the authors and not necessarily those of the NHS R&D Programme.

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Executive Summary

Background

Psoriasis is a common inflammatory skin disease, with estimates of its world prevalence ranging from 0.5 to 4.6%, and UK prevalence estimated at around 1.5%. Psoriasis generally occurs in adults; with males and females being equally commonly affected by the condition. Ethnic variations have been identified and Caucasians are more likely to suffer from the disease. Psoriasis is a chronic disorder that can be physically and emotionally debilitating and which can require life-long treatment. Plaque psoriasis, characterised by clearly demarcated, red, scaling plaques, is the most common form of psoriasis, occurring in more than 80% of cases. In the United Kingdom both etanercept (Enbrel®) and efalizumab (Raptiva®) have recently been licensed drugs for the treatment of adults with moderate to severe plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate or PUVA. Both etanercept and efalizumab are new biologic agents, which target pathologic T cell activity. Other therapies available for the treatment of moderate to severe psoriasis include phototherapy and systemic agents such as ciclosporin, methotrexate and retinoids; all of which have limitations to their use due to serious long-term adverse effects.

Methods

A systematic review evaluated the clinical efficacy and adverse effects of etanercept and efalizumab. The efficacy of other treatments for moderate to severe psoriasis was also reviewed and, where data allowed, all treatments were compared in an evidence synthesis utilising a mixed treatment comparison implemented as a Bayesian hierarchical model. Following evaluation of existing economic evaluations of etanercept and efalizumab in moderate to severe psoriasis, a new economic model was developed (the York Model), which directly utilised the results from the evidence synthesis.

Number and quality of studies

Our review of the clinical evidence identified a total of 39 published and three unpublished studies: eight randomised controlled trials of the efficacy of the interventions of interest (three of etanercept and five of efalizumab); 10 studies of the adverse effects of the interventions; and 24 randomised controlled trials of the efficacy of the other treatments for moderate to severe psoriasis.

The trials of the efficacy of the interventions were all double-blind and placebo controlled trials and generally of good quality, but three of the five efalizumab trials were poorly reported. A total of 1138 patients were included in the etanercept trials and 2963 included in the efalizumab trials.

Efficacy of the interventions

Data on the efficacy of etanercept 25 mg twice a week for 12 weeks were available from three RCTs. On average, treatment resulted in 62% of patients achieving a PASI 50 (*CiC removed*), 33% achieving a PASI 75 (RR 10.69 (95% CI: 6.15, 18.57)), 11% a PASI 90 (*CiC removed*) and 40% were assessed as clear or almost clear (RR 9.87 (95% CI: 6.00, 16.22)). Improvement in quality of life as assessed by mean percentage change in DLQI was around 59% with etanercept 25 mg twice a week compared with 9% with placebo, and all mean differences that could be calculated were statistically significantly in favour of etanercept.

Evidence from one RCT indicates that the response to etanercept is maintained, at least in the medium term, and data from uncontrolled follow-up phases reflect and extend these findings. Uncontrolled data from follow-up in one trial suggests the median duration of remission is around (*CiC removed*), with no real evidence of severe exacerbation of psoriasis after discontinuation of treatment. There is evidence from one trial that re-treatment in patients who have relapsed following an earlier treatment period does not induce a poorer response than initial treatment. Overall the trial populations may not truly reflect the difficult-to-treat patients for whom etanercept is licensed.

Efalizumab at a dose of 1 mg/kg once a week SC has been studied in five RCTs. Across these trials 12 weeks treatment resulted in an average of 55% of patients achieving PASI 50 (*CiC removed*)%, 27% achieving PASI 75 (*RR 6.34 (95% CI: 4.27, 9.42)*), 4.3% achieving PASI 90 (*RR 5.26 (0.89, 31.74)*) and 27% achieving clear or minimal psoriasis status (*RR 8.19 (95% CI: 3.78, 18.08)*). The mean change from baseline in by DLQI score averaged across four trials was (*CiC removed*)% for efalizumab-treated patients compared to (*CiC removed*)% for placebo-treated patients. There is no evidence from RCTs that the response to efalizumab 1 mg/kg once a week is maintained when treatment continues beyond 12 weeks, and long-term follow-up data relate to a range of doses and are poorly reported and so cannot be used to draw even tentative conclusions regarding the long-term efficacy of efalizumab. Uncontrolled data from trial follow-up suggest that time to relapse may be around 60 days. No data indicating the existence or absence of any rebound in psoriasis after discontinuation of efalizumab were identified. There is no evidence relating to the efficacy of efalizumab upon re-treatment. As for etanercept the trial populations may not truly reflect the difficult-to-treat patients for whom efalizumab is licensed.

Adverse effects

Injection site reactions appear to be the most common adverse effects of etanercept. Overall etanercept appears to be well tolerated in short and long-term use, although much of the long-term data are not from patients with psoriasis; data derived from patients with RA may not be applicable to those with psoriasis. As identified from earlier reviews, the main areas of concern relate to uncommon but serious adverse events, but their significance is not readily discernable from the published reports of clinical trials.

Headache, chills and, to a lesser extent, nausea, myalgia, pain and fever are the common adverse events associated with efalizumab. Overall withdrawal rates due to adverse events are low. Longer-term data for efalizumab are not readily available for evaluation, but the adverse events data up to three years appear to reflect those over 12 weeks and to remain stable. Unfortunately, few data for serious infections and serious adverse events with efalizumab are available.

Other treatments for moderate to severe psoriasis

Despite widespread use and numerous trials, it is difficult to draw firm conclusions regarding the efficacy of the treatments available for the relief of moderate to severe psoriasis. Only infliximab and ciclosporin have had their efficacy demonstrated in placebo-controlled RCTs, and even then these data are relatively few, with most trials having included a small number of patients and only a short treatment period. Whilst clinical experience has demonstrated excellent efficacy of PUVA and methotrexate, no placebo-controlled trials have been conducted. In clinical trials, methotrexate appears to be as effective as ciclosporin. The trials of other treatments, acitretin, Re-PUVA, and NBUVB, in comparison with PUVA, provide only limited evidence, demonstrating some degree of effectiveness but making it difficult to draw firm conclusions regarding relative efficacy.

Evidence synthesis

To enable indirect comparisons between all treatments for moderate to severe psoriasis, a meta-analysis of the PASI 50, 75 and 90 response rates from the randomised trials was performed. The endpoints were jointly modelled using an ordered probit model. The available data permitted the inclusion of etanercept (25 mg and 50 mg), efalizumab, infliximab, ciclosporin, methotrexate, Fumaderm and placebo in this mixed-treatment comparison which was implemented as a Bayesian hierarchical model.

In terms of mean response rate, when response is taken as PASI 75, infliximab appears the most effective followed by methotrexate and ciclosporin, then etanercept 50 mg. Etanercept 25 mg has a higher response rate than efalizumab, which has a lower mean response rate than all other therapies except Fumaderm and supportive care. As shown by the credible intervals around the mean response rates, which overlap considerably, there is uncertainty around these response rates. This is also shown in terms of the relative risks of each option (compared to placebo) and their confidence intervals. These findings for the PASI 75 level of response are mirrored in the results for the PASI 50 and PASI 90.

Summary of benefits

Etanercept is more efficacious than placebo in the treatment of moderate to severe psoriasis over a 12- week treatment period and the response is maintained up to 24 weeks. Efalizumab is also efficacious in the treatment of moderate to severe psoriasis, but there is no evidence from RCTs that the response to efalizumab 1 mg/kg once a week is maintained when treatment continues beyond 12 weeks. Etanercept and efalizumab do not appear to be more efficacious than older therapies for moderate to severe psoriasis.

Cost-effectiveness

One published article was identified looking at the cost-effectiveness of biological therapy in psoriasis, but its methods and US focus give it limited relevance to UK practice. Therefore, the cost-effectiveness of etanercept and efalizumab was informed by models submitted by the two manufacturers, together with a *de novo* model from the assessment team (the York Model). The company models compare only each manufacturer's product with non-systemic therapy. In contrast, the York Model compares various therapeutic strategies based on etanercept and efalizumab, and supportive care. In a secondary analysis, the York Model also includes other systemic therapies (infliximab, ciclosporin, methotrexate and Fumaderm). The York Model uses efficacy data taken directly from the evidence synthesis. Health effects are expressed in terms of quality-adjusted life-years (QALYs), where utilities for alternative PASI response categories are derived from a 'mapping' exercise. The focus of the York Model is to establish the most cost-effective *sequence* of therapies based on alternative threshold values for cost-effectiveness.

For the primary analysis comparing etanercept, efalizumab and supportive care, the results of the York Model suggest that the biologic therapies would only be cost-effective for all patients with moderate to severe psoriasis if the NHS is willing to pay over £60,000 per QALY gained. In patients with poor baseline quality of life (4th quartile DLQI), efalizumab, etanercept 25mg (intermittent), etanercept 25mg (continuous) and etanercept 50mg (intermittent) would be cost-effective as part of a treatment sequence if the NHS is willing to pay £45,000, £35,000, £45,000 and £65,000 per QALY gained, respectively. In patients who are also at high risk of in-

patient hospitalisation (21 days per annum), these therapies would be cost-effective as part of a sequence as long as the NHS is willing to pay £25,000, £20,000, £25,000 and £45,000 per QALY gained, respectively.

As part of a secondary analysis including a wider range of systemic therapies as comparators, it would only be cost-effective to use etanercept and efalizumab in a sequence after methotrexate, ciclosporin and Fumaderm.

Notes on the generalisability of the findings

For both etanercept and efalizumab, the trial populations may not truly reflect the difficult-to-treat patients for whom these two biologics are licensed. In addition, the results of both the clinical and economic evaluations relate to induction of remission rather than long-term effectiveness in the treatment of psoriasis.

Conclusions

Clinical trial data indicate that both etanercept and efalizumab are efficacious in patients who are eligible for systemic therapy. However, the economic evaluation demonstrates that these biologics are likely to be cost-effective only in patients with poor baseline quality of life and who are at risk of hospitalization if not responding to therapy.

Recommendations for further research

- Efficacy trials conducted in the specific population for which etanercept and efalizumab are licenced are required, i.e. patients with moderate to severe disease in whom conventional therapy has failed or is inappropriate.
- Long-term comparisons of etanercept and efalizumab with other treatments for moderate to severe psoriasis - particularly infliximab, methotrexate and ciclosporin are warranted.
- Long-term efficacy trials to provide data on how etanercept and efalizumab perform as maintenance therapies are required.
- Long term safety/tolerability data collected from patients with psoriasis are required.

- Randomised controlled trials of various combination therapies are warranted.
- Psoriasis is a heterogeneous group of diseases; trials to identify specific subtypes that respond better to one drug compared to another are warranted.
- Research on the rate of in-patient hospitalisation in patients with moderate to severe psoriasis is warranted, and the effect of treatment on this rate.

List of Abbreviations

AE	Adverse event
ANA	Antinuclear antibodies
Anti-TNF	Anti-tumour necrosis factor
BIW	Biweekly
BSA	Body surface area
CEAC	Cost effectiveness acceptability curve
CHF	Congestive heart failure
CI	Confidence interval
CSA	Ciclosporin
DB	Double blind
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying anti-rheumatic drugs
DMFAE	Dimethylfumaric acid ester
EQ-5D	EuroQol-5D
FCE	Finished consultant episodes
GA	Global Assessment
GP	General Practitioner
HEED	Health Economic Evaluation Database
HES	Hospital episode statistics
HRGs	Healthcare resource groups
HRQOL	Health-Related Quality of Life
IAGI	Investigator's Assessment of Global Improvement
ICER	Incremental cost-effectiveness ratio (e.g. incremental cost per QALY gained)
INB	Incremental net benefit
MD	Mean difference
MEFAE	Monoethylfumaric acid ester
MEFAE-Mg	Magnesium salt of monoethylfumaric acid ester
MEFAE-Na	Sodium salt of monoethylfumaric acid ester
MEFAE-Zn	Zinc salt of monoethylfumaric acid ester
MeSH	Medline Thesaurus
MRA	Minimal residual activity

MTX	Methotrexate
NBUVB	Narrow band UVB
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Clinical Excellence
NRR	National Research Register
NSAIDS	Nonsteroidal anti-inflammatory drugs
OHFAE	Octyl hydrogen fumaric acid ester
OLS	Ordinary Least Squares
OLS	Overall Lesion Severity scale
PASI	Psoriasis Area and Severity Index
PDI	Psoriasis Disability Index
PGA	Physician's Global assessment
PsA	Psoriatic arthritis
PSA	Psoriasis Symptom Assessment
PSI	Psoriasis Severity Index
PUVA	Photochemotherapy
QALYs	Quality adjusted life years
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RePUVA	Retinoid plus PUVA
RR	Relative risk
SAPASI	Self Administered Psoriasis Area and Severity Index
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLE	Systemic lupus erythematosus
TMP	Trimethoxypsoralen
TSS	Total Severity Score
UVA	Ultraviolet radiation band A
UVB	Ultraviolet radiation band B
VAS	Visual Analogue Scale
Wks	Weeks
WMD	Weighted mean difference

Definitions of Terms

Acitretin

A synthetic derivative of vitamin A that is taken orally. It is indicated for severe psoriasis.

Adverse effect

An abnormal or harmful effect caused by and attributable to exposure to a chemical (e.g. a drug), which is indicated by some result such as death, a physical symptom or visible illness. An effect may be classed as adverse if it causes functional or anatomical damage, causes irreversible change in the homeostasis of the organism, or increases the susceptibility of the organism to other chemical or biological stress.

Biologic therapies (biologicals)

Medical preparations derived from living organisms. In psoriasis, this category of pharmaceuticals may target the immune system.

Ciclosporin

A medication originally developed to prevent the immune system from rejecting transplanted organs, which has also proved helpful in treating psoriasis.

Coal tar

Tar distilled from bituminous coal applied to the skin to treat psoriasis. Often used with UV light therapy.

Confidence interval (CI)

The typical ('Classical' or 'Frequentist') definition is the range within which the "true" value (e.g. size of effect of an intervention) would be expected to lie if sampling could be repeated a large number of times (e.g. 95% or 99%).

Corticosteroid

A synthetic hormone similar to that produced naturally by the adrenal glands that is available in pill, topical, and injectable forms.

Cost-benefit analysis

An economic analysis that converts the effects or consequences of interventions into the same monetary terms as the costs and compares them using a measure of net benefit or a cost-benefit ratio

Cost-effectiveness analysis

An economic analysis that expresses the effects or consequences of interventions on a single dimension. This would normally be expressed in 'natural' units (e.g. cases cured, life-years gained, additional strokes prevented). The difference between interventions in terms of costs and effects is typically expressed as an incremental cost-effectiveness ratio (e.g. the incremental cost per life-year gained).

Cost-utility analysis

The same as a cost-effectiveness analysis but the effects or consequences of interventions are expressed in generic units of health gain, usually quality-adjusted life years (QALYs).

Credible intervals

Bayesian version of confidence intervals. It is the range within which the "true" value (e.g. size of effect of an intervention) is expected to lie with a given degree of certainty (e.g. 95% or 99%).

Effect size

A generic term for the estimate of effect for a study.

Emollient

An agent that holds moisture in the skin, and by doing so softens or soothes it.

Erythrodermic psoriasis

The least common form of psoriasis in which the skin of almost the entire body

becomes red and fiery, and may cause difficulty regulating the body's temperature and heart rate. People with this type of psoriasis may require hospitalization.

Fixed effect model

A statistical model that stipulates that the units under analysis (e.g. people in a trial or study in a meta-analysis) are the ones of interest, and thus constitute the entire population of units. Only within-study variation is taken to influence the uncertainty of results (as reflected in the confidence interval) of a meta-analysis using a fixed effect model.

Generalised pustular psoriasis

Generalised pustular psoriasis is an acute generalised inflammatory form of psoriasis with many of the same problems as erythrodermic psoriasis and usually requires hospital admission.

Goeckerman regimen

A psoriasis treatment consisting of crude coal tar together with UVB phototherapy, usually administered in a hospital or a psoriasis clinic.

Guttate psoriasis

A type of psoriasis characterized by drop-like lesions on the trunk, limbs, and scalp. Characteristically, it is triggered by a preceding streptococcal infection such as tonsillitis.

Heterogeneity

In systematic reviews heterogeneity refers to variability or differences between studies in the estimates of effects. A distinction is sometimes made between "statistical heterogeneity" (differences in the reported effects), "methodological heterogeneity" (differences in study design) and "clinical heterogeneity" (differences between studies in key characteristics of the participants, interventions or outcome measures).

Hydroxyurea

One of the older anti-cancer drugs that is sometimes used in the treatment of psoriasis. When used, either in combination or alone, it requires careful blood monitoring.

Immunomodulator

A substance that alters the body's immune response.

Ingram regimen

Daily UVB phototherapy followed by application of dithranol (anthralin) paste to the skin. This treatment was developed for in-patient use but is now often administered in a day-case setting.

Intention-to-treat

An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not.

Inverse (flexural) psoriasis

Psoriasis that occurs in the skin folds such as the underarm or groin area, which can cause significant discomfort when one part of the skin rubs against another. When this occurs in the genital area, it can cause sexual difficulties.

Malignant melanoma

A potentially fatal form of skin cancer. Psoriasis patients who have received PUVA should be carefully monitored for this complication, which is increased some tenfold over the expected rate in the general population and may develop many years after completing therapy.

Methotrexate

One of the oldest chemotherapy drugs used to treat cancer; used in the treatment of psoriasis.

Mixed treatment comparison

Mixed treatment comparison is a form of meta-analysis used to strengthen inference concerning the relative efficacy of two treatments. It uses data based on direct comparisons (A vs. B and B vs. C trials) and indirect comparisons (A vs C trials) also, it facilitates simultaneous inference regarding all treatments in order to select the best treatments.

Monoclonal antibody

An antibody produced in a laboratory from a single clone that recognizes only one antigen.

Narrow-band UVB

Ultraviolet light in a narrow band of 311 nm to 313 nm, thought to be faster acting, and possibly safer than other UV light treatments.

Palmoplantar pustular psoriasis

Palmoplantar pustular psoriasis or palmoplantar pustulosis is limited to the palms and soles and appears to have different genetics from psoriasis vulgaris. Only a minority of patients have psoriasis elsewhere.

PASI score

Psoriasis Area Severity Index score, a number representing the extent, redness, thickness, and scaliness of a person's psoriasis.

Photochemotherapy

The addition of drugs to light therapy in order to intensify its effects.

Phototherapy

The use of natural or artificial UV light to treat disease.

Placebo

An inactive substance or procedure administered to a patient, usually to compare its effects with those of a real drug or other intervention, but sometimes for the psychological benefit to the patient through a belief that s/he is receiving treatment.

Plaque psoriasis

The most common form of psoriasis, also known as psoriasis vulgaris, recognized by red, raised lesions covered by silvery scales. About 80% of psoriasis patients have this type.

Psoralen

A photosensitizing drug used in combination with UVA to treat psoriasis (also known as PUVA therapy).

Psoriasis

A chronic skin disease characterized by inflammation and scaling. Scaling occurs when cells in the outer layer of skin reproduce faster than normal and pile up on the skin's surface. It is understood to be a disorder of the immune system.

Psoriatic arthritis

This disease is characterized by stiffness, pain, and swelling in the joints, especially of the hands and feet. Early diagnosis and treatment can help inhibit the progression of joint deterioration.

Pustular psoriasis

There are two important types of pustular psoriasis: generalised pustular psoriasis and palmoplantar pustular psoriasis or palmoplantar pustulosis.

PUVA

Psoralen plus ultraviolet A is a psoriasis treatment that combines exposure to ultraviolet A (UVA) light with psoralens. Psoralens are naturally occurring compounds that interact with UVA light; they may be taken orally or applied directly to the skin (e.g. as in bath PUVA).

Quality Adjusted Life Year (QALY)

An index of health gain where survival duration is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Quality of Life

A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity as well as other factors which might affect their physical, mental and social well-being.

Random effects model

A statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.

Randomised controlled trial (RCT) (Synonym: randomised clinical trial)

An experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared.

Relative Risk (RR) (synonym: risk ratio)

The ratio of the proportion of the intervention group experiencing an event to the proportion of the control group experiencing the event. The event can be adverse, e.g. developing cancer, or beneficial e.g. responding to therapy. For adverse outcomes a relative risk of less than one indicates a beneficial effect of the intervention. For beneficial outcomes a relative risk of more than one indicates a beneficial effect of the intervention. A relative risk of one indicates no difference between intervention and control.

Remission

The state of a disease being inactive or under control.

Retinoids

Vitamin A derivatives often used in topical or oral psoriasis therapy.

Rheumatoid arthritis

A chronic autoimmune disease characterized by pain, stiffness, inflammation, swelling, and, sometimes, destruction of joints.

Sensitivity analysis

An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Statistical significance

An estimate of the probability of an association (effect) as large or larger than what is observed in a study occurring by chance, usually expressed as a P-value.

Squamous cell carcinoma

A form of cancer that may affect the skin of people who have had excessive exposure to ultraviolet light particularly PUVA.

Systemic

Affecting the entire body internally.

Systemic treatment

A treatment given internally, usually by mouth or injection.

T cell

A type of white blood cell that is part of the immune system that normally helps protect the body against infection and disease.

Tars

Natural, sticky substances used to treat psoriasis as in coal tar shampoos, topical creams, and ointments.

Thrombocytopenia

A disorder sometimes associated with abnormal bleeding in which the number of platelets (cells that help blood to clot) is abnormally low.

Topical agent

A treatment such as a cream, salve, or ointment that is applied to the surface of the skin.

Toxicity

The potential of a drug or treatment to cause harmful side effects.

Tumor necrosis factor (TNF)

One of the cytokines, or messengers, known to be fundamental to the disease process that underlies psoriasis. It is believed to play a key role in the onset and the continuation of skin inflammation.

Ultraviolet (UV) light

UV light or, more correctly, UV radiation is an important part of the energy emitted by the sun but can be produced artificially; it has a shorter wavelength than visible light and can cause profound biological effects. The shortest UV wavelengths (UVC) do not usually reach the earth's atmosphere; UVB (290-320 nm) is responsible for acute sunburn but when carefully controlled can be useful for treating psoriasis; long wavelength UV (UVA: 320-400 nm) penetrates deeper into the skin than UVB and contributes to sun-induced skin aging. Certain chemicals including psoralens (q.v.) interact with UVA, a property which is used in PUVA (q.v.) treatment of psoriasis.

UVB phototherapy

Treatment involving measured doses of UV light in the UVB wavelength. Two types are broadband UVB, and the increasingly used narrow-band UVB. Both are used to achieve clearance of psoriasis.

Variance

A measure of the variation shown by a set of observations, defined by the sum of the squares of deviations from the mean, divided by the number of degrees of freedom in the set of observations.

Visual analogue scale

Direct rating where raters are asked to place a mark at a point between two anchor states appearing at either end of the line. It is used as a method of valuing health states.

Weighted mean difference (in meta-analysis)

A method of meta-analysis used to combine measures on continuous scales, where the mean, standard deviation and sample size in each group are known. The weight given to each study is determined by the precision of its estimate of effect and, is equal to the inverse of the variance. This method assumes that all of the trials have measured the outcome on the same scale.

1 Aim of the review

To evaluate the clinical effectiveness, safety, tolerability and cost-effectiveness of etanercept and efalizumab for the treatment of moderate to severe chronic plaque psoriasis.

2 Background

2.1. Description of underlying health problem

Epidemiology

Psoriasis is a common inflammatory skin disease, with estimates of its world prevalence ranging from 0.5 to 4.6%.¹ There are few data on the prevalence and incidence of psoriasis in the UK. The only nationally representative data comes from the Morbidity Statistics from General Practice,² which covered a 1% sample of the population in England and Wales and collected data from 60 general practitioner (GP) practices. For 1991/92, the study reported a prevalence rate for ‘psoriasis and similar disorders’ of 24 per 10,000 persons (i.e. 0.24%) and an incidence rate of 48 per 10,000 years at risk. Two local surveys conducted in London (1975) and Leicestershire (1995) found prevalence point rates of 1.6%³ and 1.48%⁴ respectively.

Psoriasis generally occurs in adults; a survey conducted in the USA reported a median age of onset of 28 years.¹ However the same survey found that one quarter of those affected had experienced symptoms before the age of 18 years.¹ Males and females are equally commonly affected by the condition, however, females are more likely to regard their disease as severe.¹ Ethnic variations have been identified and Caucasians are more likely to suffer from the disease.¹

Plaque psoriasis or psoriasis vulgaris, characterised by clearly demarcated, red, scaling plaques, is the most common form of psoriasis, occurring in more than 80% of cases.¹

2.2 Aetiology, pathology and prognosis

Psoriasis is considered multifactorial disease in which several genetic and environmental factors interact.¹ Large scale epidemiological studies investigating family links and studies of twins provide observational evidence for a genetic component for psoriasis.⁵ A specific psoriasis gene has not yet been identified but research has identified several chromosomal locations associated with a predisposition to psoriasis. However, possession of a 'psoriatic gene' does not necessarily lead to the onset of psoriasis; it is well established that in some cases an external trigger, such as emotional stress or an infection, is responsible for initiating the disease.⁵

Psoriasis is both an epidermal and an immunological disease.¹ It was for many years considered to be primarily a disorder that involved the proliferation of keratinocytes with secondary inflammation.⁶ However, the success of the immuno-suppressive agent ciclosporin in the treatment of psoriasis led to the understanding that it is a disorder of the immune system, involving the abnormal activation of T cells.⁷ T cells are key surveillance elements of the immune system that proliferate during a first encounter with an infectious agent or other foreign antigen.⁷ The normal activity of T cells in maintaining immunity is amplified in psoriasis patients, in whom activated T cells are pathogenic. Once the pathogenic T cells have entered the skin, they become activated and release cytokines and chemokines to attract other immune cells to perpetuate the inflammatory cascade, leading to the inflammation of the skin and excessive production of skin cells.⁷

Plaque psoriasis is characterised by well-demarcated erythematous scaling plaques.⁸ Psoriatic plaques occur most often symmetrically on elbows, knees, lower back, and buttocks. In addition the scalp, nails, intertriginous areas, and genitalia are often involved.⁸ The extent of involvement can escalate to full body coverage in more severe cases. When only small areas are involved, lesions are often asymptomatic. Extensive body coverage with very thick, or more inflamed lesions is more likely to itch, be tender, or bleed.⁸

Other forms of psoriasis include inverse psoriasis, characterised by erythematous scaling plaques in flexural sites such as axillae; guttate psoriasis, which often arises after a streptococcal infection and is characterised by numerous erythematous scaling papules; palmoplantar pustular psoriasis (palmoplantar pustulosis), characterised by painful erythema with pustules involving the palms and soles; generalised pustular psoriasis characterised by sterile pustules covering large portions of the trunk and extremities, which in severe cases can become confluent, and erythrodermic psoriasis, where the majority of the skin surface is acutely inflamed.¹ The latter two forms of psoriasis may be associated with generalised systemic symptoms including malaise, high fever, and heart failure; they may be precipitated by withdrawal of systemic corticosteroids.¹

Psoriasis is usually classified as mild, moderate or severe, according to the proportion of the skin affected and the redness, thickness and scaling of the plaques. Assessment of psoriasis severity is not an exact science and the definition of 'severe' will inevitably differ, both amongst and between dermatologists and patients.⁹ If one adheres to strict clinical criteria then moderate psoriasis could be defined as psoriasis affecting at least 10% of skin surface area or having a Psoriasis Area Severity Index (PASI) score of 10-20. Severe psoriasis could be defined as psoriasis affecting at least 20% of skin surface area or having a Psoriasis Area Severity Index (PASI) score of >20. Understandably this is a subjective assessment and furthermore, the effect of psoriasis on the patient's quality of life has to be taken into account. It is important to realise that difficult to treat psoriasis does not necessarily equate with disease severity or extent. For instance a patient with relatively minimal extent psoriasis may be severely psychosocially disabled by the disease and have unrealistic expectations of cure or response to treatment. Another patient with moderate disease may have failed to respond to and/or to tolerate a variety of treatments. A holistic approach may incorporate psychosocial disability and historical response to treatment as well as clinical extent in the definition of severe psoriasis.⁹

Psoriasis is a chronic, life-long disease that varies in severity even when not treated. To date there are few treatments that induce very long-term remissions. The majority of patients with psoriasis will have limited areas of affected skin, which are amenable to topical treatment. However, many patients do require additional treatment, either

because of the severity or extent of disease or because of the detrimental effect it has on their psychosocial health.

Significance in terms of ill-health

It is unclear whether psoriasis is associated directly with excess mortality¹ but there may be an association through increased rates of smoking and alcohol consumption.¹⁰ The health-related quality of life (HRQOL) of people with psoriasis has been shown to be significantly worse than that of healthy adults.^{11, 12} In a Norwegian study of adults with psoriasis, scores were statistically significantly lower than those of the general population on all dimensions of the SF-36 (see table 2.1), after adjusting for age, gender, educational level and marital status. The largest difference between the two groups was on the 'role, emotional' scale.¹³

The extent to which psoriasis affects HRQOL is similar to that of other chronic diseases, such as depression, post myocardial infarction, hypertension, congestive heart failure or type II diabetes.¹⁴ Psoriasis has a particularly negative impact on mental health, although its physical impact appears greater than for people with hypertension or diabetes.¹⁴ Compared with other dermatological diseases, psoriasis appears to have less impact on HRQOL than atopic dermatitis,^{15, 16} but more impact than acne, basal cell carcinoma or viral warts.¹¹

There appears to be a broad, inverse correlation between psoriasis severity and HRQOL,^{14, 17} but this does not account for all or even most of the variability in HRQOL.¹² A small US study found no correlation between disease severity, measured by the PASI or SAPASI, and quality of life, as measured by the EQ-5D, the SF-36 or the subjective well-being scale (SWB).¹⁸ Research in the UK also found no relationship between severity and HRQOL (as measured by the EQ-5D VAS).¹⁹ However, these studies may have been too small to detect any true between-group differences. The impact of disease on people with psoriasis appears not to be directly related to body surface area affected or to sign scores (e.g. degree of scaling), but rather to the site affected and to patient attitudes.²⁰ HRQOL appears to be directly related to sufferers' ability to cope with social aspects of the disease,²¹ and the anticipation of stigmatization is an important predictor of disability.²²

Evidence for associations between the impact of psoriasis on HRQOL and demographic factors is mixed. There is some evidence, all based on US research, that the impact of psoriasis varies with age: the psychosocial impact of psoriasis appears greater in younger people, whilst its physical impact is greater in those over 55.^{23, 24} Psychosocial effects may be greater in women than in men,¹⁵ although evidence for this is mixed.²⁴ One study found that gender correlated with only two of the eight scales on the SF-36, namely 'physical functioning' and 'role emotional'.¹² UK researchers used the SF-36 and the Psoriasis Disability Index to demonstrate an inverse association between social class and degree of disability.²⁵ However, a US study of 87 patients at a tertiary medical clinic, in which three quality of life instruments were assessed, found no relationship between HRQOL and any demographic variable, including age, gender and education.²⁶

The economic impact of psoriasis in terms of out-of-pocket expenses increases with severity²⁷ and the effect is greater in lower income groups.²³ A UK study of people with severe psoriasis found that around 60% had taken time off work in the previous year as a direct result of their condition. The average (median) time off work was 20 days, although this ranged from one day to 100 days.²⁸ US research focusing on people with severe disease found that almost one-third had suffered some financial distress as a result of their psoriasis.²³ Men apparently face greater work-related stress as a result of their psoriasis, reporting a higher incidence of criticism than women for taking time off work for medical appointments.²⁴

2.3 Outcome Measures

Assessment of the severity of psoriasis and its response to treatment is not straightforward. In our review we have focused on data derived using the PASI score, primarily because it is the assessment measure used in clinical trials. In clinical practice the ideal endpoint of treatment is clearance of psoriasis. Phototherapy, in particular PUVA and NBUVB can induce clearance of psoriasis in a majority of patients and the proportion of patients achieving clearance is therefore a reasonable measure of the relative efficacy of phototherapies. Unfortunately, phototherapy is not suitable for all types of psoriasis nor all patients and furthermore, due to an increased

risk of skin cancer there is a limited lifetime exposure to phototherapy. Unfortunately, the systemic therapies available cannot generally be expected to induce clearance²⁹ and so some other lesser, but still clinically meaningful measure of response is required.

The Psoriasis Area and Severity Index (PASI) has become the most common form of assessing psoriasis activity in psoriasis trials. Although it is widely used, it is acknowledged to have many deficiencies: its constituent parameters have never been properly defined; it is insensitive to change in mild to moderate psoriasis; estimation of disease extent is notoriously inaccurate; and the complexity of the formula required to calculate the final score further increases the risk of error. It combines an extent and a severity score for each of four body areas (head, trunk, upper extremities and lower extremities). The extent score of 0-6 is allocated according to percentage skin involvement such that 0 and 6 represent no psoriasis and 90-100% involvement respectively. The severity score of 0-12 is derived by adding scores of 0-4 for each of the qualities erythema (redness), induration and desquamation representative of the psoriasis within the affected area. It is probable but usually not specified in trial reports that most investigators take induration to mean plaque thickness without adherent scale and desquamation to mean thickness of scale rather than severity of scale shedding. The severity score for each area is multiplied by the extent score and the resultant body area scores, weighted according to the percentage of total body surface area which that body area represents (10% for head, 30% for trunk, 20% for upper extremities and 40 % for lower extremities), are added together to give the PASI score. Although PASI can theoretically reach 72, scores in the upper half of the range (above 36) are uncommon even in severe psoriasis.

In clinical trials of psoriasis treatments no definitive measure of treatment success has been identified,³⁰ The majority of recent trials of systemic therapy of psoriasis with drugs such as ciclosporin or oral retinoids have used a 75% reduction in baseline PASI score (PASI 75) as the primary success criterion and may also report PASI 90 (a 90% reduction in baseline PASI score), which equates to clear or minimal residual activity as reported in many phototherapy trials. More recently the Medical Advisory Board of the National Psoriasis Foundation in the USA concluded that a 50% reduction in baseline PASI score (PASI 50) can be considered to represent a clinically

significant improvement and is associated with improvements in quality of life scores.³¹ Also in clinical trials PASI 50 has been demonstrated discriminatory power between active treatment and placebo.³¹ However the use of PASI 50 as a primary measure of efficacy in psoriasis remains controversial and is not accepted by the European Medicines Evaluation Agency (EMA). Consequently our review will take PASI 75 as the primary outcome measure but will also examine trial data using a range of success criteria derived from PASI including PASI 90.

This still leaves the question of what constitutes a good level of efficacy for a given intervention: for example should a drug be considered effective if 50% of patients achieve a PASI 50? It could be taken that any statistically significant benefit over placebo is evidence of efficacy,³⁰ but this is unlikely to gain general acceptance.

Whatever the problems with PASI, it does offer some degree of objective assessment of psoriasis severity. PASI does not, however, correlate with the patients' perceived quality of life, which can differ among all degrees of disease severity. Assessing HRQOL in people with psoriasis is important for three main reasons. First, it encourages patient-centred care by acknowledging patients' views, conveying the physician's interest in the patient and informing consultations.^{32,33} Second, HRQOL measurement can help clinicians, by informing decision-making³³ and helping to determine the effectiveness of treatments in routine practice.¹¹ Third, HRQOL measures can be decision tools for policy makers who need to allocate limited resources.^{11,32} Table 2.1 gives an overview of the generic, dermatology-specific and psoriasis-specific HRQOL measures used in international psoriasis research. Measures vary considerably in the number of items and domains included, as well as in the assessment period used.

The Dermatology Life Quality Index (DLQI) is frequently used to measure quality of life in adult psoriasis sufferers (aged 16 and above). This questionnaire consists of 10 questions that cover 6 areas of the patient's life that may be affected by the disease; these include symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. The worst possible quality of life score is 30, the best being 0.³⁴

Table 2.1: Quality of life measures used in psoriasis

Type of Instrument	Name of instrument	Acronym	Items (domains)	Assessment period	Studies
Generic	ALLTAG questionnaire on everyday life	ALLTAG	40 (6)	1 week	Augustin, 1999 ¹⁶
	EuroQol	EQ-5D	(-) 5	Current	Weiss, 2002 ¹⁸ ; Kernick, 2000 ¹⁹
	General Health Questionnaire	GHQ	12 (-)	Recent experience	Finlay, 1990 ³⁵ ; Sampogna, 2004 ³⁶
Dermatology-specific	Medical Outcomes Study 36-item Short Form Health Survey	SF-36	36 (8)	Typical day 4 weeks	Nichol, 1996 ³⁷ ; De Korte, 2002 ³⁸ ; Finlay, 2003 ³⁹ ; Lundberg, 1999 ⁴⁰
	Nottingham Health Profile	NHP	38 (6) + impact on daily life	General experience	Morgan, 1997 ⁵ ; Badia, 1999 ⁴¹
	Sickness Impact Profile	SIP	136 (12)	Current	De Korte, 2002 ³⁸ ; Finlay, 1997 ⁴²
	WHO Quality of Life Index	WHOQOL	96 (6) + 4 'general items'	Current	Momberts, 1997 ¹⁷ ; WHOQOL group, 1998 ⁴³
	Adjustment to Chronic Skin Disease Questionnaire	ACS	51 (5)	Current	Augustin, 1999 ¹⁶ ; Stangier, 2003 ⁴⁴
	Children's Dermatology Life Quality Index	CDLQI	10 (-)	1 week	Lewis-Jones, 1995 ⁴⁵
	Dermatology Life Quality Index	DLQI	10 (-)	1 week	Nichol, 1996 ³⁷ ; De Korte, 2002 ³⁸ ; Finlay, 1994 ¹¹
	Dermatology Quality of Life Scales	DQOLS	41(3)	Current / 1 week	Finlay, 2003 ³⁹ ; Morgan, 1997 ¹⁵
	Dermatology Specific Quality of Life Instrument	DSQL	52 (7)	4 weeks	De Korte, 2002 ³⁸ ; De Tiedra, 1998 ⁴⁶
	Freiburg Life Quality Assessment for Chronic Skin Disease	FLQA-d	54 (6)	Unclear	Augustin, 1999 ¹⁶
	Qualita di Vita Italiana	QUAVIDERM	11 (-)	4 weeks	De Tiedra, 1998 ⁴⁶
Psoriasis-specific	Skindex-29	-	29 (3)	4 weeks	De Korte, 2002 ³⁸ ; De Tiedra, 1998 ⁴⁶
	Impact of Psoriasis Questionnaire	IPSO	16 (3)	4 weeks	McKenna, 1997 ⁷ ; Sampogna, 2004 ³⁶
	Psoriasis Disability Index	PDI	15 (5)	Unclear	Koo, 2002 ³² ; Finlay, 1990 ^{35, 37} ; Finlay, 1995 ²⁸
	Psoriasis Disability Scale	PLSI	36 (-)	Unclear	Momberts, 1997 ¹⁷ ; Nichol, 1996 ³⁷
	Psoriasis Life Stress Inventory	PLSI	15 (-)	4 weeks	Fleischer, 1997 ⁴⁸
	Psoriasis Quality of Life	POOL	41 (2)	Current	Koo, 2002 ³² ; Fortune, 1997 ⁴⁹ ; Sampogna, 2004 ³⁶
	Psoriasis(-related) Stressor Scale	PRSS	20 (-)	Unclear	Fleischer, 1997 ⁴⁸

Although assessment of treatment efficacy in psoriasis is difficult and complex the outcome measures used in this review, namely PASI 50, PASI 75, PASI 90, clearance and DLQI cover the most important aspects of the impact of psoriasis on health, and all have discriminatory ability and are generally accepted measures of efficacy.

2.4 Current service provision

There are many different treatment options for psoriasis sufferers depending on the severity of the condition, the extent of body surface area affected, and the response to prior treatment. Topical applications are generally used as a first line approach to alleviating symptoms, especially in mild cases of psoriasis. Topical agents that are currently used in practice include; emollients (for mild limited disease), corticosteroids, salicylic acid, coal tar, vitamin D analogues, retinoids, and dithranol. These treatments are non-invasive and the main safety concern is skin atrophy, which is associated with the use of potent corticosteroids. When psoriasis is refractory to topical treatments or too widespread, phototherapy or systemic therapies are indicated.¹ Topical agents are commonly used as an adjunct to systemic therapy.

It has been known for much longer than psoriasis has been recognised as an entity that natural sunlight (heliotherapy) may be beneficial for skin disease. The value of natural sunlight is well recognised by psoriasis sufferers. Artificial sunlight in the form of broad-band ultraviolet B (UVB) emitting lamps has been used for over a century to treat psoriasis, often in combination with tar or dithranol, and has a good safety record. Ingram's regimen, which involves regular UVB exposure followed by application of dithranol (anthralin) paste to the skin, and Goeckerman's regimen, which involve UVB exposure followed by application of crude coal tar, were developed as inpatient therapies but are now more commonly administered in a day-case setting. Photochemotherapy, where a photosensitiser in the skin interacts with long-wave ultraviolet (UVA), was introduced some four decades ago in an attempt to increase efficacy of UV treatment. The most commonly used photosensitiser is a plant-derived chemical, psoralen, which can be given either as a tablet or as a topical application. Once the psoralen has penetrated into the skin, the patient receives UVA irradiation from special UVA emitting tubes (PUVA therapy). PUVA is effective at clearing psoriasis in a large proportion of treated patients and became very popular in

the 1970s and 1980s. It is still widely used but with the recognition that prolonged therapy significantly increases the risk of developing skin cancers, it is now normally limited to no more than 200 exposures in a lifetime (approximately six to nine treatment courses). More recently, a modification of broad-band UVB therapy has been introduced in an attempt to maximise the biological effects on psoriasis but reduce the overall energy required for clearing psoriasis; narrow-band UVB (NBUVB) phototherapy employs special lamps, which emit UVB in a narrow wavelength spectrum within the UVB range. It appears to have comparable efficacy to PUVA but, it is believed, will be much less likely to increase the risk of skin cancer. NBUVB is increasingly supplanting PUVA therapy in dermatology departments in the United Kingdom.

Systemic treatments that are widely used in the treatment of moderate to severe psoriasis include retinoids, methotrexate and ciclosporin. All have potential long-term side effects including hypertension and renal toxicity with ciclosporin and liver fibrosis and cirrhosis with methotrexate.^{50, 51} This may limit the length of time for which they may be used in an individual patient.

2.5 Current service cost

The cost to the NHS of treating psoriasis includes direct costs, such as the cost of drugs, clinician (nurse, GP and hospital doctor) time, the cost of daycare therapies, such as phototherapy, Ingram and Goeckerman regimens and the cost of administering and monitoring drugs. Patients may also require hospital admission, with an average length of stay of around 20 days.⁵²

In 2003, there were approximately 967,200 prescription items for psoriasis dispensed in the community at a cost of £27.8 million.⁵³ The average cost of per prescription item was £28.76, but this ranged from £1.58 for salicylic acid to £79.05 for acitretin. Drugs such as ciclosporin, methotrexate and corticosteroids have multiple indications and the expenditure on these drugs for psoriasis is not reported. Moreover, data on drug expenditure in hospitals is not available. Therefore the true cost of annual drug expenditure on psoriasis is likely to be higher than £27.8 million.

There have been a number of UK economic evaluations of treatments for psoriasis. Ashcroft and colleagues (2000)⁵⁴ compared the cost effectiveness of topical calcipotriol (annual cost, £96) against short contact dithranol (annual cost, £31). Cockayne and colleagues (1999)⁵⁵ estimated the annual cost of hospital care, comprising labour costs (medical, domestic, porter, nurse), catering, laundry, maintenance and site overhead costs. Drug costs and costs incurred by patients were excluded from the analysis. Data was derived from an audit of a day care centre, with matched inpatient controls and informed by a survey of eight dermatology departments in the UK.⁵⁶ The mean day care cost per patient was £1186 (95%CI: £971 - £1401) and the mean inpatient care cost was reported to be £2681 (95%CI: £2221 - £3141). Cork (1993)⁵⁷ estimated the annual per patient hospital costs for PUVA (£562), methotrexate (£876), and Goeckerman (£222). Davies and colleagues (1997)⁵⁶ compared the costs of ciclosporin with day care treatment using dithranol or Goeckerman treatments. Assessing direct NHS costs, including drugs, outpatient visits, day care costs and treatment of adverse events, they reported 8-month costs for ciclosporin (£2000) and day care (£3500).

Patients also incur out of pocket expenses and may need to take time off work to attend hospital appointments (see section 2.2).

2.6 Variation in services

Around 445 dermatologists work in NHS hospitals in the UK.⁵⁸ Dermatology departments range from smaller units in a local hospital to large units, which are most often located in the large teaching hospitals. A consultant dermatologist may supervise other doctors working in a dermatology unit, such as dermatological specialists from various disciplines, doctors undergoing the specialist dermatology training, and GPs with a special interest in the subject. Specialist nurses may provide certain types of intensive treatment to patients and allergy testing services.

Some centres have tertiary services for eczema and psoriasis; these take referrals from other dermatologists. The need for newer drugs is likely to be greatest in these centres.

Few UK studies have been conducted to establish variation in dermatology service provision and no survey reporting an audit of national provision for psoriasis patients was found. The British Association of Dermatologists conducted an audit of atopic eczema management in secondary care.⁵⁹ A postal survey was sent to 187 dermatology centres in England and Scotland and a response rate of 98% was achieved. Ninety-two percent of the responding centres had trained nurses, and 57% had dermatology nurses. Photo-chemotherapy units were present in 92% of centres, 90% reported rapid access facilities to a hospital specialist and 82% provided information sheets to patients. These structural features are also relevant for the treatment of psoriasis.

2.7 Description of new intervention

Treatment for psoriasis has more recently focused on eliminating activated T cells, inhibiting activated T cells, or inhibiting cytokine secretion or activity.⁷ These treatments are known as biological agents as they consist of proteins created by living cells. Due to their protein nature they cannot be given orally and are usually administered by subcutaneous, intravenous or intramuscular injection. Etanercept, one of the new biological treatments, works by binding to the postsecretory cytokine Tumor Necrosis Factor alpha (TNF α) thereby inhibiting its action; psoriasis patients are found to have increased concentrations of this factor. Etanercept is classed as a receptor antibody fusion protein.^{60, 61} Efalizumab is another biological agent that has been found to inhibit inflammatory cell function by blocking T cell activation or migration.^{60, 61}

Their agent class and therapeutic strategies are summarised below.

Generic name	Class	Target	Therapeutic strategy
Etanercept	Receptor antibody fusion protein	Binds the postsecretory cytokine TNF α *	
Efalizumab	Humanized monoclonal antibody	Anti CD11a subunit of LFA-1. Blocks T cell activation or migration	

* TNF α =Tumour necrosis factor α . This is one of a number of cytokines that stimulate the dendritic cells, macrophages and keratinocytes and maintains the inflammatory state.

(Adapted from Pariser 2003⁶¹ and Gniadecki 2002⁶⁰)

In the United Kingdom both etanercept (Enbrel®) and efalizumab (Raptiva®) are licensed for treatment of adults with moderate to severe plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other

systemic therapy including ciclosporin, methotrexate or PUVA. The product licence for etanercept⁶² states that the recommended dose for etanercept is 25 mg administered twice weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary by a dose of 25 mg twice weekly. Treatment with Enbrel® should continue until remission is achieved, for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

The product licence for efalizumab⁶³ states that treatment with efalizumab should be initiated by a physician specialised in dermatology. An initial single dose of 0.7 mg/kg body weight is given followed by weekly injections of 1.0 mg/kg body weight (maximum single dose should not exceed a total of 200 mg). The duration of therapy is 12 weeks. Therapy may be continued only in patients who respond to treatment.

Anticipated costs

The total annual per-patient drug cost for etanercept (25 mg/kg twice weekly) would be £4,290 if patients received two twelve week courses per year (i.e. 12 weeks on treatment, followed by 12 weeks off treatment).⁶⁴ If etanercept is used continuously, this cost rises to £9,296. The total annual per-patient drug cost for efalizumab (1 mg/kg once weekly) is £8798.40. There is no definitive estimate of the numbers of patients eligible for these treatments that would enable a total expected cost for the NHS to be calculated.

3 Methods

3.1 Search strategy

Searches were undertaken on the following databases to identify relevant clinical and cost-effectiveness literature. Full details of the search strategies are reported in Appendix 10.1. Searches took place over a period of time from April to July 2004 (see appendix 10.1. for dates of individual searches).

- Medline and In-Process Citations (OVID Online)
- Embase (OVID Online)
- National Research Register (NRR) (cd-rom)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the internet)
- CenterWatch (internet - <http://www.centerwatch.com/index.html>)
- Current Controlled Trials (internet - <http://controlled-trials.com/>)
- ClinicalTrials.gov (internet - <http://clinicaltrials.gov/>)
- NHS Economic Evaluation Database (NHS EED) (CRD administration database)
- Health Economic Evaluation Database (HEED) (cd-rom)
- EconLit (SilverPlatter on the web)
- ISI Science and Technology Proceedings (Web of Knowledge - <http://wos.mimas.ac.uk/>)
- Social Science Citation Index (Web of Science - <http://wos.mimas.ac.uk/>)
- Science Citation Index (Web of Science - <http://wos.mimas.ac.uk/>)

All databases were searched from their inception to the date of the search. Searches were also undertaken on several Internet resources, which are documented in Appendix 10.1.

Terminology

The terms for the search strategies were identified through discussion between an Information Officer and the research team, by scanning the background literature, and

by browsing the Medline Thesaurus (MeSH). No language or other restrictions were applied.

Management of references

As several databases were searched, some degree of duplication resulted. In order to manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into Endnote bibliographic management software to remove duplicate records.

Handsearching

The bibliographies of all included studies and industry submissions made to NICE were reviewed to identify further relevant studies. Handsearching continued throughout the project.

3.2 Inclusion and exclusion of studies

3.2.1 Study selection

Two reviewers selected the studies for the review. Discrepancies were resolved by consensus and a third reviewer was consulted when necessary.

All titles and abstracts identified by the search were screened and any references that were considered relevant by either reviewer were obtained.

No language restrictions were applied to study selection. Trials reported as full publications or unpublished full reports were included in the review. Trials reported as abstracts only were to be included if adequate information was provided. All of the data submitted by Wyeth and Serono were considered in the review.

3.2.2 Inclusion/ exclusion criteria

3.2.2.1 Efficacy of interventions

The review addressed the following questions about the efficacy of etanercept and efalizumab in the treatment of moderate to severe psoriasis:

- Is the drug effective at all?
- How effective is it?
- Can the drugs be used long-term?
- How long is remission and is there any rebound if active treatment is replaced with passive treatment?
- How effective is retreatment in patients who have relapsed following an earlier treatment period?

Studies were included in the review according to the inclusion criteria described in the following paragraphs.

Intervention

Etanercept and efalizumab administered by subcutaneous injection were the interventions of interest. Comparisons with either placebo or any other active agent were eligible for inclusion.

Participants

Studies of adults with moderate to severe psoriasis were included. These patients are usually defined as having an inadequate response to topical treatments alone and to have either received prior systemic therapy or phototherapy or are candidates for such therapy.

Study design

Only randomised controlled trials were included in the evaluation of efficacy.

Outcomes

The outcomes of primary interest were those derived from the Psoriasis Area and Severity Index (PASI). Data on the following outcomes were also eligible in the review of efficacy: Physician's Global assessment (PGA); patient-centred outcome measures; Self Administered Psoriasis Area and Severity Index (SAPASI); Psoriasis Disability Index (PDI); Total Severity Score (TSS); Investigator's Assessment of

Global Improvement (IAGI); quality of life (QoL); Dermatology Life Quality Index (DLQI); duration of remission.

3.2.2.2 Adverse effects of interventions

Adverse events data was summarised from key sources and existing reviews. This was supplemented by a systematic review of adverse events data from clinical studies. Studies were included in the systematic review according to the inclusion criteria described in the following paragraphs. The reference details and reasons for exclusion of studies are presented in Appendix 10.3.

Intervention

Etanercept and efalizumab administered by subcutaneous injection were the interventions of interest. Studies with any comparator (placebo or any other active agent) or no comparator were eligible for inclusion.

Participants

Studies of adult patients receiving treatment for any of the following indications were eligible: psoriasis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and any other indication except cancer or transplantations.

Study design

Long-term experimental and observational studies of at least 24 weeks duration and including a minimum of 100 patients were included in the review. Studies or data without a denominator were excluded from the review. In addition adverse event data from the trials of efficacy of etanercept and efalizumab were also included.

Outcomes

All adverse event data were considered in the review.

3.2.2.3 Other treatments for moderate to severe psoriasis

In an attempt to put into context the evidence base for the efficacy of etanercept and efalizumab we investigated the evidence available for other treatments for moderate to severe psoriasis. Studies were included in the review according to the inclusion criteria described in the following paragraphs.

Treatments

All of the following oral systemic agents were eligible as other treatments for moderate to severe psoriasis: ciclosporin, methotrexate, acitretin, hydroxycarbamide, Fumaderm, and infliximab. It must be noted for this review we did not assume that etretinate, the ester of acitretin was the same as acitretin and that trials of etretinate reviewed. Photochemotherapy (PUVA), RePUVA (retinoid + PUVA), Narrow-band UVB, acitretin plus calcipotriol, Ingram regimen (daily in-hospital phototherapy + dithranol (anthralin)), and Goeckerman regimen (daily in-hospital phototherapy + coal tar) were also considered relevant treatments. All of the above therapies were considered as monotherapy only, with the exception of acitretin plus calcipotriol, as this combination is recognised clinically as a single treatment. Only trials in which the control agent was placebo, etanercept, efalizumab, or any of the other treatments for moderate to severe psoriasis listed above were included in the review. Trials that compared different regimens of the same treatment or compared a treatment with or without a concomitant agent were not included in the review; all such trials identified are listed under excluded studies in Appendix 10.3.

Participants

Studies of adults with moderate to severe plaque psoriasis were included. These patients are usually defined as having an inadequate response to topical treatments alone and have either received prior systemic therapy or phototherapy or are candidates for such therapy.

Study design

Only randomised controlled trials were included in the evaluation of other treatments for moderate to severe psoriasis.

Outcomes

The outcomes of primary interest were those derived from the Psoriasis Area and Severity Index (PASI). Other outcomes included in the review are listed above under the ‘efficacy of interventions’ section.

3.2.2.4 Economic evaluations – systematic review

Studies were eligible for inclusion if they assessed both the costs and benefits of either efalizumab or etanercept and compared findings with an appropriate comparator treatment.

3.2.3 Data extraction strategy

All data were extracted by one reviewer and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus, and by consulting with a third reviewer if necessary. Data were extracted onto pre-designed forms. Data from studies with multiple publications were extracted and reported as from a single study. Any ‘commercial in confidence’ data taken from the company submission is clearly marked in the NICE report (underlined and followed by an indication of the relevant company name e.g. in brackets) and removed from the subsequent submission to the HTA.

For the efficacy trials the following details were extracted from each trial:

- Study details (author, year, country, type of publication, other publications/reports, funding, study design, setting, duration of trial follow-up, frequency of follow-up, sample size calculation, analyses);
- Participant details (number randomised and treated, age, gender, psoriasis history, duration of psoriasis, prior systemic therapy, concurrent therapies);
- Details of Intervention;
- Results and Outcomes.

For the adverse effects studies the following details were extracted:

- Study details (author, year, country, type of publication, other publications/ reports, funding, study design, duration of trial follow-up, study objective);
- Participant details (indication, inclusion criteria, number of participants, age, gender, concurrent therapies);
- Details of Intervention;
- Adverse event results (non-infectious adverse events, infectious adverse events including any serious infections, other non-infectious serious adverse events, deaths, withdrawals due to adverse events, positive test for anti-etanercept or anti efalizumab antibodies, other important adverse event results).

As the other treatments for moderate to severe psoriasis were not the primary focus of the review, we undertook only limited data extraction of the trials of these agents. The following details were extracted from each trial: study details (author, year, study design); participant details (psoriasis type, resistant to topicals/ require systemics? minimum BSA included, minimum PASI included, adult status, number of participants); details of treatment; results and outcomes.

For the economic evaluations data were extracted into a standard template, covering the timeframe used, types of costs included and their sources, measures of benefit and methods used to derive these, modelling undertaken and key findings.

3.2.4 Quality assessment strategy

3.2.4.1 Efficacy of interventions

The quality of trials was assessed by one reviewer and independently checked by a second reviewer. Disagreements were resolved through consensus, consulting a third reviewer if necessary.

The efficacy trials were assessed for quality using a checklist compiled from criteria specified in CRD Report No. 4. The quality of each study was summarised as a quality rating, classifying trials as: Excellent, Good, Satisfactory, or Poor. The checklist and quality ratings are detailed in Appendix 10.2.

3.2.4.2 *Adverse effects of interventions*

Due to the range of study designs included in the assessment and the limitation of the review to long-term large studies the quality of adverse events studies was not assessed.

3.2.4.3 *Other treatments for moderate to severe psoriasis*

The quality of the trials of other treatments for moderate to severe psoriasis was not assessed.

3.2.4.4 *Economic evaluations – systematic review*

Data were extracted into a quality assessment template, covering selection of alternatives, treatment of costs and benefits (including any modelling undertaken), use of discounting, allowance for uncertainty and presentation of results. The checklist is an updated version of that developed by Drummond et. al.⁶⁵

3.2.5 Data analysis

3.2.5.1 *Efficacy of interventions*

Full data extraction and quality assessment have been presented for each efficacy trial of etanercept and efalizumab.

Results have been summarised in tables and the effect of trial quality on the efficacy findings is discussed. Relative risks (RRs) and mean differences were calculated for the primary outcomes with 95% confidence intervals (CIs); the primary outcome variables were PASI 50, PASI 75, PASI 90, % clear/almost clear, mean PASI, % change in mean PASI from baseline, and % change in DLQI.

Clinical diversity of the trials regarding adult status, minimum PASI score, body surface area (BSA) affected, previous treatments, and concomitant medication was considered. Where the trials were not clinically diverse (heterogeneous) the data were

pooled. Statistical heterogeneity was investigated using the Chi-Squared test; where it was statistically significant data were not pooled. Where pooling was appropriate pooled RRs (95% CI) or weighted mean differences (WMD) (95% CI) were calculated using a fixed effect model. A fixed effect model was selected because a small number of trials were included in the meta-analysis, and a fixed effect model is therefore considered most appropriate due to the smaller estimation of between-study variance.⁶⁶

An evidence synthesis drawing upon data on the efficacy of etanercept, efalizumab and other treatments for moderate to severe psoriasis was conducted. Further details of this synthesis are presented in section 4.5.

3.2.5.2 Adverse effects of interventions

Results have been summarised in tables and the findings are discussed in a narrative synthesis. Adverse events data have been grouped by duration of follow-up.

3.2.5.3 Other treatments for moderate to severe psoriasis

Data extraction has been presented for each comparator trial. Results have been summarised in tables and the findings are discussed. Relative risks (RRs) and mean differences were calculated for the primary outcomes with 95% confidence intervals (CIs); the primary outcome variables were PASI 50, PASI 75, PASI 90, % clear/almost clear, mean PASI, and % change in mean PASI from baseline. Physician global assessment was used in one study in the absence of any of the above outcomes. The findings were not pooled statistically as a result of the clinical diversity of the trials and the small numbers of studies investigating the same comparison.

An evidence synthesis drawing upon data on the efficacy of etanercept, efalizumab and other treatments for moderate to severe psoriasis was conducted. Further details of this synthesis are presented in section 4.5.

3.2.5.4 *Economic evaluations – systematic review*

Only one economic evaluation of an intervention drugs was identified. The study was not amenable to analysis because incremental data were not reported.

4 Clinical evaluation

4.1 Quantity of research available

The search strategies for efficacy, adverse events and comparator trials generated a total of 2808 references. Of these 353 references were ordered and a total of 85 references met the inclusion criteria for the efficacy, adverse events or comparator section of the review. These references provided information on a total of 39 studies: five trials of the efficacy of the interventions of interest; 10 studies of the adverse effects of the interventions; and 24 trials of the efficacy of the other treatments for moderate to severe psoriasis. In addition, the company submissions from Wyeth⁶⁷ and Serono⁶⁸ provided details of three further trials of efficacy.

4.2 Efficacy of interventions

4.2.1 Efficacy of etanercept

Three RCTs were included in the review.⁶⁹⁻⁷¹ All three trials were double-blind and rated as Good according to the quality assessment (see table 4.2.1). All three trials were placebo-controlled; no trials comparing etanercept with another active treatment were identified. Trial details are summarised in table 4.2.2 and presented in the data extraction tables (Appendix 10.4.1).

Table 4.2.1. Results of quality assessment for trials of etanercept

Quality assessment criteria	Reference		
	Leonardi, 2004, ⁶⁹ USA	Elewski, 2003, ⁷⁰ USA, Canada & Europe	Gottlieb, 2003, ⁷¹ USA
Eligibility criteria specified?	Y	Y	Y
Power calculation?	Y	Y	Y
Adequate sample size?	Y	Y	Y
Number randomised stated?	Y	Y	Y
True randomisation?	Y	Y	Y
Double-blind?	Y	Y	Y
Allocation of treatment concealed?	Y	Y	Y
Treatment administered blind?	Y	Y	Y
Outcome assessment blind?	Y	Y	Y
Patients blind?	Y	Y	Y
Blinding successful?	NS	NS	NS
Adequate baseline details presented?	Y	Y	Y
Baseline comparability?	Y	Y	Y
Similar co-interventions?	Y	Y	Y
Compliance with treatment adequate?	Y	Y	Y
All randomised patients accounted for?	Y	Y	Y
Valid ITT analysis?	Y	Y	Y
≥ 80% patients in follow-up assessment?	Y	Y	Y
Quality rating	<i>Good</i>	<i>Good</i>	<i>Good</i>

Y=yes; N=no; NS=not stated

Table 4.2.2. Details of included trials of etanercept

Reference	Participants	Duration	Intervention	Comparison	Outcomes
Leonardi, 2004,⁶⁹ USA	N=652 Adults Clinically stable plaque psoriasis; ≥10% BSA; baseline PASI ≥10	12 wks	Etanercept 25mg SC once a wk (n=160) Etanercept 25mg SC twice a wk (n=162) Etanercept 50mg SC twice a wk (n=164)	Placebo (n=166)	Proportion achieving PASI 50, PASI 75, PASI 90, Clear or almost clear Mean PASI score, % change in PASI score, % change in DLQI score
Elewski, 2003,⁷⁰ USA, Canada & Europe	N=583 Adults Clinically stable plaque psoriasis; ≥10% BSA; baseline PASI ≥10	12 wks	Etanercept 25mg SC twice a wk (n=196) Etanercept 50mg SC twice a wk (n=194)	Placebo (n=178)	Proportion achieving PASI 50, PASI 75, PASI 90, Clear or almost clear Mean PASI score, % change in PASI score, % change in DLQI score
Gottlieb, 2003,⁷¹ USA	N=112 Adults Clinically stable plaque psoriasis; ≥10% BSA	24 wks	Etanercept 25mg SC twice a wk (n=57)	Placebo (n=55)	Proportion achieving PASI 50, PASI 75, PASI 90, Clear or minimal Mean PASI score, % change in PASI score, % change in DLQI score

BSA=body surface area; PASI=psoriasis area severity index; DLQI=dermatology life quality index; SC=subcutaneous; wk=week

The trials were of adult patients, with active clinically stable plaque psoriasis involving at least 10% of the body surface area, who had been previously treated with at least one systemic therapy or phototherapy or were candidates for such therapy. In two of the trials a minimum PASI score of 10 was specified in order for patients to be included.^{69, 70} The number of patients in the trials ranged from 112 to 652. Across all treatment groups (etanercept and placebo) the populations did not display clinically significant differences in terms of disease characteristics: mean duration of psoriasis ranged from 18.3 to 23 years; mean baseline PASI score ranged from 17.8 to 19.5;

mean baseline BSA involvement ranged from 26.4% to 34%; and mean baseline DLQI score ranged from 10.1 to 13.8.

All three trials investigated etanercept at a dose of 25 mg SC twice a week. In addition, two trials examined a dose of 50 mg SC twice a week,^{69, 70} and one trial also looked at a dose of 25 mg SC once a week.⁶⁹

All three trials provided outcome data on the number of patients achieving PASI 50, PASI 75, PASI 90, and Clear or almost clear (includes ‘clear to minimal status’ as reported in one trial⁷¹). They also provided data on mean PASI score, mean percentage change in PASI score from baseline, and mean percentage change from baseline in DLQI score. All three trials assessed patient outcome after 12 weeks of treatment; one trial also assessed patient outcome at 24 weeks.⁷¹ In addition, the three trials were continued for extended periods in which open-label and/ or non-randomised designs were adopted.

Given the lack of clinical heterogeneity the data were pooled by outcome, dose and follow-up period, unless this was prevented by the presence of statistical heterogeneity.

4.2.1.1 PASI 50

Table 4.2.3. Proportion of patients achieving PASI 50

Reference	Etanercept	Placebo	RR (95% CI)
12 week follow-up, Etanercept 25 mg once a week			
Leonardi 2004 ⁶⁹	65/160 (40.6%)	24/166 (14.5%)*	2.81 (1.87, 4.27)
12 week follow-up, Etanercept 25 mg twice a week			
Leonardi 2004 ⁶⁹	94/162 (58.0%)	24/166 (14.5%)*	4.01 (2.74, 5.97)
Elewski 2003 ⁷⁰	(CiC information removed)	(CiC information removed)	(CiC information removed)
Gottlieb, 2003 ⁷¹	40/57 (70.2%)	6/55 (10.9%)	6.43 (3.14, 13.99)
Pooled RR			(CiC information removed)
Test for heterogeneity			
12 week follow-up, Etanercept 50 mg twice a week			
Leonardi 2004 ⁶⁹	121/164 (73.8%)	24/166 (14.5%)*	5.10 (3.53, 7.52)
Elewski 2003 ⁷⁰	(CiC information removed)	(CiC information removed)	(CiC information removed)
Pooled RR			(CiC information removed)
Test for heterogeneity			
24 week follow-up, Etanercept 25 mg twice a week			
Gottlieb 2003 ⁷¹	44/57 (77.2%)	7/55 (12.7%)	6.07 (3.15, 12.39)

*Where a trial had more than one intervention arm, results from the placebo arm have been reported more than once

The results for PASI 50 are summarised in table 4.2.3. (*CiC information removed*). Twelve-week data were pooled for etanercept 25 mg twice a week and etanercept 50 mg twice a week. Both resultant pooled fixed effects RRs (95% CIs) were statistically significant in favour of etanercept over placebo. Although, in both cases, the Q statistic indicated a small amount of statistical heterogeneity, this was not statistically significant.

4.2.1.2 PASI 75

Table 4.2.4. Proportion of patients achieving PASI 75

Reference	Etanercept	Placebo	RR (95% CI)
12 week follow-up, Etanercept 25 mg once a week			
Leonardi 2004 ⁶⁹	23/160 (14.4%)	6/166 (3.6%)*	3.98 (1.72, 9.32)
12 week follow-up, Etanercept 25 mg twice a week			
Leonardi 2004 ⁶⁹	55/162 (34.0%)	6/166 (3.6%)*	9.39 (4.30, 20.90)
Elewski 2003 ⁷⁰	67/196 (34.2%)	6/193 (3.1%)*	11.00 (5.04, 24.38)
Gottlieb 2003 ⁷¹	17/57 (29.8%)	1/55 (1.8%)	16.40 (2.98, 95.36)
Pooled RR			10.69 (95% CI: 6.15, 18.57)
Test for heterogeneity			Q=0.281 (df=2), P=0.869
12 week follow-up, Etanercept 50 mg twice a week			
Leonardi 2004 ⁶⁹	81/164 (49.4%)	6/166 (3.6%)*	13.66 (6.35, 30.04)
Elewski 2003 ⁷⁰	96/194 (49.5%)	6/193 (3.1%)*	15.92 (7.38, 34.95)
Pooled RR			14.80 (95% CI: 8.40, 26.06)
Test for heterogeneity			Q=0.070 (df=1), P=0.791
24 week follow-up, Etanercept 25 mg twice a week			
Gottlieb 2003 ⁷¹	32/57 (56.1%)	3/55 (5.5%)	10.29 (3.67, 30.57)

*Where a trial had more than one intervention arm, results from the placebo arm have been reported more than once

The results for PASI 75 are summarised in table 4.2.4. All treatment differences were statistically significantly in favour of etanercept over placebo. Twelve-week data were pooled for etanercept 25 mg twice a week and etanercept 50 mg twice a week. Both resultant pooled fixed effects RRs (95% CIs) were statistically significant in favour of etanercept over placebo. In both cases, the test for heterogeneity was not statistically significant.

4.2.1.3 PASI 90

The PASI 90 results are summarised in table 4.2.5. (*Confidential data removed.*) However the difference between etanercept 25 mg once a week at placebo was not statistically significant. Twelve-week data were pooled for etanercept 25 mg twice a week and for etanercept 50 mg twice a week. Both resultant pooled fixed effects RRs (95% CIs) were statistically significant in favour of etanercept over placebo. In both cases, the statistical test for heterogeneity was not statistically significant.

Table 4.2.5. Proportion of patients achieving PASI 90

Reference	Etanercept	Placebo	RR (95% CI)
12 week follow-up, Etanercept 25 mg once a week			
Leonardi 2004 ⁶⁹	5/160 (3.1%)	1/166 (0.6%)*	5.19 (0.82, 33.31)
12 week follow-up, Etanercept 25 mg twice a week			
Leonardi 2004 ⁶⁹	19/162 (11.7%)	1/166 (0.6%)*	19.47 (3.39, 113.77)
Elewski 2003 ⁷⁰	CiC removed	CiC removed	CiC removed
Gottlieb 2003 ⁷¹	6/57 (10.5%)	0/55 (0%)	12.54 (1.29, 126.64)
Pooled RR			(CiC information removed)
Test for heterogeneity			
12 week follow-up, Etanercept 50 mg twice a week			
Leonardi 2004 ⁶⁹	36/164 (22.0%)	1/166 (0.6%)*	36.44 (6.47, 209.39)
Elewski 2003 ⁷⁰	CiC removed	CiC removed	CiC removed
Pooled RR			CiC removed
Test for heterogeneity			
24 week follow-up, Etanercept 25 mg twice a week			
Gottlieb 2003 ⁷¹	12/57 (21.1%)	0/55 (0%)	24.12 (2.59, 236.69)

*Where a trial had more than one intervention arm, results from the placebo arm have been reported more than once

4.2.1.4 Clear or almost clear/ Clear to minimal

All three trials reported data on the number of patients rated as clear or almost clear in severity of psoriasis according to physician global assessment; the results are summarised in table 4.2.6. (*Confidential information removed.*) Twelve-week data were pooled for etanercept 25 mg twice a week and etanercept 50 mg twice a week. (*Confidential data removed.*) In both cases, the test for heterogeneity was not statistically significant.

Table 4.2.6. Proportion of patients achieving clear or almost clear

Reference	Etanercept	Placebo	RR (95% CI)
12 week follow-up, Etanercept 25 mg once a week			
Leonardi 2004 ⁶⁹	37/160 (23.1%)	8/166 (4.8%)*	4.80 (2.36, 9.89)
12 week follow-up, Etanercept 25 mg twice a week			
Leonardi 2004 ⁶⁹	55/162 (34.0%)	8/166 (4.8%)*	7.04 (3.55, 14.21)
Elewski 2003 ⁷⁰	CiC removed	CiC removed	CiC removed
Gottlieb 2003 ⁷¹	CiC removed	CiC removed	CiC removed
Pooled RR			9.87 (95% CI: 6.00, 16.22)
Test for heterogeneity			Q=1.795 (df=2), P=0.408
12 week follow-up, Etanercept 50 mg twice a week			
Leonardi 2004 ⁶⁹	81/164 (49.4%)	8/166 (4.8%)*	10.25 (5.26, 20.38)
Elewski 2003 ⁷⁰	CiC removed	CiC removed	CiC removed
Pooled RR, p			CiC removed.
Test for heterogeneity			Q=0.705 (df=1), P=0.401
24 week follow-up, Etanercept 25 mg twice a week			
Gottlieb 2003 ⁷¹	30/57 (52.6%)	CiC removed	CiC removed

*Where a trial had more than one intervention arm, results from the placebo arm have been reported more than once

4.2.1.5 Mean PASI score and Mean percentage change in PASI score from baseline

Table 4.2.7 Mean PASI score and Mean percentage reduction in PASI score from baseline

Reference	Etanercept Mean (SD)		Placebo Mean (SD)		Mean Difference (95% CI) for % reduction in PASI score from baseline
	Final (post-treatment) PASI score	% reduction in PASI score from baseline	Final (post-treatment) PASI score	% reduction in PASI score from baseline	
12 week follow-up, Etanercept 25 mg once a week					
Leonardi 2004 ⁶⁹	CiC removed	40.9 (30.36) (n=162)	CiC removed	14.0 (33.50)* (n=166)	26.9 (19.95, 33.85)
12 week follow-up, Etanercept 25 mg twice a week					
Leonardi 2004 ⁶⁹	CiC removed	52.6 (34.37) (n=162)	CiC removed	14 (33.50)* (n=166)	38.6 (31.26, 45.94)
Elewski 2003 ⁷⁰	CiC removed	CiC removed	CiC removed	CiC removed	CiC removed
Gottlieb 2003 ⁷¹	CiC removed	CiC removed	CiC removed	CiC removed	CiC removed
12 week follow-up, Etanercept 50 mg twice a week					
Leonardi 2004 ⁶⁹	6.5 (7.68)	64.2 (30.74) (n=162)	15.8 (9.02)*	14 (33.50)* (n=166)	50.2 (43.26, 57.14)
Elewski 2003 ⁷⁰	CiC removed	CiC removed	CiC removed	CiC removed	CiC removed
24 week follow-up, Etanercept 25 mg twice a week					
Gottlieb 2003 ⁷¹	CiC removed	67.0 (30.20) (n=57)	CiC removed	1.6 (51.91) (n=55)	65.4 (49.6, 81.2)

*Where a trial had more than one intervention arm, results from the placebo arm have been reported more than once
† standard deviation not reported or calculable.

The results for mean PASI score and mean percentage change in PASI score from baseline are summarised in table 4.2.7. (Confidential data removed). However, the data were highly skewed and therefore these results must be interpreted with caution. Because of this pooled WMDs were not calculated.

4.2.1.6 Mean percentage reduction (improvement) in DLQI score from baseline

Table 4.2.8. Percentage reduction (improvement) in DLQI score from baseline

Reference	Etanercept Mean (SD)	Placebo Mean (SD)	Mean difference (95% CI)
12 week follow-up, Etanercept 25 mg once a week			
Leonardi 2004 ⁶⁹	47.2 (36.68) (n=162)	10.9 (61.84) (n=166)*	36.3 (25.21, 47.39)
12 week follow-up, Etanercept 25 mg twice a week			
Leonardi 2004 ⁶⁹	50.8 (48.37) (n=162)	10.9 (61.84)* (n=166)*	39.9 (27.87, 51.93)
Elewski 2003 ⁷⁰	CiC removed	CiC removed	CiC removed
Gottlieb 2003 ⁷¹	61.2 (CiC removed) (n=57)	10 (CiC removed) (n=55)	51.2 (CiC removed)
12 week follow-up, Etanercept 50 mg twice a week			
Leonardi 2004 ⁶⁹	61 (55.07) (n=162)	10.9 (61.84)* (n=166)*	50.1 (37.46, 62.74)
Elewski 2003 ⁷⁰	CiC removed	CiC removed	CiC removed
24 week follow-up, Etanercept 25 mg twice a week			
Gottlieb 2003 ⁷¹	64.3 (37.75)	7.2 (59.33) (n=55)	57.1 (38.75, 75.45)

*Where a trial had more than one intervention arm, results from the placebo arm have been reported more than once

The results and calculated mean differences for the mean percentage change in DLQI score from baseline are summarised in table 4.2.8. (*CiC information removed*).

However, the data were highly skewed and pooled WMDs were not calculated.

4.2.1.7 Summary of findings for licensed doses

Data on the efficacy of etanercept 25 mg twice a week for 12 weeks were available from three good quality RCTs. On average, treatment resulted in 62% of patients achieving a PASI 50, 33% achieving a PASI 75, (*CiC removed*) a PASI 90 and (*CiC removed*) were assessed as clear or almost clear. These results were all statistically significantly better than placebo with pooled relative risks from three trials of (*CiC removed*), 10.69, (*CiC removed*) and (*CiC removed*) respectively. These findings were reflected in results for mean PASI after treatment and for mean percentage change in PASI from baseline. Across the three trials the post-treatment mean PASI score was (*CiC removed*) for etanercept-treated patients compared to a (*CiC removed*) for placebo-treated patients; reflecting the respective mean changes from baseline in PASI of 58.8% and 5.1% with placebo. All mean differences calculated were statistically significant in favour of etanercept. Similarly the mean percentage change in DLQI was around 59% with etanercept 25 mg twice a week compared with 9% with placebo and again all mean differences that could be calculated were statistically significantly in favour of etanercept.

Longer-term, 24 week data for etanercept 25 mg twice a week were only available from one small RCT, but the results do reflect the 12 week data.

Data on the efficacy of etanercept 50 mg twice a week for 12 weeks were available from two good quality placebo-controlled RCTs. Across the two trials the proportion of patients achieving PASI 50, 75, 90, and clear or almost clear was 76%, 49%, 21%, and (*CiC removed*) respectively with pooled relative risks of (*CiC removed*), 14.80, (*CiC removed*), and (*CiC removed*), all of which were statistically significant in favour of etanercept. The findings for mean PASI after treatment and for mean percentage change in PASI from baseline also demonstrated efficacy of etanercept treatment. On average the mean PASI score from the two trials was (*CiC removed*) for etanercept-treated patients compared to a (*CiC removed*) for placebo-treated

patients, with mean changes from baseline of (CiC removed) and (CiC removed) respectively. Similarly the mean percentage change in DLQI was around 66% with etanercept 50 mg twice a week compared with 9% with placebo. The mean differences indicated a statistically significant treatment benefit with etanercept 50 mg twice a week.

The findings of good quality, but short term, clinical trials demonstrate that etanercept at its licensed dose of 25 mg twice per week is clinically and statistically significantly more effective than placebo in the treatment of moderate to severe psoriasis. Etanercept 50 mg twice a week has also demonstrated its efficacy, and is possibly more efficacious than the lower dose. This is discussed further in the evidence synthesis (Section 4.5).

4.2.1.8 Etanercept long-term follow-up data from RCTs

Follow-up on open-label treatment

One trial provided long-term follow-up after the RCT phase of the trial during which all patients were treated in an open-label fashion with etanercept 25 mg/kg twice a week, giving a total study duration of 36 weeks.⁷⁰ Thus half the patients received etanercept at a dose of 25 mg/kg twice a week for the whole 36 week study, and half received 50 mg/kg twice a week for 12 weeks and then had the dose halved for the remaining 24 weeks. The data are summarised in table 4.2.9 by the dose of etanercept taken during the RCT phase of the study. Data for patients who were in the placebo group during the RCT phase are not reported here as their response to etanercept was not established under RCT conditions and also the duration of etanercept treatment for those patients will have been shorter.

Table 4.2.9 Summary of open-label follow-up from RCTs

Outcome and duration of treatment*	Etanercept 25 mg BIW	Etanercept 50 mg BIW
PASI 75 24 wks	CiC removed	CiC removed
PASI 50 24 wks	CiC removed	CiC removed
	36 wks	CiC removed
PASI 90 24 wks	CiC removed	CiC removed
	36 wks	CiC removed
Mean (SE) PASI score 24 wks	(n=177) 5.8 (CiC removed)	(n=179) 5.6 (CiC removed)
Improvement in PASI score from wk 12 to 24	(n=177) 2.0 (CiC removed)	(n=179) -0.1 (CiC removed)
Clear or Almost Clear 24 wks	CiC removed	CiC removed
	36 wks	CiC removed
DLQI% (SE) change in total score from baseline		
	24 wks	CiC removed
	36 wks	CiC removed

*Duration of treatment is total time on etanercept regardless of dose.

The results at 36 weeks do not indicate any lessening of response to etanercept over time. Patients who remained on the 25 mg/kg dose of etanercept throughout the study had an improvement in mean PASI score (2.0 (*Confidential data removed*)). Those who had received the 50 mg/kg dose up to week 12 showed on average a slight deterioration in mean PASI score (-0.1 (*Confidential data removed*)), giving a treatment difference of 2.10 (95% *Confidential information removed*). (*Confidential information removed*).⁷⁰

Follow-up after discontinuation of etanercept

Two trials followed-up patients after discontinuation of etanercept (table 4.2.10).^{69, 71} It is unclear in both trials whether the treatment blinding of the RCT phase was continued during this discontinuation phase, i.e. did patients and researchers know from which treatment they had been discontinued?

Table 4.2.10 Summary of follow-up after discontinuation (RCTs only)

Trial	Dose	Duration of treatment	Definition of relapse	n	Median time to relapse (75 th and 25 th percentiles)
Gottlieb 2003 ⁷¹	CiC removed	CiC Removed	CiC removed	CiC removed	CiC removed
Leonardi 2004 ⁶⁹	25 mg BIW	24 wks	Loss of half the PASI improvement achieved by end of treatment	107	85 days (56, 169)
	50 mg BIW	24 wks	Loss of half the PASI improvement achieved by end of treatment	122	91 (60, 169)

(*Confidential information removed.*) In the other trial⁶⁹ a total of 409 patients who had received treatment with etanercept 25 mg or 50 mg twice a week for up to 24 weeks

and who had achieved at least a PASI 50, had their treatment withdrawn and patients followed to assess time to relapse. Data were available on 227 patients (table 4.2.10) and the time to relapse was not dose related. Few patients experienced any significant exacerbation of their psoriasis: three patients relapsed to a PASI score of 125% or more of baseline score, (*CiC information removed*).

Retreatment after relapse

One trial provided data on the efficacy of etanercept upon retreatment after relapse.⁶⁹ Of a total of 409 patients who had received treatment with etanercept 25 mg once or twice a week or 50 mg twice a week for up to 24 weeks and who had achieved at least a PASI 50 had had their treatment withdrawn, 297 were re-treated with etanercept (at each patient's original dose). The efficacy of retreatment was assessed as the difference in the PASI score at week 12 of retreatment with the PASI score at week 12 of initial treatment. Across all doses the mean difference was -0.5 (SE 0.3) (95% CI: -1.1, 0.0), with no indication of a poorer treatment response upon retreatment.

4.2.1.9 Summary of efficacy of etanercept in the treatment of moderate to severe psoriasis

- There is evidence from three good quality double-blind, placebo-controlled trials that etanercept is efficacious in the treatment of moderate to severe psoriasis.
- The evidence demonstrates that the level of efficacy to be achieved with etanercept 25 mg/kg twice a week is good with a clinically significant proportion of patients achieving PASI 75 or clear/almost clear status after 12 weeks therapy. The efficacy of a higher dose of etanercept (50 mg/kg) may be greater.
- Evidence from one good quality double-blind, placebo-controlled trial indicates that the response to etanercept is maintained, at least in the medium term. Conclusions to be drawn are limited by the small sample size of this trial and the limited duration of follow-up (24 weeks). Data from uncontrolled follow-up phases reflect and extend these findings. However such data may be unreliable.

- There are no data from RCTs to inform the duration of remission. Uncontrolled data from follow-up in one trial suggests the median duration is around 90 days. Little evidence of severe exacerbation of psoriasis after discontinuation of treatment was reported.
- There is evidence from one trial that retreatment in patients who have relapsed following an earlier treatment period does not induce a poorer response than initial treatment.
- The trial populations may not truly reflect the difficult to treat patients from whom etanercept is licenced.

4.2.2 Efficacy of efalizumab

Five randomised controlled trials were included in the review.⁷²⁻⁷⁶

The results of the quality assessment of trials of efalizumab are reported in table 4.3.11. It is important to note that the quality rating may not necessarily have been an accurate reflection of the true quality of studies due to inadequacies in reporting in the trials. More information was available for some trials presented in both publications and industry trial reports than for other trials for which industry trial reports and, in some cases, publications were unavailable. Of the five trials of efalizumab, three were presented in the industry submission only, which reported very little information about the trials. These trials received a quality rating of Poor; reflecting the poor reporting rather than the trial quality.⁷⁴⁻⁷⁶ Of the two studies reported in publications, one was rated as Good,⁷³ and the other was rated as Satisfactory.⁷²

Table 4.2.11. Results of quality assessment for trials efalizumab

Quality assessment criteria	Reference				
	Lebwohl, 2003, ⁷²	Gordon, 2003, ⁷³	ACD2058g, 2004, ⁷⁴	ACD2600g, 2004, ⁷⁵	IMP24011, 2004, ⁷⁶
Eligibility criteria specified?	Y	Y	Y	CiC Removed	CiC Removed
Power calculation?	Y	Y	NS	CiC Removed	CiC Removed
Adequate sample size?	Y	Y	Y	CiC Removed	CiC Removed
Number randomised stated?	Y	Y	Y	Y	Y
True randomisation?	Y	Y	NS	CiC Removed	CiC Removed
Double-blind?	Y	Y	Y	Y	Y
Allocation of treatment concealed?	NS	Y	NS	CiC Removed	CiC Removed
Treatment administered blind?	NS	Y	NS	CiC Removed	CiC Removed
Outcome assessment blind?	NS	Y	NS	CiC Removed	CiC Removed
Patients blind?	Y	Y	Y	Y	Y
Blinding successful?	NS	NS	NS	CiC Removed	CiC Removed
Adequate baseline details presented?	N	Y	N	CiC Removed	CiC Removed
Baseline comparability?	Y	Y	NS	CiC Removed	CiC Removed
Similar co-interventions?	NS	Y	NS	CiC Removed	CiC Removed
Compliance with treatment adequate?	Y	Y	NS	CiC Removed	CiC Removed
All randomised patients accounted for?	Y	Y	Y	CiC Removed	CiC Removed
Valid ITT analysis?	Y	Y	Y	CiC Removed	CiC Removed
≥ 80% patients in follow-up assessment?	Y	Y	Y	CiC Removed	CiC Removed
Quality rating	<i>Satisfactory</i>	<i>Good</i>	<i>Poor</i>	<i>Poor</i>	<i>Poor</i>

All five trials were placebo-controlled; no trials comparing efalizumab with another active treatment were identified. One additional randomised placebo controlled trial examined the effects of a different formulation of efalizumab: intravenously delivered at 0.1 mg/kg and 0.3 mg/kg once a week.⁷⁷ This trial is not considered here. Full trial details are presented in the data extraction tables (Appendix 10.4.2).

Table 4.2.12 Details of included trials of efalizumab

Reference	Participants	Duration	Intervention	Comparison	Outcomes
Lebwohl, 2003,⁷² USA	N=597 Adults Clinically stable moderate to severe plaque psoriasis; $\geq 10\%$ BSA; baseline PASI ≥ 12	12 wks	Efalizumab 1mg/kg SC once a wk (n=232) Efalizumab 2mg/kg SC once a wk (n=243)	Placebo (n=122)	Proportion achieving PASI 50; PASI 75; PASI 90 Mean % change in PSA frequency, PSA severity, Itching score, DLQI score, PASI score
Gordon, 2003,⁷³ USA	N=556 Adults Clinically stable moderate to severe plaque psoriasis; $\geq 10\%$ BSA; baseline PASI ≥ 12	12 wks	Efalizumab 1mg/kg SC once a wk (n=369)	Placebo (n=187)	Proportion achieving PASI 50; PASI 75; Clear or minimal; Excellent or clear physician rating Mean % change in PSA frequency, PSA severity, Itching score, DLQI score
ACD2058g, 2004,⁷⁴	N=332 Adults Clinically stable moderate to severe plaque psoriasis; $\geq 10\%$ BSA; baseline PASI ≥ 12	12 wks	Efalizumab 1mg/kg SC once a wk (n=162)	Placebo (n=170)	Proportion achieving PASI 50 Mean % change in PSA frequency, PSA severity, Itching score, DLQI score
ACD2600g, 2004,⁷⁵	N=686 Adults Clinically stable moderate to severe plaque psoriasis; (<i>CiC removed</i>)	12 wks	Efalizumab 1mg/kg SC once a wk (n=450)	Placebo (n=236)	Proportion achieving PASI 50 (<i>CiC removed</i>)
IMP24011, 2004,⁷⁶	N=793 Adults Clinically stable moderate to severe plaque psoriasis; (<i>CiC removed</i>)	12 wks	Efalizumab 1mg/kg SC once a wk (n=529)	Placebo (n=264)	Proportion achieving PASI 50; PASI 75 (<i>CiC removed</i>)

BSA=body surface area; PASI=psoriasis area severity index; PSA=psoriasis severity area; DLQI=dermatology life quality index; SC=subcutaneous; wk=week

The trials were of adult patients with clinically stable moderate to severe plaque psoriasis affecting at least 10% of the body surface area and with a minimum PASI score of 12, who had received prior systemic therapy or were candidates for such therapy. The number of patients in the trials ranged from 145 to 793. In the two trials reporting such details,^{72, 73} mean duration of psoriasis was 19 years, and mean baseline PASI scores were 20⁷² and 19.⁷³

All five trials assessed patient outcome after 12 weeks of treatment. Two trials were continued for extended periods in which open-label and/ or non-randomised designs were adopted.^{72, 74}

All five trials investigated efalizumab at a dose of 1mg/kg body weight administered SC once a week. In addition, one trial examined a higher dose of 2mg/kg body weight administered SC once a week.⁷²

Overall the trials provided data on the proportion of patients achieving PASI 50, PASI 75, PASI 90 data, and proportion of patients rated as minimal or clear, mean percentage change from baseline in PASI score, and mean percentage change from baseline in total DLQI score. Other outcomes reported included proportion of patients rated excellent or cleared, and mean percentage change from baseline in PSA frequency, PSA severity, and itching scores; these data are presented in the data extraction tables (Appendix 10.4.2).

The trial populations were not considered to be clinically heterogenous and data were pooled according to outcome, dose and follow-up duration unless prevented by statistical heterogeneity.

4.2.2.1 PASI 50

Table 4.2.13. Proportion of patients achieving PASI 50

Reference	Efalizumab	Placebo	RR (95% CI)
<i>12 week follow-up, Efalizumab 1 mg/kg once a week</i>			
Lebwohl, 2003, ⁷² USA	120/232 (51.7%)	19/122 (15.6%)*	3.32 (2.20, 5.15)
Gordon, 2003, ⁷³ USA	216/369 (58.5%)	26/187 (13.9%)	4.21 (2.95, 6.11)
ACD2058g, 2004, ⁷⁴	99/162 (61.1%)	25/170 (14.7%)	4.16 (2.87, 6.12)
ACD2600g, 2004, ⁷⁵	234/450 (52.0%)	33/263 (12.5%)	4.14 (3.00, 5.80)
IMP24011, 2004, ⁷⁶	CiC Removed	CiC Removed	CiC Removed
Pooled RR			<i>(CiC removed)</i>
Test for heterogeneity			Q=1.013 (df=4), P=0.908
<i>12 week follow-up, Efalizumab 2 mg/kg once a week</i>			
Lebwohl, 2003, ⁷² USA	138/243 (59.0%)	19/122 (15.6%)*	3.65 (2.42, 5.64)

*Where a trial had more than one intervention arm, results from the placebo arm have been reported more than once

The results for patients achieving PASI 50 are summarised in table 4.2.13. All comparisons with placebo were (*CiC removed*). Data for efalizumab 1 mg/kg once a week were pooled from all five trials. The resultant pooled fixed effects RR (95% CI) was (*CiC removed*). The statistical test for heterogeneity was not significant.

4.2.2.2 PASI 75

Table 4.2.14. Proportion of patients achieving PASI 75

Reference	Efalizumab	Placebo	RR (95% CI)
<i>12 week follow-up, Efalizumab 1 mg/kg once a week</i>			
Lebwohl, 2003, ⁷² USA	52/232 (22.4%)	6/122 (4.9%)*	4.56 (2.02, 10.31)
Gordon, 2003, ⁷³ USA	98/369 (26.6%)	8/187 (4.3%)	6.21 (3.09, 12.49)
IMP24011, 2004, ⁷⁶	163/529 (31.0%)	11/264 (4%)	7.40 (4.09, 13.37)
Pooled RR			6.34 (95% CI: 4.27, 9.42)
Test for heterogeneity			Q=0.89 (df=2), P=0.64
<i>12 week follow-up, Efalizumab 2 mg/kg once a week</i>			
Lebwohl, 2003, ⁷² USA	69/243 (28.4%)	6/122 (4.9%)*	5.77 (2.68, 12.78)

*Where a trial had more than one intervention arm, results from the placebo arm have been reported more than once

Three trials reported data on the number of patients achieving PASI 75 (table 4.2.14). All treatment differences were statistically significant in favour of efalizumab over placebo. Data for efalizumab 1 mg/kg once a week were pooled from both trials and the pooled fixed effects was statistically significant in favour of efalizumab. There was no significant statistical heterogeneity.

4.2.2.3 PASI 90

Table 4.2.15 Proportion of patients achieving PASI 90

Reference	Efalizumab	Placebo	RR (95% CI)
<i>12 week follow-up, Efalizumab 1 mg/kg once a week</i>			
Lebwohl, 2003, ⁷² USA	10/232 (4.3%)	1/122 (0.8%)*	5.26 (0.89, 31.74)
<i>12 week follow-up, Efalizumab 2 mg/kg once a week</i>			
Lebwohl, 2003, ⁷² USA	15/243 (6.2%)	1/122 (0.8%)*	7.53 (1.30, 44.48)

*Where a trial had more than one intervention arm, results from the placebo arm have been reported more than once

One trial reported data on the number of patients achieving PASI 90 (table 4.2.15). The RR in favour of efalizumab over placebo was statistically significant for the high (2 mg/kg) dose of efalizumab but not for the 1 mg/kg dose.

4.2.2.4 Clear or minimal

Table 4.2.16. Proportion of patients achieving Clear or minimal status

Reference	Efalizumab	Placebo	RR (95% CI)
<i>12 week follow-up, Efalizumab 1 mg/kg once a week</i>			
Gordon, 2003, ⁷³ USA	98/369 (26.6%)	8/187 (4.3%)	8.19 (3.78, 18.08)

This trial only provided data rounded to the nearest percentage of patients who were clear or minimal for each arm. The corresponding numbers of patients were calculated for each arm from this data, assuming the highest possible number to have achieved the outcome. These were the numbers from which the RR (95% CI) was calculated.

One trial of reported data on the proportion of patients rated as clear or minimal according to the Overall Lesion Severity Scale as assessed by the physician (table

4.2.16). The RR (95% CI) was statistically significant in favour of efalizumab over placebo.

4.2.2.5 Mean percentage change in PASI score from baseline

One trial reported data on mean percentage change in PASI score from baseline (table 4.2.17). The mean difference could not be calculated for this trial and outcome because no measure of variance had been reported.

Table 4.2.17. Mean percentage change in PASI score from baseline

Reference	Efalizumab	Placebo
<i>12 week follow-up, Efalizumab 1 mg/kg once a week</i>		
Lebwohl, 2003, ⁷² USA	52% (†)	19% (†)

† standard deviation not reported or calculable

4.2.2.6 Mean percentage change in DLQI score from baseline

Four trials reported data on mean percentage change in DLQI score from baseline (table 4.2.18). The mean differences could not be calculated for this outcome in these trials because no measure of variance had been reported.

Table 4.2.18. Mean percentage change in DLQI score from baseline

Reference	Efalizumab	Placebo
<i>12 week follow-up, Efalizumab 1 mg/kg once a week</i>		
Lebwohl, 2003, ⁷² USA	45.4% (†)	12.3% (†)
Gordon, 2003, ⁷³ USA	47.0% (†)	14.0% (†)
ACD2058g, 2004, ⁷⁴	47.0% (†)	16.1% (†)
IMP24011, 2004, ⁷⁶	CiC Removed	CiC Removed

† standard deviation not reported or calculable

4.2.2.7 Summary of findings for licensed dose

Efalizumab at a dose of 1 mg/kg once a week SC has been studied in five RCTs. Across these trials 12 weeks treatment resulted in an average of 55% of patients achieving PASI 50, 27% achieving PASI 75, and 25% achieving PASI 90. The pooled RRs for PASI 50 and 75 were (*CiC removed*) and 5.51 respectively and (*CiC removed*). However the RR (from a single trial) for PASI 90 was not statistically significant. Only one trial reported mean change from baseline in PASI score; it was 33% for efalizumab-treated patients compared to 5% for placebo treated patients. The proportion of patients achieving clear or minimal status as reported in a single trial

was 40% (RR 8.19 (95% CI: 3.78, 18.08)). Mean change from baseline in DLQI score averaged across four trials was (CiC removed) for efalizumab-treated patients compared to (CiC removed) for placebo-treated patients.

Data on a higher dose of efalizumab (2 mg/kg once a week) were reported from a single trial. They reflected those of the 1 mg/kg dose.

The licensed dose of efalizumab 1 mg/kg once a week has been demonstrated to be clinically and statistically significantly more effective than placebo in the treatment of moderate to severe psoriasis over a 12 week treatment period. Although efalizumab appears to be similarly effective at 2 mg/kg once a week, evidence was limited to one placebo-controlled trial.

4.2.2.8 Efalizumab long-term follow-up data from RCTs

Efficacy with open-label therapy

From the company submission⁶⁸ it appears there were three RCTs which had open-label follow-up.⁷²⁻⁷⁴ Unfortunately only details of one of these trial extensions⁷² have been identified; this study had a total duration of 24 weeks.

Following a 12 week double-blind placebo controlled phase in which patients received 1 mg/kg efalizumab once a week or 2 mg/kg efalizumab once a week or placebo, patients were re-randomised to treatment according to their response to treatment and then treated for a second 12 week period.⁷² The doses in this second 12-week period were 2 mg every two weeks, 2 mg every week and 4 mg every week. Thus, although some patients will have received continuous efalizumab therapy for 24 weeks in a randomised controlled fashion, the doses under which these results were achieved are unclear and the results for this analysis (table 4.2.19) are therefore unreliable.

Table 4.2.19 Treatment response at 24 weeks

	Efalizumab 1 mg/kg/wk	Efalizumab 2 mg/kg/wk	Efalizumab 4 mg/kg/wk
<i>Patients with PASI 75 at wk 12</i>			
PASI 75	30/39 (77%)	31/40 (78%)	
PASI 50	35/39 (90%)	38/40 (95%)	
PASI 90	12/39 (31%)	13/40 (32%)	
<i>Patients with PASI 50-74 at wk 12:</i>			
PASI 75	25/47 (53%)	13/45 (29%)	
PASI 50	35/47 (74%)	30/45 (67%)	
PASI 90	1/47 (2%)	3/45 (7%)	
<i>Patients with PASI <50 at wk 12:</i>			
PASI 75	-	-	15/118 (15%)
PASI 50	-	-	47/118 (40%)
PASI 90	-	-	5/118 (4%)

In summary there are few long-term RCT-based data for efalizumab and those extensions of RCTs that have been performed have been poorly reported making it impossible to assess the efficacy of more than 12 weeks treatment with the recommended dose of efalizumab (1 mg/kg/week). No RCT-based efalizumab data were available for any period longer than 24 weeks.

Discontinuation of treatment

Two RCTs followed-up patients after discontinuation of therapy.^{72, 74}

In one RCT,⁷² prior to treatment discontinuation, patients had been treated with a range of doses of efalizumab: 2 mg every two weeks, 2 mg every week and 4 mg every week. Across all doses mean time to relapse (loss of more than 50% of improvement achieved in PASI score at week 24) in those who had achieved \geq PASI 50 was 84 days. At week 36 (end of follow-up) approximately one third of patients who had received continuous efalizumab had not relapsed.

In the other trial, the 12 week period in which patients had been treated with either 1 mg/kg efalizumab once a week (149 patients) or 2 mg/kg efalizumab once a week (145 patients), was followed by either continued treatment or re-treatment following relapse. Unfortunately further details of this trial were not available and the number of patients followed after discontinuation or the time to relapse is unknown.

The Company submission⁶⁸ states that for the two trials together the median time to relapse (defined as loss of 50% of PASI improvement achieved by end of treatment) was 59 days. Given that the dose patients were taking up to discontinuation in the first trial was not the licensed dose and is unknown for the second trial, and that the number of patients followed is unknown, this result cannot be considered reliable or informative.

In summary the limited data available do not permit conclusions to be drawn regarding the duration of response following discontinuation of efalizumab.

Retreatment after relapse

No data on retreatment with efalizumab from RCTs or follow-up extensions of RCTs were identified.

4.2.2.9 Summary of efficacy of efalizumab in the treatment of moderate to severe psoriasis

- There is evidence from five double-blind, placebo-controlled trials that efalizumab is efficacious in the treatment of moderate to severe psoriasis.
- The evidence demonstrates that the level of efficacy to be achieved with efalizumab 1 mg/kg once a week is good with around one quarter of patients achieving PASI 75 after 12 weeks treatment. However, evidence relating to efalizumab's potential to induce clearance or near clearance of psoriasis is weak.
- There is no evidence from RCTs that the response to efalizumab 1 mg/kg once a week is maintained when treatment continues beyond 12 weeks. Long-term follow-up data relate to a range of doses and are poorly reported and so cannot be used to draw even tentative conclusions regarding the long-term efficacy of efalizumab.
- There are no data from RCTs to inform the duration of remission following treatment withdrawal. Uncontrolled data from trial follow-up suggests that time to relapse may be around 60 days but this may not be reliable. No data indicating the existence or absence of any rebound in psoriasis after discontinuation of efalizumab were identified.

- There is no evidence relating to the efficacy of efalizumab upon retreatment.
- The trial populations may not truly reflect the difficult to treat patients for whom efalizumab is licenced.

4.3 Adverse events

4.3.1 Adverse Effects of Etanercept

4.3.1.1 Information from standard reference texts

A list of adverse effects of etanercept summarised from standard reference sources^{62, 64, 78, 79} was generated (see appendix 10.6.1.1). This list of adverse effects appears very comprehensive but provides only limited information on the significance of individual events.

4.3.1.2 Information from existing reviews of etanercept

In addition to the standard reference texts, there have been a large number of articles and reviews published regarding the adverse effects of etanercept.⁸⁰⁻⁸⁹ Most of the clinical experience and trial and study data drawn upon for these reviews involved patients with rheumatoid arthritis (RA), with a smaller body of evidence from patients with psoriasis and psoriatic arthritis. To date the main areas of concern relate to the potential of etanercept to increase the risk of infections, malignancy, heart failure, conditions secondary to the development of autoimmune antibodies, haematological disorders and demyelinating disease. Further details are presented in Appendix 10.6.1.2

4.3.1.3 Adverse Events for Etanercept: data from included studies

From the selection of trials for inclusion in the efficacy evaluation of etanercept three RCTs of etanercept in psoriasis provided data on the adverse effects of etanercept in psoriasis.⁶⁹⁻⁷¹ Although these trials do not meet the selection criteria for studies to be included in the adverse effects part of the review they are included in order that the data on both the harms as well as the benefits reported in the trials of efficacy are considered in this review.

In addition to the RCTs of efficacy a total of nine clinical studies that provided data on the adverse events of etanercept were identified.⁹⁰⁻⁹⁸ Details of all studies are presented in the data extraction tables (Appendix 10.5.1). Each of these nine studies had included at least 100 patients and provided at least 24 weeks data. Five of these studies were of patients treated with etanercept for rheumatoid arthritis; one was of patients with psoriasis, one was of patients with psoriatic arthritis, one study was of patients with ankylosing spondylitis and the last was of patients with either rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. Overall there are data available on the adverse effects of etanercept over 12 weeks, 24 wks (6 months), one year and 2 years or more. These data are summarised in Appendix 10.6.1.3.

Two RCTs of etanercept in psoriasis^{69, 70} provided data on the adverse effects of etanercept over a 12 week period. Note because one of the selection criterion for studies to be included in the evaluation of adverse effects was that trials should be at least 24 weeks long, only the data from the trials of efficacy in psoriasis are included in this summary of 12 week data. Both trials compared etanercept 25 mg twice weekly and etanercept 50 mg twice weekly with placebo. The number of patients studied was 358 for etanercept 25 mg, 358 for etanercept 50 mg and 359 for placebo.

The most commonly reported adverse events are summarised in Table 4.3.1. Across both trials the rate of reported adverse events was high: the proportion of patients that reported any non-infectious adverse event was around (*CiC removed*) in both etanercept dose groups and in the placebo group and the reported rate of infections was around (*CiC removed*) to 30% in all treatment groups with no difference between

active and placebo treatment. Withdrawals due to adverse events were low (1 to *CiC removed*%) and not different from those on placebo (1 to *CiC removed*%).

Table 4.3.1 Adverse events reported most frequently during 12 or 24 weeks treatment with etanercept

Time period	Adverse event	Etanercept 25 mg	Etanercept 50 mg	Placebo
12 weeks**	Any non-infectious	CiC Removed	CiC Removed	CiC Removed
	Injection site reaction	13 to 17%	13 to 18%	6 to 7%
	Headache	CiC removed to 12%	7 to CiC removed	7 to CiC removed%
	Any infection	CiC Removed to 30%	CiC removed to 29%	29 to CiC removed
	URT infection	9 to CiC removed	5 to CiC removed	11 to CiC removed
	Serious AE*	1 to CiC removed%	2 to CiC removed%	1 to CiC removed%
	Withdrawals due to AE	1 to CiC removed%	1%	1 to CiC removed%
24 wks***	Any non-infectious	CiC removed to 64%	-	CiC removed to 66%
	Injection site reaction	3.6 to 49%	-	0 to 13%
	Headache	5 to 16%	-	5 to 13%
	Any infection	40 to CiC removed%	-	CiC removed to 43%
	URT infection	10 to 35%	-	12 to 23%
	Serious AE*	CiC removed to 6.7%	-	CiC removed%
	Withdrawals due to AE	0 to 5.6%	-	0 to 11%

* Serious AE including serious infection, cancer, death and any other non-infectious AE.

** All RCT data

*** Some data uncontrolled.

In both trials the most commonly occurring non-infectious adverse event was injection site reaction; this occurred at a rate of around 15% in patients receiving etanercept with no discernable difference between the two doses, and 6.5 % in placebo patients. No other common adverse event occurred more frequently in etanercept treated patients than in placebo treated patients. Upper respiratory tract infections occurred in 5% to *CiC removed*% of all patients and (*CiC removed*). Other non-serious infections were reported by less than (*CiC removed*) of all etanercept patients.

Serious infections and serious adverse events adverse occurred in *CiC removed*. A total of *CiC removed* patients reported some form of cancer on etanercept treatment compared to *CiC removed* on placebo. Given the small number of patients and the very short duration of the trials this could indicate a serious problem with etanercept.

CiC removed

24 weeks treatment with etanercept 25 mg twice weekly was also associated with a high rate of adverse events, but again this rate was not demonstrably higher than that seen in placebo treated patients (table 4.3.1). Withdrawals across the trials were not consistently higher than on placebo. The highest withdrawal rate over 24 weeks treatment was 5.6%, reported in an uncontrolled study in RA.⁹⁸ Only injection site reactions (including ecchymosis, bruising or bleeding at the injection site) and possibly an increased in respiratory tract infections are clearly linked to etanercept. The overall rate of infections with etanercept is high but not necessarily higher than that on placebo. Serious infections have been reported at a rate of approximately (*CiC removed*)% of patients and represent a concern with etanercept therapy. In clinical trials the rate of withdrawals due to adverse events was no higher than with placebo, indicating that generally the drug was well tolerated. Data from one study indicate that the higher dose of etanercept (50 mg BIW) is also well tolerated.

Data regarding anti-etanercept antibodies are also scarce, with few studies reporting them. The rates reported indicated that up to 6% of patients might develop antibodies.

Most long-term data for two years or more for etanercept are from patients with RA. Furthermore published long-term data are poorly reported and thus of limited value. With longer term use neurological adverse events are reported and haematological effects such as neutropaenia appear. However it is unclear how treatment related such affects are.

4.3.1.4 Summary of adverse events for etanercept

Injection site reactions appear to be the most common adverse effects of etanercept. Overall etanercept appears to be well tolerated in short and long-term use, although much of the long-term data is not from patients with psoriasis; data derived from patients with RA may not be applicable to those with psoriasis. As identified from earlier reviews, the main areas of concern relate to uncommon but serious adverse

events: the potential of etanercept to increase the risk of serious infections, malignancy, heart failure, conditions secondary to the development of autoimmune antibodies, haematological disorders and demyelinating disease. Their significance is not readily discernable from the published reports of clinical trials.

4.3.2 Adverse Effects of Efalizumab

4.3.2.1 Information from standard reference texts

No information from standard texts other than from the Summary of Product Characteristics for Raptiva⁶³ was available for efalizumab. In brief the most frequent symptomatic adverse events reported during efalizumab therapy are mild to moderate dose-related acute flu-like symptoms; these are associated with the first few doses of efalizumab. Infections are common in efalizumab treated patients, but not more so than on placebo treatment. Other adverse events very common with efalizumab are leukocytosis and lymphocytosis. Common adverse events include psoriasis, arthralgia, psoriatic arthritis (exacerbation/flare), hypersensitivity reactions, back pain, asthenia, elevation of alkaline phosphatase, and elevation of ALT. Thrombocytopenia, urticaria, and injection site reactions appear to be uncommon adverse events. Antibodies to efalizumab were detected in only 6% of patients. Experience with efalizumab has not shown evidence of risk of developing malignancy exceeding that expected in the psoriasis population. Safety data beyond 12 weeks in the target population were not yet available. Further details are given in Appendix 10.6.2.1.

4.3.2.2 Information from existing reviews of efalizumab

Little has been published on the adverse effects of efalizumab. Two overviews^{99, 100} summarise the clinical trials data. These data are evaluated as part of the systematic review below and are therefore not discussed further here.

4.3.2.3 Adverse events for efalizumab: data from included studies

In addition to the five trials already identified for the assessment of the efficacy of efalizumab in psoriasis,⁷²⁻⁷⁶ there was one long-term follow-up study also in patients

with psoriasis⁹³ that provided information on the adverse effects of efalizumab SC. Although the five efficacy trials do not necessarily meet the selection criteria for studies to be included in the adverse effects part of the review, they are included in order that the data on both the harms as well as the benefits reported in the trials of efficacy are considered in this review. In addition one trial of an intravenous formulation of efalizumab was also found.⁷⁷ Details of all studies are presented in the data extraction tables (Appendix 10.5.2). No data for efalizumab from studies of indications other than psoriasis met the inclusion criteria.

The five trials of efalizumab at a dose of 1mg/kg administered SC once a week were all double-blind placebo-controlled RCTs conducted in patients with plaque psoriasis. One of these trials also evaluated a higher dose of 2 mg/kg, administered once a week.⁷² All five trials provided adverse events data for a 12-week treatment period, with a total number of 1740 patients treated with efalizumab 1 mg/kg once a week, 243 treated with efalizumab 2 mg once a week, and 979 treated with placebo. The most common adverse events reported are summarised in Table 4.3.2 with further details in 10.6.2.3. In addition, two trials^{72, 74} provided data for a further 12 weeks in selected patients (number not reported) and one these trials⁷² provided data for a treatment free follow-up period of 12 weeks (171 with efalizumab and 158 with placebo). The data from these studies is summarised in Appendix 10.6.2.3.

Table 4.3.2 Adverse events reported most frequently during 12 weeks treatment with efalizumab

Time period	Adverse event	Efalizumab 1mg/kg*	Efalizumab 2mg/kg**	Placebo
12 weeks**	Any adverse event	CiC removed to 86%	85%	CiC removed to 77%
	Headache	CiC removed to 35%	38%	CiC removed to 30%
	Chills	CiC removed to 16%	13%	2 to 6%
	Nausea	CiC removed to 15%	14%	CiC removed to 9%
	Myalgia	CiC removed to 10%	9%	CiC removed
	Serious non-infectious AE (Not including cancer)	2%	3%	1%
	Cancer**	0.5%	-	0
	Any infection	22 to CiC removed	-	CiC removed
	Serious infection**	0.5%	-	0.5%
	Withdrawals due to AE	CiC removed	3%	1 to 3.5%

* From RCTs

** From 1 RCT only.

Across the trials the proportion of patients reporting at least one adverse event during 12 weeks treatment with efalizumab 1 mg/kg was high (range CiC removed to 86%). However the rate on placebo was also high ranging from CiC removed to 77% of patients. Withdrawals due to adverse events were at a rate of around CiC removed on efalizumab compared to around 2% on placebo. Adverse events more common on efalizumab than placebo were headache, with the proportion of patients reporting headache with efalizumab 1 mg/kg ranging from CiC removed to 35%, chills (CiC removed to 16% of patients) and nausea, myalgia, pain and fever, which were reported by at least CiC removed of patients in all or almost all trials and the rates were generally higher in the groups who received active rather than placebo treatment. Infection was reported in around CiC removed of patients on efalizumab compared to around CiC removed on placebo and no specific infection was reported more commonly with efalizumab than with placebo. Unfortunately the rate of serious infections was not reported so whether or not there is any tendency for efalizumab to increase these relatively rare events cannot be discerned from these trial data.

The rate of serious adverse events with efalizumab was low at around 2%, but again data are sparse with only two trials reporting them.^{72, 73} There were no deaths associated with 12 weeks of efalizumab treatment and most trials did not report

cancer data. Rates of around 1% to 5% for patients who developed anti-efalizumab antibodies were reported.

Two trials^{72, 74} evaluated 24 weeks of efalizumab treatment but unfortunately, one of these trials evaluated only the higher dose of efalizumab for the second 12 weeks,⁷² and in the other it is unclear which dose was studied.⁷⁴ For both the level of detail available from the available reports is very limited and the total number of patients treated with efalizumab was only 171 in one trial⁷² and not reported in the other.⁷⁴ (*CiC removed*). These limited data indicate that adverse events were similar or less than for the initial 12 week period and one trial⁷² reported adverse events leading to withdrawal were more common in patients receiving placebo. Infection was the most common adverse event occurring at a rate of around (*CiC removed*). Arthritis and headache were the only two adverse events that occurred in at least (*CiC removed*) of these patients.

One long-term study provided data on 339 patients who had responded to efalizumab and who were then followed for up to three years.⁹³ These data indicate that the clinically significant adverse events were non-specific infections (mostly colds and upper respiratory tract), accidental injury, increased cough, rhinitis and sinusitis. Clinically significant including serious adverse events remained generally stable between each 3 month period of the whole study period. The rate of serious adverse events per 3 month period ranged from 1% to 5.5%. The average frequency of skin cancer per 3 month period ranged from 0 to 3.3%: the higher figure representing one month's atypical high rate. Withdrawals during any period of the follow-up were at a rate of 3.4% or less.

4.3.2.4 Summary of adverse events data for efalizumab

Headache, chills, and to a less extent, nausea, myalgia, pain and fever are the common adverse events associated with efalizumab. Overall withdrawal rates due to adverse events are low. Longer-term data for efalizumab are not readily available for evaluation but the adverse events periods up to three years appear to reflect those over 12 weeks and to remain stable. Unfortunately few data for serious infections and serious adverse events with efalizumab are available. The available published reports

of the efalizumab trials did not reveal leukocytosis and lymphocytosis as common adverse consequences of therapy. (*CiC removed*) developed anti-bodies, but this did not appear to be associated with any increased risk of adverse events.

Overall, the publicly available information for efalizumab indicates that the drug is well tolerated over a 12 week period and in the long-term, however, few data for long-term treatment are available for detailed evaluation.

4.4 Other treatments for moderate to severe psoriasis

In 2000, Griffiths et al. published a systematic review of treatments for severe psoriasis.¹⁰¹ The present updated review has added to some of the findings from the Griffiths review with a focus on those treatments identified as comparators for etanercept and efalizumab in clinical practice. Studies eligible for inclusion in this update were RCTs that consisted of twenty or more patients, and investigated a therapeutic dose, as advised by a clinical expert. The outcome measure PASI 75 has been used where available; in its absence an alternative PASI measure has been discussed, otherwise the primary outcomes have been reported. Studies identified from the Griffiths review and this updated review that did not meet these criteria have not been discussed in this report.

Of the 24 trials that met the inclusion criteria of this review 14 were found in the Griffiths et al. (2000) report and an additional 10 trials were identified by this updated review. Details of each trial can be found in the data extraction tables (Appendix 10.7). They are summarised in Table 4.3.3, which presents diagrammatically all the available treatment comparisons of the other treatments for moderate to severe psoriasis.

Table 4.3.3 Complete list of trials of other treatments for moderate to severe psoriasis

Study reference	Placebo	Ciclosporin	Methotrexate	Acitretin	Acitretin + calcipotriol	PUVA	Re-PUVA	NBUB	NBUB + dithranol	Infliximab	Fumaderm
Ellis 1991 ¹⁰²	√	√									
Guenther 1991 ¹⁰³	√	√									
Meffert 1997 ¹⁰⁴	√	√									
van Joost 1988 ¹⁰⁵	√	√									
Sandhu, 2003 ¹⁰⁶		√	√								
Heydendael, 2003 ¹⁰⁷		√	√								
Goldfarb 1988 ¹⁰⁸	√			√							
Lassus 1987 ¹⁰⁹	√			√							
Caca-Biljanovska, 2002 ¹¹⁰				√		√					
Saurat 1988 ¹¹¹						√	√				
Sommerburg 1993 ¹¹²						√	√				
Tanew 1991 ¹¹³						√	√				
Dogan, 1999 ¹¹⁴						√	√				
van de Kerkhof 1998 ¹¹⁵				√	√						
Rim, 2003 ¹¹⁶				√	√						
Van Weelden 1990 ¹¹⁷						√		√			
Gordon, 1999 ¹¹⁸						√		√			
Markham, 2003 ¹¹⁹						√		√			
Dawe, 2003 ¹²⁰						√		√			
Storbeck 1993 ¹²¹								√	√		
Chaudhari, 2001 ¹²²	√									√	
Gottlieb, 2004 ¹²³	√									√	
Altmeyer 1994 ¹²⁴	√										√
Nugteren Huying 1990 ¹²⁵	√										√

4.4.1 Trials involving ciclosporin

Six trials investigated the efficacy of ciclosporin, of which four compared ciclosporin with placebo,¹⁰²⁻¹⁰⁵ and two compared ciclosporin with methotrexate (Table 4.3.4).^{106, 107} A range of doses were studied from 2.5 mg/kg/day to 5.5 mg/kg/day. All but one trial were of at least eight weeks duration. The number of patients included in each study was small, with a total of only 113 patients treated with ciclosporin in placebo-

controlled trials. Despite their small sample sizes two of the four placebo-controlled trials found a statistically significant treatment effect for ciclosporin over placebo.¹⁰²¹⁰³ The other two placebo-controlled trials also indicated a beneficial effect of ciclosporin, but their ability to discriminate between treatments was hampered by their small sample sizes.¹⁰⁴¹⁰⁵ Most of the trials used doses lower than that considered to be optimal (5mg/kg/day) and this may also have contributed to their failure to demonstrate clearly efficacy with ciclosporin.

Table 4.3.4 Details of trials including ciclosporin as a comparator

Studies	Comparison	Population	Dose (treatment duration)	Outcome measure	Results
Ellis 1991 ¹⁰²	Ciclosporin vs. placebo	Plaque Min BSA >25% Min PASI not stated	3 mg/kg/day (8 wks)	Mean PASI	Ciclosporin (n=25) 6.2 (SE range 4-7) Placebo (n=25) 6.1 (SE range 5-7) Mean difference not calculable
				Clearance	Ciclosporin 36% (9/25) Placebo: 0% (0/25) RR 19.00 (1.17, 309.77)
			5 mg/kg/day (8 wks)	Mean PASI	Ciclosporin (n=25) 6.5 (SE range 5-7) Placebo: 6.1 (SE range 5-7) Mean difference not calculable
				Clearance	Ciclosporin 65% (13/20) Placebo: 0% (0/25) RR 33.43 (2.11, 530.00)
Guenther 1991 ¹⁰³		Psoriasis type not stated Min BSA not stated Min PASI >12	2.5 mg/kg/day (10wks)	PASI 50	Ciclosporin 12/12 Placebo 1/11 RR 11.00 (1.70, 71.28)
				Mean PASI	Ciclosporin (n=12): (wk0) mean 23, (wk10) mean 2. Placebo (n=11): (wk0) mean 21, (wk10) mean 16. Mean difference not calculable
Meffert 1997 ¹⁰⁴		Plaque Min BSA not stated Min PASI 8 to 25	2.5 mg/kg/day (10wks)	PASI 75	Ciclosporin 10% (n=41) Placebo 5% (n=43) RR 2.10 (0.41, 10.84)
van Joost 1988 ¹⁰⁵		Plaque Min BSA not stated Min PASI >20	5.5 mg/kg/day (4 wks)	PASI 75	Ciclosporin 7/10 Placebo 0/10 RR 15.00 (0.97, 231.84)
Sandhu, 2003 ¹⁰⁶	Ciclosporin vs. methotrexate	Plaque and erythrodermic Min BSA >40% Mean baseline PASI: trtmt 29.6, ctrl 27.6	Ciclosporin: 3-4 mg/kg/day MTX: 35 mg/wk (12 wks)	PASI 75	Ciclosporin 14/15 Methotrexate 15/15 RR 0.93 (0.82, 1.07)
Heydendael, 2003 ¹⁰⁷		Plaque Min BSA not stated Min PASI >8	Ciclosporin: 3-5 mg/kg/day MTX: 15-22.5 mg/wk (16 wks)	PASI 75	Ciclosporin 30/42 Methotrexate 26/43 RR 1.18 (0.87, 1.61)

Two trials compared ciclosporin (range 3 to 5 mg/kg/day) with methotrexate (range 15 to 35 mg/wk). The Sandhu 2003¹⁰⁶ trial included only very severely affected

patients (minimum BSA 40%). The trials found that over 70% of patients achieved a PASI 75 with ciclosporin and that both drugs were equally efficacious. Overall ciclosporin appears to be effective in the treatment of moderate to severe psoriasis but there is only limited evidence from RCTS.

4.4.2 Trials involving methotrexate

A total of two trials were identified that investigated the efficacy of methotrexate; both were comparisons with ciclosporin and are discussed in the paragraph above. No placebo-controlled trials of methotrexate were identified. The dose of methotrexate used in two trials and particularly in the Sandhu 2003 trial¹⁰⁶ (35 mg/week) is much higher than that currently used in the UK for treatment of psoriasis. Furthermore the Sandhu trial involved a very severely affected population (minimum BSA of 40%). The trials are therefore of limited utility in informing clinical practice. At the doses utilised methotrexate appears to be effective in the treatment of moderate to severe psoriasis.

4.4.3 Trials involving acitretin

There were five trials that looked at the effect of acitretin (Table 4.3.5).^{108-110, 115, 116} Three trials considered the drug as a monotherapy compared with placebo^{108, 109} or PUVA,¹¹⁰ and the other two trials investigated the combination of acitretin with calcipotriol compared with acitretin alone.^{115, 116} There are additional trials of etretinate versus placebo¹⁰¹, however, in this review we did not assume that etretinate equated with acitretin and these trials have not been included.

Of the two trials that compared acitretin with placebo,^{108, 109} data were extractable from only one.¹⁰⁹ This one trial found acitretin at 50 mg and 75 mg doses to be significantly more effective in terms of physician global assessment than placebo, but acitretin at 25 mg was not.¹⁰⁸

Table 4.3.5 Details of trials including acitretin as a comparator

Studies	Comparison	Population	Dose	Outcome measure	Results
Goldfarb 1988 ¹⁰⁸	Acitretin vs. placebo	Psoriasis type not stated Min BSA >10% Min PASI not stated	25 mg	Physician Global Assessment (0-6) 0=absent or clear, 6=severe (mean (SD))	Acitretin (n=5): 1 (SD 0.67) Placebo (n=12): 0.5 (SD 1.04) Mean difference 0.5 (-0.33, 1.33)
			50 mg (8 wks)		Acitretin (n=11): 1.6 (SD 1.33) Placebo (n=12): 0.5 (SD 1.04) Mean difference 1.10 (0.12, 2.08)
			75 mg (8 wks)		Acitretin (n=5): 3 (SD 1.79) Placebo (n=12): 0.5 (SD 1.04) Mean difference 2.50 (0.82, 4.18)
Lassus 1987 ¹⁰⁹		Plaque, erythrodermic, pustular Min BSA not stated Min PASI not stated	25 mg (8 wks)	Reduction in PASI	Data not extractable
			50 mg (8 wks)		Data not extractable
Caca-Biljanovska 2002 ¹¹⁰	PUVA vs. Acitretin	Plaque Min BSA >30 Mean baseline PASI: trtmt 24.06 (SD 3.62); ctrl 24.56 (SD 3.40)	PUVA: 4/wk for 6 wks + 2/wk for 2 wks Acitretin: 30 mg/day	Mean PASI	PUVA (n=20): Mean change from baseline 22.37 (SD 14.84) Acitretin (n=20): Mean change from baseline 23.66 (SD 8.48) Mean difference 1.29 (-6.20, 8.78)
				Clearance	PUVA: 7/20 Acitretin: 10/20 RR 0.70 (0.33, 1.47)
van de Kerkhof 1998 ¹¹⁵	Acitretin + calcipotriol vs. acitretin	Plaque Min BSA not stated Mean (SD) baseline PASI: trtmt 17.8 (8.9); ctrl 17.4 (8.6)	Acitretin 20-70 mg/day + calcipotriol 2/day (12 wks)	Mean PASI	Acitretin + calcipotriol (n=76) mean reduction 13.2 Acitretin (n=59): mean reduction 8.8 Mean difference not calculable – standard deviations not reported
			Acitretin 20-70 mg/day + placebo (12 wks)	Clearance	Acitretin + calcipotriol: 51/76 Acitretin: 24/59 RR 1.65 (1.17, 2.33)
Rim, 2003 ¹¹⁶		Plaque Min BSA >5% Mean baseline PASI: trtmt 21.6, ctrl 24.3	Acitretin 10-40 mg/day + calcipotriol 50 mg 2/day (12 wks) Acitretin: 10-40 mg/day (12 wks)	Clearance	Acitretin + calcipotriol: 16/40 Acitretin: 3/20 RR 2.67 (0.88, 8.09)

The one trial that compared acitretin (30 mg/day) to PUVA (4x/week for 6 weeks)¹¹⁰ found no statistically significant difference in the reduction of mean PASI or clearance between the treatments at week eight.

Two trials compared acitretin with a combination of acitretin plus calcipotriol.^{115, 116} One trial found clearance was achieved significantly more often with combination therapy than with acitretin and placebo¹¹⁵, but the other trial did not.¹¹⁶

Overall, the few data available indicate that acitretin has some efficacy in the treatment of psoriasis and this might be enhanced when use in combination with calcipotriol.

There were four trials that compared acitretin in combination with PUVA with PUVA alone, these are discussed below under phototherapy.

4.4.4 Trials involving phototherapy

In total, ten studies looked at the efficacy of a phototherapy regimen (Table 4.3.6). Four trials investigated the efficacy of PUVA compared with narrow-band UVB,¹¹⁷⁻¹²⁰ one study compared PUVA with acitretin,¹¹⁰ four trials compared PUVA plus acitretin (rePUVA) with PUVA alone,¹¹¹⁻¹¹⁴ and one trial investigated the effect of NBUVB in combination with dithranol compared with NBUVB alone.

Although clinical opinion would generally consider PUVA more powerful than NBUVB, only one of four trials comparing PUVA with NBUVB reported a greater rate of clearance with PUVA.¹¹⁸ Thus, from the limited data available the efficacy of the two forms of phototherapy treatment appears to be similar.

PUVA was compared with acitretin in one trial which found no difference between the two treatments in reduction of mean PASI or clearance.¹¹⁰ This study is also discussed above under the acitretin section.

Four trials were identified that compared the efficacy of acitretin in combination with PUVA (known as rePUVA, representing the combination of a retinoid with PUVA) with PUVA alone.¹¹¹⁻¹¹⁴ These trials appear to show no marked differences in the outcomes of each treatment arm. In general, patients receiving the combination therapy appear to have a better rate of improvement in a variety of outcomes, however, the difference is not statistically significant.

Table 4.3.6 Details of trials including phototherapy as a comparator

Studies	Comparison	Population	Dose	Outcome measure	Results
Van Weelden 1990 ¹¹⁷	PUVA vs. NBUVB	Plaque Min BSA not stated Min PASI not stated	PUVA: 2/wk NBUVB: 2/wk (4 wks)	Overall impression	Data not extractable
Gordon, 1999 ¹¹⁸		Plaque Min BSA not stated Min PASI not stated	PUVA: (oral) 2/wk NBUVB: 2/wk (Until clearance)	Clearance	PUVA (n=49): (after 16 treatments) 41/49 NBUVB (n=51): (after 16 treatments) 32/51 RR 1.33 (1.04, 1.70)
Markham, 2003 ¹¹⁹		Plaque Min BSA ≥8% PASI baseline range 11 to 19	PUVA: (oral 8-MOP) 2/wk NBUVB 3/wk Until clearance	Clearance	PUVA (n=29): (3mths) 23/29 NBUVB (n=25): (3mths) 18/25 RR 1.10 (0.81, 1.50)
Dawe, 2003 ¹²⁰		Plaque Min BSA not stated Min PASI not stated	PUVA: (bathTMP) 2/wk NBUVB: 3/wk	Reduction in PASI	PUVA (n=28): mean 17.5 NBUVB (n=28): mean 20 Mean difference not calculable – standard deviations not reported
Caca-Biljanovska2002 ¹¹⁰	PUVA vs. Acitretin	Plaque Min BSA >30 Mean baseline PASI: trtmt 24.06 (SD 3.62); ctrl 24.56 (SD 3.40)	PUVA: 4/wk for 6 wks + 2/wk for 2 wks Acitretin: 30 mg/day (8 wks)	Mean PASI	PUVA (n=20): (Mean change from baseline 22.37 (SD 14.84) Acitretin (n=20): (Mean change from baseline 23.66 (SD 8.48) Mean difference 1.29 (-6.20, 8.78)
				Clearance	PUVA: 7/20 Acitretin: 10/20 RR 0.70 (0.33, 1.47)
Saurat 1988 ¹¹¹	RePUVA vs. PUVA	Plaque, erythrodermic Min BSA >20% Min PASI not stated	Acitretin 50 mg/day + PUVA (12 wks) PUVA + placebo (12 wks)	PASI 90	17/20 16/22 RR 1.17 (0.85, 1.60)
Sommerburg 1993 ¹¹²		Plaque, guttate or nummularis Min BSA not stated Min PASI not stated	Acitretin 25 mg/day + PUVA (8 wks) PUVA + placebo 3-5/wk (8 wks)	>75% decrease in PSI	34/44 26/44 RR 1.31 (0.98, 1.75)
				Clearance	Acitretin + PUVA: 17/18 (94%) PUVA: 16/20 (80%) RR 1.18 (0.92, 1.51)
Tanew 1991 ¹¹³		Plaque, guttate or erythrodermic Min BSA ≥20% Min PASI not stated	PUVA 4/wk + Acitretin 1 mg/kg a day PUVA 4/wk + placebo Both 11 wks or until complete clearing	90% clearance	22/30 20/30 RR 1.10 (0.79, 1.53)
Dogan, 1999 ¹¹⁴		Psoriasis type not stated Min BSA ≥15% Mean baseline PASI 12	Acitretin: 50 mg/day for 15 days, 25mg/day thereafter plus PUVA (oral psoralen) 3/wk PUVA: 3/wk Both for 3 months or until clearance	PASI 50	RePUVA: 20/20 PUVA: 29/30 RR 1.03 (0.97, 1.11)
	Clearance			RePUVA: 6/20 PUVA: 25/30 RR 0.36 (0.18, 0.72)	
Storbeck 1993 ¹²¹	NBUVB vs. NBUVB + dithranol	Plaque, guttate or erythroderma Min BSA not stated Min PASI not stated	NBUVB: 3-5/wk + dithranol NBUVB: 3-5/wk Both until non-compliance	PASI	Data not extractable

In summary, PUVA has not been compared to placebo, but the available trials data indicate a degree of efficacy which is comparable with that achieved with NBUVB and with acitretin and which may be only slightly enhanced by addition of acitretin.

Narrow-band UVB in combination with dithranol was compared with NBUVB alone in one trial.¹²¹ However as it was not possible to extract the data from the report no conclusions can be drawn about the relative efficacy of these treatments.

4.4.5 Trials involving infliximab

Two trials were identified that compared infliximab with placebo (Table 4.3.7).^{122, 123} Across the two trials infliximab was tested at doses of 3 mg, 5 mg and 10 mg. At all three doses of infliximab the proportion of patients achieving PASI 75 was significantly higher than those receiving placebo.¹²² Overall there is evidence of efficacy with infliximab in the treatment of moderate to severe psoriasis.

Table 4.3.7 Details of trials including infliximab as a comparator

Studies	Comparison	Population	Dose	Outcome measure	Results
Chaudhari, 2001 ¹²²	Infliximab vs. placebo	Plaque Min BSA >5% Mean baseline PASI: trtmt 5mg/kg 22.1; mean trtmt 10mg/kg 26.6; ctrl 20.3	5 mg/kg (10 wks)	PASI 75	Infliximab: 9/11, 10mg/kg: 8/11 Placebo: 2/11 RR 4.50 (1.25, 16.25)
			10 mg/kg (10 wks)		Infliximab: 8/11 Placebo: 2/11 RR 4.00 (1.08, 14.75)
Gottlieb, 2004 ¹²³		Plaque Min BSA ≥10% Min PASI ≥12	3 mg/kg	PASI 75	Infliximab: 71/99 Placebo: 3/51 RR 12.19 (4.04, 36.80)
			5 mg/kg		Infliximab: 87/99 Placebo: 3/51 RR 14.94 (4.97, 44.89)

4.4.6 Trials involving Fumaderm

Two studies compared Fumaderm with placebo (Table 4.3.8).^{124, 125} One study found a significant number of patients achieving clearance in the Fumaderm group at 16 weeks although the 95% confidence interval for the relative risk is wide.¹²⁴ The second trial found no significant difference in clearance between the treatment arms.¹²⁵

Table 4.3.8 Details of trials including Fumaderm as a comparator

Studies	Comparison	Population	Dose	Outcome measure	Results
Altmeyer 1994 ¹²⁴	Fumaderm vs. placebo	Plaque, guttate or erythrodermic Min BSA >10% Min PASI not stated	Fumaderm 105 escalating to 1290mg/day (16 wks)	Mean PASI	Fumaderm (n=49): 10.77 Placebo (n=51): 23 <i>Mean difference not calculable – standard deviations not reported</i>
				Clearance	Fumaderm: 12/49 Placebo: 1/51 <i>RR 12.49 (1.69, 92.47)</i>
Nugteren Huying 1990 ¹²⁵		Psoriasis type not stated Min BSA >10% Min PASI not stated	DMFAE 120 mg; MEFAE-Ca 87 mg; MEFAE-Mg 5 mg; MEFAE-Zn 3 mg. (16 wks) OHFAE 284 mg; MEFAE-Mg 5 mg; MEFAE-Zn 3 mg. (16 wks)	Clearance	DMFAE: 6/12 OHFAE: 0/10 Placebo: 0/12 <i>DMFAE: RR 13.00 (0.81, 207.84)</i> OHFAE: not estimable

4.4.7 Summary of efficacy of other treatments for moderate to severe psoriasis

Despite widespread use and numerous trials, it is difficult to draw firm conclusions regarding the efficacy of the treatments available for the relief of moderate to severe psoriasis. Only infliximab and ciclosporin have had their efficacy demonstrated in placebo-controlled RCTs, and even then these data are relatively few, with most trials having included a small number of patients and only a short treatment period.

Whilst clinical experience has demonstrated excellent efficacy of PUVA and methotrexate, no placebo-controlled trials have been conducted. In clinical trials methotrexate appears to be as effective as ciclosporin. The trials of other treatments: acitretin, Re-PUVA, and NBUVB, in comparison with PUVA provide only limited evidence, demonstrating some degree of effectiveness but making it difficult to draw firm conclusions regarding the relative efficacy.

All data provide evidence of induction of remission rather than long-term effectiveness in the treatment of psoriasis.

4.4.8 Adverse events of other treatments for moderate to severe psoriasis

Ciclosporin

Dose related hypertension and renal toxicity are associated with the use of ciclosporin.^{50, 51} These adverse effects have been found to increase over time resulting in discontinuation of the treatment.⁵¹ Malignancies have also been associated with the use of ciclosporin, specifically cutaneous malignancies such as squamous and basal cell carcinoma.⁵⁰ Where ciclosporin is used as an immunosuppressant, at higher doses than used for psoriasis, such malignancies are not uncommon. In psoriasis the risk of squamous cell carcinoma is higher in patients treated with ciclosporin and a history of PUVA therapy.⁵⁰

Methotrexate

Myelosuppression, a potentially fatal adverse effect of methotrexate, is related to dose and occurs more frequently in the elderly.⁵¹ Liver fibrosis and cirrhosis are serious long-term adverse events associated with the use of methotrexate.^{50, 51} The likelihood of these events is thought to be dose dependent with a greater chance of development associated with increased alcohol consumption,⁵¹ and much of clinical experience with methotrexate is with doses far higher than those used for the treatment of psoriasis. However, there is some evidence that patients with psoriasis maybe more susceptible to liver toxicity.^{126, 127} Acute or chronic pneumonitis may occur with the use of methotrexate although it is rare. Haematological toxicity can occur and is particularly associated with drug-interactions, for example with drugs that inhibit folate metabolism (e.g. sulphonamides) or which increase the bioavailability of methotrexate (e.g. NSAIDS).^{50, 51} When administered in combination with PUVA, methotrexate has been associated with an increased risk of squamous cell carcinoma.⁵¹ An increased risk of lymphoma may also be associated with methotrexate.

Acitretin

The primary concern with acitretin and other retinoids is its teratogenicity, and acitretin must therefore not be used by pregnant women.⁵⁰ Acitretin may be metabolised partly to etretinate which is eliminated from the body very slowly. Mucocutaneous adverse events are commonly reported when using acitretin, including cheilitis, dry skin, and conjunctivitis, but these are generally mild.^{50, 51} An increase in serum lipids including cholesterol and triglyceride is also commonly reported.^{50, 51} Low grade hepatotoxicity can occur and acute hepatitis has been reported although its incidence is rare.^{50, 51} Patients taking acitretin over a long time period have been reported to develop hypertrophy of bone ligaments, tendons and other tissues.^{50, 51}

PUVA

Serious adverse events associated with PUVA are squamous and basal cell carcinoma, and there is a possibility that malignant melanoma may also be related.^{50, 51} Pruritus is also associated with PUVA therapy as well as a sun-burn like reaction⁵⁰ and premature photoaging.⁵¹ Cataracts can develop when UVA eyeglasses are not worn after ingesting psoralen.^{50, 51} Gastrointestinal effects including nausea have been experienced.⁵⁰

NBUVB

Photoaging and an increased risk of skin cancer are associated with UVB treatment, however it has been estimated that the excess annual risk of non-melanoma skin cancer associated with UVB radiation was likely to be less than 2%.

Infliximab

Infliximab has been associated with acute infusion-related reactions, including, anaphylactic shock and delayed hypersensitivity. Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions.

Other common adverse events associated with infliximab are: infusion-related reactions (including fever, chills, pruritus, urticaria, chest pain, dyspnoea, flushing, headache, hypotension (dizziness/fainting)), viral infection (e.g. influenza, herpes infections), serum sickness-like reactions, lupus-like syndrome, respiratory tract allergic reactions, anaphylactic reactions, headache, vertigo/dizziness, flushing, upper respiratory tract infection, lower respiratory tract infection (e.g. bronchitis, pneumonia), sinusitis, nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, rash, increased sweating, dry skin, fatigue, myalgia, and elevated hepatic transaminases.^{64, 78, 79, 128}

Fumaderm

Gastrointestinal adverse effects and flushing are commonly related to treatment with Fumaderm. Eosinophilia is also associated with Fumaderm.⁵¹ There have been reports of renal failure but as yet no link has been clearly established. Other adverse events reported by patients receiving Fumaderm include oropharyngeal irritation, taste disturbances, rash, insomnia, nausea and pruritus, potential paradoxical bronchospasm, epigastric pain, diarrhoea, constipation, faecal impaction, nephrotoxicity, reversible elevation of transaminases, reversible lymphopenia, and osteomalacia.^{64, 129}

Calcipotriol

Skin irritation has been linked to the use of calcipotriol. Dose related effects include hypercalcaemia and hypercalciuria.⁵¹ Calcipotriol may also cause skin rash, atrophy of skin, folliculitis and worsening of psoriasis.⁷⁸

Goeckerman treatment

Localised irritation is associated with Goeckerman regimen.⁵¹

Ingram regimen

Localised irritation is associated with Ingram treatment.⁵¹ Adverse effects of dithranol include staining of the skin, burning and smell.⁵¹ Frequently occurring events

associated with dithranol that require medical attention are redness and skin irritation. Allergic reactions are rare but would require medical attention if observed.^{64, 78, 79, 129}

Summary of adverse events of other treatments for moderate to severe psoriasis

All comparator treatments are associated with risks of serious and long-term adverse events. However, much of the available information is derived from patients with illnesses other than psoriasis or from the use of higher doses than those employed in UK practice.

4.5 Evidence synthesis

4.5.1 Purpose

The purpose of the evidence synthesis is to bring together the clinical evidence regarding the efficacy of etanercept, efalizumab and other treatments of moderate to severe psoriasis as identified and extracted (as detailed in Sections 4.2 and Section 4.4). The synthesis is primarily for purposes of decision making, so its focus is to generate parameter estimates for the cost-effectiveness modelling described in Section 6.

4.5.2 Methods

4.5.2.1 Estimation of Response Rates

The trials reported a variety of endpoints including mean change in PASI score and PASI 50, 75 and 90 endpoints. Changes in utility arising from treatment were estimated based on the PASI 50, 75 and 90 response data as reported. The available trials have been listed in earlier sections (Table 4.2.1, Table 4.2.12 and Table 4.3.3). The trials of etanercept and efalizumab were placebo controlled. The trials including the other systemic therapies included both placebo and a variety of active treatments as controls.

4.5.2.2 *Specification of the synthesis*

It can be seen from the tables of clinical trials (Table 4.2.1, Table 4.2.12 and Table 4.3.3) that there were no head-to-head trials comparing all the treatments. Therefore, the synthesis used the methods of mixed treatment comparisons.¹³⁰ In general terms, this consists of identifying a chain of evidence between the treatments. For example, although Fumaderm and infliximab have not been directly compared in a trial, they can be *indirectly* compared as both have been assessed against a placebo common comparator.

Etanercept and efalizumab were linked to most other therapies via a placebo control. Most other therapies (i.e. those listed in Table 4.3.3) were also linked through a placebo control. Methotrexate had not been compared with placebo, but links into the chain of evidence through having been compared with ciclosporin, which in turn had been investigated in placebo-controlled trials. Treatments that could not be linked into the chain of evidence were: acitretin, acitretin plus calcipotriol, PUVA, Re-PUVA, NBUVB and NBUVB plus dithranol. Of these six treatments, only acitretin had been compared with placebo; all the others had been compared to acitretin or each other. Unfortunately, the link to the chain of evidence through the acitretin-placebo comparison could not be made because no usable measure of response was recorded in either of the two placebo-controlled acitretin trials.^{108, 109}

The pattern of comparisons available for those trials that comprised the chain of evidence is shown in Table 4.5.1. The populations investigated in these trials were all adults suffering from moderate to severe psoriasis as defined by having a minimum BSA of 10, a minimum baseline PASI of 10 or a mean baseline PASI of at least 10. Table 4.5.2 summarises the data extracted from the clinical trials.

Table 4.5.1 Treatment comparisons comprising the chain of evidence

		Treatment Option						
		Placebo	Ciclosporin	Fumaderm	Methotrexate	Infliximab	Etanercept	Efalizumab
Trials	Meffert 1997	■	■					
	Van Joost 1988	■	■					
	Ellis 1991	■	■					
	Guenther 1991	■	■					
	Altmeyer 1994	■		■				
	Chaudari 2001	■				■		
	Gottlieb 2004	■				■		
	Heydendal 2003		■		■			
	Elewski 2003	■					■	
	Leonardi 2004	■					■	
	Gottlieb 2003	■					■	
	IMP24011	■						■
	ACD 2058g	■						■
	Lebwohl 2003	■						■
	ACD 2600g	■						■
	Gordon 2003	■						■

To enable indirect comparisons between all the comparators, a meta-analysis of the PASI 50, 75 and 90 response rates from the randomised trials was performed. Where the proportion of patients reported as ‘clear’ or ‘almost clear’ was reported these were assumed to be equivalent to the PASI 75 endpoint. The endpoints were jointly modelled using an ordered probit model.^{131, 132}

With this method, the ordered probit model is designed to model a discrete dependant variable that takes ordered multinomial outcomes, for example $y = 0,1,2,3,\dots$ etc. The ordered probit model can be expressed in terms of an underlying latent variable y^* . This could be interpreted as the individual’s underlying percentage reduction in PASI score from baseline. The higher the value of y^* , the more likely they are to report a higher category of PASI response. For trials reporting the PASI 50, 75 and 90 endpoints, subjects may be in one of four mutually exclusive categories; no response, PASI 50 to PASI 75 response, PASI 75 to PASI 90 response, and PASI 90 and greater response. So the range of y^* values is divided into 4 intervals corresponding to these categories. The threshold values (c ’s) correspond to the cut-offs where an individual moves from reporting one category to another. The lowest value is set at minus

infinity, the highest value is set at plus infinity and the upper bound on the first interval (c_{50}) set to zero. The remaining thresholds (c_{75} and c_{90}) were estimated bases on the data. The treatment effects are introduced by making the latent variable, y^* , a linear function of the treatment effect and intercept and a normally distributed error term. For trials reporting other patterns of endpoints, the appropriate mutually exclusive categories were modelled; for instance, if a trial only reported the PASI 90 endpoint, patients may be in one of two mutually exclusive categories (no response and PASI 90 or greater response).

The model was implemented as a Bayesian hierarchical model. The likelihood takes the form:

$$\prod_j p_{j,m(j)}^{n_j}$$

$$p_{j,1} = \Phi(y_j^*)$$

$$p_{j,2} = \Phi(y_j^* + c_{75}) - \Phi(y_j^*)$$

$$p_{j,3} = \Phi(y_j^* + c_{90}) - \Phi(y_j^* + c_{75})$$

$$p_{j,4} = 1 - \Phi(y_j^* + c_{90})$$

$$p_{j,5} = 1 - \Phi(y_j^* + c_{75})$$

$$p_{j,6} = 1 - \Phi(y_j^*)$$

$$p_{j,7} = \Phi(y_j^* + c_{75})$$

$$y_j^* = \mu_{s(j)} + \beta_{s(j)}^{t(j)}$$

$$\mu_{s(j)} = N(\mu, 1/\tau_\mu)$$

$$\beta_{s(j)}^t = N(\beta_t, 1/\tau_\beta)$$

where:

n_j is the number of subjects in the m^{th} category represented by the j^{th} datapoint

where:

$p_{j,m(j)}$ is the probability of observing subjects in the m^{th} category represented by the j^{th} data point.

$p_{j,1}$ is the probability of observing subjects not having a PASI 50 response for the j^{th} data point.

$p_{j,2}$ is the probability of observing subjects having between a PASI 50 and a PASI 75 response for the j^{th} data point.

$p_{j,3}$ is the probability of observing subjects having between a PASI 75 and a PASI 90 response for the j^{th} data point.

$p_{j,4}$ is the probability of observing subjects having between a PASI 90 response for the j^{th} data point.

$p_{j,5}$ is the probability of observing subjects having a PASI 75 response for the j^{th} data point.

$p_{j,6}$ is the probability of observing subjects having a PASI 50 response for the j^{th} data point.

$p_{j,7}$ is the probability of observing subjects having less than a PASI 75 response for the j^{th} data point.

$\mu_{s(j)}$ is the intercept for the k^{th} study represented by the j^{th} data point

$\beta_{s(j)}^{t(j)}$ is the treatment co-efficient for the t^{th} treatment and s^{th} study represented by the j^{th} data point

β^l is constrained to zero

Φ is the standard normal cumulative density function (CDF)

The following vague priors were defined:

$$c_{75} \sim U(0,10)$$

$$c_{90} \sim U(c_{75}, c_{75}+10)$$

$$\beta^t \sim N\left(\frac{1}{0.001}\right)$$

$$\mu \sim N\left(\frac{1}{0.001}\right)$$

$$sd \sim U(0,10)$$

$$\tau_{\mu} = 1/sd^2$$

$$sd_{tx} \sim U(0,10)$$

$$\tau_{\beta} = 1/sd_{tx}^2$$

The predicted mean probabilities of PASI 50 response for the t^{th} treatment were estimated as:

$$P_t^{pasi50} = 1 - \Phi(\mu + \beta^t)$$

and PASI 75 as:

$$P_t^{pasi75} = 1 - \Phi(\mu + \beta^t + c_{75})$$

and PASI 90 as:

$$P_t^{pasi90} = 1 - \Phi(\mu + \beta^t + c_{90})$$

The meta-analysis then provided estimates for response rates for each of the treatments based on all observed comparisons adjusting for (implicit) variation in placebo response rates on the log-odds scale. These estimates of response rates were used in the cost-effectiveness model. The meta-analysis was conducted using WinBUGS version 1.4.¹³³ A burn-in period of 50,000 simulations was used to allow convergence followed by 100,000 simulations for estimation. As a degree of auto-correlation was observed in some of the model parameters the model was ‘thinned’ so every 10th simulation was retained. Caterpillar plots of the estimated parameters were checked to ensure that the model converged satisfactorily. A range of initial values was also tested. A comparison of predicted probabilities with the original data indicated a reasonable fit for the model. The deviance for the random effects was 6975 and deviance information criteria (DIC) 7004.¹³⁴ A fixed treatment effects model was also tried, but was found to fit the data less well, deviance 6990, DIC 7025. The WinBUGS code is reproduced in Appendix 10.8.

Table 4.5.2. Summary of the response data extracted from the clinical trials and used in the evidence synthesis

Trial (Author year)	Citation no.	Treatment	Outcome (Percentage Change In PASI)	Outcome Code Used in Model	n
					CiC removed
Elewski 2003	70	Supportive Care	<50	1	
					CiC removed
Elewski 2003	70	Supportive Care	50-75	2	
Elewski 2003	70	Supportive Care	75-90	3	CiC removed
Elewski 2003	70	Supportive Care	>=90	4	CiC removed
Elewski 2003	70	Etanercept 50mg	<50	1	CiC removed
Elewski 2003	70	Etanercept 50mg	50-75	2	CiC removed
Elewski 2003	70	Etanercept 50mg	75-90	3	CiC removed
Elewski 2003	70	Etanercept 50mg	>=90	4	CiC removed
Elewski 2003	70	Etanercept 25mg	<50	1	CiC removed
Elewski 2003	70	Etanercept 25mg	50-75	2	CiC removed
Elewski 2003	70	Etanercept 25mg	75-90	3	CiC removed
Elewski 2003	70	Etanercept 25mg	>=90	4	CiC removed
Gottlieb 2003	71	Supportive Care	<50	1	49
Gottlieb 2003	71	Supportive Care	50-75	2	5
Gottlieb 2003	71	Supportive Care	75-90	3	1
Gottlieb 2003	71	Supportive Care	>=90	4	0
Gottlieb 2003	71	Etanercept 50mg	<50	1	17
					23
Gottlieb 2003	71	Etanercept 50mg	50-75	2	
Gottlieb 2003	71	Etanercept 50mg	75-90	3	11
Gottlieb 2003	71	Etanercept 50mg	>=90	4	6
Lebwohl 2003	72	Supportive Care	<50	1	103
Lebwohl 2003	72	Supportive Care	50-75	2	13
Lebwohl 2003	72	Supportive Care	75-90	3	5
Lebwohl 2003	72	Supportive Care	>=90	4	1
Lebwohl 2003	72	Efalizumab	<50	1	112
Lebwohl 2003	72	Efalizumab	50-75	2	68
Lebwohl 2003	72	Efalizumab	75-90	3	42
Lebwohl 2003	72	Efalizumab	>=90	4	10
Leonardi 2004	69	Supportive Care	<50	1	142
Leonardi 2004	69	Supportive Care	50-75	2	18
Leonardi 2004	69	Supportive Care	75-90	3	5
Leonardi 2004	69	Supportive Care	>=90	4	1
Leonardi 2004	69	Etanercept 50mg	<50	1	43
Leonardi 2004	69	Etanercept 50mg	50-75	2	40
Leonardi 2004	69	Etanercept 50mg	75-90	3	45
Leonardi 2004	69	Etanercept 50mg	>=90	4	36
Leonardi 2004	69	Etanercept 25mg	<50	1	68
Leonardi 2004	69	Etanercept 25mg	50-75	2	39
Leonardi 2004	69	Etanercept 25mg	75-90	3	36
Leonardi 2004	69	Etanercept 25mg	>=90	4	19
Gordon 2003	73	Supportive Care	<50	1	161
Gordon 2003	73	Supportive Care	50-75	2	18
Gordon 2003	73	Supportive Care	>=75	5	8
Gordon 2003	73	Efalizumab	<50	1	153
Gordon 2003	73	Efalizumab	50-75	2	118
Gordon 2003	73	Efalizumab	>=75	5	98
ACD2058g 2004	68	Supportive Care	<50	1	145

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Trial (Author year)	Citation no.	Treatment	Outcome (Percentage Change In PASI)	Outcome Code Used in Model	n
ACD2058g 2004	68	Supportive Care	>=50	6	25
ACD2058g 2004	68	Efalizumab	<50	1	63
ACD2058g 2004	68	Efalizumab	>=50	6	99
ACD2600g 2004	68	Supportive Care	<50	1	230
ACD2600g 2004	68	Supportive Care	>=50	6	33
ACD2600g 2004	75	Efalizumab	<50	1	216
ACD2600g 2004	75	Efalizumab	>=50	6	234
Guenther 1991	103	Supportive Care	<50	1	10
Guenther 1991	103	Supportive Care	>=50	6	1
Guenther 1991	103	Ciclosporin	<50	1	0
Guenther 1991	103	Ciclosporin	>=50	6	12
IMP24011 2004	76	Supportive Care	<50	1	CiC removed
IMP24011 2004	76	Supportive Care	>=50	6	CiC removed
IMP24011 2004	76	Efalizumab	<50	1	CiC removed
IMP24011 2004	76	Efalizumab	>=50	6	CiC removed
Altmeyer 1994	124	Supportive Care	<Clear	9	50
Altmeyer 1994	124	Supportive Care	>=Clear	5	1
Altmeyer 1994	124	Fumaderm	<Clear	9	37
Altmeyer 1994	124	Fumaderm	>=Clear	5	12
Chaudari 2001	122	Supportive Care	<75	9	9
Chaudari 2001	122	Supportive Care	>=75	5	2
Chaudari 2001	122	Infliximab	<75	9	2
Chaudari 2001	122	Infliximab	>=75	5	9
Ellis 1991	102	Supportive Care	<Clear	9	25
Ellis 1991	102	Supportive Care	>=Clear	5	0
Ellis 1991	102	Ciclosporin	<Clear	9	9
Ellis 1991	102	Ciclosporin	>=Clear	5	9
Ellis 1991	102	Ciclosporin	<Clear	9	7
Ellis 1991	102	Ciclosporin	>=Clear	5	13
Gottlieb 2004	123	Supportive Care	<75	9	48
Gottlieb 2004	123	Supportive Care	>=75	5	3
Gottlieb 2004	123	Infliximab	<75	9	28
Gottlieb 2004	123	Infliximab	>=75	5	71
Gottlieb 2004	123	Infliximab	<75	9	12
Gottlieb 2004	123	Infliximab	>=75	5	87
Heydendael 2003	107	Methotrexate	<75	9	17
Heydendael 2003	107	Methotrexate	>=75	5	26
Heydendael 2003	107	Ciclosporin	<75	9	12
Heydendael 2003	107	Ciclosporin	>=75	5	30
Meffert 1997	104	Supportive Care	<75	9	41
Meffert 1997	104	Supportive Care	>=75	5	2
Meffert 1997	104	Ciclosporin	<75	9	37
Meffert 1997	104	Ciclosporin	>=75	5	4
Van Joost 1988	105	Supportive Care	<75	9	10
Van Joost 1988	105	Supportive Care	>=75	5	0
Van Joost 1988	105	Ciclosporin	<75	9	3
Van Joost 1988	105	Ciclosporin	>=75	5	7

4.5.2.3 Key assumptions

The estimation of response rates from the mixed treatment comparisons relies on two assumptions. First, that the treatment effects are constant across endpoints on the probit scale. The second assumption is that the treatment effects can be considered exchangeable between the trials. The randomization process (should) ensure exchangeability between patients within a randomised trial. If the treatments had been randomised between the trials this would ensure the exchangeability of the effect estimates within the mixed treatment comparison. However, because they are not, we cannot exclude the possibility of systematic differences between the sets of trials comparing say different treatments.

4.5.2.4 Results

Table 4.5.3 summarises the results of the evidence synthesis in terms of absolute response rates. The placebo arm was regarded as representing ‘supportive care’, i.e. the patient receives no systemic therapy. In terms of mean response rate, when response is taken as PASI 75, infliximab appears the most effective followed by methotrexate and ciclosporin, the etanercept 50 mg. Etanercept 25 mg has a higher response rate than efalizumab, which has a lower mean response rate than all other therapies except Fumaderm and supportive care. As shown by the credible intervals (i.e. Bayesian confidence intervals) around the mean response rates, which overlap considerably, there is uncertainty around these response rates. This is also shown in terms of the relative risks of each option (compared to placebo) and their credible intervals. These findings for the PASI 75 level of response are also reflected in the results for the PASI 50 and PASI 90.

Table 4.5.3. Results of the evidence synthesis

Treatment	Probability of a Response			Relative Risks		
	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI
<i>Response = PASI 50</i>						
Supportive Care	14%	12%	16%	1.00	1.00	1.00
Etanercept 50mg	73%	53%	89%	5.42	3.83	6.86
Etanercept 25mg	62%	36%	85%	4.62	2.66	6.48
Efalizumab	55%	37%	71%	4.04	2.72	5.40
Ciclosporin	81%	65%	93%	5.98	4.64	7.31
Fumaderm	53%	17%	87%	3.90	1.23	6.56
Infliximab	93%	80%	99%	6.92	5.62	8.16
Methotrexate	82%	50%	98%	6.05	3.58	7.76
<i>Response = PASI 75</i>						
Supportive Care	3%	2%	4%	1.00	1.00	1.00
Etanercept 50mg	46%	25%	68%	14.49	7.62	22.46
Etanercept 25mg	34%	13%	61%	10.92	4.17	20.04
Efalizumab	27%	14%	42%	8.44	4.38	13.60
Ciclosporin	55%	36%	75%	17.58	10.85	25.68
Fumaderm	27%	4%	65%	8.63	1.33	20.79
Infliximab	79%	54%	95%	25.03	16.00	33.89
Methotrexate	59%	23%	90%	18.76	6.86	30.51
<i>Response = PASI 90</i>						
Supportive Care	0%	0%	1%	1.00	1.00	1.00
Etanercept 50mg	19%	7%	37%	49.14	17.10	99.40
Etanercept 25mg	12%	3%	30%	31.90	7.10	79.90
Efalizumab	8%	3%	16%	20.53	7.58	41.69
Ciclosporin	26%	12%	45%	67.84	29.53	126.90
Fumaderm	9%	1%	34%	24.18	1.47	87.10
Infliximab	52%	24%	80%	136.00	57.96	237.10
Methotrexate	31%	6%	68%	81.53	14.50	188.11

4.5.2.5 Summary

The results of the analysis indicate that efalizumab is less effective than etanercept 25mg, and both are less effective than infliximab, methotrexate and ciclosporin. Importantly, the 50mg dose of etanercept appears clearly more effective than the 25mg dose.

The quantity and quality of data included in this analysis was not equal across all treatments compared. Efalizumab and ciclosporin have been the most investigated with five RCTs each, compared with Fumaderm and methotrexate for which only one trial each was able to contribute data.

It is important to note that this analysis is limited by the data available. Importantly it only draws conclusions regarding short-term use; relative efficacy at 12 weeks for treatment of a life-long condition is not ideal. It is also very important because not only is it not known if efficacy might continue (there is some evidence of tachyphylaxis with continued use of infliximab), but that long-term efficacy might improve with some agents and not others. However, this lack of information reflects the evidence base for all treatments, not just the new biologics. What is lacking with all the newer drugs compared with the older treatments is, of course, long-term clinical experience.

The evidence synthesis also omits the adverse effects of the various treatments. Due to long experience with the other treatments it is well known that they are associated with long-term serious adverse effects and how these have to be managed (see Section 4.3). The relative efficacy of the new biologics needs to be considered in the light of what is known about their safety profiles; so far they appear well tolerated and safe; however, much more experience of use with these agents is required before a clear picture emerges.

5 Economic review

5.1 Published economic evaluations

5.1.1 Economic evaluations of etanercept or efalizumab for psoriasis

The search strategy (see Appendix 10.1) yielded 117 hits. Of these, just one study met the inclusion criteria.¹³⁵ No economic evaluation of efalizumab was found.

Details of the economic data extracted from the included study and its quality appraisal are given in Appendix 10.9.

5.1.1.1 Results from the Economic Evaluation

Overview

The paper estimated the cost per treatment success of eight antipsoriatic therapies used to treat patients with severe psoriasis, where severe psoriasis was defined as needing phototherapy or systemic treatment. The setting for the study was managed care in the US.

Summary of effectiveness data

Effectiveness was defined as the percentage of patients achieving a 75% improvement in their PASI score from baseline. Data on effectiveness was drawn from a review of the literature, based on a Medline search for 'recent' papers reporting effectiveness data for the biologics and on two existing reviews. Details of the search strategy used were not reported. Head-to-head trials were not found, so the analysis was based on a comparison of findings from placebo-controlled trials. However, estimates of effectiveness for active treatments were not adjusted by the placebo estimates of effectiveness. Where different measures of effect were reported in the literature for any of the active drugs, expert consensus was used to select baseline values for the analysis. The impact of high and low estimates of effect on cost-effectiveness was explored using deterministic sensitivity analysis.

Summary of resource utilisation and cost data

All relevant direct costs were included in the analysis, including clinician time (proxied by cost/visit), laboratory tests, drug costs and hospitalisation for biopsy. The cost of liver transplantation was explicitly excluded, although the authors acknowledged that this could have an impact on the findings.

Several sources were used to derive estimates of treatment doses, treatment durations and the frequency of office visits and laboratory tests. These included published clinical guidelines, manufacturers' guidelines and expert opinion.

National Medicare fee schedules provided unit costs for provider costs, laboratory tests, intravenous infusion and UVB treatment. Local Medicare fee schedules were used to estimate day hospital costs for liver biopsy. The Drug Topics Red Book provided drug acquisition costs. Although the authors state that indirect costs were estimated, details of the methods used and estimates obtained were not reported and it is unclear whether these were used in the analysis.

Summary of cost-effectiveness

Defining cost-effectiveness as the cost per treatment success, the paper reports average (rather than incremental) cost-effectiveness ratios. A probabilistic analysis was not conducted.

The base-case analysis found UVB phototherapy to be the most cost-effective option, followed by methotrexate. Although infliximab was the most cost-effective of the three biologics considered, it was still less cost-effective than any non-biological therapy. Alefacept (given intravenously) was the least cost-effective therapy overall, and remained so when sensitivity analysis was used to explore the impact of different effectiveness estimates. However, a probabilistic sensitivity analysis was not undertaken and so the uncertainty around estimates of cost-effectiveness is unclear.

Comments

The authors highlight many limitations to their economic evaluation and advise caution in interpreting the findings. Problems include the absence of head-to-head

effectiveness data and of long-term data for both effectiveness and safety. The chosen time frame of 12 months is acknowledged to be inadequate for modelling the treatment of a chronic disease, but this reflects the availability of long-term data. The shortcomings of the PASI 75 are discussed and the authors acknowledge that quality of life, compliance and patient satisfaction have not been addressed.

The comparators chosen reflect the availability of treatments in the US. The type and frequency of laboratory tests also reflect US clinical practice. For purposes of NHS decision-making, the study therefore has several limitations: it does not report health gain in terms of a generic measure (i.e. QALYs); findings relate to US clinical practice and US costs; and of the uncertainty in the findings was not reported.

Quality Assessment of the Economic Evaluation

Feldman and colleagues clearly state their reasons for selecting the alternatives to be used in the economic analysis, namely that these reflect clinical practice in the US. Weaknesses in the evidence base for effectiveness estimates are stated and explored using sensitivity analysis. The costing methodology is generally explicit, although the authors' treatment of indirect costs is unclear. There is incomplete reporting of the modelling undertaken and it appears that parameter uncertainty was not explored using probabilistic sensitivity analysis.

5.2 Company submissions

5.3 Company submissions

Two cost-effectiveness models were received from manufacturers, one for etanercept (from Wyeth) and one for efalizumab (from Serono).

5.3.1 Wyeth's cost-effectiveness model

Details of Wyeth's model are presented in Appendix 10.10 in terms of a data extraction table and a quality assessment.

5.3.1.1 Summary

Methods. The analysis assesses the cost-effectiveness of etanercept 25mg (twice per week), etanercept 50mg (twice per week) and an option of “no systemic therapy” (i.e. topical therapy only). These three alternatives are considered over a time horizon of 12 weeks (based on follow-up in the registration trials: Studies 20021632, 20021639 and 20021642). Costs are assessed from the perspective of the NHS, and outcomes are expressed in terms of QALYs.

Two longer-term etanercept strategies are also evaluated over a time horizon of 96 weeks: the use of continuous etanercept 25mg or 50mg; and the use of intermittent etanercept 25mg. With continuous therapy, patients were assessed at 12-weekly intervals (8 treatment periods) in terms of their PASI response. Patients experiencing an improvement of PASI 50 or better continue treatment, otherwise therapy is stopped and they move to no active systemic therapy. At 24 weeks after treatment initiation etanercept therapy is maintained only in patients who achieve a PASI 75. In addition, when patients move to no systemic therapy, their psoriasis can improve (i.e. spontaneous remission) following observations in the placebo arms of the registration trials.

The intermittent strategy relates to etanercept 25mg only, which is compared with no systemic therapy. The model is similar to continuous therapy: it is based on a 96-week time horizon with response assessment at 12-week intervals. However, with intermittent therapy, therapy is stopped for all patients 12 weeks following initiation. Only patients who show a response at 12 weeks (in terms of PASI 50) are considered for re-initiation of therapy if and when efficacy wears off. The strategy follows the treatment strategy used in study 20021639, modified to allow patients to be withdrawn from therapy if adequate response is achieved after 12 weeks.

The short-term (12-week) analysis is based on patient-level data from the trials. Resource use and costs relate to the cost of etanercept and of adverse events observed in the trials. No utility data were collected directly in the registration trials. Therefore, a ‘mapping’ exercise was undertaken to estimate the relationship between psoriasis-related quality of life (as measured by the DLQI) and utility (using the EQ-

5D). This mapping analysis was based on a survey of psoriasis patients treated at a single acute NHS hospital in Cardiff over a 2-year period. Patients were asked to complete the DLQI and the EQ5D, and PASI data were taken from clinical notes. The regression analysis found a statistically significant association between utility and DLQI and estimated each one-point increase in the DLQI to be associated with a fall of 0.0248 in patient utility. Patients' DLQI scores at each visit were converted into utility scores using the algorithm:

$$\text{EQ5D utility score} = 0.956 - [0.0248 \times (\text{DLQI total score})]$$

QALYs were computed, for each patient, using area-under-the-curve methods based on change in utility (predicted from DLQI) between baseline and 12 and 24 weeks.

For the longer-term extrapolation analyses used to evaluate strategies based on continuous and intermittent etanercept, simple Markov models were used. These were populated with cost and QALY data adapted from the 12-week analyses, and response rates at 12 and 24 weeks taken from the registration trials. Between 24 and 96 weeks (when no trial evidence existed) extrapolation was apparently based on the assumption of constant transition rates with assumptions about withdrawal of therapy.

The cost-effectiveness results were presented for patients with the mix of baseline characteristics in the three registration trials. In addition, extensive scenario analyses were presented to indicate how the cost-effectiveness of etanercept varies according to severity (in terms of PASI) and quality of life (in terms of DLQI) at baseline. Little analysis was undertaken regarding parameter uncertainty in the analysis, either stochastic analysis based on patient-level data, or deterministic or probabilistic sensitivity analysis on the models.

Results. The results of the short-term (12 week) analysis are shown in Table 5.2.1 below. This indicates that the cost of the etanercept itself is by far the largest cost component. Over a 12-week time horizon, the additional cost of etanercept is high relative to the QALYs gained when compared to topical therapy only. This is reflected in the magnitude of the ICERs.

The results for the longer-term extrapolation model for continuous etanercept therapy are shown in Table 5.2.2. The table shows the results for all patients and for those with relatively severe psoriasis and quality of life at baseline. It can be seen that the ICER of etanercept (compared to no systemic therapy) declines markedly for the relatively severe sub-group. It is also worth noting that the higher dose therapy becomes dominated in this sub-group (the possible reasons for this are not explored in the submission).

The results for the longer-term extrapolation for intermittent etanercept therapy (25mg twice per week) are shown in Table 5.2.3. Note the slightly different definition of 'relatively severe' patients in this analysis compared to that for continuous therapy. The same picture emerges as for continuous therapy: the ICER falls in the relatively severe sub-group of patients.

Table 5.2.1. Results of the 12-week trial analysis as part of the Wyeth submission

Treatment	Costs (UK, £)					TOTAL	QALY gain	ICER (UK £)
	Drug	Initial visit	Follow-up visit	Adverse events				
No systemic therapy	0	0	55	18	72		0.011	-
Etanercept 25mg	2,043	76	218	15	2,352		0.029	124,732
Etanercept 50mg	4,160	76	218	9	4,474		0.031	1,255,840

ICER – incremental cost-effectiveness ratio

Table 5.2.2. Results of the long-term (96 week) extrapolation model for two dosages of continuous etanercept therapy as part of the Wyeth submission

Treatment	All patients				ICER (UK £)
	Cost (UK, £)	QALY gain	ICER (UK £)	Cost (UK £)	
No systemic therapy	578	0.084	-	578	-
Etanercept 25mg	8635	0.236	53,056	8655	25,926
Etanercept 50mg	12,175	0.264	127,464	10,867	Dominated

Table 5.2.3. Results of the long-term (96 week) extrapolation model for intermittent etanercept therapy (25mg twice per week) as part of the Wyeth submission

Treatment	All patients				ICER (UK £)
	Cost (UK £)	QALY gain	ICER (UK £)	Cost (UK £)	
No systemic therapy	563	0.093	-	563	-
Etanercept 25mg	5,274	0.220	37,199	5,274	24,229

5.3.2 Limitations of the Wyeth model

The Wyeth model seems generally well conducted. The availability of patient-level data from the three regulatory trials is an important strength of the analysis. The mapping exercise between the DLQI and utility is far from ideal. However, it is difficult to see an alternative way of expressing health effects in terms of QALYs given the absence of patient-level EQ5D (or similar) data collection in any of the registration trials. There are some specific methodological weaknesses in the analysis (see detailed quality assessment in Appendix 10.10). Some of the more important weaknesses are discussed below.

- *Comparators.* The Wyeth analysis compares various dosages of etanercept, using alternative strategies, with an option of no systemic therapies. Given the licence for etanercept, which suggests the use of the treatment when other (non-biologic) systemic therapies have been tried, this comparison seems reasonable. It remains the case, however, that, in routine clinical practice, biologic therapies may be considered before some systemic therapies, and this decision is not informed by the Wyeth analysis. More importantly, there is no comparison with efalizumab, an alternative biologic therapy being considered as part of this assessment. The key decision question is (a) whether either therapy should be used in preference to no systemic therapy; and (b) which should be tried first. Another limitation of the analysis is that it does not formally compare continuous and intermittent use of etanercept.
- *Modelling.* Not surprisingly, the ICER of etanercept (compared to no systemic therapy) is relatively high over the period of follow-up in the registration trials (12 or 24 weeks). The rationale for extrapolation modelling is that it facilitates estimates of cost-effectiveness which can reflect more accurately how etanercept would be used in routine clinical practice. In particular, it can reflect the likelihood that clinicians will make assessments of how patients are responding to the drug, and withdraw or maintain therapy as appropriate. A key issue relates to the assumptions used to implement this longer-term modelling. An important assumption is the use of the PASI 50 as definition of response and as a threshold to determine whether patients remain on therapy at 12 weeks (for continuous

therapy) or are considered for further therapy if necessary (for intermittent therapy). Clinical advice to the Assessment Team suggests that some clinicians would not consider PASI 50 as an adequate threshold of response. Ideally, the Wyeth analysis would have used scenario analysis to explore the implications of using a range of possible definitions of response – these are, of course, an element of defining alternative treatment strategies. A second key modelling assumption relates to the basis of extrapolation beyond the trial period for which data are available (12 or 24 weeks). It is not spelled out in detail how this extrapolation is implemented, but it seems to result in a large proportion of patients going into spontaneous remission when not on systemic therapy. Greater clarity and use of sensitivity analysis to explore alternative assumptions would have been warranted here.

- *Uncertainty.* An important limitation of the Wyeth model (which has already been referred to above) is the limited amount of uncertainty analysis undertaken. This relates to parameter uncertainty (the precision with which the various parameters in the analysis are estimated and its implications for cost-effectiveness), where no deterministic or probabilistic sensitivity analysis appears to have been undertaken. There is also no use of scenario analysis in order to assess the importance of the key assumptions used in the analysis.

5.3.3 Serono's cost-effectiveness model

Details of Serono's model are presented in Appendix 10.10 in terms of a data extraction table and a quality assessment.

5.3.3.1 Summary

Methods. The Serono analysis compares two general management strategies for patients with moderate to severe psoriasis: a strategy starting with efalizumab and one starting with topical therapy based on calcipotriol or bethamethasone. The analysis uses PASI 50 as the criterion for treatment response. It is assumed that patients are assessed for response 12 weeks after initiation of therapy (based on the design of the registration trials). Those who are not responding with efalizumab or who experience adverse events with that treatment are assumed to discontinue therapy and move to

topicals. Those who do not respond to, or suffer adverse events from topical therapy are assumed to move to emollients which are taken as conferring no response in terms of PASI 50. Responders to treatment at 12 weeks are assumed to maintain that response (and the gain in quality of life associated with it) over a 10 year period unless they discontinue therapy for reasons not related to lack of efficacy or adverse events. Mortality is not considered in the model despite a 10-year time horizon. In terms of structure, the model is implemented as a simple decision tree as shown in figure 5.2.1. Costs are assessed from the perspective of the NHS, and health effects are expressed in terms of successfully-treated years (defined in terms of PASI 50) and QALYs.

The evidence used to populate the Serono model is taken largely from 5 registration trials: ACD2058g, ACD2059g, ACD2390g, ACD2600g and IMP24011 (see Section 4.2 for more details of these trials). These studies are used to derive response rates and rates of adverse events, as well as discontinuation from therapy for reasons other than lack of response or adverse events. In addition, a review of trials of calcipotriol and bethamethasone is used to generate similar estimates for topical therapy. A key input into the analysis is related to the utilities which are used to translate treatment response (in terms of PASI 50) to QALYs. Serono had no primary sources of utility data for this purpose (for example, from trials). Instead, a literature search identified a study by Zug *et al*²⁶ which elicited utilities, based on the time trade-off instrument, from 87 patients with psoriasis. Serono argues that non-response in their model can appropriately be given a utility value which accords with Zug *et al*'s 'severe' state (0.59 on a 0 (equivalent to death) to 1 (equivalent to good health) scale). They assume that response is valued at 0.945 which is an average of full health (1.0) and the utility estimated for 'mild' psoriasis by Zug *et al* (0.89). Resource use data are taken from a mixture of the trials and assumptions. Unit costs are taken from routine NHS sources.

Results. Serono presents total costs (with no disaggregation between different components) for efalizumab and topical therapy for three different time horizons. These costs are shown in Table 5.2.4. Over an apparent 10 year time horizon, expected 'quality-adjusted response-years' with efalizumab are reported as 1.39 compared to 0.36 for a strategy starting with topical therapy. These are not the same

as 10-year QALYs and it is not clear how they have been derived, but they do appear to be used to derive the 10-year incremental cost per QALY gained for efalizumab of £25,582.

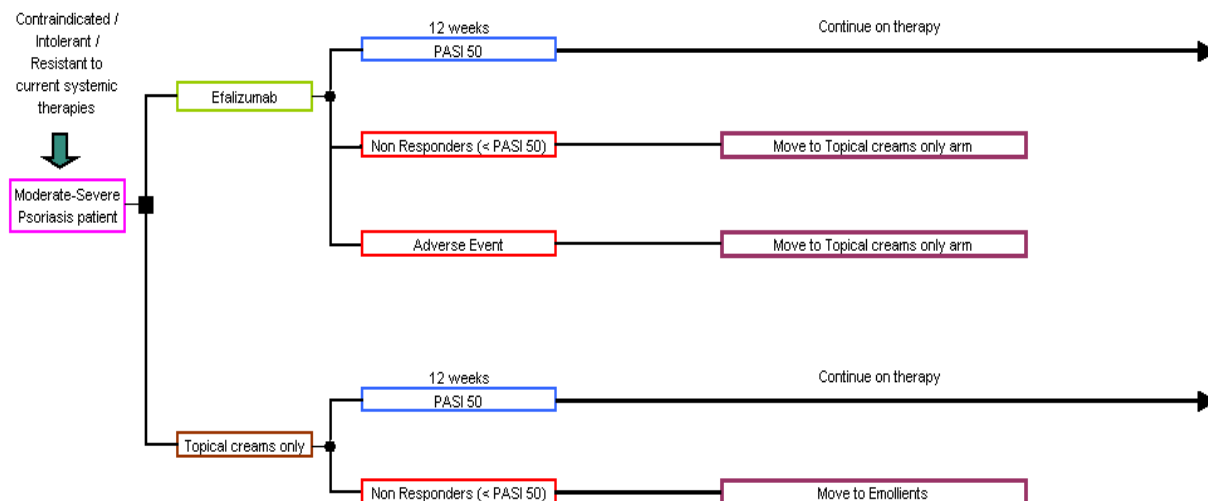


Figure 5.2.1. The decision tree used in the Serono model

Table 5.2.4. Total cost results from the Serono model over 3 different time horizons (£ UK)

Time horizon	Efalizumab	Topical therapy
1 year	27,032	453
5 years	18,488	303
10 years	5,611	123

A range of deterministic sensitivity analyses is reported. Most are one-way analyses which show the ICER remaining below £30,000 under all scenarios. The exception is a two-way analysis looking at utility values for responders and non-responders to therapy and the impact of the differences in these utilities on the ICER of efalizumab. This sensitivity analysis is reproduced in Table 5.2.5.

Table 5.2.5. Results of the two-way sensitivity analysis undertaken by Serono looking at the effect on the ICER of efalizumab of variation in the utilities associated with treatment response and non-response

Responder utility	Non-responder utility				
	0.40	0.50	0.59	0.60	0.70
1.00	£15,237	£18,628	£22,439	£22,836	£30,415
0.95	£16,801	£20,643	£25,473	£26,764	£37,559
0.90	£18,253	£22,964	£29,402	£30,397	£46,409
0.89	£18,604	£23,559	£30,710	£31,896	£48,144
0.80	£22,850	£30,581	£43,573	£45,824	£92,001
0.70	£30,397	£45,576	£83,937	£91,486	-

It can be seen that, depending on the assumptions about the two utilities in the model, the cost per QALY gained from efalizumab can vary between £15,237 and £92,001.

5.3.3.2 Limitations of the Serono model

The Serono analysis has the strength of using efficacy data from five registration trials for efalizumab. It does, however, have some important weaknesses.

- *Comparators.* As for etanercept, given the licence for efalizumab, which suggests the use of the treatment when other (non-biological) systemic therapies have been tried, it seems reasonable for Serono to compare efalizumab against topical therapy rather than one or more other systemic therapies. As described above in the context of Wyeth’s model, however, in routine clinical practice there is likely to be a choice between biologic therapy and other systemic therapies, and this decision is not informed by the Serono analysis. There is also no comparison with etanercept. The Serono analysis cannot inform decisions about whether to use efalizumab or etanercept or, more realistically, in what order to use these therapies.
- *Utilities.* Probably the most important weakness of the Serono analysis is the utility data linking response to QALYs. This is taken from a previously published study in which utilities were elicited directly from patients. The difference between the utility of a responder and non-responder is, in the base-case, taken to

be 0.455. This may be considered to be an implausibly high difference for this disease. To put this into context, with the EQ-5D index this difference would accord with that between full health and a health state characterised by moderate problems in mobility, self care, ability to undertake usual activities and pain/discomfort. As shown in Table 5.2.5 above, variation in utilities can have a major impact on the ICER of efalizumab.

- *Modelling.* A major assumption with the model is that those patients who are responding at 12 weeks (in terms of PASI 50) will continue to respond for a further 10 years with the exception of a small proportion of patients who discontinue therapy for reasons unrelated to efficacy or adverse events. This is a strong extrapolation assumption which may be considered unrealistic clinically. Furthermore, together with the assumption about the difference between responders and non-responders in terms of utility, it will have a major effect on the ICER of efalizumab.

6 Economic modelling

6.1 Introduction

The review of the company cost-effectiveness models in Section 5 above indicates a number of weaknesses. Perhaps the most fundamental is that neither considers all relevant treatment options; indeed, neither even compares the cost-effectiveness of both the licensed biologic therapies. For this reason, it is considered necessary to develop a *de novo* cost-effectiveness model (hereafter referred to as ‘the York Model’). Its aim is to assess the cost-effectiveness of efalizumab and etanercept within their licensed indications for the treatment of psoriasis.

Excerpts from the summaries of product characteristics (SPC) for efalizumab and etanercept (currently in draft) that are relevant to the economic analysis are given in boxes 6.1. and 6.2. These details are pivotal to various decisions that have been made about the specification of the cost-effectiveness model.

Box 6.1. Excerpt from SPC for Efalizumab & Etanercept Efalizumab SPC

Indication:

...Treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to or who have a contraindication to or are intolerant of other systemic therapies including cyclosporin, methotrexate and PUVA...

Dosage:

...Treatment with Raptiva should be initiated by a physician specialised in dermatology. An initial single dose of 0.7 mg/kg body weight is given followed by weekly injections of 1.0 mg/kg body weight (maximum single dose should not exceed a total of 200 mg). The volume to be injected should be calculated as follows: Dose Volume to be injected per 10 kg body weight Single initial dose: 0.7 mg/kg 0.07 ml Subsequent doses: 1 mg/kg 0.1 ml The duration of therapy is 12 weeks. Therapy may be continued only in patients who responded to treatment (PGA good or better). For discontinuation guidance see section 4.4...

Special warnings and special precautions for use:

...During treatment with Raptiva, cases of exacerbation of psoriasis, including pustular, erythrodermic, and guttate subtypes, have been observed (see section 4.8). In such cases, it is recommended to discontinue treatment with Raptiva. Abrupt discontinuation of treatment may cause a recurrence or exacerbation of plaque psoriasis including erythrodermic and pustular psoriasis...

...Management of patients discontinuing Raptiva includes close observation. In case of recurrence or exacerbation of disease, the treating physician should institute the most appropriate psoriasis treatment as necessary. In case re-treatment with Raptiva is indicated the same guidance should be followed as under Posology and method of administration. Re-treatment may be associated with lower or inadequate response to Raptiva than in the earlier treatment periods. Therapy may be continued only in those patients who respond adequately to treatment...

Box 6.2. Excerpt from SPC for Etanercept

Etanercept SPC

Indication:

...Treatment of adult patients with moderate to severe chronic plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate and PUVA...

Dosage:

...The recommended dose of Enbrel is 25mg administered twice weekly. Alternatively, 50mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25mg twice weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks...

Psoriasis is a common, chronic, relapsing, inflammatory skin disorder. The extent and duration of the disease is highly variable from patient to patient. If an individual patient does not respond to or tolerate a particular treatment option an alternate one may be tried; in other words, treatments are ‘trialled’ on individual patients. If an effective treatment is not found, then a patient will receive some form of supportive care. If the available treatments were only considered to be mutually exclusive options, this would leave the decision-maker with no information as to which treatment should be selected if the initial treatment failed and may not correctly identify the treatment that should be ‘trialled’ first. The York Model must, therefore consider *treatment sequences*.

A cost-effectiveness analysis may require the comparison of hundreds of alternative sequences. In addition, the optimum treatment sequence for an individual patient will depend on an individual patient’s characteristics including medical history, renal and hepatic function, treatment history and associated response and adverse events, impact of current disease and willingness to accept the risk of specific side effects.

Therefore, it may not be useful to provide estimates of the expected cost-effectiveness of specific individual treatment sequences as not all of these may be relevant to an individual patient, the optimum treatment sequence identified may not be suitable, and the decision-maker may be left without information as to the cost-effectiveness of alternative treatment sequences for the patient. To consider all possible treatments for all possible patient sub-populations may not be feasible. Therefore, this analysis seeks to identify an optimum overall *ordering* of treatments, from which the treatments suitable for an individual patient can be selected.

6.2 Methods

6.2.1 Comparators

Based on the indications described in the SPCs, a primary analysis was conducted comparing efalizumab, etanercept and supportive care. A secondary analysis was conducted to provide context for the use of the efalizumab and etanercept. This analysis included the following additional systemic therapies: ciclosporin, Fumaderm, methotrexate and infliximab. Although Fumaderm and infliximab are not licensed in the UK for psoriasis, they are used for selected patients in clinical practice. Therefore, the secondary analysis seeks to offer a pragmatic basis for NHS decision-making.

6.2.1.1 Dose ranges

The doses considered in the analysis for the comparators are shown in Table 6.2.1. These are based on licensed or anticipated licensed doses except for Fumaderm and infliximab where current guidelines are used.¹³⁶⁻¹³⁸ Only trial data corresponding to these dose ranges were included in the cost-effectiveness analysis. An exception was made for Fumaderm where the only trial evidence available lay outside the guideline range.

Treatments are often licensed over a range of doses. In clinical practice, a clinician may select an initial dose based on an individual patient's characteristics such as renal and hepatic function, severity of disease and response to previous treatments. For chronic diseases, the clinician may modify the subsequent dose of a drug based on patient response and the occurrence of adverse events. This is reflected in the trials for ciclosporin, Fumaderm and methotrexate, which frequently allowed dose titration (see Tables 4.3.2 & 4.3.7). Due to the wide range of doses and dose schedules employed in the trials, and considering clinical practice where individual dose selection and titration are to be expected, the trial results for different doses are grouped together in the analysis. It was assumed that the patterns of doses seen in the trials would reflect those in clinical practice. An exception was made for etanercept

where the results of the 25 mg and 50 mg trials were considered separately as this was one of the comparators in the primary analysis.

Table 6.2.1 Licensed or guideline doses used in the economic analysis

Treatment	Dose
Etanercept	25-50 mg administered twice weekly until remission
Efalizumab	Initial single dose of 0.7 mg/kg, Weekly injections of 1.0 mg/kg body
Ciclosporin	2.5-5mg/kg/day
Fumaderm	120-240mg 3 times per day
Methotrexate	10-25 mg/week
Infliximab	Loading dose of 3 infusions during first six weeks (3 – 5 mg/kg) then every 8 weeks or as needed

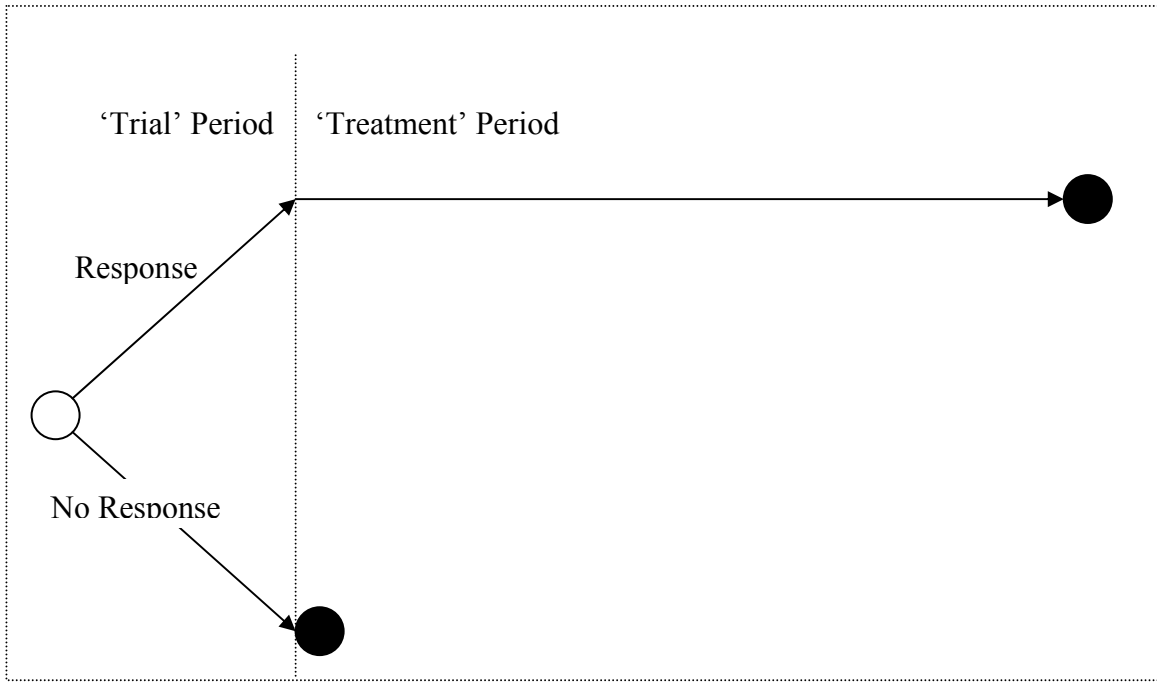
6.2.1.2 Continuous or intermittent use

Some treatments such as methotrexate are given continuously following the initial remission of disease and some treatments such as ciclosporin may be stopped following remission and the treatment used intermittently. In this analysis, it is assumed that all treatments are used continuously except for infliximab, which is given intravenously at discrete intervals, and etanercept, where the SPC specifies that treatment should continue until remission is achieved. The SPC for efalizumab specifically mentions that abrupt discontinuation of treatment may cause a recurrence or exacerbation of plaque psoriasis and re-treatment may be associated with lower or inadequate response than in the earlier treatment periods. Efalizumab is, therefore, probably unsuitable for intermittent use.

6.2.2 The model

The cost-effectiveness analysis was conducted by comparing estimates of expected costs and health effects per unit time for each treatment, incorporating both patients who ‘respond’ and continue treatment after a ‘trial’ period and those who do not ‘respond’ and stop treatment. This is illustrated in Figure 6.2.1.

Figure 6.2.1 Illustration of the structure of the cost-effectiveness analysis



To compute the expected costs and effects per unit time of interventions requires estimates of the proportion of patients responding and the costs, effects and total duration of treatment for responding and non-responding patients. The model can be specified based on the following equations:

$$u^{placebo} = u_{oo} \times (1 - p_{placebo}^{pasi50}) + u_{50} \times (p_{placebo}^{pasi50} - p_{placebo}^{pasi75}) u_{75} \times (p_{placebo}^{pasi75} - p_{placebo}^{pasi90}) + u_{90} \times (p_{placebo}^{pasi90})$$

$$u_t^{responders} = (u_{75} \times (p_t^{pasi75} - p_t^{pasi90}) + u_{90} \times (p_t^{pasi90})) / p_t^{pasi75}$$

$$u_t^{all} = u_{oo} \times (1 - p_t^{pasi50}) + u_{50} \times (p_t^{pasi50} - p_t^{pasi75}) u_{75} \times (p_t^{pasi75} - p_t^{pasi90}) + u_{90} \times (p_t^{pasi90})$$

$$Qaly_t = \frac{d_t^{trial} \times (u_{tx}^{all} - u^{placebo}) + p_t^{pasi75} \times d_t^{treatment, effect} \times (u_t^{responders} - u^{placebo})}{d_t^{trial} + p_t^{pasi75} \times d_t^{treatment, effect}}$$

$$c^{placebo} = c^{hospital} \times (1 - p_{placebo}^{pasi75})$$

$$Cost_t = \frac{c_t^{trial} + p_t^{pasi75} \times d_t^{treatment, cost} \times c_t^{treatment} + (1 - p_t^{pasi75}) \times c^{hospital} \times d_t^{trial} - (d_t^{trial} + p_t^{pasi75} \times t_t^{treatment}) \times c^{placebo}}{d_t^{trial} + p_t^{pasi75} \times d_t^{treatment, cost}}$$

Where the model outputs are:

$Cost_t$ = mean incremental cost per year for the t^{th} treatment compared to ‘supportive care’.

$Qalys_t$ = mean incremental qalys per year for the t^{th} treatment compared to ‘supportive care’.

The various parameters going into these equations are defined in Table 6.2.2.

6.2.3 Decision rule

The health effects of the alternative treatments are expressed as quality-adjusted life-years (QALYs). This is a generic measure of health effect and allows the decision to allocate resources to the treatments for psoriasis to be based on the opportunity cost of the treatments they displace, which could be based in other specialties.

The most cost-effective order of treatments will be to use them in order of decreasing expected net-benefit (NB_{tx}) per unit time, where:

$$E[NB_{tx}] = E[Qalys_{tx}] \times \lambda - E[Cost_{tx}]$$

λ is the maximum threshold for cost-effectiveness (per additional QALY). As there is no single value for this threshold, the analysis will vary it across a wide range.

If any of the active treatments has an expected net-benefit per unit time less than that for supportive care, its use is not cost-effective.

Table 6.2.2 Definition of parameters used in the York Model, summary of sources and indication of how uncertainty assessed.

Parameter	Description	Source	Uncertainty
$c^{hospital}$	Yearly cost of hospitalisation for non-responding patient	Assumption based on survey data	Scenario analysis
c_t^{trial}	Cost of treatment with the t^{th} treatment for the 'trial' period	BNF 48 ⁶⁴	Fixed
$c_t^{treatment}$	Yearly cost of treatment with tx	BNF 48 ⁶⁴	Gamma distribution
d_t^{trial}	Duration (in years) of the 'trial' period for the t^{th} treatment	Assumption based on clinical trial designs and BNF recommendations	Fixed
$d_t^{treatment,cost}$	Mean duration (in years) of the 'treatment' period for the calculation of costs for the t^{th} treatment	Assumption based on limited observational data	Scenario analysis of patient attrition rate and cost discount rate
$d_t^{treatment,effect}$	Mean duration (in years) of the 'treatment' period for the calculation of effects for the t^{th} treatment	Assumption based on limited observational data	Scenario analysis of patient attrition rate and effect discount rate
u_{00}	Utility for a patient not achieving a PASI50 response	Pooled clinical trial and HODaR data	Normal distribution
u_{50}	Utility for a patient achieving a PASI50 response but not a PASI75 response	Pooled clinical trial and HODaR data	Normal distribution
u_{75}	Utility for a patient achieving a PASI75 response but not a PASI90 response	Pooled clinical trial and HODaR data	Normal distribution
u_{90}	Utility for a patient achieving a PASI90 response	Pooled clinical trial and HODaR data	Normal distribution
p_t^{pasi50}	Probability of a PASI 50 response for treatment tx	Bayesian hierarchical model of clinical trial data (see Section 4.3)	Simulated posterior distribution from MCMC analysis of trial data
p_t^{pasi75}	Probability of a PASI 75 response for treatment tx	Bayesian hierarchical model of clinical trial data (see Section 4.3)	Simulated posterior distribution from MCMC analysis
p_t^{pasi90}	Probability of a PASI 90 response for treatment tx	Bayesian hierarchical model of clinical trial data (see Section 4.3)	Simulated posterior distribution from MCMC analysis

BNF: British National Formulary

MCMC: Markov Chain Monte Carlo

If we maximise the expected net-benefit per unit time for a treatment sequence, we will maximise the total expected net-benefit for a patient. As there will be attrition due to successful treatment or termination of treatment, the proportion of patients receiving a treatment will decline as we proceed along the treatment sequence; therefore, we will maximise the expected net for the treatment sequence by using the treatments in order of their individual expected net-benefit per unit time. This approach requires that a patient only receives benefit while they receive treatment; for example, it assumes that the treatments do not alter for the progression of the disease. A more detailed description of this analytic approach is included in Appendix 10.12.

6.2.4 Input parameter estimates

The model assumes no difference between the treatments in terms of mortality. The model requires estimates of the following parameters for each of the treatments being compared:

- Response rates
- Duration of the ‘trial’ and ‘treatment’ periods
- Costs
- The utility improvement associated with the various PASI response categories.

6.2.4.1 Response rates

The predicted response rates used in the model are taken directly from the evidence synthesis reported in Section 4.5. If the trial only reported ‘clear’ or ‘almost clear’ as the endpoint, this was taken to be equivalent to a PASI 75 response.

The increased decision uncertainty arising from uncertainty in the predicted response rates was estimated by directly exporting the simulated posterior distribution from the Markov Chain Monte Carlo analysis in WinBUGS to the cost-effectiveness model preserving any correlations. This has been termed a *comprehensive* decision model.¹³⁹

6.2.4.2 ‘Trial’ period and ‘treatment’ duration for responders

The ‘trial’ period was estimated based on the period over which response was assessed in the efficacy trials for each treatment option and ‘expert’ opinion. The mean ‘treatment’ duration for responding patients was estimated based on an assumed annual drop-out rate for responding patients receiving treatment and a maximum assumed treatment period based on published guidelines if appropriate.^{140, 141} The mean treatment response period was then estimated from a 10-year Markov model with an annual cycle (figure 6.2.2).

The estimated ‘trial’ and ‘treatment’ periods are shown on Table 6.2.3. There is very little experimental or observational evidence to inform these parameters and they are consequently subject to a great deal of uncertainty. These parameters were entered into the model as fixed values and sensitivity analysis of the annual withdrawal conducted.

The mean treatment period for intermittent use of etanercept was estimated to be 85 days based on the results of the 20021639 re-challenge study.¹⁴²

Cost and effect discount rates were incorporated into the model by estimating separate ‘treatment’ durations for the estimation of cost and effects. Annual discount rates of 6% on costs and 1.5% on outcomes were applied.¹⁴³

Figure 6.2.2. Markov model of ‘treatment’ period

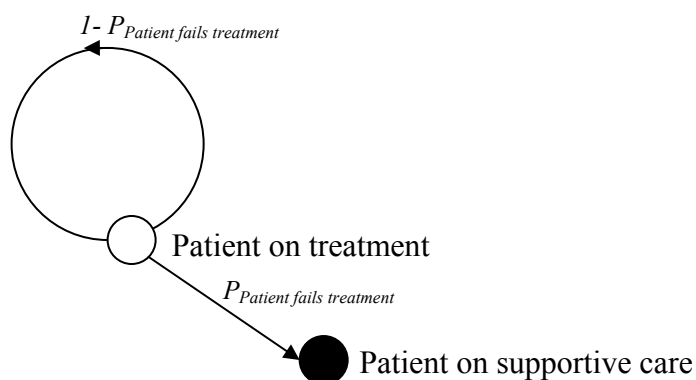


Table 6.2.3. Estimated duration of ‘trial’ and ‘treatment’ periods.

Treatment	'Trial' period (Weeks)	Maximum 'treatment' period (Years)	Annual drop-out rate	Mean 'treatment' period for responders (Weeks)
Etanercept 25mg	12	10	0.2	186
Etanercept 50mg	12	10	0.2	186
Efalizumab	12	10	0.2	186
Ciclosporin	12	2	0.2	75
Fumaderm	16	10	0.2	186
Methotrexate	16	10	0.2	186
Infliximab	10	10	0.2	186

6.2.4.3 Resource use and costs

Resource use. Direct costs incurred by the NHS were assessed. The analysis included the cost of drugs and of their administration and monitoring, the cost of outpatient visits and of inpatient stays.

The cost of tests undertaken solely to screen patients for eligibility for treatment was excluded from the analysis, such as chest x-rays and HEAF tests for tuberculosis (etanercept and infliximab) or biopsies of lesions atypical of psoriasis (ciclosporin). The reason for excluding these costs is that only a proportion of patients undergo these tests, and that this proportion is unknown and, for tuberculosis tests, likely to

vary geographically.¹³⁸ We also excluded the cost of folic acid (used in conjunction with methotrexate), because its annual cost was so low (under £1). We did not estimate the costs of treating adverse events, due to a lack of data on treatment pathways and resource use. Details of the adverse events associated with each drug can be found section 4.3 and Appendix 10.6.

Estimates of resource use (quantities) were derived from several sources. Drug dosage and titration rates were based on information in the September 2004 edition of the British National Formulary.⁶⁴ For the biological drugs, we referenced the manufacturers' SPCs^{62, 63, 128} and the British Society of Rheumatology's guidelines.¹³⁷ Two drugs are not licensed for use in the UK. For Fumaderm, a Manchester protocol provided titration rates and doses (see Appendix 10.11).¹³⁶ For infliximab, we assumed that re-treatment intervals would match those of the drug's use for psoriatic arthritis, namely that infusions would take place at 0, 2, and 6 weeks and then at 8-week intervals thereafter (i.e. 8 infusions in the first year, 6.5 infusions per year for maintenance treatment). There is some limited evidence to suggest that infliximab may require less frequent re-treatment intervals for psoriasis patients,¹²³ and trials are underway to validate this finding.

It was assumed that there were no significant additional treatment costs associated with 'supportive care' compared to the other systemic treatment being considered. It was assumed that patients receiving supportive care would have two outpatient visits annually. The main additional cost associated with 'supportive care' in the model resulted from the increased rate of hospitalisation due to the lower rate of PASI 75 response associated with supportive care. No data were available to inform an estimate of the rate of hospitalisation, so estimates were based on a range of scenarios, based on expert opinion, about the rate of hospitalisation and included the cost of outpatient visits and inpatient care.

The same sources provided some estimates of the types and frequency of laboratory tests undertaken for each drug.^{62-64, 128, 136, 137} Clinician and nurse time for clinical examinations (such as blood pressure) were not estimated because this was assumed to be included in the care covered by a standard outpatient visit. However, the time

taken in administering drugs was estimated for etanercept, efalizumab and infliximab. We assumed that to educate patients to self-inject efalizumab or etanercept would involve three one-hour sessions of nurse time during the 'trial period'. We based our estimates for infliximab infusions on the BSR guidelines,¹³⁷ which recommend that, for the first four two-hour infusions, the monitoring period is two hours, reduced to one hour thereafter.

Length of stay for an inpatient admission was based on Department of Health, Hospital Episode Statistics (2002/03) for psoriasis, which gave a mean of 19.6 days.⁵² This statistic was supported by evidence from recent audits of two local hospitals, which had average lengths of stay of 22.3 days and 22.7 days respectively (Personal communications: K. Swindells (Hope Hospital, Salford) and A. Woods (St John's Institute of Dermatology, London)).

The frequency of liver biopsy with methotrexate, with or without concurrent use of the PIIINP test, was based on estimates from a recent economic evaluation.¹⁴⁴ The re-treatment intervals for intermittent etanercept were based on a clinical trial report.¹⁴⁵ Expert opinion was used to generate the remaining estimates including the frequency of outpatient visits, drug tablet sizes commonly used, monitoring requirements and titration rates not available from the published literature.

Unit costs. Prices (unit costs) of drugs were taken, where available, from the BNF No. 48.⁶⁴ The price of Fumaderm was obtained through a personal communication with the Director of Pharmacy of the Greater Manchester Dermatology Service. The cost of efalizumab was based on information from the manufacturers (Table 6.2.3).

Prices of monitoring tests were obtained from the Biochemistry Department at York NHS Trust. The cost of the PIIINP test and the cost of a liver biopsy for patients were based on a recent economic evaluation.¹⁴⁴ The cost of nurse time educating patients to self inject was based on the PSSRU cost per patient related hour (PSSRU, Table 13.3).¹⁴⁶ The cost of an infusion visit was based on the latest available NHS Reference Cost category 'Other attendance with other investigation or procedure (J09op)', which is the same cost as for intensive topical hospital treatment.¹⁴⁷

Outpatient visits were based on NHS Reference Cost category ‘Other attendance without other investigation or procedure (J10op)’. The cost of an inpatient day was based upon two NHS Reference Cost categories. An average of the categories ‘Elective inpatient HRG data, major dermatological conditions J39 (>69 or w cc) (>69 or w cc: aged over 69 or with co-morbidities or complications)’ and ‘Elective inpatient HRG data, major dermatological conditions J40 (<70 or w/o cc)’ was estimated, weighted by number of Finished Consultant Episodes.

Where necessary, costs were updated to the year 2003/04, the latest available year, using the PSSRU inflation index.¹⁴⁶ Remaining prices relate to the year 2004/05.

Costs and quantities were estimated for one year’s maintenance treatment of each drug; discounting of costs was therefore unnecessary. For ciclosporin, only continuous treatment was costed: although intermittent treatment is recommended as a first line option,¹⁴¹ no trial providing adequate data was identified. Moreover, patients with recalcitrant disease, which reflects the population indicated for etanercept or efalizumab, are more likely to be candidates for long-term continuous ciclosporin therapy.¹⁴¹

For etanercept, both continuous treatment (with 25 mg) and intermittent treatment (with 25 mg or 50 mg) were included in the economic evaluation. The SPC for etanercept treatment states the treatment should be continued until the patient responds. Treatment will then be repeated when the patient relapses. This was incorporated in the model by adjusting the cost of treatment to account for this pattern of usage. (Confidential data removed.) The time to loss of response, and hence the cost of treatment with etanercept, will vary between patients. Continuous treatment with etanercept was also included as an option in the model. All other treatments were assumed to be administered continuously.

The costs of treatment with methotrexate with or without the PIIINP test were also estimated separately. Methotrexate without the PIIINP test was included in the model as it was considered to represent standard methotrexate therapy. The unit costs used in the model are given in Tables 6.2.4 to 6.2.6, and the resource use quantities are

shown in Tables 6.2.7 and 6.2.8. Tables 6.2.9 and 6.2.10 show the total ‘trial’ period and total annual per-patient costs for each drug respectively. Parameter uncertainty in drug costs are reflected in terms of a gamma distribution.

Table 6.2.4 Unit costs: drug costs, 2004/05

Drug	Price per mg	Price per tablet / vial	Source
	2004/05	2004/05	
Ciclosporin, 25 mg	£0.03	£0.68	BNF 48
Ciclosporin, 100 mg	£0.03	£2.54	BNF 48
Efalizumab, 125 mg	£1.35	£169.20	(see note)
Etanercept, 25 mg	£3.58	£89.38	BNF 48
Fumaderm, initial (30 mg)	£0.08	£2.39	(see note)
Fumaderm (120 mg)	£0.02	£2.03	(see note)
Infliximab	£4.51	£451.20	BNF 48
Methotrexate, 2.5 mg	£0.05	£0.12	BNF 48

Note:

The price for efalizumab was provided by the manufacturer (communication from Serono, 21/12/04).

Prices for Fumaderm were provided by the Greater Manchester Dermatology Service.

Table 6.2.5 Unit costs: laboratory costs, 2004/05

Test	Cost/test	Source
	2004/05	
Blood glucose	£0.43	York NHS Trust
Blood lipid profile	£2.93	York NHS Trust
Full blood count with differential	£2.42	York NHS Trust
Liver Biopsy with overnight stay	£479.67*	Chalmers et al, 2004 ¹⁴⁴ (mean)
Liver function test	£0.61	York NHS Trust
PIIINP (serum procollagen III aminopeptide)	£21.64	Chalmers et al, 2004 ¹⁴⁴ ; York NHS Trust
Serum creatinine	£0.31	York NHS Trust
Total Protein	£0.43	York NHS Trust
U&E	£1.12	York NHS Trust

Notes:

*Price year 2003/04

FBC: Full blood count with differential

LFT: liver function test

PIIINP: serum procollagen III aminopeptide

U&E: urea and electrolytes (includes test for serum creatinine)

Excludes cost of tests undertaken to determine eligibility, i.e. TB HEAF test; chest X-ray (etanercept / infliximab)

Table 6.2.6 Unit costs: hospital visit costs

	Category	2003/04	Source
Cost / inpatient day	Elective inpatient HRG data, major dermatological conditions. Weighted average of J39 (>69 or w cc) and J40 (<70 or w/o cc)	£248.31*	NHS Reference Costs 2003 and National Tariff 2004
Cost/outpatient visit	Major dermatological conditions; other attendance without other investigation or procedure (J10op)	£56.60*	NHS Reference Costs 2003 and National Tariff 2004
Cost/outpatient visit	Major dermatological conditions; other attendance with other investigation or procedure (J09op)	£78.21*	NHS Reference Costs 2003 and National Tariff 2004
Cost/patient educational hour	Cost per patient related hour, staff nurse	£34.00	PSSRU Unit Costs of Health and Social Care 2004

*Updated to 2003/04 prices using PSSRU inflation index¹⁴⁶

Table 6.2.7 Resource use: number of annual laboratory tests

	Efalizumab	Etanercept	Etanercept	Fumaderm	Infliximab	MTX	MTX
	CsA	Continuous	Intermittent			With PIINP	No PIINP
FBC	4-8	2-4	2-4	Up to 15	4	4 to 5	4 to 5
Liver Biopsy						0.04/ pt/year	0.28/ pt/year
LFT				Up to 15	4	4 to 5	4 to 5
PIINP						4	0
Serum creatinine	6 to 14						
Total Protein	4-8	2-4	2-4				
U&E	6 to 14	4-8	2-4	Up to 15	4	4 to 5	4 to 5*

* U&E, FBC and LFT: expert opinion suggests 8 to 9 tests in the first year of treatment, reducing to 4 to 5 annually thereafter.

Acronyms:

CsA: ciclosporin
FBC: Full blood count with differential
LFT: liver function test
PIINP: serum procollagen III aminopeptide (test)
MTX: methotrexate
U&E: urea and electrolytes

Sources:

BNF 48⁶⁴
RCN and BSR Guideline^{137, 138}
SPCs^{62, 63, 128}
Fumaderm protocol¹³⁶ (see Appendix 10.11)
Expert opinion

Table 6.2.8 Resource use: number of outpatient visits

	Number visits Week 0 to week 12	Number visits Annually (maintenance)	Source
CsA, continuous	5 to 6	6 to 7	Expert opinion
Efalizumab	3	4	Manufacturer's submission
Etanercept, intermittent	3	4	Assumption
Fumaderm	3 to 4	5 to 6	Expert opinion
Infliximab*	4 to 5	5 to 6	Expert opinion
Methotrexate	4 to 5	4 to 5	Expert opinion
Supportive care	-	2	Assumption

* To avoid double counting, the analysis adjusted the number of outpatient visits for infliximab by the number of infusion visits

Table 6.2.9 Total per-patient costs: 'Trial Period'* , 2004/05

DRUG	Type of treatment	Drug Cost	Administration Cost	Monitoring Cost	Outpatient visits	Total Cost
'Supportive Care'	-	-	-	-	-	-
Ciclosporin	Continuous	£643.89	£0.00	£8.96	£311.29	£964.14
Efalizumab	Continuous	£2,199.60	£102.00	£15.88	£169.79	£2,487.27
Etanercept, 25 mg	Continuous	£2,145.12	£102.00	£8.30	£169.79	£2,425.21
Etanercept, 25 mg	Intermittent	£2,145.12	£102.00	£8.30	£169.79	£2,425.21
Etanercept, 50 mg	Intermittent	£4,290.24	£102.00	£8.30	£169.79	£4,570.33
Fumaderm, 120 mg-240 mg TD	Continuous	£803.67	£0.00	£49.80	£198.09	£1,051.56
Infliximab, 3 mg/kg	Continuous	£4,060.80	£234.62	£8.30	£56.60	£4,360.32
Infliximab, 5 mg/kg	Continuous	£5,414.40	£234.62	£8.30	£56.60	£5,713.92
Methotrexate, 10-25 mg Without PIIINP	Continuous	£9.87	£0.00	£20.75	£254.69	£285.31
Methotrexate, 10-25 mg PIIINP and reduced liver biopsy rate	Continuous	£9.87	£0.00	£63.34	£254.69	£327.90

* Length of trial period varies by drug and is based on figures in Table 6.2.2

Table 6.2.10 Total per-patient annual ‘treatment period’ costs, 2004/05

Drug	Type Of Treatment	Drug Cost	Administration Cost	Monitoring Cost	Outpatient visits	Total Cost
‘Supportive Care’	-	-	-	-	113.20	113.20
Ciclosporin	Continuous	£3,717.27	£0.00	£6.72	£367.89	£4,091.88
Efalizumab		£8,828.61	£0.00	£15.88	£226.39	£9,070.89
Etanercept, 25 mg	Continuous	£9,327.44		£8.30	£226.39	£9,562.13
Etanercept, 25 mg	Intermittent	£6,933.67		£8.30	£226.39	£7,168.37
Etanercept, 50 mg	Intermittent	£13,867.35		£8.30	£226.39	£14,102.04
Fumaderm, 120 mg TD	Continuous	£2,224.37	£0.00	£49.80	£311.29	£2,585.46
Fumaderm, 240 mg TD	Continuous	£4,448.75	£0.00	£49.80	£311.29	£4,696.64
Infliximab, 3 mg/kg	Continuous	£8,798.40	£508.35	£8.30	£56.60	£9,371.65
Infliximab, 5 mg/kg	Continuous	£11,731.20	£508.35	£8.30	£56.60	£12,304.45
Methotrexate, 10 mg	Continuous	£24.37		£153.89	£254.69	£432.96
Without PIINP						
Methotrexate, 25 mg	Continuous	60.94		£153.89	£254.69	£469.53
Without PIINP						

Except for the annual cost of treatment, these parameters were entered into the model as fixed values. For the annual cost of treatment, the mean costs were estimated as the average of the minimum and maximum cost, and the standard error estimated as the difference between the minimum and maximum divided by 1.96. Uncertainty in the mean cost was then represented as a gamma distribution parameterised using the estimated mean cost and standard error method of moments estimates.

6.2.4.4 Utility

The utilities associated with treatment were based on proportion of patients in the different PASI categories and the change in utility from baseline associated with the different PASI response categories. These were estimated from an analysis of data from the three etanercept regulatory trials and the HODaR Database (<http://www.hodar.co.uk/>). The estimation process consisted of two stages.

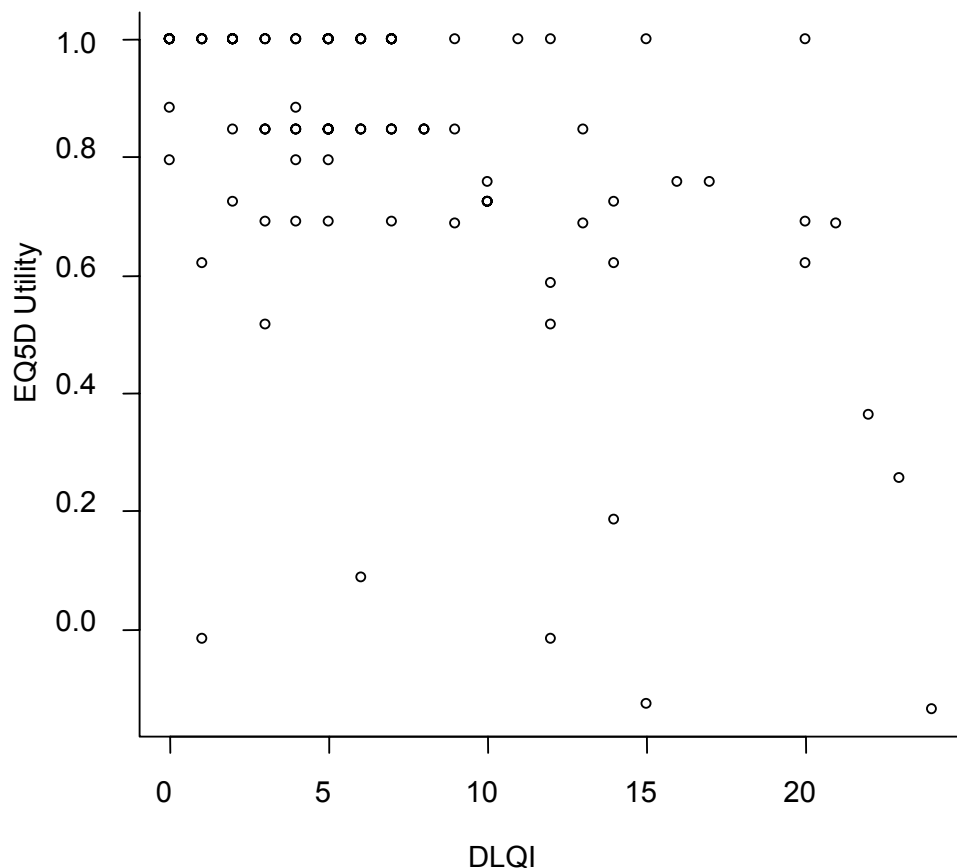
In the first stage, the mean change in the Dermatology Life Quality Index (DLQI) score between baseline and week 12 was estimated for patients from etanercept trials with different levels of PASI response and different baseline DLQI scores. This analysis was facilitated by access to patient-level data by Wyeth, and the placebo and treatment groups were pooled. The results of this stage are shown in Table 6.2.11. Higher scores on the DLQI indicate worse quality of life.

Table 6.2.11 Mean change in DLQI between baseline and week 12 by PASI response and baseline DLQI

PASI - DLQI Data:		PASI Response				
		<50	>=50 and <75	>=75 and <90	>=90	ALL
Baseline DLQI	1st quartile	Mean	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	Δ	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	DLQI	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	SD	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	N	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	2nd quartile	Mean	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	Δ	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	DLQI	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	SD	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	N	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	3rd quartile	Mean	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	Δ	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	DLQI	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	SD	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	N	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	4th quartile	Mean	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	Δ	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	DLQI	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	SD	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
	N	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
All	Mean	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	
Δ	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	
DLQI	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	
SD	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	
N	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)	

Data within the HODaR database included patients who had completed both the DLQI and EQ-5D. These data were used to ‘map’ the change in DLQI associated with PASI responses to changes in EQ-5D utility. A scatterplot of DLQI and EQ5D data are shown in Figure 6.2.3.

Figure 6.2.3. A scatterplot of DLQI and EQ5D data from the HODaR database. Higher DLQI and lower EQ5D utilities indicate worse quality of life.



An ordinary least squares (OLS) linear regression analysis of the DLQI-EQ5D data from HODaR produced the following results (values in parenthesis are standard errors, n=86):

$$\text{EQ5D utility} = (\text{CiC information removed})$$

Based on these data, the mean gain in utility was estimated for the various PASI response categories. These results are shown in Table 6.2.12 and are reported for all patients and for those with the worst baseline quality of life (4th quartile DLQI). The probabilistic sensitivity analysis has used the standard error from the OLS regression

of EQ5D and DLQI and the standard error from the change in DLQI conditional on PASI response and assumed normal distributions in both instances.

Table 6.2.12. Estimated gains in utility for the different PASI response categories. Results are shown for all patients and for those with the worst baseline quality of life (4th quartile DLQI).

PASI Response Category	Gains in utility (mean (se))	
	All Subjects	4 th Quartile DLQI
<50	0.05(0.01)	0.12(0.03)
>=50 and <75	0.17(0.04)	0.29(0.06)
>=75 and <90	0.19(0.04)	0.38(0.08)
>=90	0.21(0.05)	0.41(0.09)

There are three key assumptions in how QALYs have been derived for the cost-effectiveness model. The first is that the PASI response is a perfect proxy for the change in utility arising from treatment. In effect, if we condition on PASI response, utility is independent of treatment. Secondly, that if we condition on DLQI change, utility is independent of PASI response. These are assumptions of conditional independence. The third assumption is that the relationship between DLQI and utility is linear. In addition, we do not account for the impact of any adverse events on utility.

6.2.5 Analysis

All decision modelling was undertaken in the programming language R (see Appendix 10.8 for the code). The results of the York model are presented as expected average costs and QALYs over the period of treatment for each drug. The ICER comparing all drugs only relates to a situation when the decision-maker can only choose one treatment and cannot try other treatments if that fails. This is not useful for decision making as it does not identify which drugs should be included in a treatment sequence for a given threshold value for cost-effectiveness or in which order they should be tried. The ICER comparing all drugs with ‘supportive care’ is also given, this indicates the cost-effectiveness threshold at which a drug would be included somewhere in the sequence but does not indicate where.

In addition, tables are given which indicate the most cost-effective order in which to give the therapies based on the estimated average cost and QALYs associated with

each treatment. These vary according to the threshold value of cost-effectiveness. These should not be interpreted as a strict sequence which all patients should adhere to. Rather, the order shows that, if a patient is unable to have a particular therapy (e.g. due to contraindications or intolerance), (s)he would move to the next treatment in the order. Decision uncertainty, based on the results of the probabilistic sensitivity analysis, is presented as the probability that each treatment would be included in the optimum treatment sequence and the probability that each treatment would be first in the sequence as a function of the threshold value of cost-effectiveness.

The cost-effectiveness results vary considerably according to two important baseline characteristics of a given patient. The first is their baseline quality of life, as assessed using the DLQI. The second is the probability of the patient being hospitalised if they fail to respond to treatment. Below, results are presented using various scenarios regarding these two baseline variables.

6.3 Results

6.3.1 Base-case results

The base-case results relate to all patients (regardless of baseline quality of life in terms of DLQI) and assume that patients not responding to therapy are not hospitalised. The base-case analysis focuses only on etanercept, efalizumab and supportive care. The base-case results are shown in Table 6.3.1. The ICERs in the last column, relative to supportive care, indicate the ICER at which the particular therapy might enter a sequence. Under base-case assumptions, these ICERs are relatively high ranging from £66,703 (etanercept 25mg) to £120,855 (etanercept 50mg).

Table 6.3.1. Results of the base-case analysis including only etanercept, efalizumab and supportive care and related to all patients (regardless of baseline DLQI) and assuming patients not responding to therapy are not hospitalised. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

	QALYs				Costs				ICER	ICER against Supportive Care
	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI	ICER			
Supportive Care	0	0	0	0	0	0	0	0	-	-
Etanercept 25mg	0.116	0.064	0.17	7743	7437	8337	66703	66703	66703	66703
Efalizumab	0.112	0.064	0.162	9382	9238	9602	Dominated	Dominated	84018	84018
Etanercept 25mg Continuous	0.116	0.064	0.17	9665	9569	9851	Dominated	Dominated	83258	83258
Etanercept 50mg	0.123	0.071	0.178	14860	14569	15365	1035121	1035121	120855	120855

Table 6.3.2. Most cost-effective ordering of therapies for base-case results as a function of the threshold value of cost-effectiveness. Analysis includes only etanercept, efalizumab and supportive care and relates to all patients (regardless of baseline DLQI) and assuming patients not responding to therapy are not hospitalised. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

Threshold value of cost-effectiveness	Sequence	
	1 st in sequence	2 nd in sequence
0	Supportive Care	
5000	Supportive Care	
10000	Supportive Care	
15000	Supportive Care	
20000	Supportive Care	
25000	Supportive Care	
30000	Supportive Care	
35000	Supportive Care	
40000	Supportive Care	
45000	Supportive Care	
50000	Supportive Care	
55000	Supportive Care	
60000	Supportive Care	
65000	Supportive Care	
70000	Etanercept 25mg	Supportive Care
75000	Etanercept 25mg	Supportive Care

The more informative results are shown in Table 6.3.2, which indicates the most cost-effective sequence of therapies conditional on the threshold value of cost-effectiveness. The fact that supportive care is the only form of management listed until the threshold reaches £70,000 per QALY gained indicates that, under base-case assumptions, neither biologic therapy would be sufficiently cost-effective to enter the sequence until that threshold.

Table 6.2.3 shows the results of the probabilistic sensitivity analysis for the base-case analysis. This is presented for each of the therapies conditional on the threshold value of cost-effectiveness. For each therapy, two probabilities are shown: (i) the probability of being the first treatment in the sequence; and (ii) the probability of being in the sequence at all. Only when the threshold reaches £50,000 per QALY do the biologic therapies have a non-zero probability of being first in sequence or in the sequence at all but, even at this threshold, the probability is only 0.09 for etanercept 25mg and remains zero for the other biologic therapies.

Table 6.3.3 Results of probabilistic sensitivity analysis for the base-case showing probabilities that each therapy is first in sequence and included in the sequence at all conditional on the threshold value of cost-effectiveness. Analysis includes only etanercept, efalizumab and supportive care and relates to all patients (regardless of baseline DLQI) and assumes patients not responding to therapy are not hospitalised. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

Threshold value of cost-effectiveness		Etanercept 25mg	Etanercept 50mg	Efalizumab	Etanercept 25mg Continuous	Supportive Care
20000	Probability first in sequence	0.00	0.00	0.00	0.00	1.00
30000	Probability first in sequence	0.00	0.00	0.00	0.00	1.00
50000	Probability first in sequence	0.09	0.00	0.00	0.00	0.91
20000	Probability included in sequence	0.00	0.00	0.00	0.00	1.00
30000	Probability included in sequence	0.00	0.00	0.00	0.00	1.00
50000	Probability included in sequence	0.09	0.00	0.00	0.00	1.00

6.3.2 Alternative Scenario I: 4th quartile DLQI at baseline

A series of alternative scenarios is run to contrast with the base-case results. In the first, patients with poor baseline quality of life (in terms of DLQI) are considered. The results of the gains in utility by PASI response categories, conditional on baseline DLQI, in Table 6.2.11, show that the utility gains are greater in patients who have worse baseline DLQI. In this scenario, there are no hospitalisations on supportive care as in the base-case.

Table 6.3.4. Results of the Alternative Scenario I including only etanercept, efalizumab and supportive care and relating only to patients with the worst quality of life (4th quartile DLQI) at baseline, and assuming patients not responding to therapy are not hospitalised. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

	QALYs				Costs				ICER against Supportive Care
	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI	ICER		
Supportive Care	0	0	0	0	0	0	0	-	
Etanercept 25mg	0.222	0.124	0.324	7743	7437	8337	34834	34834	
Efalizumab	0.214	0.122	0.311	9382	9238	9602	Dominated	43821	
Etanercept 25mg Continuous	0.222	0.124	0.324	9665	9569	9851	Dominated	43479	
Etanercept 50mg	0.235	0.137	0.34	14860	14569	15365	539083	63103	

Table 6.3.4 shows the expected costs, QALYs and incremental cost-effectiveness of this scenario. The ICERs against supportive care are lower than in the base-case reflecting that the therapies will enter the most cost-effective sequence at lower ICER levels. Table 6.3.5 shows the most cost-effective sequence of therapies conditional on the threshold value of cost-effectiveness. It can be seen that the biologic therapies appear much earlier in these sequences than was the case under base-case assumptions. The first to appear is etanercept 25mg, which is first in the sequence at a threshold of £35,000 per QALY gained. Etanercept 25mg (continuous) and efalizumab appear in the sequence at a threshold of £45,000 and above. Etanercept 50mg appears in a cost-effective sequence at a threshold of £65,000 and above. Table 6.3.6 shows the results of the probabilistic sensitivity analysis for this scenario, and indicates that the probabilities of being first in sequence and of appearing in the sequence at all are higher than under the base-case assumptions

Table 6.3.5. Most cost-effective ordering of therapies for base-case results as a function of the cost-effectiveness threshold. Analysis includes only etanercept, efalizumab and supportive care and relates only to patients with the worst quality of life (4th quartile DLQI) at baseline and assumes patients not responding to therapy are not hospitalised. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

Threshold value of cost-effectiveness	Sequence				
	1 st in sequence	2 nd in sequence	3 rd in sequence	4 th in sequence	5 th in sequence
0	Supportive Care				
5000	Supportive Care				
10000	Supportive Care				
15000	Supportive Care				
20000	Supportive Care				
25000	Supportive Care				
30000	Supportive Care				
35000	Etanercept 25mg	Supportive Care			
40000	Etanercept 25mg	Supportive Care			
45000	Etanercept 25mg	Continuous	Efalizumab	Supportive Care	
50000	Etanercept 25mg	Continuous	Efalizumab	Supportive Care	
55000	Etanercept 25mg	Continuous	Efalizumab	Supportive Care	
60000	Etanercept 25mg	Continuous	Efalizumab	Supportive Care	
65000	Etanercept 25mg	Continuous	Efalizumab	Etanercept 50mg	Supportive Care
70000	Etanercept 25mg	Continuous	Efalizumab	Etanercept 50mg	Supportive Care
75000	Etanercept 25mg	Continuous	Efalizumab	Etanercept 50mg	Supportive Care

Table 6.3.6 Results of probabilistic sensitivity analysis for Alternative Scenario I showing probabilities that each therapy is first in sequence and included in the sequence at all conditional on the threshold value of cost-effectiveness. Analysis includes only etanercept, efalizumab and supportive care and relates only to patients with the worst quality of life (4th quartile DLQI) at baseline, and assumes patients not responding to therapy are not hospitalised. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

Threshold value of cost-effectiveness		Etanercept 25mg	Etanercept 50mg	Efalizumab	Etanercept 25mg Continuous	Supportive Care
20000	Probability first in sequence	0.00	0.00	0.00	0.00	1.00
30000	Probability first in sequence	0.25	0.00	0.00	0.00	0.75
50000	Probability first in sequence	0.86	0.00	0.05	0.00	0.09
20000	Probability included in sequence	0.00	0.00	0.00	0.00	1.00
30000	Probability included in sequence	0.25	0.00	0.02	0.03	1.00
50000	Probability included in sequence	0.90	0.12	0.70	0.71	1.00

Table 6.3.7. Results of Alternative Scenario II including only etanercept, efalizumab and supportive care and relating to all patients (regardless of baseline DLQI) and assuming patients not responding to therapy are hospitalised for 21 days per year. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

	QALYs				Costs				ICER against Supportive Care
	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI	ICER		
Supportive Care	0	0	0	0	0	0	0	-	
Etanercept 25mg	0.116	0.065	0.168	3415	2623	4971	29420	29420	
Efalizumab	0.112	0.065	0.162	5232	4656	6116	Dominated	46866	
Etanercept 25mg Continuous	0.116	0.065	0.168	5337	4753	6484	Dominated	45975	
Etanercept 50mg	0.123	0.073	0.176	10258	9696	11248	984856	83378	

6.3.3 Alternative Scenario II: patients with any DLQI at baseline and 21 days annual in-patient hospitalisation when not responding to therapy

The second alternative scenario considers all patients in terms of baseline quality of life but now assumes that patients not responding to therapy spend 21 days per year as hospital in-patients. This figure is a mean length of stay for a single hospitalisation and is based on an average of that from the Hospital Episode Statistics (2002/03) for psoriasis and two local audits (see section 6.2.4.3). The assumption is effectively that non-responding patients experience one hospitalisation per annum consisting of a 21-day stay.

Table 6.3.7 shows expected QALYs, costs and ICERs for this alternative scenario. Compared to the base-case assumptions, the ICERs against supportive care are lower indicating that the biologics would enter a sequence at lower ICERs. These ICERs are not greatly different to those in Alternative Scenario I.

Table 6.3.8. Most cost-effective ordering of therapies for Alternative Scenario II as a function of the threshold value for cost-effectiveness. Analysis includes only etanercept, efalizumab and supportive care and relates to all patients (regardless of baseline DLQI) and assumes patients not responding to therapy are hospitalised for 21 days per year. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

Threshold value of cost-effectiveness	Sequence			
	1 st in sequence	2 nd in sequence	3 rd in sequence	4 th in sequence
0	Supportive Care			
5000	Supportive Care			
10000	Supportive Care			
15000	Supportive Care			
20000	Supportive Care			
25000	Supportive Care			
30000	Etanercept 25mg	Supportive Care		
35000	Etanercept 25mg	Supportive Care		
40000	Etanercept 25mg	Supportive Care		
45000	Etanercept 25mg	Supportive Care		
50000	Etanercept 25mg	Continuous	Efalizumab	Supportive Care
55000	Etanercept 25mg	Continuous	Efalizumab	Supportive Care
60000	Etanercept 25mg	Continuous	Efalizumab	Supportive Care
65000	Etanercept 25mg	Continuous	Efalizumab	Supportive Care
70000	Etanercept 25mg	Continuous	Efalizumab	Supportive Care
75000	Etanercept 25mg	Continuous	Efalizumab	Supportive Care

Table 6.3.8 shows the most cost-effective sequence of therapies conditional on the threshold value of cost-effectiveness. As for Alternative Scenario I, the biologic therapies appear much earlier in these sequences than was the case under base-case assumptions. Again, the first to appear is etanercept 25mg (at £30,000 per QALY gained). Etanercept 25mg (continuous) and efalizumab appear in the sequence at a threshold of £50,000 and above. Etanercept 50mg does not appear in a sequence based on the thresholds shown. Table 6.3.9 shows the results of the probabilistic sensitivity analysis for this scenario, and indicates that the probabilities of being first in sequence and of appearing in the sequence at all are higher than under the base-case assumptions.

Table 6.3.9. Results of probabilistic sensitivity analysis for Alternative Scenario II showing probabilities that each therapy is first in sequence and included in the sequence at all conditional on the threshold value of cost-effectiveness. Analysis includes only etanercept, efalizumab and supportive care and relates to all patients (regardless of baseline DLQI) and assumes patients not responding to therapy are hospitalised for 21 days per year. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

Threshold value of cost-effectiveness		Etanercept 25mg	Etanercept 50mg	Efalizumab	Etanercept 25mg Continuous	Supportive Care
20000	Probability first in sequence	0.09	0.00	0.00	0.00	0.91
30000	Probability first in sequence	0.56	0.00	0.00	0.00	0.44
50000	Probability first in sequence	0.91	0.00	0.04	0.00	0.05
20000	Probability included in sequence	0.09	0.00	0.00	0.00	1.00
30000	Probability included in sequence	0.56	0.00	0.02	0.03	1.00
50000	Probability included in sequence	0.93	0.00	0.60	0.63	1.00

6.3.4 Alternative Scenario III: 4th quartile DLQI and 21 days annual in-patient hospitalisation when not responding to therapy

The third alternative scenario effectively combines the first and second by including a sub-group of patients with poor baseline quality of life (highest quartile DLQI) and high in-patient hospitalisation when not responding to therapy (21 days per year).

Table 6.3.10 shows the expected QALYs, costs and ICERs for all therapies. It can be seen that the ICERs compared to supportive care are lower than the base-case and the two previous alternative scenarios, indicating that biologic therapies will enter a cost-effective sequence at lower ICERs.

Table 6.3.11 shows the most cost-effective sequence of therapies conditional on the threshold value of cost-effectiveness. Compared to the base-case and earlier scenarios, the biologic therapies appear much earlier in these sequences. Again, the first to appear is etanercept 25mg (at £20,000 per QALY gained). Etanercept 25mg (continuous) and efalizumab appear in the sequence at a threshold of £25,000 and above. Etanercept 50mg appears in the sequence at a threshold of £45,000 per QALY gained. Table 6.3.12 shows the results of the probabilistic sensitivity analysis for this scenario, and indicates that the probabilities of being first in sequence and of appearing in the sequence at all are the highest of all the scenarios.

Table 6.3.10. Results of Alternative Scenario III including only etanercept, efalizumab and supportive care and relating to patients with the worst quality of life (4th quartile DLQI) at baseline and assuming patients not responding to therapy are hospitalised for 21 days per year. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

	QALYs				Costs				ICER against Supportive Care
	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI	ICER		
Supportive Care	0	0	0	0	0	0	0	-	
Etanercept 25mg	0.223	0.126	0.326	3415	2623	4971	15297	15297	
Efalizumab	0.215	0.127	0.312	5232	4656	6116	Dominated	24346	
Etanercept 25mg Continuous	0.223	0.126	0.326	5337	4753	6484	Dominated	23905	
Etanercept 50mg	0.236	0.141	0.342	10258	9696	11248	521054	43395	

Table 6.3.11. Most cost-effective ordering of therapies for Alternative Scenario III as a function of threshold value for cost-effectiveness. Analysis includes only etanercept, efalizumab and supportive care, relates to patients with the worst quality of life (4th quartile DLQI) at baseline and assumes patients not responding to therapy are hospitalised for 21 days per year. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

Threshold value of cost-effectiveness	Sequence				
	1 st in sequence	2 nd in sequence	3 rd in sequence	4 th in sequence	5 th in sequence
0	Supportive Care				
5000	Supportive Care				
10000	Supportive Care				
15000	Supportive Care				
20000	Etanercept 25mg	Supportive Care			
25000	Etanercept 25mg	Etanercept 25mg	Efalizumab	Supportive Care	
30000	Etanercept 25mg	Etanercept 25mg	Efalizumab	Supportive Care	
35000	Etanercept 25mg	Etanercept 25mg	Efalizumab	Supportive Care	
40000	Etanercept 25mg	Etanercept 25mg	Efalizumab	Supportive Care	
45000	Etanercept 25mg	Etanercept 25mg	Efalizumab	Etanercept 50mg	Supportive Care
50000	Etanercept 25mg	Etanercept 25mg	Efalizumab	Etanercept 50mg	Supportive Care
55000	Etanercept 25mg	Etanercept 25mg	Efalizumab	Etanercept 50mg	Supportive Care
60000	Etanercept 25mg	Etanercept 25mg	Efalizumab	Etanercept 50mg	Supportive Care
65000	Etanercept 25mg	Etanercept 25mg	Efalizumab	Etanercept 50mg	Supportive Care
70000	Etanercept 25mg	Etanercept 25mg	Efalizumab	Etanercept 50mg	Supportive Care
75000	Etanercept 25mg	Etanercept 25mg	Efalizumab	Etanercept 50mg	Supportive Care

Table 6.3.12. Results of probabilistic sensitivity analysis for Alternative Scenario III showing probabilities that each therapy is first in sequence and included in the sequence at all conditional on the threshold value of cost-effectiveness. Analysis includes only etanercept, efalizumab and supportive care and relates to patients with the worst quality of life (4th quartile DLQI) at baseline and assumes patients not responding to therapy are hospitalised for 21 days per year. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

Threshold value of cost-effectiveness		Etanercept 25mg	Etanercept 50mg	Efalizumab	Etanercept 25mg Continuous	Supportive Care
20000	Probability first in sequence	0.80	0.00	0.02	0.00	0.18
30000	Probability first in sequence	0.92	0.00	0.05	0.00	0.02
50000	Probability first in sequence	0.92	0.00	0.08	0.00	0.00
20000	Probability included in sequence	0.81	0.00	0.20	0.24	1.00
30000	Probability included in sequence	0.96	0.03	0.78	0.80	1.00
50000	Probability included in sequence	0.99	0.72	0.99	0.98	1.00

6.3.5 Alternative Scenario IV: comparison of biologics with other systemic therapies (patients with any baseline DLQI and assumption that non-responding patients are hospitalised for 21 days per year)

The final scenario widens the basis of comparison to include all systemic therapies for which effectiveness parameters could be estimated in the evidence synthesis (see Section 4.5). As well as supportive care and therapies based on etanercept and efalizumab, this scenario includes methotrexate, ciclosporin, Fumaderm and infliximab. By way of illustration, the scenario is run for all patients (regardless of baseline DLQI) and assuming that patients not responding to therapy are hospitalised for 21 days per annum.

Table 6.3.13 shows the expected QALYs, costs and ICERs for this scenario. As a result of their higher effectiveness (compared to supportive care) and lower acquisition costs (compared to the biologics), methotrexate, ciclosporin and

Fumaderm all dominate supportive care. The ICERs for etanercept-based therapies and efalizumab, compared to supportive care, are similar to those in Alternative Scenario II. The ICER of infliximab, compared to supportive care, lies between those for etanercept 25mg (continuous) and etanercept 50mg.

Table 6.3.14 show the most cost-effective treatment sequences, conditional on the threshold for cost-effectiveness, for this broader comparison. It shows that methotrexate, ciclosporin and Fumaderm would be the first three treatments in the sequence whatever threshold value is used. The first biologic to appear is etanercept 25mg (4th in sequence at £30,000 per QALY gained). Etanercept 25mg (continuous) and efalizumab appear 5th and 6th in the sequence, respectively, at a threshold of £50,000 and above. Etanercept 50mg does not appear in any sequence at the thresholds used in the analysis. Table 6.3.15 shows the results of the probabilistic sensitivity analysis for this scenario, and indicates that the probabilities of being first in sequence and of appearing in the sequence are highest for methotrexate, ciclosporin and Fumaderm.

Table 6.3.13. Results of the base-case analysis including supportive care and full range of systemic therapies. Includes all patients (regardless of baseline DLQI) and assumes that patients not responding to therapy are hospitalised for 21 days per year. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

	QALYs						Costs						ICER against Supportive Care	
	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI	Mean	2.5% CI	97.5% CI		ICER
Methotrexate	0.126	0.072	0.182	-4223	-4604	-3224	-	-	-	-	-	-	-	Dominates
Ciclosporin	0.122	0.072	0.175	-452	-795	41	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Fumaderm	0.101	0.036	0.16	-162	-2192	2309	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Supportive Care	0	0	0	0	0	0	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	-
Etanercept 25mg	0.116	0.065	0.168	3415	2623	4971	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	29451
Efalizumab	0.112	0.066	0.161	5232	4656	6116	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	46893
Etanercept 25mg Continuous	0.116	0.065	0.168	5337	4753	6484	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	46025
Infliximab	0.134	0.079	0.192	6918	4396	9850	1393179	9850	9850	9850	9850	9850	1393179	51748
Etanercept 50mg	0.123	0.072	0.176	10258	9696	11248	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	83477

Table 6.3.14. Most cost-effective ordering of therapies for Alternative Scenario IV as a function of threshold value for cost-effectiveness. Analysis includes supportive care and full range of systemic therapies. Includes all patients (regardless of baseline DLQI) and assumption that patients not responding to therapy are hospitalised for 21 days per annum. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

Threshold value of cost-effectiveness	Sequence							
	1 st in sequence	2 nd in sequence	3 rd in sequence	4 th in sequence	5 th in sequence	6 th in sequence	7 th in sequence	8 th in sequence
0	Methotrexate	Ciclosporin	Fumaderm	Supportive Care				
5000	Methotrexate	Ciclosporin	Fumaderm	Supportive Care				
10000	Methotrexate	Ciclosporin	Fumaderm	Supportive Care				
15000	Methotrexate	Ciclosporin	Fumaderm	Supportive Care				
20000	Methotrexate	Ciclosporin	Fumaderm	Supportive Care				
25000	Methotrexate	Ciclosporin	Fumaderm	Supportive Care				
30000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25mg	Supportive Care			
35000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25mg	Supportive Care			
40000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25mg	Supportive Care			
45000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25mg	Supportive Care			
50000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25mg	Etanercept 25mg	Efalizumab	Supportive Care	
55000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25mg	Etanercept 25mg	Efalizumab	Infliximab	Supportive Care
60000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25mg	Etanercept 25mg	Efalizumab	Infliximab	Supportive Care
65000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25mg	Etanercept 25mg	Efalizumab	Infliximab	Supportive Care
70000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25mg	Etanercept 25mg	Efalizumab	Infliximab	Supportive Care
75000	Methotrexate	Ciclosporin	Fumaderm	Etanercept 25mg	Etanercept 25mg	Efalizumab	Infliximab	Supportive Care

Table 6.3.15. Results of probabilistic sensitivity analysis for Alternative Scenario IV showing probabilities that each therapy is first in sequence and included in the sequence at all conditional on the threshold value of cost-effectiveness. Analysis includes supportive care and full range of systemic therapies. Includes all patients (regardless of baseline DLQI) and assumption that patients not responding to therapy are hospitalised for 21 days per annum. All etanercept therapies are intermittent unless stated and efalizumab is continuous.

Threshold value of cost-effectiveness	Etanercept 25mg	Etanercept 50mg	Efalizumab	Supportive Care	Ciclosporin	Methotrexate	Funaderm	Infliximab	Etanercept 25mg Continuous
Probability first in sequence	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Probability first in sequence	0.00	0.00	0.00	0.00	0.00	0.99	0.00	0.00	0.00
Probability first in sequence	0.00	0.00	0.00	0.00	0.01	0.99	0.00	0.00	0.00
Probability included in sequence	0.09	0.00	0.00	1.00	1.00	1.00	0.92	0.00	0.00
Probability included in sequence	0.56	0.00	0.02	1.00	1.00	1.00	0.95	0.04	0.03
Probability included in sequence	0.93	0.00	0.60	1.00	1.00	1.00	0.97	0.46	0.63

7 Discussion

7.1 Clinical evaluation

The literature searches conducted for this review were comprehensive. With these and the data made available in the company submissions and clinical trial reports provided by Wyeth, we are confident that we have been able to include all the relevant RCTs in our evaluation of efficacy. We are similarly confident that all relevant studies have been included in our review of adverse events and all RCTs identified regarding the efficacy of other treatments for moderate to severe psoriasis.

It may be considered a limitation of our review that it is based firmly in the available clinical trials data and as such may not properly reflect UK clinical practice and experience. Whilst we adhered to standard systematic review practice to evaluate the best evidence from clinical trials, this review has several limitations. Firstly, there is a shortage of good quality data on the various treatment options used in moderate to severe psoriasis. Secondly, the excellent degree of efficacy seen with PUVA in clinical practice, with clearance of symptoms being the normal outcome of treatment, has resulted in a complete lack of placebo-controlled trials. We, therefore, found it impossible to compare (even indirectly) PUVA with other therapies. Similarly, trials of methotrexate are lacking. Finally, the outcome measures used in clinical trials, primarily PASI do not help to unify clinical trial evidence and clinical experience, because of its lack of relevance for and applicability to clinical practice. However, one of the most important parameters, with respect to cost-effectiveness, is the probability that a patient continues on therapy beyond an initial trial period – the PASI may be a good proxy for this.

One of the difficulties in comparing older systemic therapies with the newer biologics is that trials of older therapies report fewer and less clearly-defined outcomes than those of the biologics. However, some of the trials of the biologics place heavy emphasis on PASI 50 as an appropriate measure of effectiveness. In clinical practice, it is likely that dermatologists will consider this an insufficient definition of treatment success.

There are only limited data available for the evaluation of the efficacy of the two biological drugs reviewed: only three RCTs for etanercept and five for efalizumab. All eight trials were double-blind, placebo-controlled trials, conducted by the pharmaceutical companies developing the drugs, and as such were of a generally high standard. All eight trials provided reliable data regarding the short-term (12 weeks) use of the biologics, however, much less data are available for 24 weeks use, with only one RCT available for etanercept and none for efalizumab. There is good evidence that etanercept and efalizumab are both more efficacious than placebo in the treatment of moderate to severe psoriasis. The clinical significance of the level of efficacy is a point for debate: is the achievement with etanercept 25 mg of PASI 50 by 60% of patients treated, and PASI 75 by 33% of patients treated to be considered an acceptable level of efficacy? Clinical advice we have received suggests that UK dermatologists do not consider the PASI 50 to represent a sufficient clinical response. The level of efficacy with the 50 mg dose of etanercept, with 76% of treated patients achieving a PASI 50 and 49% achieving PASI 75 is higher, but that for efalizumab is lower, with only around 55% achieving PASI 50 and 27% PASI 75.

The degree of debility suffered by the patients to be treated with these drugs also needs to be considered. The patients included in the clinical trials can all be appropriately classified as having moderate to severe psoriasis, with baseline PASI scores of at least 10 or 12 and the populations are comparable across the trials. However, whether they are truly representative of the patients who are likely to be candidates for treatment with these agents in clinical practice is questionable. Given the product licences for both etanercept and efalizumab and the high cost of these drugs, it is likely that patients in clinical practice will be much more severely affected than those in the clinical trials and, therefore, response rates may be different.

As a chronic condition, psoriasis requires many patients to undergo continuous treatment for long periods. RCT data to support this type of use of both biologics are lacking. Uncontrolled data from long-term continuation of RCTs of etanercept do suggest that for up to 36 weeks at least, the short-term efficacy is maintained. Unfortunately, similar data for efalizumab are not available. Intermittent treatment of psoriasis is often advocated, with short treatment periods to induce remission and then a treatment-free period until relapse, upon which active therapy is again introduced.

There are some limited data to support this with etanercept, with relapse occurring on average some three months after treatment. Importantly, the data indicate that there is no rebound psoriasis upon withdrawal of treatment, nor any loss of efficacy upon re-treatment in patients who have relapsed. However, it must be stressed that these findings for intermittent use of etanercept may not be reliable as they are based on uncontrolled data. Supporting evidence for intermittent use of efalizumab is even weaker. The time to relapse is possibly shorter than that for etanercept at around two months and, although the efalizumab SPC states that efficacy may be reduced upon re-treatment, we found no RCT or RCT-extension data to support or confirm this.

Overall, both drugs have clearly demonstrated some degree of efficacy for the short-term (12 weeks) treatment of moderate to severe psoriasis but only for etanercept did we find any real evidence that longer-term (24 weeks) or intermittent use is an effective therapy option.

In the context of the etanercept product licence for use up to 24 weeks, the adverse effects profile of etanercept appears acceptable and is supported by long-term data from other clinical indications. However, given that clinical use is likely to be intermittent over a very long period, probably years, then long-term effects specifically in psoriasis patients are relevant and further information is required. The publicly available information for efalizumab indicates that the drug is well tolerated when used to treat psoriasis patients over a 12-week period with a low rate of withdrawals. As yet unpublished data from Serono's submission indicate that efalizumab(*CiC removed*), however, those data were not evaluable in this review. For both etanercept and efalizumab it must be remembered that patients with moderate to severe psoriasis will have been exposed to the nephrotoxicity of methotrexate, the hepatotoxicity of ciclosporin, and the increased risk of skin cancer with PUVA, before being treated with either biologic agent. The significance of the serious adverse events reported in association with etanercept or efalizumab is not readily discernable from the published reports of clinical trials.

Despite widespread use and numerous trials, it is difficult to draw firm conclusions regarding the efficacy of the treatments available for the relief of moderate to severe psoriasis. Only infliximab and ciclosporin have had their efficacy demonstrated in

placebo-controlled RCTs, and even these data are relatively few, with most trials having included a small number of patients and only a short treatment period. Whilst clinical experience has demonstrated excellent efficacy of PUVA and methotrexate, no placebo-controlled trials have been conducted. In clinical trials methotrexate appears to be as effective as ciclosporin. The trials of other treatments - acitretin, Re-PUVA, and NBUVB, in comparison with PUVA - provide only limited evidence, demonstrating some degree of effectiveness but making it difficult to draw firm conclusions regarding the relative efficacy. All comparator treatments are associated with serious and long-term adverse events.

By using a mixed treatment comparison analysis it was possible to make some form of comparison between etanercept and efalizumab with each other and with ciclosporin, Fumaderm, methotrexate, infliximab and placebo. Data available from trials limited the therapies that could be compared, but the majority of widely used systemic psoriasis treatments were included. Our failure to include PUVA in the analysis is not of great importance since the level of efficacy to be achieved with phototherapy is very different to that achieved with other therapies: with PUVA or NBUVB the ability to achieve clearance is the expected outcome. Unfortunately, phototherapy can only be used for a limited number of exposures over a lifetime; other therapies are only considered when the exposure limit has been reached or other factors make phototherapy unsuitable.

In a mixed treatment comparison, including etanercept, efalizumab, ciclosporin, Fumaderm, methotrexate, infliximab and placebo, infliximab appeared the most effective followed by methotrexate and ciclosporin, then etanercept 50mg. Etanercept 25mg has a higher response rate than efalizumab, which has a lower mean response rate than all other therapies except Fumaderm and supportive care. It should be emphasised, however, that response rates for all therapies were uncertain and 95% confidence intervals frequently overlapped.

It is important to note that this analysis is limited by the data available. Importantly, it only draws conclusions regarding short-term use; relative efficacy at 12 weeks for treatment of a life-long condition is not ideal. However, this lack of information reflects the evidence base for all treatments, not just the new biologics. What is

lacking with the newer drugs is, of course, long-term clinical experience. The lack of long-term data is a serious omission in the evidence base. Without such information it is impossible to understand fully the relative value of the therapies reviewed. It is unknown if short-term efficacy is maintained in the long-term or if indeed it might improve, or if, in the case of infliximab, tachyphylaxis is common with continued use.

The evidence synthesis also omits the adverse effects of the various treatments. Due to long experience with the other treatments their long-term serious adverse effects, and how these should be managed, is well known. The relative efficacy of the new biologics needs to be considered in the light of what is known about their safety profiles; so far they appear well tolerated and safe; however, much more experience of use with these agents is required before a clear picture emerges.

Another area of importance to clinical practice that has not been addressed in this report due to a lack of trial-based evidence is that of the use of combination therapies: neither of the new biologics has been studied in combination with any older treatment (except methotrexate). All systemic therapies for psoriasis are, however, complemented by use of topical preparations.

7.2 Economic evaluation

In assessing the cost-effectiveness of efalizumab and etanercept in psoriasis, little information was available in the published literature. Only one study was identified which had several methodological limitations and has little relevance to NHS decision making. It has, therefore, been necessary to rely on the economic models submitted by Wyeth and Serono, and the *de novo* York Model. How do these models compare? The models share some important features. For example, all models use PASI to determine whether, over a short-term period (usually 12 weeks, following trial evidence), patients are showing adequate response to continue therapy.

There are, however, some important differences between the three models which are likely to impact on results. The first different is a general one. Both Serono and Wyeth's models sought to estimate the cost-effectiveness of the relevant biologic

therapy, relative to a comparator of no systemic therapy, as a single mutually exclusive comparison. The premise of such an analysis is that clinicians will only be able to use one therapy and this should be the one that is identified as the most cost-effective. Although this is a fairly standard approach to economic evaluation, it has some important limitations in the context of the treatment of chronic relapsing diseases such as psoriasis. Such diseases show high variability between individuals and, if a patient does not appear to respond to (or cannot tolerate) one treatment, another will be tried. Once all active therapies have been tried, some form of ‘best supportive care’ would be the only remaining option. In this context, the comparison of mutually exclusive treatment options does not provide useful information to decision makers. Instead, the appropriate focus is to identify the most cost-effective *sequence* of therapies, and this was the objective of the York Model. The latter indicated the most cost-effective sequence of treatments conditional on a decision maker’s threshold value of cost-effectiveness (per additional QALY).

There are also some more specific differences between the manufacturers’ models and the York Model. The first is the choice of PASI response category to determine whether a patient has experienced sufficient benefit from treatment to justify continuing on that therapy. In the Serono and Wyeth models, PASI 50 is used. Clinical advice received, however, suggests that, in routine practice, dermatologists will consider this too modest a gain to justify continuation. Of course, the choice of this response threshold is one aspect of defining the most appropriate intervention/sequence. In the York Model, clinical advice has prompted the use of PASI 75 as the response criterion, but other scenarios could be run to assess the implications of using alternatives.

A second important difference between the models is the methods used to relate the measure of efficacy in the trials (PASI) with health-related quality of life and utility. The Serono model has used utility estimates from the literature and sought to ‘map’ these to general health states of ‘severe psoriasis’ and ‘treatment response to severe psoriasis’. As discussed in Section 5.3.3.2, the resulting utility gain from a PASI 50 treatment response can be considered to be unrealistically high. The Wyeth and York models have some similarity, in terms of utility, as both have used survey data to link quality of life (in terms of DLQI) to utility (in terms of EQ-5D). The Wyeth model

has linked PASI to DLQI by, in effect, averaging the DLQI changes for responders and non-responders in terms of PASI 50. On the basis of access to patient-level data supplied by Wyeth, the York analysis may be considered somewhat more sophisticated in that the changes in DLQI for all levels of PASI response are considered, and these are conditioned on baseline DLQI.

Despite the difference in modelling approach, it is possible to compare the ICERs generated by the company models with those against supportive care in the York Model. The ICER range for intermittent use of etanercept 25mg in the Wyeth model was £24,229 to £37,199 per QALY gained dependent on baseline severity. The range for the same therapy in the York Model was £15,297 to £66,703 per QALY gained depending on assumptions about baseline quality of life and the number of days in hospital for patients not responding to therapy. Hence the Wyeth range lies within the York Model range which indicates that the latter explored more extreme scenarios. This is also the case in comparing the ICERs for continuous use of etanercept 25mg (£25,926 to £53,056 per QALY gained for Wyeth and £23,905 to £83,258 per QALY gained for the York model). Etanercept 50mg was evaluated as a continuous therapy in the Wyeth model and as an intermittent therapy in the York model, so the results are not directly comparable.

In comparing the Serono and York models, two features of the former are likely to generate optimistic results for the cost-effectiveness of efalizumab. The first is the methods Serono have used to introduce utility values into their analysis, as discussed above. The second is the assumption that those patients who are responding at 12 weeks (in terms of PASI 50) will continue to respond for a further 10 years with the exception of a small proportion of patients who discontinue therapy for reasons unrelated to efficacy or adverse events. This drop out rate is set at 8% per annum compared to the 20% in the York model based on available longer-term data. These assumptions explain the base-case ICER for efalizumab from Serono of £25,582 per QALY gained (over 10 years), compared to a range of £24,346 to £84,018 for the York Model. In other words, Serono's base-case estimate for all patients is close to that from the York Model for patients with poor baseline quality of life and a 21-day annual hospitalisation for patients not responding to therapy.

An important issue with respect to cost-effectiveness is the choice of comparators against which to assess efalizumab and etanercept. In the York Model, two alternative approaches to comparators have been used. The primary analysis includes only etanercept, efalizumab and supportive care. One alternative scenario (IV) was included which assessed the cost-effectiveness of a wider set of systemic therapies which are used in routine practice and which were included in the systematic review and evidence synthesis. For purposes of decision making in a broader clinical context, it is this wider comparison which is likely to be most useful.

Some parameters in the modelling are highly uncertain. In part, this simply reiterates the point made above, in the context of the clinical evaluation, that about the limitations in the efficacy evidence. Parameters, other than those relating to efficacy, have been used in the cost-effectiveness model and are characterized by significant uncertainty. Perhaps the most important of these relate to the long-term experience with biologics including the annual drop out rate from therapy and the ‘remission’ period assumed between spells of intermittent etanercept. Another area of parameter uncertainty relates to the cost of adverse events. In the York Model, no such costs have been included for any therapy on the assumption that common adverse events generally resolve once therapy is discontinued and the latter is explicitly part of the model. The cost implications of more serious adverse events are unclear given the uncertainty about the incidence of such events.

Other parameters in the York model are highly variable. This is particularly the case with baseline quality of life and the assumed number of in-patient days spent in hospital by patients not responding to therapy. Hence the cost-effectiveness analysis results have been presented conditional on a baseline DLQI and the probability of being hospitalised. It is clear that etanercept and efalizumab are more cost-effective in patients whose psoriasis has a greater impact on their baseline quality of life and who are likely to spend more days in hospital when not responding to therapy.

7.3 Recommendations for research

- Efficacy trials conducted in the specific population for which etanercept and efalizumab are licenced are required, i.e. patients with moderate to severe disease in whom conventional therapy has failed or is inappropriate.
- Long-term comparisons of etanercept and efalizumab with other treatments for moderate to severe psoriasis - particularly infliximab, methotrexate and ciclosporin are warranted.
- Long-term efficacy trials to provide data on how etanercept and efalizumab perform as maintenance therapies are required.
- Long term safety/tolerability data collected from patients with psoriasis are required.
- Randomised controlled trials of various combination therapies are warranted.
- Psoriasis is a heterogeneous group of diseases; trials to identify specific subtypes that respond better to one drug compared to another are warranted.
- Research on the rate of in-patient hospitalisation in patients with moderate to severe psoriasis is warranted, and the effect of treatment on this rate.

8 Conclusions

- There is good evidence that etanercept is efficacious in the treatment of moderate to severe psoriasis, and that the response is maintained up to 24 weeks.
- The most common adverse effect of etanercept is injection site reaction. Other serious adverse events, as identified from earlier reviews, are uncommon and not readily identified from clinical trials.
- There is evidence that efalizumab is efficacious in the treatment of moderate to severe psoriasis. There is no evidence from RCTs that the response to efalizumab 1 mg/kg once a week is maintained when treatment continues beyond 12 weeks.
- The publicly available information for efalizumab indicates that the drug is well tolerated over a 12 week period; however, few data for any longer-term treatment are available for evaluation.
- Despite widespread use and numerous trials, it is difficult to draw firm conclusions regarding the efficacy of the other treatments available for the relief of moderate to severe psoriasis.
- All other treatments are associated with serious and possibly long-term adverse events.
- In a mixed treatment comparison, including etanercept, efalizumab, ciclosporin, Fumaderm, methotrexate, infliximab and placebo, infliximab appeared the most effective followed by methotrexate and ciclosporin, then etanercept 50 mg. Etanercept 25 mg has a higher response rate than efalizumab, which has a lower mean response rate than all other therapies except Fumaderm and supportive care. The pattern is consistent across the different PASI response categories.
- For the primary analysis comparing etanercept, efalizumab and supportive care, the results of the York Model suggest that the biologic therapies would only be cost-effective in a treatment sequence for all patients with moderate to severe psoriasis if the NHS is willing to pay over £60,000 per QALY gained.
- Efalizumab is only a cost-effective option for patients with poor baseline DLQI (4th quartile) in a treatment sequence as long as the NHS is willing to pay up to £45,000 per QALY gained. For patients who are also at high risk of hospitalisation for their psoriasis in the event of failing to respond to treatment

(21 in-patient days annually), efalizumab can be a cost-effective option as long as the NHS will pay up to £25,000 per QALY gained.

- Intermittent use of etanercept 25mg is only a cost-effective option in a treatment sequence for patients with poor baseline DLQI (4th quartile) as long as the NHS is willing to pay up to £35,000 per QALY gained. For patients who are also at high risk of hospitalisation for their psoriasis in the event of failing to respond to treatment, intermittent etanercept 25mg can be a cost-effective option as long as the NHS will pay up to £20,000 per QALY gained.
- Continuous use of etanercept 25mg is only a cost-effective option in a treatment sequence for patients with poor baseline DLQI (4th quartile) as long as the NHS is willing to pay up to £45,000 per QALY gained. For patients who are also at high risk of hospitalisation for their psoriasis in the event of failing to respond to treatment, this therapy can be a cost-effective option as long as the NHS will pay up to £25,000 per QALY gained.
- Intermittent use of etanercept 50mg is only a cost-effective option in a treatment sequence for patients with poor baseline DLQI (4th quartile) as long as the NHS is willing to pay up to £65,000 per QALY gained. For patients who are also at high risk of hospitalisation for their psoriasis in the event of failing to respond to treatment it can be a cost-effective option as long as the NHS will pay up to £45,000 per QALY gained.
- As part of a secondary analysis including a wider range of systemic therapies as comparators, the York Model found it would only be cost-effective to use etanercept and efalizumab in a sequence after methotrexate, ciclosporin and Fumaderm.
- Overall, clinical trial data indicate that both etanercept and efalizumab are efficacious in patients who are eligible for systemic therapy but, the economic evaluation demonstrates that these biologics are likely to be cost-effective only in patients with poor baseline quality of life and who are at risk of hospitalization.

9 References

1. Lebwohl M. Psoriasis. *Lancet* 2003;361:1197-204.
2. McCormick A, Flaming D, Charlton J. *Morbidity statistics from general practice: fourth national study - 1991-92*. London: HMSO, 1995.
3. Williams HC. Dermatology. In: Stevens A, Raftery J, editors. *Health care needs assessment: the epidemiologically based needs assessment reviews: second series*. Oxford: Radcliffe Medical Press, 1997. p. 261-348.
4. Nevitt GJ, Hutchinson PE. Psoriasis in the community: prevalence, severity and patients' beliefs and attitudes towards the disease. *Br J Dermatol* 1996;135:533-7.
5. Ameen M. Genetic basis of psoriasis vulgaris and its pharmacogenetic potential. *Pharmacogenomics* 2003;4:297-308.
6. Granstein RD. New treatments for psoriasis. *N Engl J Med* 2001;345:284-87.
7. Prinz JC. The role of T cells in psoriasis. *J Eur Acad Dermatol Venereol* 2003;17:257-70.
8. Stern RS. Psoriasis. *Lancet* 1997;350:349-53.
9. Kirby B, Fortune DG, Bhushan M, Chalmers RJG, Griffiths CEM. The Salford Psoriasis Index: an holistic measure of psoriasis severity. *Br J Dermatol* 2000;142:728-32.
10. Poikolainen K, Karvonen J, Pukkala E. Excess mortality related to alcohol and smoking among hospital-treated patients with psoriasis. *Arch Dermatol* 1999;135:1490-3.
11. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;19:210-6.
12. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol* 1999;41:401-7.
13. Wahl A, Loge JH, Wiklund I, Hanestad BR. The burden of psoriasis: a study concerning health-related quality of life among Norwegian adult patients with psoriasis compared with general population norms. *J Am Acad Dermatol* 2000;43:803-8.
14. Rapp SR, Feldman SR, Reboussin D, Fleischer A. Predictors of health-related quality of life in psoriasis and a comparison with other chronic diseases. *Qual Life Res* 1997;6:705.
15. Morgan M, McCreedy R, Simpson J, Hay RJ. Dermatology quality of life scales: a measure of the impact of skin diseases. *Br J Dermatol* 1997;136:202-6.
16. Augustin M, Zschocke I, Lange S, Seidenglanz K, Amon U. [Quality of life in skin diseases: methodological and practical comparison of different quality of life questionnaires in psoriasis and atopic dermatitis]. *Hautarzt* 1999;50:715-22.
17. Mombers FMC, deVries J, DeBakker ESM, Duller P. Severity of psoriasis in relationship to quality of life. *Qual Life Res* 1997;6:32.
18. Weiss SC, Kimball AB, Liewehr DJ, Blauvelt A, Turner ML, Emanuel EJ. Quantifying the harmful effect of psoriasis on health-related quality of life. *J Am Acad Dermatol* 2002;47:512-8.
19. Kernick D, Cox A, Powell R, Reinhold D, Sawkins J, Warin A. A cost consequence study of the impact of a dermatology-trained practice nurse on the quality of life of primary care patients with eczema and psoriasis. *Br J Gen Pract* 2000;50:555-8.

20. Finlay AY, Henley LA. Quality of life and cost-effectiveness of treatment. *J Dermatolog Treat* 1997;8:28-9.
21. Rapp SR, Cottrell CA, Leary MR. Social coping strategies associated with quality of life decrements among psoriasis patients. *Br J Dermatol* 2001;145:610-6.
22. Richards HL, Fortune DG, Main CJ, Griffiths CEM. Stigmatization and psoriasis. *Br J Dermatol* 2003;149:209-11.
23. Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. *Arch Dermatol* 2001;137:280-4.
24. Gupta MA, Gupta AK. Age and gender differences in the impact of psoriasis on quality of life. *Int J Dermatol* 1995;34:700-3.
25. O'Neill P, Kelly P. Postal questionnaire study of disability in the community associated with psoriasis. *BMJ* 1996;313:919-21.
26. Zug KA, Littenberg B, Baughman RD, Kneeland T, Nease RF, Sumner W, et al. Assessing the preferences of patients with psoriasis a quantitative, utility approach. *Arch Dermatol* 1995;131:561-8.
27. Feldman SR, Fleischer AB, Reboussin DM, Rapp SR, Bradham DD, Exum ML, et al. The economic impact of psoriasis increases with psoriasis severity. *J Am Acad Dermatol* 1997;37:564-9.
28. Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. *Br J Dermatol* 1995;132:236-44.
29. Al-Suwaidan SN, Feldman SR. Clearance is not a realistic expectation of psoriasis treatment. *J Am Acad Dermatol* 2000;42:796-802.
30. Krueger GG, Feldman SR, Camisa C, Duvic M, Elder JT, Gottlieb AB, et al. Two considerations for patients with psoriasis and their clinicians: What defines mild, moderate, and severe psoriasis? What constitutes a clinically significant improvement when treating psoriasis? *J Am Acad Dermatol* 2000;43:281-5.
31. Carlin CS, Feldman SR, Krueger JG, Menter A, Krueger GG. A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. *J Am Acad Dermatol* 2004;50:859-66.
32. Koo J, Kozma CM, Reinke K. The development of a disease-specific questionnaire to assess quality of life for psoriasis patients: an analysis of the reliability, validity, and responsiveness of the psoriasis quality of life questionnaire. *Dermatology & Psychosomatics* 2002;3:171-9.
33. Finlay AY. Quality of life assessments in dermatology. *Semin Cutan Med Surg* 1998;17:291-6.
34. Shikhar R, Bresnahan BW, Stone SP, Thompson C, Koo J, Revicki DA. Validity and reliability of patient reported outcomes used in psoriasis: results from two randomised clinical trials. *Health and Quality of Life Outcomes* 2003;1:53. Available from: <http://www.hqlo.com/content/1/1/53>
35. Finlay AY, Khan GK, Luscombe DK, Salek MS. Validation of Sickness Impact Profile and Psoriasis Disability Index in psoriasis. *Br J Dermatol* 1990;123:751-6.
36. Sampogna F, Sera F, Abeni D, IDI Multipurpose Psoriasis Research on Vital Experiences (IMPROVE) Investigators. Measures of clinical severity, quality of life, and psychological distress in patients with psoriasis: a cluster analysis. *J Invest Dermatol* 2004;122:602-7.
37. Nichol MB, Margolies JE, Lippa E, Rowe M, Quell J. The application of multiple quality-of-life instruments in individuals with mild-to-moderate psoriasis. *Pharmacoeconomics* 1996;10:644-53.

38. de Korte J, Mommers FM, Sprangers MA, Bos JD. The suitability of quality-of-life questionnaires for psoriasis research: a systematic literature review. *Arch Dermatol* 2002;138:1221-7.
39. Finlay AY, Salek MS, Haney J, Alefacept Clinical Study G. Intramuscular alefacept improves health-related quality of life in patients with chronic plaque psoriasis. *Dermatology* 2003;206:307-15.
40. Lundberg L, Johannesson M, Silverdahl M, Hermansson C, Lindberg M. Quality of life, health-state utilities and willingness to pay in patients with psoriasis and atopic eczema. *Br J Dermatol* 1999;141:1067-75.
41. Badia X, Mascaro JM, Lozano R, The Cavide Research Group. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensitivity to change of the DLQI. *Br J Dermatol* 1999;141:698-702.
42. Finlay AY. Quality of life measurement in dermatology: a practical guide. *Br J Dermatol* 1997;136:305-14.
43. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. *Soc Sci Med* 1998;46:1569-85.
44. Stangier U, Ehlers A, Gieler U. Measuring adjustment to chronic skin disorders: validation of a self-report measure. *Psychol Assess* 2003;15:532-49.
45. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol* 1995;132:942-9.
46. de Tiedra AG, Mercadal J, Badia X, Mascaro JM, Lozano R. A method to select an instrument for measurement of HR-QOL for cross-cultural adaptation applied to dermatology. *Pharmacoeconomics* 1998;14:405-22.
47. McKenna KE, Stern RS. The impact of psoriasis on the quality of life of patients from the 16-center PUVA follow-up cohort. *J Am Acad Dermatol* 1997;36:388-94.
48. Fleischer AB, Clark AR, Rapp SR, Reboussin DM, Feldman SR. Commercial tanning bed treatment is an effective psoriasis treatment: results from an uncontrolled clinical trial. *J Invest Dermatol* 1997;109:170-4.
49. Fortune DG, Main CJ, Osullivan TM, Griffiths CEM. Quality of life in patients with psoriasis: the contribution of clinical variables and psoriasis-specific stress. *Br J Dermatol* 1997;137:755-60.
50. McClure SL, Valentine J, Gordon KB. Comparative tolerability of systemic treatments for plaque-type psoriasis. *Drug Saf* 2002;25:913-27.
51. British Medical Journal. *Clinical Evidence [database on the Internet]*. London: British Medical Journal, 2004. Available from: <http://www.clinicalevidence.com/ceweb/conditions/index.jsp>. [cited 2004 Nov]
52. Department of Health. *Hospital episode statistics England: financial year 2002-03 [monograph on the Internet]*. Department of Health, 2003. Available from: <http://www.dh.gov.uk/assetRoot/04/06/74/03/04067403.pdf>. [cited 2004 Dec 12]
53. Department of Health. *Prescription cost analysis, England 2003: prescription items dispensed in the community in England and listed alphabetically within chemical entity by therapeutic class [web page on the Internet]*. London: Department of Health, 2004. Available from: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsStatistics/PublicationsStatisticsArticle/fs/en?CONTENT_ID=4081720&chk=kVOup3. [cited 2004 Dec 17]
54. Ashcroft DM, Li Wan Po A, Williams HC, Griffiths CE. Cost-effectiveness analysis of topical calcipotriol versus short-contact dithranol in the treatment of mild to moderate plaque psoriasis. *Pharmacoeconomics* 2000;18:469-76.

55. Cockayne SE, Cork MJ, Gawkrödger DJ. Treatment of psoriasis: day care vs. inpatient therapy. *Br J Dermatol* 1999;140:375-6.
56. Davies L, Levell N, Munro CS, Cork MJ. Short course cyclosporin therapy for psoriasis: benefits, risks and costs. *Br J Dermatol* 1997;137 Suppl 50:53.
57. Cork M. Economic considerations in the treatment of psoriasis. *Dermatology in Practice* 1993:16-20.
58. Sarkany R. *Access to care [web page on the Internet]*. London: British Association of Dermatologists, 2001. Available from: <http://www.bad.org.uk/patients/access/>. [cited 2004 Dec 17]
59. Shum KW, Lawton S, Williams HC, Docherty G, Jones J. The British Association of Dermatologists audit of atopic eczema management in secondary care. Phase 1: audit of service structure. *Br J Dermatol* 1999;141:430-7.
60. Gniadecki R, Zachariae C, Calverley M. Trends and developments in the pharmacological treatment of psoriasis. *Acta Derm Venereol* 2002;82:401-10.
61. Pariser DM. Management of moderate to severe plaque psoriasis with biologic therapy. *Manag Care* 2003;12:36-44.
62. Wyeth Pharmaceuticals. *Enbrel [summary of product characteristics] [web page on the Internet]*. Electronic Medicines Compendium, 2004. Available from: <http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=3343>. [cited 2004 Dec 15]
63. Serono Ltd. *Raptiva 100 mg/ml [summary of product characteristics] [web page on the Internet]*. Electronic Medicines Compendium, 2004. Available from: <http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=15279>. [cited 2004 Dec 15]
64. British Medical Association. *British national formulary, No. 48*. London: British Medical Association, 2004. Available from: <http://bnf.org>
65. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. 2nd ed. Oxford: Oxford Medical Publications, 1997.
66. Whitehead A. *Meta-analysis of controlled clinical trials*. Chichester: John Wiley & Sons, 2002.
67. Wyeth Pharmaceuticals. *Enbrel and psoriasis: an appraisal submission for the National Institute for Clinical Excellence [Industry submission]*. Maidenhead: Wyeth Pharmaceuticals; 2004 June 23.
68. Serono Ltd. *Clinical and cost effectiveness of efalizumab (Raptiva) for moderate to severe psoriasis*. Feltham: Serono Ltd.; 2004 July 16.
69. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003;349:2014-22.
70. Wyeth Pharmaceuticals, Immunex Corporation. *Efficacy and safety of etanercept in patients with psoriasis: results of a global phase 3 study [Industry submission]*. Poster. Philadelphia, Pa.: Wyeth Pharmaceuticals,; 2004.
71. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. *Arch Dermatol* 2003;139:1627-32.
72. Lebwohl M, Tying SK, Hamilton TK, Toth D, Glazer S, Tawfik NH, et al. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med* 2003;349:2004-13.

73. Gordon KB, Papp KA, Hamilton TK, Walicke PA, Dummer W, Li N, et al. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA* 2003;290:3073-80.
74. ACD2058g. Phase III, randomised double blind placebo-controlled study evaluating 12 weeks of therapy with XOMA1 efalizumab administered subcutaneously (SC), followed by either continued treatment for an additional 12 weeks or re-treatment for 12 weeks following relapse. In: *Clinical and cost effectiveness of efalizumab (Raptiva) for moderate to severe psoriasis. [Industry submission]*. Feltham: Serono Ltd., 2004.
75. ACD2600g. Phase IIIb, randomised, double-blind, parallel group, placebo-controlled, multicentre study evaluating 12 weeks therapy with subcutaneously administered Genentech efalizumab in adults with moderate to severe psoriasis who are candidates for systemic therapy. In: *Clinical and cost effectiveness of efalizumab (Raptiva) for moderate to severe psoriasis. [Industry submission]*. Feltham: Serono Ltd., 2004.
76. IMP24011. Phase III, randomised, double blind, placebo-controlled, multicentre study evaluating 12 weeks subcutaneous therapy with Genentech efalizumab in patients with moderate to severe psoriasis who are candidates for systemic therapy. In: *Clinical and cost effectiveness of efalizumab (Raptiva) for moderate to severe psoriasis. [Industry submission]*. Feltham: Serono Ltd., 2004.
77. Papp K, Bissonnette R, Krueger JG, Carey W, Gratton D, Gulliver WP, et al. The treatment of moderate to severe psoriasis with a new anti-CD11a monoclonal antibody. *J Am Acad Dermatol* 2001;45:665-74.
78. United States Pharmacopoeial Convention. *USPDI, vol 1: drug information for the health care professional*. Rockville, MD: United States Pharmacopoeial Convention, 2004.
79. Sweetman S. *Martindale: the complete drug reference [CD-ROM]*. London: Pharmaceutical Press, 2002. [cited 2004 Mar 30]
80. Khanna D, McMahon M, Furst DE. Safety of tumour necrosis factor-a antagonists. *Drug Saf* 2004;27:307-24.
81. Kavanaugh A, Keystone EC. The safety of biologic agents in early rheumatoid arthritis. *Clin Exp Rheumatol* 2003;21:S203-8.
82. Weisman MH. What are the risks of biologic therapy in rheumatoid arthritis? An update on safety. *J Rheumatol Suppl* 2002;65:33-8.
83. Ellerin T, Rubin RH, Weinblatt ME. Infections and anti-tumor necrosis factor a therapy. *Arthritis Rheum* 2003;48:3013-22.
84. Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *The Lancet Infectious Diseases* 2003;3:148-55.
85. Antoni C, Braun J. Side effects of anti-TNF therapy: current knowledge. *Clin Exp Rheumatol* 2002;20(6 Suppl 28):s152.
86. Keystone EC. Advances in targeted therapy: safety of biological agents. *Ann Rheum Dis* 2003;62 Suppl 2:34-6.
87. Culy CR, Keating GM. Etanercept: an updated review of its use in rheumatoid arthritis, psoriatic arthritis and juvenile rheumatoid arthritis. *Drugs* 2002;62:2493-537.
88. Bresnihan B, Cunnane G. Infection complications associated with the use of biologic agents. *Rheum Dis Clin North Am* 2003;29:185-202.
89. Goffe B, Cather JC. Etanercept: an overview. *J Am Acad Dermatol* 2003;49:S105-11.

90. Davis JC, van der Heijde D, Braun J, Dougados M, Cush J, Clegg DO, et al. Recombinant human tumor necrosis factor receptor, (etanercept) for treating ankylosing spondylitis - a randomized, controlled trial. *Arthritis Rheum* 2003;48:3230-6.
91. Klareskog L, van der Heijde D, De Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double blind randomised controlled trial. *Lancet* 2004;363:675 - 81.
92. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004;50:2264-72.
93. Gottlieb A, Hamilton TK, Caro I, Chastain R, Rundle AC, Gordon KB. *Efficacy and safety outcomes of extended efalizumab therapy in patients with moderate to severe chronic plaque psoriasis: an update [poster]*. American Academy of Dermatology, 2004. Available from: <http://www.xoma.com/pdf/GNU-04-0335%20SmmrAAD%20Gottlieb%20Final.pdf>. [cited 2004 Oct 24]
94. Geborek P, Crnkic M, Petersson IF, Saxne T, South Swedish Arthritis Treatment Group. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. *Ann Rheum Dis* 2002;61:793-8.
95. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med* 1999;130:478-86.
96. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;343:1586-93.
97. Willis RF, Pedersen R. A long-term, open-label trial of the safety and efficacy of etanercept (25 mg twice weekly) in patients with rheumatoid arthritis (interim analysis). *J Rheumatol* 2001;28:W104.
98. Phillips K, Husni ME, Karlson EW, Coblyn JS. Experience with etanercept in an academic medical center: are infection rates increased? *Arthritis Rheum* 2002;47:17-21.
99. Tam JW, Lee GJ, Song JC. Efalizumab: a new biologic therapy for the control of chronic plaque psoriasis. *Formulary* 2004;39:20-39.
100. Leonardi CL. Efalizumab: an overview. *J Am Acad Dermatol* 2003;49:S98-104.
101. Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC. A systematic review of treatments for severe psoriasis. *Health Technol Assess* 2000;4(40):1-125.
102. Ellis CN, Fradin MS, Messana JM, Brown MD, Siegel MT, Hartley AH, et al. Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. *N Engl J Med* 1991;324:277-84.
103. Guenther L, Wexler D. Inducing remission of severe psoriasis with low dose cyclosporin A. *Canad J Dermatol* 1991;3:163-7.
104. Meffert H, Brautigam M, Farber L, Weidinger G. Low-dose (1.25 mg/kg) cyclosporin A: treatment of psoriasis and investigation of the influence on lipid profile. *Acta Derm Venereol* 1997;77:137-41.
105. van Joost T, Bos JD, Heule F, Meinardi MM. Low-dose cyclosporin A in severe psoriasis. A double-blind study. *Br J Dermatol* 1988;118:183-90.

106. Sandhu K, Kaur I, Kumar B, Saraswat A. Efficacy and safety of cyclosporine versus methotrexate in severe psoriasis: a study from north India. *J Dermatol* 2003;30:458-63.
107. Heydendael VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *N Engl J Med* 2003;349:658-65.
108. Goldfarb MT, Ellis CN, Gupta AK, Tincoff T, Hamilton TA, Voorhees JJ. Acitretin improves psoriasis in a dose-dependent fashion. *J Am Acad Dermatol* 1988;18:655-62.
109. Lassus A, Geiger JM, Nyblom M, Virrankoski T, Kaartamaa M, Ingervo L. Treatment of severe psoriasis with etretin (RO 10-1670). *Br J Dermatol* 1987;117:333-41.
110. Caca-Biljanovska NG, V'Lckova-Laskoska MT. Management of guttate and generalized psoriasis vulgaris: prospective randomized study. *Croat Med J* 2002;43:707-12.
111. Saurat JH, Geiger JM, Amblard P, Beani JC, Boulanger A, Claudy A, et al. Randomized double-blind multicenter study comparing acitretin-PUVA, etretinate-PUVA and placebo-PUVA in the treatment of severe psoriasis. *Dermatologica* 1988;177:218-24.
112. Sommerburg C, Kietxmann H, Eichelberg D, Goos M, Heese A, Holze A, et al. Acitretin in combination with PUVA: a randomised double-blind placebo controlled study in severe psoriasis. *J Eur Acad Dermatol Venereol* 1993;2:303-17.
113. Tanew A, Guggenbichler A, Honigsmann H, Geiger JM, Fritsch P. Photochemotherapy for severe psoriasis without or in combination with acitretin: a randomized, double-blind comparison study. *J Am Acad Dermatol* 1991;25:682-4.
114. Dogan B, Taskapan O, Cekmen S, Karabudak O, Harmanyeri Y. PUVA-alone, bath-PUVA, and re-PUVA in the treatment of psoriasis: a clinical comparison. *Gulhane Medical Journal* 1999;41:439-42.
115. van de Kerkhof PCM, Cambazard F, Hutchinson PE, Haneke E, Wong E, Souteyrand P, et al. The effect of addition of calcipotriol ointment (50 ug/g) to acitretin therapy in psoriasis. *Br J Dermatol* 1998;199:84-9.
116. Rim JH, Park JY, Choe YB, Youn JI. The efficacy of calcipotriol + acitretin combination therapy for psoriasis: comparison with acitretin monotherapy. *Am J Clin Dermatol* 2003;4:507-10.
117. van Weelden H, Baart de la Faille H, Young E, van der Leun JC. Comparison of narrow-band UV-B phototherapy and PUVA photochemotherapy in the treatment of psoriasis. *Acta Derm Venereol* 1990;70:212-5.
118. Gordon PM, Diffey BL, Matthews JN, Farr PM. A randomized comparison of narrow-band TL-01 phototherapy and PUVA photochemotherapy for psoriasis. *J Am Acad Dermatol* 1999;41:728-32.
119. Markham T, Rogers S, Collins P. Narrowband UV-B (TL-01) phototherapy vs oral 8-methoxypsoralen psoralen-UV-A for the treatment of chronic plaque psoriasis. *Arch Dermatol* 2003;139:325-8.
120. Dawe RS, Cameron H, Yule S, Man I, Wainwright NJ, Ibbotson SH, et al. A randomized controlled trial of narrowband ultraviolet B vs bath-psoralen plus ultraviolet A photochemotherapy for psoriasis. *Br J Dermatol* 2003;148:1194-204.
121. Storbeck K, Holzle E, Schurer N, Lehmann P, Plewig G. Narrow-band UVB (311 nm) versus conventional broad-band UVB with and without dithranol in phototherapy for psoriasis. *J Am Acad Dermatol* 1993;28:227-31.

122. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet* 2001;357:1842-7.
123. Gottlieb A, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004;51:534-42.
124. Altmeyer PJ, Matthes U, Pawlak F, Hoffmann K, Frosch PJ, Ruppert P, et al. Antipsoriatic effect of fumaric acid derivatives. Results of a multicenter double-blind study in 100 patients. *J Am Acad Dermatol* 1994;30:977-81.
125. Nugteren-Huying WM, van der Schroeff JG, Hermans J, Suurmond D. Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol* 1990;22:311-2.
126. Whiting-O'Keefe QE, Fye KH, Sack KD. Methotrexate and histologic hepatic abnormalities: a meta-analysis. *Am. J. Med.* 1991;90:711-6.
127. Roenigk HH, Auerbach R, Maibach H, Weinstein G, Lebwohl M. Methotrexate in psoriasis: Consensus conference. *J Am Acad Dermatol* 1998;38:478-485.
128. Schering-Plough Ltd. *Remicade [summary of product characteristics] [web page on the Internet]*. Electronic Medicines Compendium, 2004. Available from: <http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=3236>. [cited 2004 Dec 15]
129. Dukes M, Aronson J. *Meyler's side effects of drugs: an encyclopedia of adverse reactions and interactions*. 14 ed. Amsterdam: Elsevier, 2000.
130. Higgins JPT, Whitehead J. Borrowing strength from external trials in meta-analysis. *Stat Med* 1996;15:2733-49.
131. Jones A. *Applied econometrics for health economists : a practical guide*. London: Office of Health Economics, 2001.
132. Greene WH. *Econometric analysis*. 4th ed. London: Prentice-Hall International, 2000.
133. Spiegelhalter DJ, Thomas A, Best N, Lunn D. *WinBUGS user manual: version 1.4*. Cambridge: MRC Biostatistics Unit, 2001.
134. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian measures of model complexity and fit. *J Roy Statist Soc B* 2000;64:583-640.
135. Feldman SR, Garton R, Averett W, Balkrishnan R, Vallee J. Strategy to manage the treatment of severe psoriasis: considerations of efficacy, safety and cost. *Expert Opin Pharmacother* 2003;4:1525-33.
136. Chalmers R. Protocol for use of fumaderm in psoriasis. [Personal communication, 2003 April 17].
137. McHugh N, Chandler D, Griffiths CE, Helliwell P, Lewis J, McInnes I, et al. *BSR guideline for anti-TNF α therapy in psoriatic arthritis [webpage on the Internet]*. London: British Society for Rheumatology, 2004. Available from: <https://www.msecportal.org/portal/editorial/PublicPages/bsr/536883013/FinalPsoriaticArthritisGuideline.pdf>. [cited 2004 Dec 14]
138. Royal College of Nursing Rheumatology Biologics Working Party, Arthritis and Musculoskeletal Alliance, Royal College of Nursing Paediatric Rheumatology Specialist Nurses Group. *Assessing, managing and monitoring biologic therapies for inflammatory arthritis: guidance for rheumatology practitioners. An advisory document*. London: Royal College of Nursing, 2003. Available from: <http://www.rcn.org.uk/publications/pdf/inflammatory-arthritis.pdf>. [cited 2003 Dec 14]

139. Cooper NJ, Sutton AJ, Abrams KR, Turner D, Wailoo A. Comprehensive decision analytical modelling in economic evaluation: a Bayesian approach. *Health Econ* 2004;13:203-26.
140. Sterry W, Barker J, Boehncke WH, Bos JD, Chimenti S, Christophers E, et al. Biological therapies in the systemic management of psoriasis: International Consensus Conference. *Br J Dermatol* 2004;69:3-17.
141. Griffiths CE, Dubertret L, Ellis CN, Finlay AY, Finzi AF, Ho VC, et al. Ciclosporin in psoriasis clinical practice: an international consensus statement. *Br J Dermatol* 2004;150:11-23.
142. Duggan A. *Multicenter dose-ranging study of the safety and efficacy of Enbrel in psoriasis: withdrawal and re-treatment final report (protocol no.: 20021639)*. Industry submission: Wyeth Pharmaceuticals; 2003.
143. National Institute for Clinical Excellence. *Technical guidance for manufacturers and sponsors on making a submission to a Technology Appraisal*. London: NICE; 2001.
144. Chalmers RJG, Kirby B, Smith A, Burrows P, Little R, Horan M, et al. Replacement of routine liver biopsy by procollagen III aminopeptide for monitoring psoriasis patients receiving long-term methotrexate: a multicentre audit and health economic analysis. *Br J Dermatol* Forthcoming 2004.
145. Wyeth Research. *Multicenter dose-ranging study of the safety and efficacy of Enbrel in psoriasis: withdrawal and re-treatment final report: protocol no.: 20021639 [Industry submission]*. Philadelphia, Pa.: Wyeth Research; 2003 Nov 13.
146. Curtis L, Netten A. *Unit costs of health and social care 2004*. Canterbury: The University of Kent, Personal Social Services Unit, 2004. Available from: <http://www.pssru.ac.uk/>
147. Department of Health. *NHS reference costs 2003 and national tariff 2004 (payment by results core tools 2004')*. London: Department of Health, 2004. Available from: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4070195&chk=UzhHA3. [cited 2004 Nov 23]
148. Wyeth Research. *Phase 3 study of the safety and efficacy of Enbrel in psoriasis: final 12-week report: protocol no.: 20021642 [Industry submission]*. Philadelphia, Pa: Wyeth Research; 2003 Nov 10.
149. Wyeth Research. *Phase 3 study of the safety and efficacy of Enbrel in psoriasis: open-label final report: protocol no.: 20021642 [Industry submission]*. Philadelphia, Pa: Wyeth Research; 2003 Nov 13.
150. Wyeth Pharmaceuticals, Immunex Corporation. *Efficacy of Etanercept in an integrated multi-study database of patients with psoriasis [Industry submission]*. Poster. Philadelphia, Pa.: Wyeth Pharmaceuticals; 2004 Aug 24.
151. Wyeth Pharmaceuticals, Immunex Corporation. *Safety of etanercept in an integrated multi-study database of patients with psoriasis [Industry submission]*. Poster. Philadelphia, Pa.: Wyeth Pharmaceuticals; 2004 Aug 24.
152. Wyeth Research. *Double-blind, placebo-controlled, phase 2 study of Etanercept (ENBREL®) in the treatment of psoriasis: final report: protocol no.: 016.0032 [Industry submission]*. Philadelphia, Pa.: Wyeth Research; 2003 July 31.
153. Gaspari A, Gottlieb AB, Kang S, Gordon K, Feng S. Enbrel improves the clinical and pathologic features of psoriasis. *J Invest Dermatol* 2002;119:236.
154. Gottlieb A, Matheson RT, Lowe NJ. Efficacy of Enbrel in patients with psoriasis. *J Invest Dermatol* 2002;119:234.

155. Wyeth Research. *Multicenter dose-ranging study of the safety and efficacy of Enbrel in psoriasis: withdrawal and re-treatment: final report: protocol no.:20021639 [Industry submission]*. Philadelphia, Pa.: Wyeth Research; 2003 Nov 13.
156. Wyeth Pharmaceuticals, Immunex Corporation. *Continuance on Etanercept after early incomplete response in patients with psoriasis [Industry submission]*. Poster. Philadelphia, Pa.: Wyeth Pharmaceuticals; 2004 Aug 24.
157. Wyeth Pharmaceuticals, Immunex Corporation. *Withdrawal from etanercept after successful clinical response in psoriasis patients: disease characteristics and the durability of treatment response [Industry submission]*. Poster. Philadelphia, Pa.: Wyeth Pharmaceuticals; 2004 Aug 24.
158. Menter A, Kosinski M, Bresnahan BW, Papp KA, Ware JE, Jr. Impact of efalizumab on psoriasis-specific patient-reported outcomes. Results from three randomized, placebo-controlled clinical trials of moderate to severe plaque psoriasis. *J Drugs Dermatol* 2004;3:27-38.
159. Hamilton T, Powers J, Carey W. Efficacy and safety of efalizumab (anti-CD11a) in subjects with moderate to severe plaque psoriasis. In: *61st annual meeting of the American Academy of Dermatology, 2003 March 21-26*; San Francisco, Calif.
160. ACD2390g. Phase III, randomised, placebo-controlled, double blind study evaluating 12 weeks of therapy with SC administered Genentech efalizumab. In: *Clinical and cost effectiveness of efalizumab (Raptiva) for moderate to severe psoriasis. [Industry submission]*. Feltham: Serono Ltd., 2004.
161. Gordon K, Leonardi C, Tyring S, Gottlieb A, Walicke P, Dummer W. Efalizumab (Anti-CD11a) is safe and effective in the treatment of psoriasis: pooled results of the 12-week first treatment period from 2 phase III trials. *J Invest Dermatol* 2002;119:242.
162. ACD2059g. Phase III, randomised, placebo-controlled, double blind study evaluating 12 weeks with SC administered efalizumab (approx 75% XOMA1 and 25% Genentech1), followed by a 2nd placebo-controlled period with either continued active treatment or placebo for 12 weeks. In: *Clinical and cost effectiveness of efalizumab (Raptiva) for moderate to severe psoriasis. [Industry submission]*. Feltham: Serono Ltd., 2004.
163. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002;46:1443-50.
164. Bathon JM, Genovese MC. The Early Rheumatoid Arthritis (ERA) Trial comparing the efficacy and safety of etanercept and methotrexate. *Clin Exp Rheumatol* 2003;21 Suppl 31:S195-7.
165. Wyeth Research. *Double-blind, randomized, placebo-controlled phase 3 study of etanercept (ENBREL) in the treatment of psoriatic arthritis (PsA) and psoriasis: final report: protocol 016.0030 [Industry submission]*. Philadelphia, Pa: Wyeth Research; 2001 July 25.
166. Wyeth Research. *Double-blind, randomized, placebo-controlled phase 3 study of etanercept (ENBREL) in the treatment of psoriatic arthritis (PsA) and psoriasis: radiographic results: protocol no.: 016.0030 [Industry submission]*. Philadelphia, Pa.: Wyeth Research; 2003 April 22.
167. Wyeth Pharmaceuticals. *Marketing authorisation application for Enbrel: expert report on the clinical documentation. [Industry submission]*. Philadelphia, Pa.: Wyeth Pharmaceuticals; 2001 Oct 26.

168. Ory P, Sharp JT, Salonen D, Rubenstein J, Mease PJ, Kivitiz A, et al. Etanercept (ENBREL (R)) inhibits radiographic progression in patients with psoriatic arthritis. *Arthritis Rheum* 2002;46:S196.
169. Wajdula J, Pedersen R, Sanda M. A long-term, open-label trial of the safety and efficacy of etanercept (25 mg twice weekly) in patients with rheumatoid arthritis (interim analysis). *Arthritis Rheum* 2000;43:974.
170. Gottlieb A, Blacker K, Duvic M. Efficacy and safety of efalizumab (anti-CD11a) long-term treatment: preliminary findings from an open-label trial [poster 11]. In: *61st annual meeting of the American Academy of Dermatology* 2003 March 21-26; San Francisco, Calif. Available from: <http://www.aad.org/NR/rdonlyres/9C931811-1A1D-438D-B317-B1D20D145432/0/AM03abstract.pdf>
171. Gottlieb A, Menter A, Duvic M. Induction and maintenance treatment during a 12 month trial in patients with moderate to severe plaque psoriasis: preliminary findings [poster 546]. In: *60th Annual Meeting of the American Academy of Dermatology* 2002 February 22-27; New Orleans, La. Available from: <http://www.aad.org/NR/rdonlyres/B77B2CFB-60B2-4973-8D02-E2CB5BC48F4B/0/AM02abstract.pdf>
172. ACD2243g. Ongoing phase III open-label study evaluating 12 weeks of therapy with Genentech efalizumab (in combination with topical corticosteroids for days 56-84) and up to 132 additional weeks of therapy. In: *Clinical and cost effectiveness of efalizumab (Raptiva) for moderate to severe psoriasis. [Industry submission]*. Feltham: Serono Ltd., 2004.
173. Health And Human Services Food And Drug Administration Center For Biologics Evaluation And Research: Arthritis Advisory Committee. *Safety update on TNF-a antagonists; infliximab and etanercept*. Rockville MD: US Food and Drug Administration, 2001. Available from: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3779b2_01_cber_safety%20revision2.pdf. [cited 2004 Oct 10]
174. Nieboer C, de Hoop D, van Loenen AC, Langendijk PN, van Dijk E. Systemic therapy with fumaric acid derivates: new possibilities in the treatment of psoriasis. *J Am Acad Dermatol* 1989;20:601-8.
175. Nieboer C, de Hoop D, Langendijk PN, van Loenen AC, Gubbels J. Fumaric acid therapy in psoriasis: a double-blind comparison between fumaric acid compound therapy and monotherapy with dimethylfumaric acid ester. *Dermatologica* 1990;181:33-7.
176. Engst R, Huber J. [Results of cyclosporin treatment of severe, chronic psoriasis vulgaris]. *Hautarzt* 1989;40:486-9.
177. Kingston TP, Matt LH, Lowe NJ. Etretin therapy for severe psoriasis. Evaluation of initial clinical responses. *Arch Dermatol* 1987;123:55-8.
178. Madhok R, Muller SA, Dicken CH. Treatment of psoriasis with etretin: a preliminary report. *Mayo Clin Proc* 1987;62:1084-9.
179. Olsen EA, Weed WW, Meyer CJ, Cobo LM. A double-blind, placebo-controlled trial of acitretin for the treatment of psoriasis. *J Am Acad Dermatol* 1989;21:681-6.
180. Williams R. PUVA therapy vs Goeckerman therapy in psoriasis: a pilot study. *Physiother Can* 1985;37:361-6.
181. Leavell UW, Jr., Yarbro JW. Hydroxyurea. A new treatment for psoriasis. *Arch Dermatol* 1970;102:144-50.
182. Ellis C, Gorsulowsky D, Hamilton T, Billings J, Brown M, Headington J, et al. Cyclosporine improves psoriasis in a double-blind study. *Jama* 1986;256:3110-6.

183. Brennan A, Bansback N, Reynolds A, Conway P. Modelling the cost-effectiveness of etanercept in adults with rheumatoid arthritis in the UK. *Rheumatology* 2004;43:62-72.
184. Kobelt G, Jonsson L, Young A, Eberhardt K. The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. *Rheumatology* 2003;42:326-35.

10 Appendices

10.1 Literature searches

10.1.1 Clinical Effectiveness

Searching for the clinical effectiveness component of this review was addressed by several separate searches to identify:

- Reports of randomized controlled trials (RCTs) of etanercept or efalizumab in psoriasis
- Reports of RCTs and reports of adverse events (AEs) for etanercept or efalizumab
- Reports of RCTs of comparator treatments in psoriasis
- Reports of adverse events of comparators treatments
- Reports of RCTs of infliximab in psoriasis

Separate strategies were devised for each topic. Full details of the databases searched and search strategies used are provided below.

10.1.1.1 Search A: Randomized controlled trials (RCTs) of etanercept or efalizumab in psoriasis

Medline and In-Process Citations (OVID Online - <http://www.ovid.com/>)

1966 – 2004/02 wk 3

This search retrieved 64 references.

1. randomized controlled trial.pt.
2. exp randomized controlled trials/
3. random allocation/
4. double blind method/
5. single blind method/
6. clinical trial.pt.
7. exp clinical trials/
8. controlled clinical trials/
9. clin\$ trial\$.ti,ab.
10. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.
11. placebo\$.ti,ab.
12. placebos/
13. random\$.ti,ab.
14. exp evaluation studies/
15. follow up studies/
16. exp research design/
17. prospective studies/
18. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
19. or/1-18
20. animals/
21. human/
22. 20 not (20 and 21)
23. 19 not 22

24. exp psoriasis/
25. (psoria\$ or anti psoria\$ or antipsoria\$).mp.
26. or/24-25
27. etanercept.mp.
28. enbrel.mp.
29. efalizumab.mp.
30. raptiva.mp.
31. or/27-30
32. 23 and 26 and 31
33. (letter or comment or editorial).pt.
34. 32 not 33

Embase (OVID Online - <http://www.ovid.com/>)
1980- 2004 wk 9

This search retrieved 184 references.

1. randomized controlled trial/
2. randomization/
3. double blind procedure/ or single blind procedure/
4. exp clinical trial/
5. controlled study/
6. clin\$ trial\$.ti,ab.
7. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.
8. placebo\$.ti,ab.
9. Placebo/
10. random\$.ti,ab.
11. evaluation/
12. follow up/
13. exp methodology/
14. prospective study/
15. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
16. or/1-15
17. (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
18. exp ANIMAL/
19. Animal Experiment/
20. Nonhuman/
21. Human/
22. Human Experiment/
23. or/17-20
24. 21 or 22
25. 16 not (23 not (23 and 24))
26. exp psoriasis/
27. (psoria\$ or anti psoria\$ or antipsoria\$).mp.
28. or/26-27
29. etanercept/ or etanercept.mp.
30. enbrel.mp.
31. eralizumab/ or efalizumab.mp.
32. raptiva.mp.

- 33. or/29-32
- 34. 25 and 28 and 33
- 35. (letter or note or editorial).pt.
- 36. 34 not 35

National Research Register (NRR) (cd-rom)

2004 Issue 1

This search retrieved 1 reference.

- #1 PSORIASIS explode all trees (MeSH)
- #2 (PSORIA* or (ANTI NEXT PSORIA*) or ANTIPSORIA)
- #3 (#1 or #2)
- #4 ETANERCEPT
- #5 ENBREL
- #6 EFALIZUMAB
- #7 RAPTIVA
- #8 (#4 or #5 or #6 or #7)
- #9 (#3 and #8)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the internet - <http://www.update-software.com/clubng/clublogon.htm>)

2004 Issue 1

This search retrieved 6 references.

- #1 PSORIASIS*:me
- #2 (psoria* or (anti next psoria*) or antipsoria)
- #3 (#1 or #2)
- #4 etanercept
- #5 enbrel
- #6 efalizumab
- #7 raptiva
- #8 (#4 or #5 or #6 or #7)
- #9 (#3 and #8)

ISI Science and Technology Proceedings (Web of Knowledge)

1990 - 2004 (Feb 28th update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981-2004 (Feb 29th update.)

<http://wos.mimas.ac.uk/>

The search of ISI Science and Technology Proceedings retrieved 2 references.

The search of Social Science Citation Index and Science Citation Index retrieved 24 references.

- #1 TS=((study or studies) SAME design*)

- #2 TS=((clinic* trial*) or placebo* or random* or (control* or prospectiv* or volunteer*))
- #3 TS=((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*))
- #4 #1 or #2 or #3
- #5 TS=(psoria* or antipsoria* or anti-psoria*)
- #5 TS=((etanercept or efalizumab or raptiva or enbrel))
- #7 #4 and #5 and #6
- #8 TS=((animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*))
- #9 #7 not #8

All databases were searched from inception date.
In total, 218 references were retrieved for this topic.

10.1.1.2 Search B: Randomized controlled trials (RCTs) and reports of adverse events (AEs) for etanercept or efalizumab

Medline and In-Process Citations (OVID Online - <http://www.ovid.com/>)
1966 – 2004/02 wk 3

This search retrieved 217 references.

1. Adverse Drug Reaction Reporting Systems/
2. drug eruptions/ or erythema nodosum/
3. Drug Hypersensitivity/
4. Drug Toxicity/
5. treatment emergent.tw.
6. (safe or safety).ti,ab.
7. (tolerability or toxicity or adrs or harm\$).ti,ab.
8. (hypersensiti\$ or hyper sensiti\$).ti,ab.
9. (undesirable\$ adj2 (outcome\$ or event\$ or reaction\$ or effect or effects)).ti,ab.
10. (side effects or side effect).tw.
11. (adverse adj2 (event\$ or effect or effects or outcome\$ or reaction\$)).ti,ab.
12. (po or ae or de or co or to).fs.
13. Injections/ae
14. Erythema/ci
15. Pruritus/ci
16. pain/ci
17. Headache/ci
18. Fever/ci
19. chills/ci
20. Nausea/ci
21. vomiting/ci
22. Infection/ci
23. Abdominal Pain/ci
24. Depression/ci
25. Personality Disorders/ci
26. Immunocompromised Host/
27. Immunosuppressive Agents/ae

28. Abnormalities, Drug-Induced/
29. (site reaction\$ or injection\$ reaction\$ or erythema or itching or pain or swelling or swollen or swelled).ti,ab.
30. (headache\$ or head ache\$ or head pain\$ or chill or chills or fever or temperature or nausea or nauseous or sickness or vomiting or vomit or vomited).ti,ab.
31. (myalgia or muscle\$ pain or infection\$ or immunocompromise\$ or immuno compromise\$).ti,ab.
32. (immunosuppress\$ or immuno suppress\$ or depression or depressive or depressed or personality disorder\$).ti,ab.
33. or/1-32
34. randomized controlled trial.pt.
35. exp randomized controlled trials/
36. random allocation/
37. double blind method/
38. single blind method/
39. clinical trial.pt.
40. exp clinical trials/
41. controlled clinical trials/
42. clin\$ trial\$.ti,ab.
43. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.
44. placebo\$.ti,ab.
45. placebos/
46. random\$.ti,ab.
47. exp evaluation studies/
48. follow up studies/
49. exp research design/
50. prospective studies/
51. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
52. or/34-51
53. animals/
54. human/
55. 53 not (53 and 54)
56. 33 and 52
57. 56 not 55
58. 57 not (comment or letter or editorial).pt.
59. etanercept.mp.
60. enbrel.mp.
61. efalizumab.mp.
62. raptiva.mp.
63. or/59-62
64. 58 and 63

Embase (OVID Online - <http://www.ovid.com/>)
1980- 2004 wk 9

This search retrieved 826 references.

1. randomized controlled trial/
2. randomization/

3. double blind procedure/ or single blind procedure/
4. exp clinical trial/
5. controlled study/
6. clin\$ trial\$.ti,ab.
7. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.
8. placebo\$.ti,ab.
9. Placebo/
10. random\$.ti,ab.
11. evaluation/
12. follow up/
13. exp methodology/
14. prospective study/
15. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
16. or/1-15
17. (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
18. exp ANIMAL/
19. Animal Experiment/
20. Nonhuman/
21. Human/
22. Human Experiment/
23. or/17-20
24. 21 or 22
25. 16 not (23 not (23 and 24))
26. adverse drug reaction/ or drug eruption/ or drug fatality/ or drug fever/ or drug induced disease/ or flu like syndrome/ or retinoic acid syndrome/ or drug hypersensitivity/ or side effect/
27. drug surveillance program/
28. exp Drug Toxicity/
29. drug safety/ or drug tolerability/
30. treatment emergent.tw.
31. (safe or safety).ti,ab.
32. (tolerability or toxicity or adrs or harm\$).ti,ab.
33. (hypersensiti\$ or hyper sensiti\$).ti,ab.
34. (undesirable\$ adj2 (outcome\$ or event\$ or reaction\$ or effect or effects)).ti,ab.
35. (side effects or side effect).tw.
36. (adverse adj2 (event\$ or effect or effects or outcome\$ or reaction\$)).ti,ab.
37. (si or it or ae or to or po).fs.
38. injection/
39. injection site/
40. Erythema/si {Side Effect}
41. Erythema Nodosum/si {Side Effect}
42. Pruritus/si {Side Effect}
43. Skin Tingling/si {Side Effect}
44. Pain/si {Side Effect}
45. Headache/si {Side Effect}
46. Fever/si {Side Effect}
47. Chill/si {Side Effect}
48. Nausea/si {Side Effect}
49. vomiting/si

50. Infection/si {Side Effect}
51. Abdominal Pain/si {Side Effect}
52. Depression/si {Side Effect}
53. Personality Disorder/si {Side Effect}
54. Immune Deficiency/si {Side Effect}
55. Immunosuppressive Agent/ae, it, to {Adverse Drug Reaction, Drug Interaction, Drug Toxicity}
56. (site reaction\$ or injection\$ reaction\$ or erythema or itching or pain or swelling or swollen or swelled).ti,ab.
57. (headache\$ or head ache\$ or head pain\$ or chill or chills or fever or temperature or nausea or nauseous or sickness or vomiting or vomit or vomited).ti,ab.
58. (myalgia or muscle\$ pain or infection\$ or immunocompromise\$ or immuno compromise\$).ti,ab.
59. (immunosuppress\$ or immuno suppress\$ or depression or depressive or depressed or personality disorder\$).ti,ab.
60. or/26-59
61. 25 and 60
62. etanercept/
63. etanercept.mp.
64. efalizumab/
65. efalizumab.mp.
66. (raptiva or enbrel).mp.
67. or/62-66
68. 61 and 67
69. 68 not (letter or note or editorial).pt.

National Research Register (NRR) (cd-rom)

2003 Issue 4

This search retrieved 22 references.

#1 ETANERCEPT or ENBREL or EFALIZUMAB or RAPTIVA

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the internet - <http://www.update-software.com/clubng/clublogon.htm>)

2004 Issue 1

This search retrieved 26 references.

- #1 ADVERSE DRUG REACTION REPORTING SYSTEMS single term (MeSH)
- #2 DRUG ERUPTIONS single term (MeSH)
- #3 ERYTHEMA NODOSUM single term (MeSH)
- #4 DRUG HYPERSENSITIVITY single term (MeSH)
- #5 DRUG TOXICITY single term (MeSH)
- #6 (treatment next emergent)
- #7 (safe or safety)
- #8 (tolerability or toxicity or adrs or harm*)

- #9 (hypersensiti* or (hyper next sensiti*))
- #10 ((undesirable* next outcome*) or (undesirable* next event*) or (undesirable* next reaction*) or (undesirable* next effect) or (undesirable* next effects))
- #11 ((side next effects) or (side next effect))
- #12 ((adverse next event*) or (adverse next effect) or (adverse next effects) or (adverse next outcome*) or (adverse next reaction*))
- #13 INJECTIONS {ae} single term (MeSH)
- #14 ERYTHEMA {ci} single term (MeSH)
- #15 PRURITUS {ci} single term (MeSH)
- #16 PAIN {ci} single term (MeSH)
- #17 HEADACHE {ci} single term (MeSH)
- #18 FEVER {ci} single term (MeSH)
- #19 CHILLS {ci} single term (MeSH)
- #20 NAUSEA {ci} single term (MeSH)
- #21 VOMITING {ci} single term (MeSH)
- #22 INFECTION {ci} single term (MeSH)
- #23 ABDOMINAL PAIN {ci} single term (MeSH)
- #24 DEPRESSION {ci} single term (MeSH)
- #25 PERSONALITY DISORDERS {ci} single term (MeSH)
- #26 IMMUNOCOMPROMISED HOST single term (MeSH)
- #27 IMMUNOSUPPRESSIVE AGENTS {ae} single term (MeSH)
- #28 ABNORMALITIES DRUG-INDUCED single term (MeSH)
- #29 ((site next reaction*) or (injection* next reaction*) or erythema or itching or pain or swelling or swollen or swelled)
- #30 (headache* or (head next ache*) or (head next pain*) or chill or chills or fever or temperature or nausea or nauseous or sickness or vomiting or vomit or vomited)
- #31 (myalgia or (muscle* next pain) or infection* or immunocompromise* or (immuno next compromise*))
- #32 (immunosuppress* or (immuno next suppress*) or depression or depressive or depressed or (personality next disorder*))
- #33 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
- #34 (#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33)
- #35 (etanercept or enbrel or efalizumab or raptiva)
- #36 (#34 and #35)

CenterWatch (internet - <http://www.centerwatch.com/>)

Searched 3rd March 2004

This search retrieved 110 references.

etanercept OR efalizumab OR raptiva OR enbrel {ALL-FIELDS}

Current Controlled Trials (internet - <http://controlled-trials.com/>)

Searched 3rd March 2004

This search retrieved 31 references.

etanercept OR efalizumab OR raptiva OR enbrel

ClinicalTrials.gov (internet - <http://clinicaltrials.gov/>)

Searched 3rd March 2004

This search retrieved 15 references.

etanercept OR efalizumab OR raptiva OR enbrel

ISI Science and Technology Proceedings (Web of Knowledge)

1990 - 2004 (Feb 28th update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981-2004 (Feb 29th update.)

<http://wos.mimas.ac.uk/>

The search of ISI Science and Technology Proceedings retrieved 13 reference.

The search of Social Science Citation Index and Science Citation Index retrieved 44 references.

- #1 TS=((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*)
- #2 TS=((clinic* trial*) or placebo* or random* or (control* or prospectiv* or volunteer*))
- #3 TS=((study or studies) SAME design*)
- #4 TS=((ADVERSE same REACTION*) or (DRUG same ERUPTION*) or hypersensiti* or (hyper same sensiti*))
- #5 TS=((treatment same emergent) or (safe or safety) or (tolerability or toxicity or adrs or harm*))
- #6 TS=((undesirable* same outcome*) or (undesirable* same event*) or (undesirable* same reaction*) or (undesirable* same effect) or (undesirable* same effects))
- #7 TS=((adverse same event*) or (adverse same effect) or (adverse same effects) or (adverse same outcome*) or (adverse same reaction*))
- #8 TS=(drug same ABNORMALIT*)
- #9 TS=((site same reaction*) or (injection* same reaction*) or erythema or itching or pain or swelling or swollen or swelled)
- #10 TS=(headache* or head-ache* or (head same ache*) or (head same pain*) or chill or chills or fever or temperature or nausea or nauseous or sickness or vomiting or vomit or vomited)
- #11 TS=(myalgia or (muscle* same pain) or infection* or immunocompromise* or (immuno-compromise*) or (side same effects) or (side same effect))
- #12 TS=(immunosuppress* or (immuno-suppress*) or depression or depressive or depressed or (personality same disorder*))
- #13 #1 or #2 or #3
- #14 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
- #15 #13 and #14
- #16 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
- #17 #15 not #16

- #18 TS=(etanercept or enbrel or efalizumab or raptiva)
- #19 #17 and #18

All databases were searched from inception date.

10.1.1.3 Search C: Randomized controlled trials (RCTs) of comparator treatments in psoriasis

Medline and In-Process Citations (OVID Online - <http://www.ovid.com/>)

1966 – 2004/01 wk 4

This search retrieved 381 references.

1. randomized controlled trial.pt.
2. exp randomized controlled trials/
3. random allocation/
4. double blind method/
5. single blind method/
6. clinical trial.pt.
7. exp clinical trials/
8. controlled clinical trials/
9. clin\$ trial\$.ti,ab.
10. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.
11. placebo\$.ti,ab.
12. placebos/
13. random\$.ti,ab.
14. exp evaluation studies/
15. follow up studies/
16. exp research design/
17. prospective studies/
18. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
19. or/1-18
20. animals/
21. human/
22. 20 not (20 and 21)
23. 19 not 22
24. psoriasis/
25. (psoria\$ or anti psoria\$ or antipsoria\$).mp.
26. or/24-25
27. exp Psoralens/
28. psoralen\$.tw.
29. puva.tw.
30. (phototherap\$ or photo therap\$ or photochemotherap\$ or photo chemotherap\$ or photo chemo therap\$).tw.
31. Phototherapy/
32. Heliotherapy/
33. photochemotherapy/
34. ultraviolet therapy/

35. puva therapy/
36. (puva or ultraviolet A or ultra violet A or UVA or UVB or ultraviolet B or ultra violet B).tw.
37. (NBUVB or BBUVB).tw.
38. ((narrowband or narrow band) adj1 (UVB or ultraviolet B or ultra violet B)).tw.
39. ((broadband or broad band) adj1 (UVB or ultraviolet B or ultra violet B)).tw.
40. (pnbuvb or repuva).tw.
41. MOP.ti,ab.
42. methoxypsoralen\$.tw.
43. Acitretin/
44. retinoids/
45. etretinate/
46. vitamin A/
47. tretinoin/
48. (retinoid\$ or acitretin\$ or etretinate\$ or vitamin A deriv\$).tw.
49. (synthet\$ adj1 vitamin A).tw.
50. tmp.ti,ab.
51. trimethylpsoralen.tw.
52. Cyclosporins/
53. (cyclosporin\$ or ciclosporin\$ or csa).tw.
54. Hydroxyurea/
55. hydroxyurea\$.mp. or hydroxycarbamide\$.tw.
56. (fumarate\$ or fumaric acid ester\$).tw.
57. fumaderm.tw.
58. Fumarates/
59. (dmfae or dimethylfumar\$ or monoethylfumar\$).tw.
60. (mefae-ca or mefae-mg or mefae-na or mefae-zn).ti,ab.
61. (ohfae or octyl hydrogen fumar\$).tw.
62. Anthralin/
63. (dithranol or anthralin).tw.
64. (goeckerman adj1 (therap\$ or treatment\$ or method\$ or regime\$)).tw.
65. (ingram adj1 (therap\$ or treatment\$ or method\$ or regime\$)).tw.
66. Methotrexate/
67. methotrexate.tw.
68. or/27-67
69. 23 and 26 and 68
70. limit 69 to yr=1999-2004

Embase (OVID Online - <http://www.ovid.com/>)
1980- 2004 wk 6

This search retrieved 957 references.

1. randomized controlled trial/
2. randomization/
3. double blind procedure/ or single blind procedure/
4. exp clinical trial/
5. controlled study/
6. clin\$ trial\$.ti,ab.
7. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.

8. placebo\$.ti,ab.
9. Placebo/
10. random\$.ti,ab.
11. evaluation/
12. follow up/
13. exp methodology/
14. prospective study/
15. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
16. or/1-15
17. (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
18. exp ANIMAL/
19. Animal Experiment/
20. Nonhuman/
21. Human/
22. Human Experiment/
23. or/17-20
24. 21 or 22
25. 23 not (23 and 24)
26. 16 not 25
27. exp Psoriasis/
28. (psoria\$ or anti psoria\$ or antipsoria\$).mp.
29. or/27-28
30. psoralen\$.tw.
31. puva.tw.
32. (puva or ultraviolet A or ultra violet A or UVA or UVB or ultraviolet B or ultra violet B).tw.
33. (NBUVB or BBUVB).tw.
34. ((narrowband or narrow band) adj1 (UVB or ultraviolet B or ultra violet B)).tw.
35. ((broadband or broad band) adj1 (UVB or ultraviolet B or ultra violet B)).tw.
36. (pnbuvb or repuva).tw.
37. MOP.ti,ab.
38. methoxypsoralen\$.tw.
39. (retinoid\$ or acitretin\$ or etretinate\$ or vitamin A deriv\$).tw.
40. (synthet\$ adj1 vitamin A).tw.
41. tmp.ti,ab.
42. trimethylpsoralen.tw.
43. (cyclosporin\$ or ciclosporin\$ or csa).tw.
44. hydroxyurea\$.mp. or hydroxycarbamide\$.tw.
45. (fumarate\$ or fumaric acid ester\$).tw.
46. fumaderm.tw.
47. (dmfae or dimethylfumar\$ or monoethylfumar\$).tw.
48. (mefae-ca or mefae-mg or mefae-na or mefae-zn).ti,ab.
49. (ohfae or octyl hydrogen fumar\$).tw.
50. (dithranol or anthralin).tw.
51. (goeckerman adj1 (therap\$ or treatment\$ or method\$ or regime\$)).tw.
52. (ingram adj1 (therap\$ or treatment\$ or method\$ or regime\$)).tw.
53. methotrexate.tw.
54. (phototherap\$ or photo therap\$ or photochemotherap\$ or photo chemotherap\$ or

- photo chemo therap\$.tw.
55. psoralen/ or psoralen derivative/
 56. phototherapy/ or photochemotherapy/ or puva/
 57. ultraviolet radiation/ or ultraviolet a radiation/ or ultraviolet b radiation/
 58. methoxsalen/ or methoxsalen derivative/
 59. retinoid/ or etretin/ or etretinate/
 60. retinol/ or retinol derivative/
 61. Retinoic Acid/
 62. Trimethylpsoralen/
 63. Cyclosporin/
 64. HYDROXYUREA/
 65. fumaric acid/ or fumaric acid derivative/
 66. fumaric acid dimethyl ester/ or fumaric acid ethyl ester/
 67. dithranol/ or dithranol derivative/
 68. METHOTREXATE/
 69. antipsoriasis agent/ or 4' aminomethyl 4,5',8 trimethylpsoralen/ or fumaderm/ or psoralon/ or psorin/
 70. or/30-69
 71. 26 and 29 and 70
 72. limit 71 to yr=1999-2004

National Research Register (NRR) (cd-rom)

2003 Issue 4

This search retrieved 93 references.

- #1 PSORIASIS single term (MeSH)
- #2 ((PSORIA* or ANTI-PSORIA*) or ANTIPSORIA*)
- #3 PSORALENS explode all trees (MeSH)
- #4 (PSORALEN* or (((PHOTOTHERAP* or PHOTO-THERAP*) or PHOTOCHEMOTHERAP*) or PHOTO-CHEMOTHERAP*) or PHOTO-CHEMO-THERAP*))
- #5 (PHOTOTHERAPY single term (MeSH) or HELIOTHERAPY single term (MeSH) or PHOTOCHEMOTHERAPY single term (MeSH))
- #6 (ULTRAVIOLET-THERAPY single term (MeSH) or PUVA-THERAPY single term (MeSH))
- #7 (((((((PUVA or ULTRAVIOLET-A) or ULTRA-VIOLET-A) or UVA) or UVB) or ULTRAVIOLET-B) or ULTRA-VIOLET-B) or (NBUVB or BBUVB))
- #8 ((NARROWBAND next UVB) or (NARROWBAND next ULTRAVIOLET) or (NARROW-BAND NEXT UVB) or (NARROW-BAND next ULTRAVIOLET next B))
- #9 (((NARROWBAND next UVB) or (NARROWBAND next ULTRAVIOLET)) or (NARROW-BAND next UVB)) or (NARROW-BAND next ULTRAVIOLET))
- #10 ((BROADBAND next UVB) or (BROADBAND next ULTRAVIOLET)) or (BROAD-BAND next UVB)) or (BROAD-BAND next ULTRAVIOLET)) or (PNBUVB or REPUVA))
- #11 ((MOP:TI or METHOXYPsorALEN*) or ACITRETIN single term (MeSH))

- #12 ((RETINOIDS single term (MeSH) or ETRETINATE single term (MeSH)) or VITAMIN-A single term (MeSH))
- #13 (TRETINOIN:ME or ((RETINOID* or ACITRETIN*) or ETRETINATE*))
- #14 ((TMP:TI or TRIMETHYLPORALEN) or CYCLOSPORINS:ME)
- #15 (((CYCLOSPORIN* or CICLOSPORIN*) or CSA) or HYDROXYUREA single term (MeSH))
- #16 ((HYDROXYUREA* or HYDROXYCARBAMIDE*) or (FUMARATE* or ((FUMARIC next ACID) next ESTER*)))
- #17 ((FUMADERM or FUMARATES single term (MeSH)) or ((DMFAE or DIMETHYLFUMAR*) or MONOETHYLFUMAR*))
- #18 (((MEFAE-CA or MEFAE-MG) or MEFAE-NA) or MEFAE-ZN) or (OHFAE or ((OCTYL next HYDROGEN) next FUMAR*))
- #19 (ANTHRALIN single term (MeSH) or (DITHRANOL or ANTHRALIN))
- #20 ((GOECKERMAN next METHOD*) or (GOECKERMAN next REGIME*))
- #21 ((((((INGRAM next THERAPY) or (INGRAM next THERAPIES)) or (INGRAM next TREATMENT)) or (INGRAM next TREATMENTS)) or (INGRAM next METHOD*)) or (INGRAM next REGIME*))
- #22 (METHOTREXATE single term (MeSH) or METHOTREXATE)
- #23 (((((((((#3 or #4) or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12)
- #24 (((((((((#13 or #14) or #15) or #16) or #17) or #18) or #19) or #20) or #21) or #22)
- #25 (#23 or #24)
- #26 (#1 or #2)
- #27 (#25 and #26) limited to Start Date 1999-2004

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the internet - <http://www.update-software.com/clubng/clublogon.htm>)
2004 Issue 1

This search retrieved 124 references.

- #1 PSORIASIS single term (MeSH)
- #2 (psoria* or anti-psoria* or antipsoria*)
- #3 (#1 or #2)
- #4 PSORALENS explode all trees (MeSH)
- #5 psoralen*
- #6 (phototherap* or photo-therap* or photochemotherap* or photo-chemotherap* or photo-chemo-therap*)
- #7 PHOTOTHERAPY single term (MeSH)
- #8 HELIOTHERAPY single term (MeSH)
- #9 PHOTOCHEMOTHERAPY single term (MeSH)
- #10 ULTRAVIOLET THERAPY single term (MeSH)
- #11 PUVA THERAPY single term (MeSH)
- #12 (puva or ultraviolet-a or ultra-violet-a or uva or uvb or ultraviolet-b or ultra-violet-b)
- #13 (nbuvb or bbuvb)
- #14 ((narrowband next uvb) or (narrowband next ultraviolet) or (narrow-band next uvb) or (narrow-band next ultraviolet next b))
- #15 ((broadband next uvb) or (broadband next ultraviolet) or (broad-band next uvb) or (broad-band next ultraviolet))

- #16 (pnbuvb or repuva)
- #17 mop:ti
- #18 methoxypsoralen*
- #19 ACITRETIN single term (MeSH)
- #20 RETINOIDS single term (MeSH)
- #21 ETRETINATE single term (MeSH)
- #22 vitamin-a
- #23 VITAMIN A single term (MeSH)
- #24 TRETINOIN single term (MeSH)
- #25 (retinoid* or acitretin* or etretinate*)
- #26 tmp:ti
- #27 trimethylpsoralen
- #28 CYCLOSPORINS single term (MeSH)
- #29 (cyclosporin* or ciclosporin* or csa)
- #30 HYDROXYUREA single term (MeSH)
- #31 (hydroxyurea* or hydroxycarbamide*)
- #32 (fumarate* or (fumaric next acid next ester*))
- #33 fumaderm
- #34 FUMARATES single term (MeSH)
- #35 (dmfae or dimethylfumar* or monoethylfumar*)
- #36 (mefae-ca or mefae-mg or mefae-na or mefae-zn)
- #37 (ohfae or (octyl next hydrogen next fumar*))
- #38 ANTHRALIN single term (MeSH)
- #39 (dithranol or anthralin)
- #40 ((goeckerman next therapy) or (goeckerman next treatments))
- #41 ((goeckerman next therapies) or (goeckerman next treatment))
- #42 ((goeckerman next method*) or (goeckerman next regime*))
- #43 ((ingram next therapy) or (ingram next therapies) or (ingram next treatment) or (ingram next treatments) or (ingram next method*) or (ingram next regime*))
- #44 METHOTREXATE single term (MeSH)
- #45 methotrexate
- #46 (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
- #47 (#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
- #48 (#31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
- #49 (#41 or #42 or #43 or #44 or #45 or #46 or #47 or #48)
- #50 (#3 and #49)
- #51 (#3 and #49) (1999 to current date)

CenterWatch (internet - <http://www.centerwatch.com/>)

Searched 12th February 2004

This search retrieved 309 references.

etanercept OR efalizumab OR raptiva OR enbrel {ALL-FIELDS}

Current Controlled Trials (internet - <http://controlled-trials.com/>)

Searched 12th February 2004

This search retrieved 75 references.

etanercept OR efalizumab OR raptiva OR enbrel

ClinicalTrials.gov (internet - <http://clinicaltrials.gov/>)

Searched 12th February 2004

This search retrieved 7 references.

etanercept OR efalizumab OR raptiva OR enbrel

ISI Science and Technology Proceedings (Web of Knowledge)

1990 - 2004 (February 6th update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981-2004

<http://wos.mimas.ac.uk/>

The search of ISI Science and Technology Proceedings retrieved 80 references.

The search of Social Science Citation Index and Science Citation Index retrieved 119 references.

- #1 TS=(Psoria* or anti-psoria* or antipsoria*)
- #2 TS=(psoralen* or phototherap* or photo-therap* or photochemotherap* or photo-chemotherap* or photo-chemo-therap*)
- #3 TS=(puva or ultraviolet-A or ultra-violet-A or UVA or UVB or ultraviolet-B or ultra-violet-B or NBUVB or BBUVB)
- #4 TS=((narrowband or narrow-band) SAME (UVB or ultraviolet))
- #5 TS=((broadband or broad-band) SAME (UVB or ultraviolet))
- #6 TS=(pnbuvb or repuva or MOP or methoxypsoralen* or retinoid* or acitretin* or etretinate*)
- #7 TS=((vitamin-A SAME deriv*) or (synthet* SAME vitamin-A))
- #8 TS=(tmp or trimethylpsoralen or cyclosporin* or ciclosporin* or csa or fumaderm)
- #9 TS=(hydroxyurea* or hydroxycarbamide* or fumarate* or (fumaric SAME acid SAME ester*))
- #10 TS=(dmfae or dimethylfumar* or monoethylfumar* or mefae-ca or mefae-mg or mefae-na or mefae-zn)
- #11 TS=(ohfae or (octyl SAME hydrogen SAME fumar*) or dithranol or anthralin or methotrexate)
- #12 TS=(goeckerman or ingram)
- #13 TS=((animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea))
- #14 #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
- #15 #1 and #14
- #16 #15 not #13

10.1.1.4 Search D: Reports of adverse events of comparators treatments

The following resources were examined for references to adverse events:

BMJ Publishing Group. *Clinical Evidence*. London: BMJ Publishing Group; 2004.

Dukes MNG and Aronson JK, editors. *Meyler's side effects of drugs: an encyclopedia of adverse reactions and interactions*. 14th ed. Oxford: Elsevier; 2000.

British Medical Association. *British National Formulary, No. 47*. London: British Medical Association, 2004. Available from: <http://bnf.org>.

Sweetman SC, editor. *Martindale: the complete drug reference*. {CD-ROM}. London: Pharmaceutical Press; 2000

EMC Trust. *Medicines compendium* {CD-ROM}. Alton: Virtual Hwalth Network; Version 3.4. 3rd quarter 2003

Aronson JK, editor. *Side Effects of Drugs Annual*. Oxford: Elsevier; 2004.
United States Pharmacopoeial Convention. *USPDI, vol 1: drug information for the health care professional*. Rockville: United States Pharmacopoeial Convention; 2004.

10.1.1.5 Search E: Randomized controlled trials (RCTs) of infliximab in psoriasis

Medline and In-Process Citations (OVID Online - <http://www.ovid.com/>)
1966 – 2004/03 wk 2

This search retrieved 80 references.

1. randomized controlled trial.pt.
2. exp randomized controlled trials/
3. random allocation/
4. double blind method/
5. single blind method/
6. clinical trial.pt.
7. exp clinical trials/
8. controlled clinical trials/
9. clin\$ trial\$.ti,ab.
10. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.
11. placebo\$.ti,ab.
12. placebos/
13. random\$.ti,ab.
14. exp evaluation studies/
15. follow up studies/
16. exp research design/
17. prospective studies/

18. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
19. or/1-18
20. animals/
21. human/
22. 20 not (20 and 21)
23. 19 not 22
24. exp psoriasis/
25. (psoria\$ or anti psoria\$ or antipsoria\$).ti,ab.
26. or/24-25
27. (letter or comment or editorial).pt.
28. (infliximab or remicade).mp.
29. 23 and 26 and 28
30. 29 not 27

Embase (OVID Online - <http://www.ovid.com/>)
1980- 2004 wk 11

This search retrieved 183 references.

1. randomized controlled trial/
2. randomization/
3. double blind procedure/ or single blind procedure/
4. exp clinical trial/
5. controlled study/
6. clin\$ trial\$.ti,ab.
7. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.
8. placebo\$.ti,ab.
9. Placebo/
10. random\$.ti,ab.
11. evaluation/
12. follow up/
13. exp methodology/
14. prospective study/
15. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
16. or/1-15
17. (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
18. exp ANIMAL/
19. Animal Experiment/
20. Nonhuman/
21. Human/
22. Human Experiment/
23. or/17-20
24. 21 or 22
25. 23 not (23 and 24)
26. 16 not 25
27. exp Psoriasis/
28. (psoria\$ or anti psoria\$ or antipsoria\$).ti,ab.
29. or/27-28
30. Infliximab/

- 31. (infliximab or remicade).ti,ab.
- 32. or/30-31
- 33. 26 and 29 and 32

National Research Register (NRR) (cd-rom)

2004 Issue 1

This search retrieved 1 reference.

- #1 PSORIASIS single term (MeSH)
- #2 ((PSORIA* or ANTI-PSORIA*) or ANTIPSORIA*)
- #3 (#1 or #2)
- #4 (INFLIXIMAB or REMICADE)
- #5 (#3 and #4)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the internet - <http://www.update-software.com/clibng/cliblogon.htm>)

2004 Issue 1

This search retrieved 4 references.

- #1 PSORIASIS single term (MeSH)
- #2 (psoria* or anti-psoria* or antipsoria*)
- #3 (#1 or #2)
- #4 (infliximab or remicade)
- #5 (#3 and #4)

ISI Science and Technology Proceedings (Web of Knowledge)

1990 - 2004 (March 17th update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981-2004 (March 15th update.)

<http://wos.mimas.ac.uk/>

The search of ISI Science and Technology Proceedings retrieved 19 references.

The search of Social Science Citation Index and Science Citation Index retrieved 134 references.

- #1 TS=(Psoria* or anti-psoria* or antipsoria*)
- #2 TS=(infliximab or remicade)
- #3 #1 and #2
- #4 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
- #5 #3 not #4

All databases were searched from inception date.

10.1.2 Cost-effectiveness

Searching for the cost-effectiveness component of this review was addressed by several separate searches to identify:

Reports of economic evaluations of etanercept or efalizumab in psoriasis

Reports of economic evaluations of comparator treatments in psoriasis

Reports of quality of life (QoL) measures in psoriasis

Internet searches to locate reports of economic evaluations of etanercept or efalizumab in psoriasis

Reports of treatment pathways for psoriasis

Reports of treatment pathways for psoriasis (on the internet)

Guidelines for psoriasis (on the internet)

To locate economic models for psoriasis

Separate strategies were devised for each topic. Full details of the databases searched and search strategies used are provided below.

10.1.2.1 Search 1: Economic evaluations of etanercept or efalizumab in psoriasis

Medline and In-Process Citations (OVID Online - <http://www.ovid.com/>)

1966 – 2004/02 wk 1

This search retrieved 5 references.

- 1 economics/
- 2 exp "Costs and Cost Analysis"/
- 3 VALUE OF LIFE/ec {Economics}
- 4 economics, dental/
- 5 exp economics, hospital/
- 6 economics, medical/
- 7 economics, nursing/
- 8 economics, pharmaceutical/
- 9 or/1-8
- 10 (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoconom\$).tw.
- 11 (expenditure\$ not energy).tw.
- 12 (value adj1 money).tw.
- 13 budget\$.tw.
- 14 or/10-13
- 15 9 or 14
- 16 letter.pt.
- 17 editorial.pt.
- 18 historical article.pt.
- 19 or/16-18
- 20 15 not 19
- 21 animals/
- 22 human/
- 23 21 not (21 and 22)

- 24 20 not 23
- 25 (metabolic adj cost).ti,ab,sh.
- 26 ((energy or oxygen) adj cost).ti,ab,sh.
- 27 24 not (25 or 26)
- 28 psoriasis/
- 29 psoria\$.mp.
- 30 antipsoria\$.mp.
- 31 anti psoria\$.mp.
- 32 or/28-31
- 33 etanercept.mp.
- 34 enbrel.mp.
- 35 efalizumab.mp.
- 36 raptiva.mp.
- 37 or/33-36
- 38 27 and 32 and 37

Embase (OVID Online - <http://www.ovid.com/>)
1980- 2004 wk 7

This search retrieved 113 references.

1. economics/ or exp health economics/
2. cost/ or exp health care cost/
3. exp fee/ or exp health insurance/ or exp pharmacoeconomics/ or health care organization/ or exp health care quality/
4. economic aspect/ or budget.mp.
5. economic aspect/ or budget/
6. exp disease management/
7. or/1-6
8. (econom\$ or cost or costs or costly or costing or costed or price or prices or pricing or pharmacoeconom\$).tw.
9. (expenditure\$ not energy).tw.
10. (value adj5 money).tw.
11. budget\$.tw.
12. or/9-11
13. 7 or 12
14. 13 not (editorial or letter or note).pt.
15. exp ANIMAL/ or Animal Experiment/ or Nonhuman/ or (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
16. Human/ or Human Experiment/
17. 15 not (15 and 16)
18. 14 not 17
19. (metabolic adj cost).mp.
20. ((energy or oxygen) adj cost).mp.
21. 18 not (19 or 20)
22. exp Psoriasis/
23. (psoria\$ or anti psoria\$ or antipsoria\$).mp.
24. or/22-23
25. Etanercept/

26. Efalizumab/
27. (etanercept or efalizumab or enbrel or raptiva).mp.
28. or/25-27
29. 21 and 24 and 28

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the internet - <http://www.update-software.com/clubng/clublogon.htm>)
2004 Issue 1

This search retrieved 6 references.

1. PSORIASIS single term (MeSH)
2. (psoria* or anti-psoria* or antipsoria*)
3. (#1 or #2)
4. (etanercept or efalizumab or enbrel or raptiva)
5. (#3 and #4)

NHS Economic Evaluation Database (NHS EED) (CRD administration database)
1990 – 2004/02

This search retrieved 0 references.

1. s psoria\$ or anti(w1)psoria\$ or antipsoria\$
2. s (etanercept or efalizumab or enbrel or raptiva)
3. s s1 and s2

Health Economic Evaluation Database (HEED) (cd-rom)
February 2004

This search retrieved 0 references.

Psoriasis or psoriatic or psoriatics or anti-psoriasis or anti-psoriatic or anti-psoriatics
or antipsoriasis or antipsoriatic or antipsoriatics
AND
etanercept or efalizumab or enbrel or raptiva

EconLit (SilverPlatter on the web - <http://arc.uk.ovid.com/>)
1969 – 2004/01

This search retrieved 0 references.

1. PSORIASIS
2. psoria* or anti-psoria* or antipsoria*
3. (psoria* or anti-psoria* or antipsoria*) and (PSORIASIS)
4. (etanercept or efalizumab or enbrel or raptiva)
5. ((etanercept or efalizumab or enbrel or raptiva)) and ((psoria* or anti-psoria* or antipsoria*) or (PSORIASIS))

ISI Science and Technology Proceedings (Web of Knowledge)

1990 - 2004 (February 13th update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981-2004 (February 15th update.)

<http://wos.mimas.ac.uk/>

The search of ISI Science and Technology Proceedings retrieved 0 references.

The search of Social Science Citation Index and Science Citation Index retrieved 7 references.

- #1 TS=((Psoria* or anti-psoria* or antipsoria*))
- #2 TS=(etanercept or enbrel or efalizumab or raptiva)
- #3 #1 and #2
- #4 TS=((econom* or cost or costs or costly or costing or price or prices or pricing or pharmacoconom* or budget*))
- #5 #3 and #4

All databases were searched from inception date.

10.1.2.2 Search 2: Economic evaluations of comparator treatments in psoriasis

Medline and In-Process Citations (OVID Online - <http://www.ovid.com/>)

1966 – 2004/03 wk 4

This search retrieved 89 references.

- 1. economics/
- 2. exp "Costs and Cost Analysis"/
- 3. VALUE OF LIFE/
- 4. economics, dental/
- 5. exp economics, hospital/
- 6. economics, medical/
- 7. economics, nursing/
- 8. economics, pharmaceutical/
- 9. or/1-8
- 10. (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoconom\$).ti,ab.
- 11. (expenditure\$ not energy).ti,ab.
- 12. (value adj1 money).ti,ab.
- 13. budget\$.ti,ab.
- 14. or/10-13
- 15. 9 or 14
- 16. letter.pt.
- 17. editorial.pt.
- 18. historical article.pt.
- 19. or/16-18
- 20. 15 not 19
- 21. animals/
- 22. human/

23. 21 not (21 and 22)
24. 20 not 23
25. (metabolic adj cost).ti,ab.
26. ((energy or oxygen) adj cost).ti,ab.
27. 24 not (25 or 26)
28. psoriasis/
29. psoria\$.ti,ab.
30. antipsoria\$.ti,ab.
31. anti psoria\$.ti,ab.
32. or/28-31
33. exp Psoralens/
34. psoralen\$.mp.
35. puva.ti,ab.
36. (phototherap\$ or photo therap\$ or photochemotherap\$ or photo chemotherap\$ or photo chemo therap\$).ti,ab.
37. Phototherapy/
38. Heliotherapy/
39. photochemotherapy/
40. ultraviolet therapy/
41. puva therapy/
42. (puva or ultraviolet A or ultra violet A or UVA or UVB or ultraviolet B or ultra violet B).ti,ab.
43. (NBUVB or BBUVB).ti,ab.
44. (pnbuvb or repuva).ti,ab.
45. MOP.mp.
46. methoxypsoralen\$.mp.
47. Acitretin/
48. retinoids/
49. etretinate/
50. exp vitamin A/
51. (retinoid\$ or acitretin\$ or etretinate\$ or vitamin A deriv\$).mp.
52. synthet\$ vitamin A.mp.
53. tmp.mp.
54. trimethylpsoralen.mp.
55. exp Cyclosporins/
56. (cyclosporin\$ or csa or cya or cyc-a or ciclosporin\$ or sandimmun\$).mp.
57. Hydroxyurea/
58. (hydroxyurea\$ or hydroxycarbamide\$).mp.
59. (fumarate\$ or fumaric acid ester\$).mp.
60. fumaderm.mp.
61. Fumarates/
62. (dmfae or dimethylfumar\$ or monoethylfumar\$).mp.
63. (mefae-ca or mefae-mg or mefae-na or mefae-zn).mp.
64. (ohfae or octyl hydrogen fumar\$).mp.
65. Anthralin/
66. (dithranol or anthralin).mp.
67. (goeckerman adj1 (therap\$ or treatment\$ or method\$ or regime\$)).ti,ab.
68. (ingram adj1 (therap\$ or treatment\$ or method\$ or regime\$)).ti,ab.
69. Methotrexate/ or (methotrexate or mtx).mp.
70. (infliximab or remicade).mp.

- 71. or/33-70
- 72. 27 and 32 and 71

Embase (OVID Online - <http://www.ovid.com/>)
1980- 2004 wk 13

This search retrieved 688 references.

- 1. economics/ or exp health economics/
- 2. cost/ or exp health care cost/
- 3. exp fee/ or exp health insurance/ or exp pharmacoeconomics/ or health care organization/ or exp health care quality/
- 4. economic aspect/ or budget.mp. {mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name}
- 5. economic aspect/ or budget/
- 6. exp disease management/
- 7. or/1-6
- 8. (econom\$ or cost or costs or costly or costing or costed or price or prices or pricing or pharmacoeconom\$).ti,ab.
- 9. (expenditure\$ not energy).ti,ab.
- 10. (value adj5 money).ti,ab.
- 11. budget\$.ti,ab.
- 12. or/9-11
- 13. 7 or 12
- 14. 13 not (editorial or letter or note).pt.
- 15. exp ANIMAL/ or Animal Experiment/ or Nonhuman/ or (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
- 16. Human/ or Human Experiment/
- 17. 15 not (15 and 16)
- 18. 14 not 17
- 19. (metabolic adj cost).ti,ab.
- 20. ((energy or oxygen) adj cost).ti,ab.
- 21. 18 not (19 or 20)
- 22. exp Psoriasis/
- 23. (psoria\$ or anti psoria\$ or antipsoria\$).ti,ab.
- 24. or/22-23
- 25. psoralen\$.ti,ab.
- 26. puva.ti,ab.
- 27. (puva or ultraviolet A or ultra violet A or UVA or UVB or ultraviolet B or ultra violet B).ti,ab.
- 28. (NBUVB or BBUVB).ti,ab.
- 29. (pnbuvb or repuva).ti,ab.
- 30. MOP.ti,ab.
- 31. methoxypsoralen\$.ti,ab.
- 32. (retinoid\$ or acitretin\$ or etretinate\$ or vitamin A deriv\$).ti,ab.
- 33. synthet\$ vitamin A.ti,ab.
- 34. tmp.ti,ab.
- 35. trimethylpsoralen.ti,ab.
- 36. (cyclosporin\$ or ciclosporin\$ or csa or cya or cyc-a or ciclosporin\$ or

- sandimmun\$.ti,ab.
37. (hydroxyurea\$ or hydroxycarbamide\$.ti,ab.
38. (fumarate\$ or fumaric acid ester\$.ti,ab.
39. fumaderm.ti,ab.
40. (dmfae or dimethylfumar\$ or monoethylfumar\$.ti,ab.
41. (mefae-ca or mefae-mg or mefae-na or mefae-zn).ti,ab.
42. (ohfae or octyl hydrogen fumar\$.ti,ab.
43. (dithranol or anthralin).ti,ab.
44. (goeckerman adj1 (therap\$ or treatment\$ or method\$ or regime\$)).ti,ab.
45. (ingram adj1 (therap\$ or treatment\$ or method\$ or regime\$)).ti,ab.
46. methotrexate.ti,ab.
47. (phototherap\$ or photo therap\$ or photochemotherap\$ or photo chemotherap\$ or photo chemo therap\$.ti,ab.
48. psoralen/ or psoralen derivative/
49. phototherapy/ or photochemotherapy/ or puva/
50. ultraviolet radiation/ or ultraviolet a radiation/ or ultraviolet b radiation/
51. methoxsalen/ or methoxsalen derivative/
52. retinoid/ or etretin/ or etretinate/
53. retinol/ or retinol derivative/
54. Retinoic Acid/
55. Trimethylpsoralen/
56. Cyclosporin/
57. HYDROXYUREA/
58. fumaric acid/ or fumaric acid derivative/
59. fumaric acid dimethyl ester/ or fumaric acid ethyl ester/
60. dithranol/ or dithranol derivative/
61. METHOTREXATE/
62. antipsoriasis agent/ or 4' aminomethyl 4,5',8 trimethylpsoralen/ or fumaderm/ or psoralon/ or psorin/
63. or/25-62
64. 21 and 24 and 63

National Research Register (NRR) (cd-rom)

2004 Issue 1

This search retrieved 99 references.

- #1 PSORIASIS single term (MeSH)
#2 ((PSORIA* or ANTI-PSORIA*) or ANTIPSORIA*)
#3 PSORALENS explode all trees (MeSH)
#4 (PSORALEN* or (((PHOTOTHERAP* or PHOTO-THERAP*) or PHOTOCHEMOTHERAP*) or PHOTO-CHEMOTHERAP*) or PHOTO-CHEMO-THERAP*))
#5 ((PHOTOTHERAPY single term (MeSH) or HELIOTHERAPY single term (MeSH)) or PHOTOCHEMOTHERAPY single term (MeSH))
#6 (ULTRAVIOLET-THERAPY single term (MeSH) or PUVA-THERAPY single term (MeSH))
#7 ((((((PUVA or ULTRAVIOLET-A) or ULTRA-VIOLET-A) or UVA) or UVB) or ULTRAVIOLET-B) or ULTRA-VIOLET-B) or (NBUVB or BBUVB))

- #8 ((NARROWBAND next UVB) or (NARROWBAND next ULTRAVIOLET) or (NARROW-BAND next UVB) or (NARROW-BAND next ULTRAVIOLET next B))
- #9 (((NARROWBAND next UVB) or (NARROWBAND next ULTRAVIOLET)) or (NARROW-BAND next UVB)) or (NARROW-BAND next ULTRAVIOLET))
- #10 (((((BROADBAND next UVB) or (BROADBAND next ULTRAVIOLET)) or (BROAD-BAND next UVB)) or (BROAD-BAND next ULTRAVIOLET)) or (PNBUVB or REPUVA))
- #11 ((MOP:TI or METHOXYPsorALEN*) or ACITRETIN single term (MeSH))
- #12 ((RETINOIDS single term (MeSH) or ETRETINATE single term (MeSH)) or VITAMIN-A single term (MeSH))
- #13 (TRETINOIN single term (MeSH) or ((RETINOID* or ACITRETIN*) or ETRETINATE*))
- #14 ((TMP:TI or TRIMETHYLPSORALEN) or CYCLOSPORINS single term (MeSH))
- #15 (((CYCLOSPORIN* or CICLOSPORIN* or SANDIMMUN*) or CSA) or HYDROXYUREA single term (MeSH))
- #16 ((HYDROXYUREA* or HYDROXYCARBAMIDE*) OR (FUMARATE* or ((FUMARIC next ACID) next ESTER*)))
- #17 ((FUMADERM or FUMARATES single term (MeSH)) or ((DMFAE or DIMETHYLFUMAR*) or MONOETHYLFUMAR*))
- #18 (((((MEFAE-CA or MEFAE-MG) or MEFAE-NA) or MEFAE-ZN) or (OHFAE or ((OCTYL next HYDROGEN) next FUMAR*)))
- #19 (ANTHRALIN single term (MeSH) or (DITHRANOL or ANTHRALIN))
- #20 ((GOECKERMAN next METHOD*) or (GOECKERMAN next REGIME*))
- #21 ((((((INGRAM next THERAPY) or (INGRAM next THERAPIES)) or (INGRAM next TREATMENT)) or (INGRAM next TREATMENTS)) or (INGRAM next METHOD*)) or (INGRAM next REGIME*))
- #22 (METHOTREXATE single term (MeSH) or METHOTREXATE or MTX)
- #23 (((((((((#3 or #4) or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12)
- #24 (((((((((#13 or #14) or #15) or #16) or #17) or #18) or #19) or #20) or #21) or #22)
- #25 #23 or #24
- #26 #1 or #2
- #27 #26 and #27

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the internet - <http://www.update-software.com/clubng/clublogon.htm>)
2004 Issue 1

This search retrieved 652 references.

- #1 PSORIASIS single term (MeSH)
- #2 (psoria* or anti-psoria* or antipsoria*)
- #3 (#1 or #2)
- #4 PSORALENS explode all trees (MeSH)
- #5 psoralen*
- #6 (phototherap* or photo-therap* or photochemotherap* or photo-chemotherap* or photo-chemo-therap*)

- #7 PHOTOTHERAPY single term (MeSH)
- #8 HELIOTHERAPY single term (MeSH)
- #9 PHOTOCHEMOTHERAPY single term (MeSH)
- #10 ULTRAVIOLET THERAPY single term (MeSH)
- #11 PUVA THERAPY single term (MeSH)
- #12 (puva or ultraviolet-a or ultra-violet-a or uva or uvb or ultraviolet-b or ultra-violet-b)
- #13 (nbuvb or bbuvb)
- #14 ((narrowband next uvb) or (narrowband next ultraviolet) or (narrow-band next uvb) or (narrow-band next ultraviolet next b))
- #15 ((broadband next uvb) or (broadband next ultraviolet) or (broad-band next uvb) or (broad-band next ultraviolet))
- #16 (pnbuvb or repuva or infliximab or remicade)
- #17 mop:ti
- #18 methoxypsoralen*
- #19 ACITRETIN single term (MeSH)
- #20 RETINOIDS single term (MeSH)
- #21 ETRETINATE single term (MeSH)
- #22 vitamin-a
- #23 VITAMIN A single term (MeSH)
- #24 TRETINOIN single term (MeSH)
- #25 (retinoid* or acitretin* or etretinate*)
- #26 tmp:ti
- #27 trimethylpsoralen
- #28 CYCLOSPORINS single term (MeSH)
- #29 (cyclosporin* or ciclosporin* or csa or sandimmun*)
- #30 HYDROXYUREA single term (MeSH)
- #31 (hydroxyurea* or hydroxycarbamide*)
- #32 (fumarate* or (fumaric next acid next ester*))
- #33 fumaderm
- #34 FUMARATES single term (MeSH)
- #35 (dmfae or dimethylfumar* or monoethylfumar*)
- #36 (mefae-ca or mefae-mg or mefae-na or mefae-zn)
- #37 (ohfae or (octyl next hydrogen next fumar*))
- #38 ANTHRALIN single term (MeSH)
- #39 (dithranol or anthralin)
- #40 ((goeckerman next therapy) or (goeckerman next treatments))
- #41 ((goeckerman next therapies) or (goeckerman next treatment))
- #42 ((goeckerman next method*) or (goeckerman next regime*))
- #43 ((ingram next therapy) or (ingram next therapies) or (ingram next treatment) or (ingram next treatments) or (ingram next method*) or (ingram next regime*))
- #44 METHOTREXATE single term (MeSH)
- #45 methotrexate or mtx
- #46 (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
- #47 (#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
- #48 (#31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
- #49 (#41 or #42 or #43 or #44 or #45 or #46 or #47 or #48)
- #50 (#3 and #49)

NHS Economic Evaluation Database (NHS EED) (CRD administration database)
1990 – 2004/04

This search retrieved 7 references.

1. s psoria\$ or antiw1)psoria\$ or antipsoria\$
2. s psoralen\$ or puva or phototherap\$ or photo(w)therap\$ or photochemotherap\$
3. s photo(w)chemotherap\$ or photo(w)chemo(w)therap\$ or Heliotherap\$
4. s helio(w)therapy or ultraviolet or NBUVB or BBUVB or pnbuvb or repuva
5. s MOP or methoxypsoralen\$ or Acitretin or retinoid\$ or etretinate
6. s vitamin(w1)A or tmp or trimethylpsoralen
7. s cyclosporin\$ or csa or cya or cyc(w1)a or ciclosporin\$ or sandimmun\$
8. s hydroxyurea\$ or hydroxycarbamide\$ or fumarate\$ or fumaric(w)acid(w)ester\$
9. s fumaderm or dmfae or dimethylfumar\$ or monoethylfumar\$
10. s mefae or ohfae or octyl(w)hydrogen(w)fumar\$ or dithranol or anthralin
11. s goeckerman(w2)(therap\$ or treatment\$ or method\$ or regime\$)
12. s ingram(w2)(therap\$ or treatment\$ or method\$ or regime\$)
13. s methotrexate or mtx or infliximab or remicade
14. s s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13
15. s s1 and s14

Health Economic Evaluation Database (HEED) (cd-rom)
May 2004

This search retrieved 0 references.

Psoriasis or psoriatic or psoriatics or anti-psoriasis or anti-psoriatic or anti-psoriatics or antipsoriasis or antipsoriatic or antipsoriatics

EconLit (SilverPlatter on the web - <http://arc.uk.ovid.com/>)
1969 – 2004/03

This search retrieved 1 reference.

(psoria* or anti-psoria* or antipsoria*) and (PSORIASIS)

ISI Science and Technology Proceedings (Web of Knowledge)
1990 - 2004 (March 26th update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981-2004 (March 29th update.)
<http://wos.mimas.ac.uk/>

The search of ISI Science and Technology Proceedings retrieved 1 reference.

The search of Social Science Citation Index and Science Citation Index retrieved 28 references.

- #1 TS=(Psoria* or anti-psoria* or antipsoria*)
- #2 TS=(psoralen* or phototherap* or photo-therap* or photochemotherap* or photo-chemotherap* or photo-chemo-therap*)
- #3 TS=(puva or ultraviolet-A or ultra-violet-A or UVA or UVB or ultraviolet-B or ultra-violet-B or NBUVB or BBUVB)
- #4 TS=((narrowband or narrow-band) SAME (UVB or ultraviolet))
- #5 TS=((broadband or broad-band) SAME (UVB or ultraviolet))
- #6 TS=(pnbuvb or repuva or MOP or methoxypsoralen* or retinoid* or acitretin* or etretinate*)
- #7 TS=((vitamin-A SAME deriv*) or (synthet* SAME vitamin-A))
- #8 TS=(tmp or trimethylpsoralen or cyclosporin* or ciclosporin* or csa or fumaderm)
- #9 TS=(hydroxyurea* or hydroxycarbamide* or fumarate* or (fumaric SAME acid SAME ester*))
- #10 TS=(dmfae or dimethylfumar* or monoethylfumar* or mefae-ca or mefae-mg or mefae-na or mefae-zn)
- #11 TS=(ohfae or (octyl SAME hydrogen SAME fumar*) or dithranol or anthralin or methotrexate)
- #12 TS=(goeckerman or ingram)
- #13 TS=(sandimmun* or infliximab or remicade or hydroxycarbamide)
- #14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
- #15 TS=((econom* or cost or costs or costly or costing or price or prices or pricing or pharmacoconom* or budget*))
- #16 #14 and #15
- #17 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
- #18 #16 not #17

All databases were searched from inception date.

10.1.2.3 Search 3: *Quality of life (QoL) measures in psoriasis*

Medline and In-Process Citations (OVID Online - <http://www.ovid.com/>)

1966 – 2004/02 wk 2

This search retrieved 253 references.

1. (sf36 or sf 36).tw.
2. (eq5d or eq 5d or euroqol or euro qol).tw.
3. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
4. (hrql or hrqol or h qol or hql or hqol).tw.
5. (hye or hyes or health\$ year\$ equivalent\$ or health utilit\$).tw.
6. health related quality of life.tw.
7. rosser.tw.
8. (standard gamble\$ or time trade off or time tradeoff or tto or willingness to pay).tw.
9. (utilities or utility or daly or disability adjusted life).tw.
10. quality of life/ or (quality of life or life quality).tw.
11. health status indicators/

12. quality adjusted life year/
13. (qaly\$ or quality adjusted).tw.
14. (qwb\$ or hui or hui1 or hui2 or hui3 or qwi).tw.
15. (quality of wellbeing or quality of well being).tw.
16. preference based.tw.
17. (dermatology life quality index or health status).tw.
18. (state adj2 (value or values or valuing or valued)).tw.
19. (dlqi or hspv).ti,ab.
20. general health questionnaire.tw.
21. nottingham health profile.tw.
22. patient generated index.tw.
23. sickness impact profile.tw.
24. (ghq or nhp or pgi or sip or uksip or wtp).ti,ab.
25. psoriasis/
26. psoria\$.mp.
27. antipsoria\$.mp.
28. anti psoria\$.mp.
29. or/25-28
30. or/1-24
31. 30 and 29
32. limit 31 to yr=1990-2004
33. animals/
34. human/
35. 33 not (33 and 34)
36. 32 not 35
37. 36 not (letter or editorial or comment).pt.

Embase (OVID Online - <http://www.ovid.com/>)

1980- 2004 wk 8

This search retrieved 320 references.

1. (sf36 or sf 36).tw.
2. (eq5d or eq 5d or euroqol or euro qol).tw.
3. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
4. (hrql or hrqol or h qol or hql or hqol).tw.
5. (hye or hyes or health\$ year\$ equivalent\$ or health utilit\$).tw.
6. health related quality of life.tw.
7. rosser.tw.
8. (standard gamble\$ or time trade off or time tradeoff or tto or willingness to pay).tw.
9. (utilities or utility or daly or disability adjusted life).tw.
10. (qaly\$ or quality adjusted).tw.
11. (qwb\$ or hui or hui1 or hui2 or hui3 or qwi).tw.
12. (quality of wellbeing or quality of well being).tw.
13. preference based.tw.
14. (dermatology life quality index or health status).tw.
15. (state adj2 (value or values or valuing or valued)).tw.
16. (dlqi or hspv).ti,ab.
17. general health questionnaire.tw.

18. nottingham health profile.tw.
19. patient generated index.tw.
20. sickness impact profile.tw.
21. (ghq or nhp or pgi or sip or uksip or wtp).ti,ab.
22. (quality of life or life quality).tw.
23. quality of life/ or quality adjusted life year/
24. or/1-23
25. exp Psoriasis/
26. (psoria\$ or anti psoria\$ or antipsoria\$).mp.
27. or/25-26
28. 24 and 27
29. exp ANIMAL/ or Animal Experiment/ or Nonhuman/ or (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
30. Human/ or Human Experiment/
31. 29 not (29 and 30)
32. 28 not 31
33. 32 not (editorial or letter or note).pt.
34. limit 33 to yr=1990-2004

National Research Register (NRR) (cd-rom)
2003 Issue 4

This search retrieved 24 references.

- #1 PSORIASIS single term (MeSH)
- #2 ((PSORIA* or ANTIPSORIA*) or ANTI-PSORIA*)
- #3 (#1 or #2)
- #4 (((((SF36 or SF-36) or EQ5D) or EQ-5D) or EUROQOL) or EURO-QOL)
- #5 (((((SHORT next FORM-36) or SHORTFORM-36) OR (SF next THIRTY-SIX)) or (SF next THIRTY-SIX))
- #6 (((((SHORTFORM next THIRTY-SIX) or (SHORTFORM next THIRTY-SIX)) or ((SHORT next FORM) next THIRTY-SIX)) or ((SHORT next FORM) next THIRTY-SIX))
- #7 (((((((HRQL or HRQOL) or H-QOL) or HQL) or HQOL) or HYE) or HYES) or ((HEALTH* next YEAR*) next EQUIVALENT*)) or (HEALTH next UTILIT*))
- #8 (((((((HEALTH next RELATED) next QUALITY) next LIFE) or ROSSER) or (STANDARD next GAMBLE*)) or ((TIME next TRADE) next OFF))
- #9 (((((((TIME next TRADEOFF) or TTO) or (WILLINGNESS next PAY)) or UTILITIES) or UTILITY) or DALY) or ((DISABILITY next ADJUSTED) next LIFE))
- #10 ((QUALITY next LIFE) or (LIFE next QUALITY))
- #11 QUALITY-OF-LIFE single term (MeSH)
- #12 QUALITY-ADJUSTED-LIFE-YEARS single term (MeSH)
- #13 HEALTH-STATUS-INDICATORS single term (MeSH)
- #14 (((((((QALY* or (QUALITY next ADJUSTED)) or QWB*) or HUI) or HUI1) or HUI2) or HUI3) or QWI)
- #15 (((QUALITY next WELLBEING) or (QUALITY next WELL-BEING)) OR

- (PREFERENCE next BASED))
- #16 (((DERMATOLOGY next LIFE) next QUALITY) next INDEX) or (HEALTH next STATUS))
- #17 (DLQI or HSPV)
- #18 (((GENERAL next HEALTH) next QUESTIONNAIRE) or ((NOTTINGHAM next HEALTH) next PROFILE)) or ((PATIENT next GENERATED) next INDEX))
- #19 (((((((SICKNESS next IMPACT) next PROFILE) or GHQ) or NHP) or PGI) or SIP) or UKSIP) or WTP)
- #20 (((STATE next VALUE) or (STATE next VALUES)) or (STATE NEXT VALUING)) or (STATE NEXT VALUED))
- #21 (((((((((#4 or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12) or #13)
- #22 (((((((((#14 or #15) or #16) or #17) or #18) or #19) or #20) or #21)
- #23 (#3 and #22)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the internet - <http://www.update-software.com/clubng/clublogon.htm>)
2004 Issue 1

This search retrieved 913 references.

- #1 (sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol)
- #2 ((short next form-36) or shortform-36 or (sf next thirtysix) or (sf next thirty-six))
- #3 ((shortform next thirtysix) or (shortform next thirty-six) or (short next form next thirtysix) or (short next form next thirty-six))
- #4 (hrql or hrqol or h-qol or hql or hqol or hqe or hyes or (health* next year* next equivalent*) or (health next utilit*))
- #5 ((health next related next quality next life) or rosser or (standard next gamble*) or (time next trade next off))
- #6 ((time next tradeoff) or tto or (willingness next pay) or utilities or utility or daly or (disability next adjusted next life))
- #7 ((quality next life) or (life next quality))
- #8 QUALITY OF LIFE single term (MeSH)
- #9 QUALITY-ADJUSTED LIFE YEARS single term (MeSH)
- #10 HEALTH STATUS INDICATORS single term (MeSH)
- #11 (qaly* or (quality next adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)
- #12 ((quality next wellbeing) or (quality next well-being) or (preference next based))
- #13 ((dermatology next life next quality next index) or (health next status))
- #14 (dlqi or hspv)
- #15 ((general next health next questionnaire) or (nottingham next health next profile) or (patient next generated next index))
- #16 ((sickness next impact next profile) or ghq or nhp or pgi or sip or uksip or wtp)
- #17 ((state next value) or (state next values) or (state next valuing) or (state next valued))
- #18 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
- #19 (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
- #20 (psoria* or antipsoria* or anti-psoria*)
- #21 PSORIASIS single term (MeSH)

- #22 (#20 or #21)
#23 #22 and #19 (1990 to current date)

NHS Economic Evaluation Database (NHS EED) (CRD administration database)
1990 – 2004/02

This search retrieved 6 references.

1. s sf36 or sf(w)36 or eq5d or eq(w)5d or euroqol or euro(w)qol
2. s short(w)form(w)36 or shortform(w)36 or sf(w)thirtysix or sf(w)thirty(w)six
3. s shortform(w)thirtysix or shortform(w)thirty(w)six or short(w)form(w)thirtysix
4. s short(w)form(w)thirty(w)six or hrql or hrqol or h(w)qol or hql or hqol or hye or hyes
5. s health\$(w)year\$(w)equivalent\$ or health(w)utilit\$ or health(w)related(w)quality(w)life
6. s rosser or standard(w)gamble\$ or time(w)trade(w)off or time(w)tradeoff
7. s tto or willingness(w)pay or utilities or utility or daly or disability(w)adjusted(w)life
8. s quality(w2)life or life(w)quality
9. s health(w)status(w)indicator\$ or quality(w)adjusted(w)life(w)year\$
10. s qaly\$ or quality(w)adjusted or qwb\$ or hui or hui1 or hui2 or hui3 or qwi
11. s quality(w2)wellbeing or quality(w2)well(w)being or preference(w)based
12. s dermatology(w)life(w)quality(w)index or health(w)status
13. s (state(w2)(value or values or valuing or valued)) or dlqi or hspv
14. s general(w)health(w)questionnaire or nottingham(w)health(w)profile
15. s patient(w)generated(w)index or sickness(w)impact(w)profile
16. s ghq or nhp or pgi or sip or uksip or wtp
17. s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14
18. s s15 or s16 or s17
19. s psoria\$ or antipsoria\$ or anti(w)psoria\$
20. s s18 and s19
21. s 1990:2004/xyr
22. s s20 and s21

Health Economic Evaluation Database (HEED) (cd-rom)
February 2004

This search retrieved 0 references.

Psoriasis or psoriatic or psoriatics or anti-psoriasis or anti-psoriatic or anti-psoriatics or antipsoriasis or antipsoriatic or antipsoriatics

EconLit (SilverPlatter on the web - <http://arc.uk.ovid.com/>)
1969 – 2004/01

This search retrieved 1 reference.

1. (sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol or (short form-36) or

- shortform-36 or (sf thirtysix) or (sf thirty-six))or((shortform thirtysix) or (shortform thirty-six) or (short form thirtysix) or (short form thirty-six))or(hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* year* equivalent*) or (health utilit*))
2. ((health related quality life) or rosser or (standard gamble*) or (time trade off) or (time tradeoff))or(tto or (willingness pay) or utilities or utility or daly or (disability adjusted life) or (quality of life))or((life quality) or qaly* or (quality adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)
 3. ((quality wellbeing) or (quality well-being) or (preference based) or (dermatology life quality index))or((health status) or (state value) or (state values) or (state valuing) or (state valued) or dlqi or hspv)
 4. ((general health questionnaire) or (nottingham health profile) or (patient generated index))or((sickness impact profile) or ghq or nhp or pgi or sip or uksip or wtp)
 5. (((general health questionnaire) or (nottingham health profile) or (patient generated index))or((sickness impact profile) or ghq or nhp or pgi or sip or uksip or wtp)) or (((quality wellbeing) or (quality well-being) or (preference based) or (dermatology life quality index))or((health status) or (state value) or (state values) or (state valuing) or (state valued) or dlqi or hspv)) or (((health related quality life) or rosser or (standard gamble*) or (time trade off) or (time tradeoff))or(tto or (willingness pay) or utilities or utility or daly or (disability adjusted life) or (quality of life))or((life quality) or qaly* or (quality adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)) or ((sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol or (short form-36) or shortform -36 or (sf thirtysix) or (sf thirty-six))or((shortform thirtysix) or (shortform thirty-six) or (short form thirtysix) or (short form thirty-six))or(hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* year* equivalent*) or (health utilit*)))
 6. psoria* or antipsoria* or anti-psoria*
 7. (psoria* or antipsoria* or anti-psoria*) and ((((general health questionnaire) or (nottingham health profile) or (patient generated index))or((sickness impact profile) or ghq or nhp or pgi or sip or uksip or wtp)) or (((quality wellbeing) or (quality well-being) or (preference based) or (dermatology life quality index))or((health status) or (state value) or (state values) or (state valuing) or (state valued) or dlqi or hspv)) or (((health related quality life) or rosser or (standard gamble*) or (time trade off) or (time tradeoff))or(tto or (willingness pay) or utilities or utility or daly or (disability adjusted life) or (quality of life))or((life quality) or qaly* or (quality adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)) or ((sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol or (short form-36) or shortform-36 or (sf thirtysix) or (sf thirty-six))or((shortform thirtysix) or (shortform thirty-six) or (short form thirtysix) or (short form thirty-six))or(hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* year* equivalent*) or (health utilit*))))

ISI Science and Technology Proceedings (Web of Knowledge)

1990 - 2004 (February update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981-2004 (February 22nd update.)

<http://wos.mimas.ac.uk/>

The search of ISI Science and Technology Proceedings retrieved 27 references.

The search of Social Science Citation Index and Science Citation Index retrieved 302 references.

- #1 TS=(sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol or (short SAME form-36) or shortform-36 or (sf SAME thirtysix) or (sf SAME thirty-six))
- #2 TS=((shortform SAME thirtysix) or (shortform SAME thirty-six) or (short SAME form SAME thirtysix) or (short SAME form SAME thirty-six))
- #3 TS=(hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* SAME year* SAME equivalent*) or (health SAME utilit*))
- #4 TS=(tto or (willingness SAME to SAME pay) or utilities or utility or daly or (disability SAME adjusted SAME life) or (quality SAME of SAME life))
- #5 TS=((quality SAME of SAME wellbeing) or (quality SAME of SAME well-being) or (preference SAME based) or (dermatology SAME life SAME quality SAME index))
- #6 TS=((health SAME status) or (state SAME value) or (state SAME values) or (state SAME valuing) or (state SAME valued) or dlqi or hspv)
- #7 TS=((health SAME related SAME quality SAME life) or rosser or (standard SAME gamble*) or (time SAME trade SAME off) or (time SAME tradeoff))
- #8 TS=((life SAME quality) or qaly* or (quality SAME adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)
- #9 TS=((general SAME health SAME questionnaire) or (nottingham SAME health SAME profile) or (patient SAME generated SAME index))
- #10 TS=((sickness SAME impact SAME profile) or ghq or nhp or pgi or sip or uksip or wtp)
- #11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
- #12 TS=(psoria* or antipsoria* or anti-psoria*)
- #13 #11 and #12
- #14 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
- #15 #13 not #14

All databases were searched from inception date.

10.1.2.4 Search 4: Internet searches to locate economic evaluations of etanercept or efalizumab in psoriasis

Google (<http://www.google.co.uk>)

Searched 8th March 2004

This search retrieved 1851 references.

The simple search interface was used. Due to the high volume of hits, a pragmatic cut-off point was used. The first hundred references were saved from each set. The following keywords were searched in combination:

Etanercept	Psoriasis	Economic
------------	-----------	----------

Efalizumab Raptiva Enbrel	Psoriatic	Economics Cost Costs Costly Costing Price Prices Pricing Pharmacoeconomic Pharmacoeconomics
---------------------------------	-----------	--

Organising Medical Networked Information (OMNI) (<http://www.omni.ac.uk>)

Searched 8th March 2004

This search retrieved 3 references.

etanercept AND (economic OR cost or price OR pricing OR pharmacoeconomic)
 OR
 efalizumab AND (economic OR cost or price OR pricing OR pharmacoeconomic)
 OR
 enbrel AND (economic OR cost or price OR pricing OR pharmacoeconomic)
 OR
 raptiva AND (economic OR cost or price OR pricing OR pharmacoeconomic)

Copernic (<http://www.copernic.com>)

Searched 4th March 2004

This search retrieved 68 references.

(economics or economic or cost or costs) and (etanercept or efalizumab or enbrel or raptiva)
 OR
 (costly or costing or price or prices) and (etanercept or efalizumab or enbrel or raptiva)
 OR
 (pricing or pharmacoeconomics or pharmacoeconomic) and (etanercept or efalizumab or enbrel or raptiva)

10.1.2.5 Search 5: Treatment pathways for psoriasis

Medline and In-Process Citations (OVID Online - <http://www.ovid.com/>)

1966 – 2004/02 wk 1

This search retrieved 112 references.

1. guideline.pt.
2. practice guideline.pt.
3. exp guidelines/
4. health planning guidelines/
5. treatment\$ pathway\$.mp.
6. treatment\$ path way\$.mp.
7. care pathway\$.mp.
8. care path way\$.mp.
9. clinical pathway\$.mp.
10. clinical path way\$.mp.
11. treatment\$ path\$.mp.
12. (treatment\$ route\$ or guideline\$ or guide line\$).mp.
13. or/1-12
14. psoriasis/
15. psoria\$.mp.
16. antipsoria\$.mp.
17. anti psoria\$.mp.
18. or/14-17
19. 13 and 18

Embase (OVID Online - <http://www.ovid.com/>)
1980- 2004 wk 7

This search retrieved 220 references.

1. exp practice guideline/
2. (treatment pathway\$ or treatment path way\$).mp.
3. (care pathway\$ or care path way\$).mp.
4. (clinical path way\$ or clinical pathway\$).mp.
5. (treatment\$ path\$ or treatment\$ route\$).mp.
6. (guide line\$ or guideline\$).mp.
7. or/1-6
8. exp Psoriasis/
9. (psoria\$ or anti psoria\$ or antipsoria\$).mp.
10. or/8-9
11. 7 and 10
12. limit 11 to yr=1990-2004

National Research Register (NRR) (cd-rom)
2003 Issue 4

This search retrieved 7 references.

- #1 PSORIASIS single term (MeSH)
- #2 ((PSORIA* or ANTIPSORIA*) or ANTI-PSORIA*)
- #3 (#1 or #2)
- #4 GUIDELINES explode all trees (MeSH)
- #5 HEALTH-PLANNING-GUIDELINES single term (MeSH)
- #6 ((TREATMENT next PATH*) or (TREATMENTS next PATH*))

- #7 (((CARE next PATH*) or (CLINICAL next PATH*)) or GUIDELINE*
or GUIDE-LINE*)
- #8 ((TREATMENT next ROUTE*) or (TREATMENTS next ROUTE*))
- #9 (((#4 or #5) or #6) or #7) or #8)
- #10 (#3 and #9) (limited to start date = 1990-2004)

**Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library
via the internet - <http://www.update-software.com/clibng/cliblogon.htm>)
2004 Issue 1**

This search retrieved 9 references.

- #1 GUIDELINES explode all trees (MeSH)
- #2 HEALTH PLANNING GUIDELINES single term (MeSH)
- #3 ((treatment next pathway*) or (treatment next path-way*) or (treatments next
pathway*) or (treatments next path-way*))
- #4 ((care next pathway*) or (care next path-way*) or (clinical next pathway*) or
(clinical next path-way*))
- #5 ((treatment next path*) or (treatments next path*) or (treatment next route*) or
(treatments next route*))
- #6 (guideline* or guide-line*)
- #7 (#1 or #2 or #3 or #4 or #5 or #6)
- #8 PSORIASIS single term (MeSH)
- #9 (psoria* or antipsoria* or anti-psoria*)
- #10 (#8 or #9)
- #11 (#7 and #10)
- #12 #11 (1990 to current date)

**NHS Economic Evaluation Database (NHS EED) (CRD administration database)
1990 – 2004/02**

This search retrieved 7 references.

- 1. s treatment\$(w)pathway\$ or treatment\$(w)path(w)way\$
- 2. s care(w)pathway\$ or care(w)path(w)way\$
- 3. s clinical(w)pathway\$ or clinical(w)path(w)way\$
- 4. s treatment\$(w)path\$ or treatment\$(w)route\$ or guideline\$ or guide(w)line\$
- 5. s s1 or s2 or s3 or s4
- 6. s psoria\$ or antipsoria\$ or anti(w)psoria\$
- 7. s s5 and s6
- 8. s 1990:2004/xyr
- 9. s s7 and s8

**Health Economic Evaluation Database (HEED) (cd-rom)
February 2004**

This search retrieved 7 references.

Psoriasis or psoriatic or psoriatics or anti-psoriasis or anti-psoriatic or anti-psoriatics or antipsoriasis or antipsoriatic or antipsoriatics

EconLit (SilverPlatter on the web - <http://arc.uk.ovid.com/>)

1969 – 2004/01

This search retrieved 0 references.

1. PSORIASIS
2. psoria* or antipsoria* or anti-psoria*
3. (psoria* or antipsoria* or anti-psoria*) or (PSORIASIS)
4. pathway* or path-way* or route* or guideline* or guide-line* or path*
5. (pathway* or path-way* or route* or guideline* or guide-line* or path*) and ((psoria* or antipsoria* or anti-psoria*) or (PSORIASIS))

ISI Science and Technology Proceedings (Web of Knowledge)

1990 - 2004 (Februray 15th update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981-2004 (Februray 15th update.)

<http://wos.mimas.ac.uk/>

The search of ISI Science and Technology Proceedings retrieved 7 references.

The search of Social Science Citation Index and Science Citation Index retrieved 244 references.

- #1 TS=((treatment* same pathway*) or (treatment* same path-way*) or (care same pathway*) or (care same path-way*))
- #2 TS=((clinical same pathway*) or (clinical same path-way*) or (treatment* same path*) or (treatment* same route*))
- #3 TS=(guideline*)
- #4 TS=(guide-line*)
- #5 #1 or #2 or #3 or #4
- #6 TS=(psoria* or antipsoria* or anti-psoria*)
- #7 #5 and #6

All databases were searched from 1990 to date.

10.1.2.6 Search 6: Internet searches to locate reports of treatment pathways for psoriasis

Google (<http://www.google.co.uk>)

Searched 8th March 2004

This search retrieved 1600 references.

The simple search interface was used. Due to the high volume of hits, a pragmatic cut-off point was used. The first hundred references were saved from each set. The following keywords were searched in combination:

Psoriasis Psoriatic	Guideline Guidelines Path Paths Pathway Pathways Route Routes
------------------------	--

Organising Medical Networked Information (OMNI) (<http://www.omni.ac.uk>)

Searched 8th March 2004

This search retrieved 2 references.

psoriasis and (path or paths or pathways or pathway or path-way or path-ways or route or routes or guideline or guidelines or guide-line or guide-lines)

OR

Psoriatic and (path or paths or pathways or pathway or path-way or path-ways or route or routes or guideline or guidelines or guide-line or guide-lines)

Copernic (<http://www.copernic.com>)

Searched 8th March 2004

This search retrieved 48 references.

psoriasis and (path or paths or pathways or pathway or path-way or path-ways or route or routes or guideline or guidelines or guide-line or guide-lines)

OR

Psoriatic and (path or paths or pathways or pathway or path-way or path-ways or route or routes or guideline or guidelines or guide-line or guide-lines)

All resources were searched from inception date.

10.1.2.7 Search 7: Internet searches to locate guidelines for psoriasis

The following websites were searched using these keywords:

Psoriasis

Psoriatic

NeLH Guidelines Finder

<http://rms.nelh.nhs.uk/guidelinesfinder/>
Searched 9th March 2004

This search retrieved 2 references.

eGuidelines
<http://www.eguidelines.co.uk/>
Searched 9th March 2004

This search retrieved 25 references.

Health Services/Technology Assessment Text (HSTAT)
<http://hstat.nlm.nih.gov/hq/Hquest/screen/HquestHome/s/52877>
Searched 11th March 2004

This search retrieved 14 references.

National Guidelines Clearinghouse
<http://www.guideline.gov/>
Searched 11th March 2004

This search retrieved 6 references.

Scottish Intercollegiate Guidelines Network (SIGN)
<http://www.sign.ac.uk/index.html>
Searched 11th March 2004

This search retrieved 3 references.

Clinicians Health Channel
<http://www.clinicians.vic.gov.au/guidelines/index.html>
Searched 12th March 2004

This search retrieved 0 references.

Medical Services Advisory Committee (MSAC)
<http://www.health.gov.au/msac/msacapps.htm>
Searched 12th March 2004

This search retrieved 0 references.

New Zealand Health Technology Assessment (NZHTA)
<http://nzhta.chmeds.ac.nz/>
Searched 12th March 2004

This search retrieved 1 reference.

National Health and Medical Research Council (NHMRC)
<http://www.health.gov.au/nhmrc/publications/cphome.htm>
Searched 12th March 2004

This search retrieved 0 references.

New Zealand Guidelines Group (NZGG)
<http://www.nzgg.org.nz/>
Searched 12th March 2004

This search retrieved 0 references.

Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP)
<http://www.surgeons.org/asernip-s/>
Searched 12th March 2004

This search retrieved 0 references.

Centre for Clinical Effectiveness (CCE - Monash)
<http://www.med.monash.edu.au/healthservices/cce/>
Searched 12th March 2004

This search retrieved 1 reference.

All resources were searched from inception date.

10.1.2.8 Search 8: economic models for psoriasis

Medline and In-Process Citations (OVID Online - <http://www.ovid.com/>)
1966 – 2004/02 wk 4

This search retrieved 85 references.

1. exp decision support techniques/ or exp survival analysis/
2. exp models, economic/ or decision trees/
3. markov.mp. or exp models, statistical/
4. (decision analytic model\$ or decision tree\$ or simulation model\$ or decision analysis).ti,ab.
5. (explanatory model\$ or statistical model\$ or monte carlo or decision model\$).ti,ab.
6. (survival analy\$ or mathematical model\$).ti,ab.
7. or/1-6
8. psoriasis/
9. (psoria\$ or antipsoria\$ or anti-psoria\$).mp.
10. or/8-9
11. 7 and 10

12. animals/
13. human/
14. 12 not (12 and 13)
15. 11 not 14
16. 15 not (letter or editorial or comment).pt.

Embase (OVID Online - <http://www.ovid.com/>)
1980- 2004 wk 9

This search retrieved 61 references.

1. decision support system/
2. medical decision making/
3. decision theory/
4. survival/
5. statistical model/
6. probability/
7. monte carlo method/
8. (decision support technique\$ or economic model\$ or decision tree\$).tw.
9. (decision analytic model\$ or simulation model\$ or decision analysis).tw.
10. (explanatory model\$ or markov or statistical model\$ or monte carlo or decision model\$).tw.
11. (survival analy\$ or mathematical model\$).tw.
12. or/1-11
13. exp psoriasis/
14. (psoria\$ or antipsoria\$ or anti-psoria\$).mp.
15. 13 or 14
16. 12 and 15
17. 16 not (editorial or letter or note).pt.
18. exp ANIMAL/ or Animal Experiment/ or Nonhuman/ or (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
19. Human/ or Human Experiment/
20. 18 not (18 and 19)
21. 17 not 20

National Research Register (NRR) (cd-rom)
2003 Issue 4

This search retrieved 1 reference.

- #1 PSORIASIS single term (MeSH)
- #2 ((PSORIA* or ANTIPSORIA*) or ANTI-PSORIA*)
- #3 (#1 or #2)
- #4 DECISION-SUPPORT-TECHNIQUES explode all trees (MeSH)
- #5 SURVIVAL-ANALYSIS explode all trees (MeSH)
- #6 MODELS-ECONOMIC explode all trees (MeSH)
- #7 DECISION-TREES single term (MeSH)
- #8 MODELS-STATISTICAL explode all trees (MeSH)

- #9 MARKOV
- #10 (((((DECISION next ANALYTIC) next MODEL*) or (SIMULATION next MODEL*)) or (DECISION next ANALYSIS)) or (DECISION next TREE*))
- #11 (((EXPLANATORY next MODEL*) or (STATISTICAL next MODEL*)) or (MONTE next CARLO)) or (DECISION next MODEL*)
- #12 ((SURVIVAL next ANALY*) or (MATHEMATICAL next MODEL*))
- #13 (((((((#4 or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12)
- #14 (#3 and #13)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the internet - <http://www.update-software.com/clibng/cliblogon.htm>)

2004 Issue 1

This search retrieved 9 references.

- #1 DECISION SUPPORT TECHNIQUES explode all trees (MeSH)
- #2 SURVIVAL ANALYSIS explode all trees (MeSH)
- #3 MODELS ECONOMIC explode all trees (MeSH)
- #4 DECISION TREES single term (MeSH)
- #5 MODELS STATISTICAL explode all trees (MeSH)
- #6 (markov:ti or markov:ab)
- #7 ((decision next analytic next model*) or (simulation next model*) or (decision next analysis) or (decision next tree*))
- #8 ((explanatory next model*) or (statistical next model*) or (monte next carlo) or (decision next model*))
- #9 ((survival next analy*) or (mathematical next model*))
- #10 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
- #11 PSORIASIS single term (MeSH)
- #12 (psoria* or antipsoria* or anti-psoria*)
- #13 (#11 or #12)
- #14 (#10 and #13)

NHS Economic Evaluation Database (NHS EED) (CRD administration database) 1990 – 2004/03

This search retrieved 4 references.

1. s decision(w)analytic(w)model\$ or simulation(w)model\$ or decision(w)analysis or decision(w)tree\$
2. s explanatory(w)model\$ or statistical(w)model\$ or monte(w)carlo or decision(w)model\$
3. s survival(w)analy\$ or mathematical(w)model\$ or markov
4. s s1 or s2 or s3
5. s psoria\$ or antipsoria\$ or anti(w)psoria\$
6. s s4 and s5

Health Economic Evaluation Database (HEED) (cd-rom) February 2004

This search retrieved 0 references.

Psoriasis or psoriatic or psoriatics or anti-psoriasis or anti-psoriatic or anti-psoriatics or antipsoriasis or antipsoriatic or antipsoriatics

EconLit (SilverPlatter on the web - <http://arc.uk.ovid.com/>)
1969 – 2004/02

This search retrieved 0 references.

1. (psoria* or antipsoria* or anti-psoria*)
2. ((decision analytic model*) or (simulation model*) or (decision analysis) or (decision tree*))or((explanatory model*) or (statistical model*) or (monte carlo) or (decision model*))or((survival analy*) or (mathematical model*) or markov)
3. (((decision analytic model*) or (simulation model*) or (decision analysis) or (decision tree*))or((explanatory model*) or (statistical model*) or (monte carlo) or (decision model*))or((survival analy*) or (mathematical model*) or markov)) and ((psoria* or antipsoria* or anti-psoria*))

ISI Science and Technology Proceedings (Web of Knowledge)

1990 - 2004 (February 28th update)

The same strategy was also used to search **Social Science Citation Index** and **Science Citation Index (Web of Science)** 1981-2004 (February 29th update.)

<http://wos.mimas.ac.uk/>

The search of ISI Science and Technology Proceedings retrieved 5 references.

The search of Social Science Citation Index and Science Citation Index retrieved 21 references.

- #1 TS=((decision same analytic same model*) or (simulation same model*) or (decision same analysis) or (decision same tree*))
- #2 TS=((explanatory same model*) or (statistical same model*) or (monte same carlo) or (decision same model*))
- #3 TS=((survival same analy*) or (mathematical same model*) or markov)
- #4 #1 or #2 or #3
- #5 TS=((psoria* or antipsoria* or anti-psoria*))
- #6 #4 and #5
- #7 TS=((animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*))
- #8 #6 not #7

All databases were searched from inception date.

10.2 Quality assessment tool

All of the criteria listed below should be scored with one of the following responses:

Yes (Y);
No (N);
Partial (P);
Not stated (NS);
Not applicable (NA);
Unclear (U).

Study:

1	Were the eligibility criteria for the study adequately specified? <i>Adequate: study population clearly defined</i>	
2	Was an a priori power calculation for adequate sample size performed?	
3	Was the sample size adequate for the analysis of the primary outcome variable?	
4	Was the number of participants who were randomised stated?	
5	Was the method used to assign participants to treatment groups truly random? <i>Adequate: computer generated random numbers, random number tables</i> <i>Inadequate: alternation, case record numbers, birth dates, days of the week</i>	
6	Was the trial described as double-blind?	
7	Was allocation of treatment concealed? <i>Adequate: centralised or pharmacy controlled assignment, serially numbered containers, serially numbered opaque envelopes, on-site computer-based systems where assignment is unreadable until after allocation, other robust measures to prevent revelation of a participant's treatment</i> <i>Inadequate: alternation, case record numbers, days of the week, open random number lists</i>	
8	Were the individuals administering the treatment blinded to the treatment allocation?	
9	Were the outcome assessors blinded to the treatment allocation?	
10	Were the participants blinded to the treatment allocation?	
11	Was the blinding procedure successful?	
12	Were adequate details of the treatment groups at baseline presented? <i>Adequate: information on age, nature and severity of psoriasis, previous treatments</i>	
13	Were the treatment groups comparable at baseline? <i>Answer 'Yes' if no important differences or if appropriate adjustments had been made for any differences in the baseline characteristics of the treatment groups</i>	
14	Were the treatment groups similar in terms of co-interventions that could influence the results?	
15	Was participant compliance with the assigned treatment adequate?	
16	Were all participants who were randomised accounted for at the end of the trial?	
17	Was a valid ITT analysis performed? <i>Adequate: all participants randomised included in efficacy analysis, all randomised participants who took at least one dose of trial medication included in efficacy analysis</i>	
18	Were at least 80% of those randomised included in the follow-up assessment? <i>Answer 'Yes' if at least 80% of those randomised provided complete data with regard to the primary outcome(s)</i>	

Quality rating =

Excellent: The answer is 'Yes' to all of the criteria.

Good: The answer is 'Yes' to all of the following criteria: 1, 3, 4, 6, 10, 12-14, 16-18.

Satisfactory: The answer is 'Yes' to all of the following criteria: 1, 3, 6, 13, 17.

Poor: The answer is NOT 'Yes' to one or more of the criteria listed for 'Satisfactory'.

10.3 Excluded studies

Cameron H, R. S. , Dawe S, Yule I, Man SH, Ibbotson I, Ferguson AD. A comparison of 2x and 3x weekly narrow-band (TL-OI) UVB phototherapy in the treatment of chronic plaque psoriasis Abstract. *Br J Dermatol* 2001;144:655.

Cameron H, Dawe RS, Yule S, Murphy J, Ibbotson SH, Ferguson J. A randomized, observer-blinded trial of twice vs three times weekly narrowband ultraviolet B phototherapy for chronic plaque psoriasis. *Br J Dermatol* 2002;147:973-8.

Cooper EJ, Herd RM, Priestley GC, Hunter JA. A comparison of bathwater and oral delivery of 8-methoxypsoralen in PUVA therapy for plaque psoriasis. *Clin Exp Dermatol* 2000;25:111-4.

Dawe RS, Cameron H, Yule S, Man I, Ibbotson SH, Ferguson J. UV-B phototherapy clears psoriasis through local effects. *Arch Dermatol* 2002;138:1071-1076.

Griffiths CEM, George SA, Harris PV, Goodfield M, Kemmett D, Lewis H, et al. Intermittent short courses of cyclosporin for psoriasis unresponsive to topical therapy: a one year multicentre, randomised study Abstract. *Br J Dermatol* 1999;141:73.

Kirkup MES, R. A. , Kavanagh GM, Downs AMR, Sansom JE, DeBerker DARD, M. G. S. , Kennedy CTC, et al. Twice daily versus once daily inpatient dithranol for psoriasis. Abstract. *Br J Dermatol* 1999;141:72.

Kirkup ME, Sabroe RA, Kavanagh GM, Downs AM, Sansom JE, de Berker DA, et al. Twice-daily vs once-daily inpatient dithranol for psoriasis. *Clin Exp Dermatol* 2002;27:695-9.

McBride SR, Walker P, Reynolds NJ. Optimizing the frequency of outpatient short-contact dithranol treatment used in combination with broadband ultraviolet B for psoriasis: A randomized, within-patient controlled trial. *Br J Dermatol* 2003;149:1259-1265.

Ohtsuki M, Nakagawa H, Sugai J, Ozawa A, Ohkido M, Nakayama J, et al. Long-term continuous versus intermittent cyclosporin: therapy for psoriasis. *J Dermatol* 2003;30:290-8.

Thaci D, Brautigam M, Kaufmann R, Weidinger G, Paul C, Christophers E. Body-weight-independent dosing of cyclosporine micro-emulsion and three times weekly maintenance regimen in severe psoriasis A randomised study. *Dermatology* 2002;205:383-8.

10.4 Data extraction tables: intervention efficacy

10.4.1 Data extraction tables: intervention efficacy – etanercept

Study details and design	Participant details	Intervention/outcome/an alyses details	Results
<p>Elewski, 2003,⁷⁰ USA, Canada and Europe</p> <p>Type of publication Conference poster</p> <p>Other publications/ reports Kim, 2003,¹⁴⁸ Industry trial report Kim, 2003,¹⁴⁹ Industry trial report Gordon,¹⁵⁰ Conference poster Gottlieb,¹⁵¹ Conference poster Industry submission (study no. 20021642), 2004,⁶⁷</p> <p>Funding Immunex Corp. (wholly-owned subsidiary of Amgen Inc.); Wyeth Pharmaceuticals Inc.</p> <p>Study design Double-blind RCT, parallel with open follow-up Monotherapy</p> <p>The trial was conducted in two stages: Stage 1 RCT; Stage 2 open follow-up</p> <p>Setting Outpatient</p> <p>Duration of follow-up Stage 1: 12wks Stage 2: 36 wks</p> <p>Frequency of follow-up</p>	<p>Inclusion/exclusion criteria Active clinically stable plaque psoriasis involving $\geq 10\%$ BSA, minimum PASI score of 10, previously treated with at least one systemic therapy or phototherapy or to be a candidate for such therapy. Aged > 18 yrs. Those previously treated with etanercept or with antibodies to TNF or who had received investigational drugs, biologicals, systemic psoriasis therapy, systemic corticosteroids or PUVA within previous 4 wks or had received UVB topical steroids, topical Vitamin A or D analogues or anthralin within 2 wks were excluded.</p> <p>Number randomised and treated 583</p> <p>Age <i>Mean age (SD)</i> Etanercept 25 mg: 45.4 (CiC removed) yrs; Etanercept 50 mg: 45.2 (CiC removed) yrs; Placebo: 44.8 (CiC removed) yrs; Total 45.2 (CiC removed) yrs</p> <p>Gender Etanercept 25 mg: male 65%; (CiC removed) Etanercept 50 mg: male 67%; (CiC removed) Placebo: male 64%; (124/193) Total: male 66% (382/583)</p> <p>Psoriasis history</p>	<p>Stage 1 Intervention Etanercept Dose regimen: 25 mg SC twice a wk; Length of treatment: 12 wks No. randomised: 196 No. completed: CiC removed</p> <p>Intervention Etanercept Dose regimen: 50mg SC twice a wk Length of treatment: 12 wks No. randomised: 194 No. completed: CiC Removed</p> <p>Comparator Placebo Dose regimen: equivalent Length of treatment: 12 wks No. randomised: 193 No. completed: CiC removed</p> <p>Stage 2 Etanercept Dose regimen: 25 mg SC twice a wk Length of treatment: 36 wks No.: 557</p> <p>Primary Outcome PASI 75 at wk 12</p>	<p>Stage 1 PASI 75 Etanercept 25 mg 12 wks: 67/196 (34%); Etanercept 50 mg 12 wks: 96/194 (49%); Placebo 12 wks: 6/193 (3%); $p < 0.0001$ for placebo vs. both etanercept doses; $p = 0.002$ for etanercept 25mg vs 50 mg</p> <p>PASI 50 (CiC removed)</p> <p>PASI 90 (CiC removed)</p> <p>Clear or Almost Clear (CiC removed)</p> <p>PASI score (CiC removed)</p> <p>Mean PASI score (CiC removed)</p> <p>Stage 2 Note: all patients were on etanercept 25 mg twice a week. The stated group denotes the treatment participants were on in stage 1 (from week 0 to week 12)</p> <p>PASI 75 Etanercept 25 mg 24 wks: (CiC removed) Etanercept 50 mg 24 wks: (CiC removed); Placebo 24 wks: (CiC removed)</p> <p>PASI 50 Etanercept 25 mg 24 wks: (CiC removed); 36 wks: (CiC removed) Etanercept 50 mg 24 wks: (CiC removed); 36 wks: (CiC removed) Placebo 24 wks: (CiC removed); 36 wks: (CiC removed)</p> <p>PASI 90 Etanercept 25 mg 24 wks: (CiC removed); 36 wks: (CiC removed) Etanercept 50 mg 24 wks: (CiC removed); 36 wks: (CiC removed)</p>

<p>Stage 1: 0, 2, 4, 8 and 12 wks; Stage 2: 18, 20, 24, (CiC removed) Removed) 36 (CiC removed) wks Extracted by: Nerys Checked by: AK</p>	<p><i>Duration of psoriasis (mean (SD))</i> Etanercept 25 mg: 22.2 yrs (CiC removed); Etanercept 50 mg: 19.9 yrs (CiC removed); Placebo: 19.4 yrs (CiC removed) Prior systemic therapy Patients were permitted to have received previous systemic therapy or phototherapy; CiC removed</p> <p><i>PASI score (mean)</i> Etanercept 25 mg: 19.1 (CiC removed) Etanercept 50 mg: 19.5 (CiC removed) Placebo: 18.6 (CiC removed)</p> <p>Patient Global Score Etanercept 25 mg: 68 Etanercept 50 mg: 70 Placebo: 71</p> <p>BSA involved Etanercept 25 mg: 28.6% Etanercept 50 mg: 28.8% Placebo: 26.4%</p> <p><i>Psoriatic Arthritis</i> % (SD): Etanercept 25 mg: CiC removed Etanercept 50 mg: CiC removed Placebo: CiC removed</p> <p>DLQI Mean (SD): Etanercept 25 mg: CiC removed Etanercept 50 mg: CiC removed Placebo: CiC removed</p> <p>Concurrent therapies CiC removed.</p> <p>Comments (CiC removed); 583 treated</p>	<p>Sample size calculation Based on PASI 75 at wk 12 assuming % on etanercept and placebo would be 30% and 5% respectively, 200 patients per group gives >99% power to detect this difference at the 5% level (2-sided Fisher's exact test).</p> <p>Statistical analyses CiC removed</p> <p>ITT analysis CiC removed</p> <p>Comments</p>	<p>Placebo: 24 wks (CiC removed); 36 wks; (CiC removed)</p> <p>Mean (SE) PASI score Etanercept 25 mg (n=177) 24 wks: 5.8 (CiC removed); improvement from wk 12 to 24: 2.0 (CiC removed) Etanercept 50 mg (n=179) 24 wks: 5.6 (CiC removed); improvement from wk12 to 24: -0.1 (CiC removed) Placebo (n=166) 12 wks: 18.5; 24 wks: 7.4 (CiC removed); improvement from wk 12 to 24: 11.1 (CiC removed)</p> <p>Clear or Almost Clear Etanercept 25 mg 24 wks: (CiC removed); 36 wks: (CiC removed) Etanercept 50 mg 24 wks: (CiC removed); 36 wks: (CiC removed) Placebo 24 wks: (CiC removed); 36 wks: (CiC removed)</p> <p>DLQI (CiC removed)</p> <p>Patient assessment of psoriasis at Wks 24 and 36 CiC removed</p> <p>Adverse events Stage 1 Adverse events occurring in >3% of patients in any treatment group Placebo (n=193) Etanercept 25mg (n=196) Etanercept 50 mg (n=194) (CiC removed)</p> <p>Exposure-adjusted rate/100 patient yrs</p> <p>Non-infectious adverse events CiC Removed Injection Site reaction 11 (6%) 26 (13%) 35 (18%) CiC Removed</p> <p>Infectious adverse events including any serious infections Placebo (n=193) Etanercept 25mg (n=196) Etanercept 50 mg (n=194) 55 (29%) 58 (30%) 56 (29%)</p> <p>Any infection CiC removed.</p> <p>Other non-infectious serious adverse events (no.) (CiC removed).</p> <p>Deaths (no.) None</p>
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			<p>Withdrawals due to adverse events Etanercept 25 mg: 3 withdrawals (1.5%); CiC removed Etanercept 50 mg: 2 withdrawals (1%); CiC Removed CiC Removed</p> <p>Positive test for anti-etanercept antibody Etanercept 25 mg CiC removed; etanercept 50 mg CiC removed; placebo CiC removed</p> <p>Other important adverse event results None</p> <p><i>Stage 2</i> *All patients on etanercept 25 mg twice /wk Results expressed as exposure-adjusted rate/100 patient yrs CiC removed</p> <p>Non-infectious adverse events CiC removed</p> <p>Infectious adverse events including any serious infections CiC removed</p> <p>Serious infections (no.): CiC removed.</p> <p>Cancer CiC removed.</p> <p>Other non-infectious serious adverse events (no.) CiC removed.</p> <p>Deaths (no.) CiC removed</p> <p>Withdrawals due to adverse events CiC removed</p> <p>Positive test for anti-etanercept antibody CiC removed</p> <p>Other important adverse event results CiC removed</p>
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*York Technology Assessment Group
Efalizumab And Eianercept For The Treatment Of Psoriasis*

			Comments <i>(CiC removed)</i>

Study details and design	Participant details	Intervention/outcome/analyses details	Results
<p>Gottlieb, 2003,⁷¹ USA</p> <p>Type of publication Full publication</p> <p>Other publications/ reports Gaspari, 2003,¹⁵² Industry trial report Gaspari, 2002,¹⁵³ Abstract Gottlieb, 2002,¹⁵⁴ Abstract Gordon,¹⁵⁰ Conference poster Gottlieb,¹⁵¹ Conference poster Industry submission (study no. 20021632), 2004,⁶⁷</p> <p>Funding Immunex Corp. (a subsidiary of Amgen Inc.)</p> <p>Study design Double-blind RCT, parallel Monotherapy. The study was in 2 stages: Stage 1: RCT Stage 2: Follow-up after discontinuation of study treatments</p> <p>Setting Outpatient</p> <p>Duration of follow-up Stage 1: 24 wks Stage 2: CiC removed</p> <p>Frequency of follow-up Stage 1: Baseline, 2, 4, 8, 12, 16, 20, and 24 wks Stage 2: CiC removed</p>	<p>Inclusion/exclusion criteria Patients aged at least 18 years, with active stable plaque psoriasis involving 10% or more of the body surface area. Patients were excluded if they had guttate, erythrodermic, or pustular psoriasis; other skin conditions; or other significant medical conditions that might interfere with evaluations of the effect of study medications on psoriasis. Patients were to have had at least one previous systemic psoriasis therapy or phototherapy. PUVA and systemic psoriasis therapy were not allowed within 4 weeks of the trial; and UVB, topical corticosteroids, vitamin A or D analogues, or anthralin were not allowed within 2 weeks of baseline measurements.</p> <p>Number randomised and treated 112</p> <p>Age <i>Mean (range/SD)</i> Etanercept: 48.2 yrs (25-72 yrs/(CiC removed)) Placebo: 46.5 yrs (18-77 yrs/(CiC removed))</p> <p>Gender Etanercept: Male 58% (33/57) Placebo: Male 67% (37/55)</p> <p>Psoriasis history <i>Duration of psoriasis</i> Mean (SE/SD) Etanercept: Mean 23 yrs (1.6/12.1) Placebo: Mean 20 yrs (1.7/12.2)</p> <p>Prior systemic therapy Yes</p> <p>Baseline PASI <i>Mean (SE/SD) score at baseline:</i> Etanercept: 17.8 (1.1/8.5)</p>	<p>Intervention Etanercept Dose regimen: 25mg SC, twice a wk Length of treatment: 24 wks No. randomised: 57 No. completed: 12 wks: 53 (93%); 24 wks: 48 (84%)</p> <p>Comparator Placebo Dose regimen: Equivalent Length of treatment: 24 wks No. randomised: 55 No. completed: 12 wks: 40 (73%); 24 wks: 12 (22%)</p> <p>Stage 2: Etanercept n=17 Placebo n=3</p> <p>Primary Outcome PASI 75 at 12 wks</p> <p>Sample size calculation Assuming PASI 75 response rates of 10% in the placebo group and 35% in the treatment group, the sample size of 50 patient per group afforded over 80% power to detect a significant difference in the primary endpoint between treatments using a 2-sided $\alpha=0.05$ (Fisher exact test)</p> <p>Statistical analyses χ^2 test was used to analyse PASI response rate. For binary endpoints, the χ^2 test was used to compare the two treatment groups with respect to the proportion who met criteria for psoriasis efficacy response. The Fisher exact test was substituted if more appropriate. Non-parametric tests</p>	<p>PASI 75 Etanercept: 12 wks: 17/57 (30%); Placebo: 12 wks: 1/55 (2%); p<0.001; treatment difference: 28% (95% CI: 16%, 40%) Etanercept: 24 wks: 32/57 (56%); Placebo: 24 wks: 3/55 (5%); p<0.001; treatment difference 51% 95% CI (36%, 65%)</p> <p>PASI 50 Etanercept: 12 wks: 40/57 (70%); Placebo: 12 wks: 6/55 (11%); p<0.001 Etanercept: 24 wks: 44/57 (77%); Placebo: 24 wks: 7/55 (13%); p<0.001</p> <p>PASI 90 Etanercept: 12 wks: 6/57 (11%); Placebo: 12 wks: 0/55 (0%); p=0.03 Etanercept: 24 wks: 12/57 (21%); Placebo: 24 wks: 0/55 (0%); p<0.001</p> <p>Mean PASI score Etanercept: 12 wks: (CiC removed); Placebo: 12 wks: (CiC removed) Etanercept: 24 wks: (CiC removed); Placebo: 24 wks: (CiC removed)</p> <p>PASI Mean (SE) improvement from baseline Etanercept: 12wks:(CiC removed) ; Placebo: 12 wks: (CiC removed) Etanercept: 24wks: 67% (4%); Placebo: 24 wks: 1% (7%); p<0.001</p> <p>Median improvement from baseline CiC Removed</p> <p>Physician GA Mean (SE) improvement from baseline Etanercept: 24wks: 46% (4%); Placebo: 24 wks: -2 (4%); p<0.001</p> <p>Clear or minimal Number (%) clear or minimal for assessment of psoriasis Etanercept: 12wks: 26 (46%); Placebo: 12 wks: 1 (2%); p<0.0001 Etanercept: 24wks: 30 (53%); CiC removed</p> <p>Patient GA Mean (SE) improvement from baseline Etanercept: 24wks: 62% (5%); Placebo: 24wks: 7% (5%); p<0.001</p> <p>DLQI Mean (SE) improvement from 4 wks</p>

<p>Extracted by: AK Checked by: NW</p>	<p>Placebo: 19.5 (1.3/9.4) BSA affected Mean (SE/SD) %: Etanercept: 30 (2.3/17.7) Placebo: 34 (3.0/21.9) DLQI CiC removed Psoriatic arthritis Number of patients: Etanercept: 16 (28%) Placebo: 19 (35%) Physician GA Mean (SE) score: Etanercept: 2.8 (0.1) Placebo: 2.9 (0.1) Patient GA Mean (SE) score: Etanercept: 4.1 (0.1) Placebo: 4.2 (0.1) Concurrent therapies Tar compounds and steroid-free topical emollients were allowed during the study. Some topical preparations (such as lower-potency corticosteroids and tar-based shampoo) were allowed to continue at stable doses during therapy on the scalp, axilla, and groin. Comments 118 patients were randomised; 112 received treatment</p>	<p>were used for other endpoints. ITT analysis Yes. All patients who received at least one study dose were evaluated for safety and efficacy. <u>(CiC removed)</u> If a patient discontinued treatment before the end of the study, the last observation was carried forward. <u>(CiC removed)</u> Comments</p>	<p>Etanercept: 12wks:(CiC removed); Placebo: 24wks: (CiC removed) Etanercept: 24wks: 64.3% (5.0%); Placebo: 24wks: 7.2% (8.0%); p<0.001 BSA affected Mean (SE) improvement from baseline Etanercept: 24wks: 63% (5%); Placebo: 24wks: -12% (7%); p<0.001 Target Lesions CiC removed Adverse events N (%) adverse events occurring in ≥ 5% of groups combined Etanercept (n=57) Placebo (n=55) Non-infectious adverse events Any non-infectious (CiC removed) headache 9 (16%) 7 (13%) bruise at injection site 6 (11%) 5 (9%) sinusitis 8 (14%) 4 (4%) pain 4 (7%) 4 (7%) peripheral oedema 1 (2%) 5 (9%) hypertension 4 (7%) 2 (4%) accidental injury 4 (7%) 2 (4%) injection site reaction 5 (9%) 0 (0%) CiC Removed CiC removed CiC removed CiC removed CiC removed CiC removed Infectious adverse events including any serious infections any infection CiC removed upper respiratory tract infection 20 (35%) 11 (20%) bronchitis CiC removed cellulitis CiC removed herpes simplex CiC removed Serious infections (no.): Etanercept: appendicitis: 1/57 Placebo: pharyngitis: 1/55 Cancer</p>
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*York Technology Assessment Group
Efalizumab And Etanercept For The Treatment Of Psoriasis*

		<p>CiC removed</p> <p>Other non-infectious serious adverse events (no.) Etanercept: motor vehicle crash: 1/57 Placebo: stroke: 1/55; pustular psoriasis: 1/55</p> <p>Deaths (no.) CiC removed</p> <p>Withdrawals due to adverse events Etanercept: 2/57 Placebo: 6/55</p> <p>Positive test for anti-etanercept antibody No patients developed antibodies to etanercept: all samples negative for anti-etanercept antibodies.</p> <p>Other important adverse event results Number of patients reporting adverse events was similar between the two groups (CiC removed)</p> <p>Comments</p>
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Study details and design	Participant details	Intervention/outcome/analyses details	Results
<p>Leonardi, 2004,⁶⁹ USA</p> <p>Type of publication Full publication</p> <p>Other publications/reports Duggan, 2003,¹⁴⁵ Industry trial report Duggan, 2003,¹⁵⁵ Krueger,¹⁵⁶ Conference poster Gottlieb,¹⁵⁷ Conference poster Gordon,¹⁵⁰ Conference poster Gottlieb,¹⁵¹ Conference poster Industry submission (study no. 20021639), 2004,⁶⁷</p> <p>Funding Immunex (wholly-owned subsidiary of Amgen)</p> <p>Study design Stage 1: Double-blind RCT, parallel Monotherapy Stage 2: Double-blind follow-up Stage 3: Discontinuation of treatment (for responders, i.e., those who achieved PASI 50) or open-label etanercept (for incomplete responders, i.e., those who did not achieve PASI 50) Stage 4: Retreatment</p>	<p>Inclusion/exclusion criteria Aged at least 18 yrs, with active clinically stable plaque psoriasis involving $\geq 10\%$ BSA and a PASI score of ≥ 10; previously received systemic or phototherapy for psoriasis or had been a candidate for such therapy. Patients with other forms of psoriasis or those who had previously received etanercept were excluded. Patients were excluded if they had received anti-CDA antibodies or interleukin-2 in the previous 6 months, other biologic or other investigational therapy or PUVA, systemic corticosteroids or systemic psoriasis therapy in previous 4 weeks, or UVB, topical steroids, Vitamin A or D analogues or anthralin in previous 2 weeks or antibiotics in previous week.</p> <p>Number randomised and treated 652</p> <p>Age <i>Mean age (SE/SD)</i> Etanercept 25 mg once a wk: 44.4 (0.9/12.0) yrs; Etanercept 25 mg twice a wk: 45.4 (1.0/13.1) yrs; Etanercept 50 mg twice a wk: 44.8 (0.8/10.8) yrs; Placebo: 45.6 (1.0/12.9)</p>	<p>Stage 1 Intervention Etanercept Dose regimen: 25 mg SC once a wk; Length of treatment: 12 wks No. randomised: 160 No. completed: <u>CiC removed</u> (94% of total study population)</p> <p>Intervention Etanercept Dose regimen: 25 mg SC twice a wk Length of treatment: 12 wks No. randomised: 162 No. completed: <u>CiC removed</u> (94% of total study population)</p> <p>Intervention Etanercept Dose regimen: 50 mg SC twice a wk Length of treatment: 12 wks No. randomised: 164 No. completed: <u>CiC removed</u> (94% of total study population)</p> <p>Comparator placebo Dose regimen: equivalent Length of treatment: 12 wks No. randomised: 166 No. completed: <u>CiC removed</u> (94% of total study population)</p> <p>Stage 2 Patients continued on same doses of etanercept. Those on placebo in Stage 1 switched to etanercept 25 mg twice a wk.</p>	<p>Stage 1 PASI 75 Etanercept 25 mg once a wk 12 wks: 23/160 (14%); Etanercept 25 mg twice a wk 12 wks: 55/162 (34%); Etanercept 50 mg twice a wk 12 wks: 81/164 (49%); Placebo 12 wks: 6/166 (4%); p<0.001 for placebo vs. all etanercept doses</p> <p>Etanercept 25 mg once a wk 24 wks: 40/160 (25%); Etanercept 25 mg twice a wk 24 wks: 71/162 (44%); Etanercept 50 mg twice a wk 24 wks: 97/164 (59%). <u>CiC removed</u></p> <p>PASI 50 Etanercept 25 mg once a wk 12 wks: 65/160 (41%); Etanercept 25 mg twice a wk 12 wks: 94/162 (58%); Etanercept 50 mg twice a wk 12 wks: 121/164 (74%); Placebo 12 wks: 24/166 (14%); p<0.0001 for placebo vs. all etanercept doses</p> <p>Etanercept 25 mg once a wk 24 wks: 92/160 (58%); Etanercept 25 mg twice a wk 24 wks: 113/162 (70%); Etanercept 50 mg twice a wk 24 wks: 127/164 (77%). <u>CiC removed</u></p> <p>PASI 90 Etanercept 25 mg once a wk 12 wks: 5/160 (3%); Etanercept 25 mg twice a wk 12 wks: 19/162 (12%); Etanercept 50 mg twice a wk 12 wks: 36/164 (22%); Placebo 12 wks: 1/166 (1%); p<0.0001 for placebo vs. two higher etanercept doses</p> <p>Etanercept 25 mg once a wk 24 wks: 9/160 (6%); Etanercept 25 mg twice a wk 24 wks: 32/162 (20%); Etanercept 50 mg twice a wk 24 wks: 49/164 (30%). <u>CiC removed</u></p> <p>Clear or almost clear Etanercept 25 mg once a wk 12 wks: 37/160 (23%); Etanercept 25 mg twice a wk 12 wks: 55/162 (34%); Etanercept 50 mg twice a wk 12 wks: 81/164 (49%); Placebo 12 wks: 8/166 (5%); p<0.0001 for placebo vs. all etanercept doses.</p> <p>Etanercept 25 mg once a wk 24 wks: 41/160 (26%); Etanercept 25 mg twice a wk 24 wks: 63/162 (39%); Etanercept 50 mg twice a wk 24 wks: 90/164 (55%). <u>CiC removed</u></p> <p>After 12 wks re-treatment (n=297): Etanercept 25 mg once a wk 12 wks: (CiC removed); Etanercept 25 mg twice a wk 12 wks: (CiC removed); Etanercept 50 mg twice a wk 12 wks: (CiC removed); Etanercept 25 mg twice a wk (Ex-Placebo) 12 wks: (CiC removed)</p> <p>PASI score mean (SE) % improvement from baseline Etanercept 25 mg once a wk 12 wks: 40.9 (2.4); Etanercept 25 mg twice a wk 12 wks: 52.6 (2.7); Etanercept 50 mg twice a wk 12 wks: 64.2 (2.4); Placebo 12 wks: 14.0 (2.6); p<0.0001 for placebo vs. all etanercept doses</p> <p>Etanercept 25 mg once a wk 24 wks: 50.3 (2.5); Etanercept 25 mg twice a wk 24 wks: 62.1 (2.5); Etanercept 50 mg twice a wk 24 wks: 71.1 (2.2). <u>CiC removed</u></p>

<p>Setting Outpatients</p> <p>Duration of follow-up Total: 72 wks Stage 1: 12 wks Stage 2: 12 wks Stage 3: Variable duration with follow-up until relapse (for responders); 48 wks (for incomplete responders) Stage 4: 24 wks or until study conclusion</p> <p>Frequency of follow-up Stage 1: 0, 2, 4, 8, 12 wks Stage 2: 16, 20, 24 wks Stages 3 and 4: 36, 48, 60 wks</p> <p>Extracted by: NFW Checked by: AK</p>	<p>Gender Etanercept 25 mg once a wk: male 74% (119/160) Etanercept 25 mg twice a wk: male 67% (109/162) Etanercept 50 mg twice a wk: male 65% (106/164) Placebo: male 63% (104/166) Total: male 67% (438/652)</p> <p>Psoriasis history Duration of psoriasis (mean (SE/SD)) Etanercept 25 mg once a wk: 19.3 (0.9/11.0) yrs; Etanercept 25 mg twice a wk: 18.5 (0.9/11.2) yrs; Etanercept 50 mg twice a wk: 18.6 (0.9/11.2) yrs; Placebo: 18.4 (0.9/11.6) yrs; Total 18.7 yrs</p> <p>Prior systemic therapy (n (%)) CIC removed Total 76%</p> <p>BSA (mean (SE/SD)) Etanercept 25 mg once a wk: 27.7% (1.5/18.8); Etanercept 25 mg twice a wk: 28.5%(1.6/20.2) yrs; Etanercept 50 mg twice a wk: 29.9% (1.6/19.9) yrs; Placebo: 28.8% (1.4/18.5); Total 28.7% (not stated)</p> <p>PASI score (mean (SE/SD)) Etanercept 25 mg once a wk: 718.2 (0.7/8.6); Etanercept 25 mg twice a wk: 18.5 (0.7/8.6); Etanercept 50 mg twice a wk: 18.4 (0.7/8.4); Placebo: 18.3 (0.6/7.5); Total 18.4 (not stated)</p>	<p>Nos. completed 24 wks CIC removed Total: 573 (88%)</p> <p>Stage 3 157 patients who had not achieved a PASI 50 by 24 wks: open label etanercept 25mg SC twice a wk</p> <p>409 patients who achieved a PASI 50 by 24 wks had etanercept stopped (i.e. no treatment).</p> <p>Stage 4 Of those responders who underwent treatment withdrawal in Stage 3, those whose disease relapsed (i.e. lost >50% of their initial treatment response) were re-treated with their original blinded dose of etanercept (n=297)</p> <p>CIC removed</p> <p>Primary Outcome Stage 1 and Stage 2: PASI 75 at wk 12 of first phase. Stage 3: duration of treatment response during withdrawal. Stage 4: difference in PASI 75 at wk 12 of re-treatment and PASI 75 at wk 12 of Stage 1</p> <p>Sample size calculation Sample size (CIC removed) was calculated to give 99% power to detect a difference of 25% between etanercept and placebo (CIC removed)</p>	<p>PASI Score Mean (SE) CIC removed</p> <p>PASI score Median (range) Etanercept 25 mg once a wk 12 wks: 9.6 (0.7 – 70.8); Etanercept 25 mg twice a wk 12 wks: 6.5 (0.0-51.9); Etanercept 50 mg twice a wk 12 wks: 4.2 (0.0-48.0); Placebo 12 wks: 14.4 (1.6- 49.1).</p> <p>Etanercept 25 mg once a wk 24wks: 7.0 (0.0-54.0); Etanercept 25 mg twice a wk 24 wks: 4.8 (0.0-29.4); Etanercept 50 mg twice a wk 24 wks: 3.0 (0.0-48.0). CIC removed</p> <p>% change from baseline in total DLQI score(mean (SE)) Etanercept 25 mg once a wk 12 wks: 47.2 (2.9); Etanercept 25 mg twice a wk 12 wks: 50.8 (3.8); Etanercept 50 mg twice a wk 12 wks: 61.0 (4.3); Placebo 12 wks: 10.9 (4.8); p<0.0001 for placebo vs. all etanercept doses</p> <p>Etanercept 25 mg once a wk 24wks: 54.0 (3.0); Etanercept 25 mg twice a wk 24 wks: 59.4 (3.6); Etanercept 50 mg twice a wk 24 wks: 73.8 (2.8). CIC removed</p> <p>Patient global assessment Wk 12 distribution on 6-point scale favoured all doses of etanercept over placebo (p<0.0001) CIC removed</p> <p>Responses over time CIC removed</p> <p>Stage 3 Duration of treatment response (time to loss of <50% PASI improvement achieved between baseline and wk 24 > 50% for all responders after withdrawal of treatment (median (75th percentile, 25th percentile)) (n=409) (CIC removed)</p> <p>Time to relapse after withdrawal of etanercept (loss of half of PASI improvement achieved by Wk 24) (median (75th percentile, 25th percentile))(n=409) Etanercept 25 mg once a wk (n=85): 70 days (56, 113 days); Etanercept 25 mg twice a wk (n=107): 85 days (56, 169 days); Etanercept 50 mg twice a wk (n=122): 91 days (60, 169 days); Etanercept 25 mg twice a wk (Ex-Placebo) (n=95): 85 days (57, 143 days) Median time for all patients from wk 24 to study visit when relapse identified: 85 days</p> <p>Time to loss of PASI 50 after withdrawal of etanercept in those with PASI 75 or better at week 24 (CIC removed) (n=252) Etanercept 25 mg once a wk (n=37): 85 days (CIC removed); Etanercept 25 mg twice a wk (n=69): 87 days (CIC removed); Etanercept 50 mg twice a wk (n=91): 112 days (CIC removed); Etanercept 25 mg twice a wk (Ex-Placebo): 106 days (CIC removed) Median time for all patients from wk 24 to study visit when loss of PASI 50 identified: 91 days</p> <p>Rebound psoriasis</p>
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	<p>DLQI score (mean (SE/SD)) Etanercept 25 mg once a wk: 12.2 (0.5/6.6); Etanercept 25 mg twice a wk: 12.7 (0.5/7.0) yrs: Etanercept 50 mg twice a wk: 11.3 (0.5/6.4); placebo: 12.8 (0.6/7.3)</p> <p>Psoriatic arthritis Etanercept 25 mg once a wk: CiC removed Etanercept 25 mg twice a wk: CiC removed Etanercept 50 mg twice a wk: CiC removed placebo: CiC removed Total: 22% (146/652)</p> <p>Concurrent therapies Stable doses of low or moderate potency topical steroids on scalp, axilla and groin were permitted. CiC removed</p> <p>Comments 672 randomised, 652 received one dose of study drug</p>	<p>for PASI 75 at Wk 12 of Stage 1</p> <p>Statistical analyses Pearson's chi-squared test, Fisher's exact test for binary endpoints; Mantel-Haenszel for ordinal endpoints and non-parametric tests for continuous endpoints. Hochberg's set-up procedure for multiple comparisons was used on comparisons up to 12 wks.</p> <p>ITT analysis All patients who took at least one dose of medication included in all safety and efficacy analyses. Last observation carried forward used for missing data.</p> <p>Comments</p>	<p>Of those patients who had received 24 wks etanercept therapy (n=409) 1 patient (who had been in the Etanercept 25 mg once a wk group) developed a PASI score of 125% or more of baseline score. (CiC removed). No patient developed a PASI score of 150% or more of baseline score</p> <p>Stage 4</p> <p>CiC removed</p> <p>Adverse events</p> <p>Stage 1 At Wk 12 occurring in at least 3% of patients in any group</p> <table border="1"> <thead> <tr> <th></th> <th>Placebo n=166</th> <th>E25mg/wk n=160</th> <th>E25 mg 2/wk n=162</th> <th>E50 mg 2/wk n=164</th> </tr> </thead> <tbody> <tr> <td>Non-infectious adverse events</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>CiC removed</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Injection site reaction</td> <td>12 (7%)</td> <td>17 (11%)</td> <td>28 (17%)</td> <td>22 (13%)</td> </tr> <tr> <td>Headache</td> <td>11 (7%)</td> <td>5 (3%)</td> <td>19 (12%)</td> <td>11 (7%)</td> </tr> <tr> <td>Inject site ecchymosis</td> <td>6 (4%)</td> <td>11 (7%)</td> <td>4 (2%)</td> <td>8 (5%)</td> </tr> <tr> <td>Asthma</td> <td>5 (3%)</td> <td>7 (4%)</td> <td>6 (4%)</td> <td>3 (2%)</td> </tr> <tr> <td>Myalgia</td> <td>4 (2%)</td> <td>3 (2%)</td> <td>6 (4%)</td> <td>3 (2%)</td> </tr> <tr> <td>Accidental injury</td> <td>7 (4%)</td> <td>6 (4%)</td> <td>5 (3%)</td> <td>7 (4%)</td> </tr> <tr> <td>CiC removed</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Simusitis</td> <td>1 (1%)</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Nausea</td> <td>2 (1%)</td> <td>5 (3%)</td> <td>4 (2%)</td> <td>3 (2%)</td> </tr> <tr> <td>Rash</td> <td>4 (2%)</td> <td>4 (3%)</td> <td>4 (2%)</td> <td>5 (3%)</td> </tr> <tr> <td>Infectious adverse events including any serious infections</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>CiC removed</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>U. resp infection</td> <td>19 (11%)</td> <td>16 (10%)</td> <td>15 (9%)</td> <td>9 (5%)</td> </tr> <tr> <td>CiC removed</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>CiC removed</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Deaths (no.) (CiC removed).</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Withdrawals due to adverse events CiC removed</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Positive test for anti-etanercept antibody (CiC removed)</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Other important adverse event results</td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>		Placebo n=166	E25mg/wk n=160	E25 mg 2/wk n=162	E50 mg 2/wk n=164	Non-infectious adverse events					CiC removed					Injection site reaction	12 (7%)	17 (11%)	28 (17%)	22 (13%)	Headache	11 (7%)	5 (3%)	19 (12%)	11 (7%)	Inject site ecchymosis	6 (4%)	11 (7%)	4 (2%)	8 (5%)	Asthma	5 (3%)	7 (4%)	6 (4%)	3 (2%)	Myalgia	4 (2%)	3 (2%)	6 (4%)	3 (2%)	Accidental injury	7 (4%)	6 (4%)	5 (3%)	7 (4%)	CiC removed					Simusitis	1 (1%)	0	0	0	Nausea	2 (1%)	5 (3%)	4 (2%)	3 (2%)	Rash	4 (2%)	4 (3%)	4 (2%)	5 (3%)	Infectious adverse events including any serious infections					CiC removed					U. resp infection	19 (11%)	16 (10%)	15 (9%)	9 (5%)	CiC removed					CiC removed					Deaths (no.) (CiC removed).					Withdrawals due to adverse events CiC removed					Positive test for anti-etanercept antibody (CiC removed)					Other important adverse event results				
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Positive test for anti-etanercept antibody (CiC removed)																																																																																																																	
Other important adverse event results																																																																																																																	

		<p>Stage 2 Adverse events from Wk 13 to Wk 24: occurring in at least 3% of patients in any group</p> <table border="0"> <tr> <td>E25mg2/wk (was Placebo) n=153</td> <td>E25mg1/wk n=150</td> <td>E25 mg 2/wk n=149</td> <td>E50 mg 2/wk n=159</td> </tr> </table> <p>Non-infectious adverse events</p> <p>Any non-infectious CiC removed</p> <p>Rash 0 CiC removed</p> <p>Headache 8 (5%) 5 (3%) 2 (1%) 3 (2%) 6 (4%)</p> <p>Simusitis 5 (3%) 3 (2%) 3 (2%) 5 (3%) 6 (4%)</p> <p>Asthemia 2 (1%) 3 (2%) 5 (3%) 6 (4%)</p> <p>Myalgia 3 (2%) 5 (3%) 6 (4%) 4 (3%)</p> <p>Accidental injury 6 (4%) 6 (4%) 4 (3%) 4 (3%)</p> <p>CiC removed</p> <p>Infectious adverse events including any serious infections</p> <p>Any infectious (CiC removed) 9 (6%)</p> <p>U. resp infection 8 (5%) 9 (6%) 11 (7%)</p> <p>Serious infections (no.): (CiC removed)</p> <p>Cancer (CiC removed)</p> <p>Other non-infectious serious adverse events (no.) CiC removed</p> <p>Deaths (no.)</p> <p>Withdrawals due to adverse events Etanercept 25 mg once a wk: (CiC removed); Etanercept 25 mg twice a wk: (CiC removed); Etanercept 50 mg twice a wk: (CiC removed); placebo: (CiC removed)</p> <p>Over the 24 week study 27 patients withdrew due to adverse events</p> <p>Positive test for anti-etanercept antibody 8/520 etanercept patients for whom paired baseline-24 week (or study withdrawal) samples were available had serum samples tested positive for non-neutralising anti-etanercept antibodies.</p> <p>Other important adverse event results CiC removed</p>	E25mg2/wk (was Placebo) n=153	E25mg1/wk n=150	E25 mg 2/wk n=149	E50 mg 2/wk n=159
E25mg2/wk (was Placebo) n=153	E25mg1/wk n=150	E25 mg 2/wk n=149	E50 mg 2/wk n=159			

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		<p>Stage 3 Adverse events at Wk 60 Of the 157 treated with open label etanercept 25 mg twice a wk in Stage 3, 72% received 48 wks therapy and 38% received 60 wks. (CiC removed) Exposure adjusted rates of adverse events, infections and serious adverse events were similar to those in the first phase: (number (exposure-adjusted event rate per 100 patient years)) (CiC removed)</p> <p>Serious adverse events Any: (CiC removed) Serious infection: (CiC removed)</p> <p>Withdrawals due to adverse events (CiC removed)</p> <p>Stage 4 (CiC removed)</p> <p>Serious adverse events (CiC removed)</p> <p>Withdrawals due to adverse events (CiC removed)</p> <p>Serious adverse events (CiC removed)</p> <p>Withdrawals due to adverse events (CiC removed)</p> <p>Comments Further sub-group analyses and further results relating to the re-treatment phase are reported in the Industry Trial Report</p>
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10.4.2 Data extraction tables: intervention efficacy – efalizumab

Study details and design	Participant details	Intervention/outcome/analyses details	Results
<p>Gordon, 2003,⁷³ USA</p> <p>Type of publication Full publication</p> <p>Other publications/ reports Menter, 2004,¹⁵⁸ Full publication Hamilton, 2003,¹⁵⁹ Abstract ACD2390g, 2004,¹⁶⁰ Industry submission</p> <p>Funding Genentech Inc.</p> <p>Study design Double-blind RCT, parallel Multicentre</p> <p>Setting Outpatient</p> <p>Duration of follow-up 12 wks</p> <p>Frequency of follow-up Baseline, 2, 4, 6, 8, 10, 12</p> <p>Extracted by: Zarnie</p> <p>Checked by: Nerys</p>	<p>Inclusion/exclusion criteria Patients aged between 18 to 75 years with moderate to severe plaque psoriasis for at least 6 months, with at least 10% of total BSA affected, with a minimum PASI score of 12 and candidates for systemic therapy.</p> <p>Number randomised and treated 556</p> <p>Age <i>Mean age (range)</i> Efalizumab: 45 yrs (18-75 yrs) Placebo: 45 yrs (20-75 yrs)</p> <p>Gender Efalizumab: Male 68% (251/369) Placebo: Male 71% (132/187)</p> <p>Psoriasis history <i>Duration of psoriasis</i> Efalizumab: mean 19 yrs (1-62 yrs) Placebo: mean 19 yrs (1-53 yrs)</p> <p><i>Prior systemic therapy</i> Efalizumab: Yes 77% (283/369) Placebo: Yes 74% (139/187)</p> <p>Baseline PASI score (range) Efalizumab: 19 (10-59) Placebo: 19 (11-50)</p> <p><i>% BSA affected (range)</i> Efalizumab: 28 (10-95) Placebo: 27 (10-90)</p>	<p>Intervention Efalizumab Dose regimen: 1 mg/kg SC once a wk Length of treatment: 12 wks No. randomised: 369 No. completed: 345</p> <p>Comparator Placebo Dose regimen: Equivalent Length of treatment: 12 wks No. randomised: 187 No. completed: 175</p> <p>Primary Outcome PASI 75 at wk 12</p> <p>Sample size calculation A planned sample size of 333 patients receiving Efalizumab and 167 receiving placebo produced 99% power to detect a difference between assumed placebo response rate of 5%, and Efalizumab response rate of 25%.</p> <p>Statistical analyses Dichotomous outcomes including the PASI 75 were compared using the 2-sided Fisher exact test. Continuous data was analysed using 2-sided t-test or non-parametric test (Wilcoxon rank sum test) as appropriate. Hochberg-Bonferroni adjustment for multiple comparisons used for secondary end points.</p>	<p>PASI 75 Efalizumab: 12 wks: 27% (98/369); Placebo: 12 wks: 4% (8/187); p<0.001. Treatment effect: 22.3% (95% CI: 15.8%, 29.5%)</p> <p>PASI 50 Efalizumab: 12 wks: 59% (216/369); Placebo: 12 wks: 14% (26/187); p<0.001.</p> <p>PASI Mean % improvement from baseline Efalizumab: 12 wks: 52%; Placebo: 12 wks: 19%; p<0.001.</p> <p>Clear or Almost Clear Efalizumab: 12 wks: 26%; Placebo: 12 wks: 3%; p<0.001.</p> <p>Physician's global assessment Proportion excellent or cleared Efalizumab: 12 wks: 33%; Placebo: 12 wks: 5%; p<0.001.</p> <p>DLQI (Mean % improvement) Mean % improvement from baseline Efalizumab: 12 wks: 47%; Placebo: 12 wks: 14%; p<0.001.</p> <p>PSA frequency (Mean % improvement) Efalizumab 12 wks: 46.9%; placebo 12 wks: 18.4%; p<0.001</p> <p>PSA severity (Mean % improvement) Efalizumab 12 wks: 47.3%; placebo 12 wks: 17.3%; p<0.001</p> <p>Itching scores (Mean % improvement) Efalizumab 12 wks: 37.7%; placebo 12 wks: 11.2%; p<0.001</p> <p>Adverse events Adverse events occurring in ≥ 5% of all patients Efalizumab (n=368) 296 (80%) 163 (44%) Placebo (n=187) 133 (71%) 47 (25%)</p>

	<p>Concurrent therapies Tar and salicylic acid preparations were permitted for the scalp, and low-potency topical corticosteroids were allowed for the face, hands, feet, groin, and axillae.</p> <p>Comments Patients were permitted to use emollients.</p>	<p>ITT analysis Yes. For primary and secondary endpoints, consisting of all patients who were randomised. Safety analyses were performed on the as-treated population.</p> <p>Comments After 12 weeks all patients were enrolled in a separate long-term open label extension study.</p>	<p>Non-infectious adverse events</p> <table border="0"> <tr><td>Headache</td><td>123 (33%)</td><td>39 (21%)</td></tr> <tr><td>Chills</td><td>44 (12%)</td><td>10 (5%)</td></tr> <tr><td>Nausea</td><td>39 (11%)</td><td>13 (7%)</td></tr> <tr><td>Myalgia</td><td>38 (10%)</td><td>8 (4%)</td></tr> <tr><td>Pain</td><td>37 (10%)</td><td>9 (5%)</td></tr> <tr><td>Fever</td><td>25 (7%)</td><td>3 (2%)</td></tr> <tr><td>Rhinitis</td><td>23 (6%)</td><td>11 (6%)</td></tr> <tr><td>Asthenia</td><td>22 (6%)</td><td>9 (5%)</td></tr> <tr><td>Diarrhoea</td><td>20 (5%)</td><td>10 (5%)</td></tr> <tr><td>Unintentional injury</td><td>17 (5%)</td><td>19 (10%)</td></tr> <tr><td>Accidental injury</td><td>17 (5%)</td><td>19 (10%)</td></tr> </table> <p>Infectious adverse events including any serious infections</p> <table border="0"> <tr><td>Any infection</td><td>27%</td><td>23%</td></tr> <tr><td>Infection not specified</td><td>46 (13%)</td><td>23 (12%)</td></tr> <tr><td>Pharyngitis</td><td>27 (7%)</td><td>10 (5%)</td></tr> <tr><td>Flulike syndrome</td><td>27 (7%)</td><td>7 (4%)</td></tr> <tr><td>Herpes simplex</td><td>17 (5%)</td><td>7 (4%)</td></tr> <tr><td>Gastroenteritis</td><td>5 (1%)</td><td>10 (5%)</td></tr> </table> <p>Serious infections (no.): Efalizumab: 0.5%; Placebo: 0.5% Opportunistic infections: none</p> <p>Cancer 2 cases in efalizumab treated patients (squamous cell cancer at day 2; basal cell cancer at day 77)</p> <p>Other non-infectious serious adverse events (no.) Serious adverse events: Efalizumab: 2% (9/368); Placebo: 1% (1/187)</p> <p>Deaths None</p> <p>Withdrawals due to adverse events Efalizumab: 12 (3%); Placebo: 2 (1%)</p> <p>Positive test for anti-efalizumab antibody Efalizumab: 8 (2%); Placebo: 0</p> <p>Other important adverse event results No clinically significant laboratory abnormalities or pattern of changes were observed during efalizumab therapy</p>	Headache	123 (33%)	39 (21%)	Chills	44 (12%)	10 (5%)	Nausea	39 (11%)	13 (7%)	Myalgia	38 (10%)	8 (4%)	Pain	37 (10%)	9 (5%)	Fever	25 (7%)	3 (2%)	Rhinitis	23 (6%)	11 (6%)	Asthenia	22 (6%)	9 (5%)	Diarrhoea	20 (5%)	10 (5%)	Unintentional injury	17 (5%)	19 (10%)	Accidental injury	17 (5%)	19 (10%)	Any infection	27%	23%	Infection not specified	46 (13%)	23 (12%)	Pharyngitis	27 (7%)	10 (5%)	Flulike syndrome	27 (7%)	7 (4%)	Herpes simplex	17 (5%)	7 (4%)	Gastroenteritis	5 (1%)	10 (5%)
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Study details and design	Participant details	Intervention/outcome/analyses details	Results
<p>Lebwohl, 2003,⁷² USA</p> <p>Type of publication Full publication</p> <p>Other publications/ reports Menter, 2004,¹⁵⁸ Full publication Gordon, 2002,¹⁶¹ Abstract ACD2059g, 2004,¹⁶² Industry submission</p> <p>Funding Genentech</p> <p>Study design Double-blind RCT, parallel Monotherapy</p> <p>The study was in 3 stages: Stage 1: RCT Stage 2: Further RCT dependant on response of participants after completion of first stage Stage 3: Follow-up after discontinuation of study treatments</p> <p>Setting Outpatient</p> <p>Duration of follow-up Total: 36 wks Stage 1: 12 wks Stage 2: 12 wks Stage 3: 12 wks</p> <p>Frequency of follow-up Main assessments every 12 wks for 36 wks.</p> <p>Extracted by: NFW Checked by: AK</p>	<p>Inclusion/exclusion criteria Aged 18-70 yrs, plaque psoriasis stable for ≥ 3 mths and PASI score ≥ 12, covering $\geq 10\%$ BSA and candidate for systemic therapy. Patients with uncontrolled infection, cancer, hepatic or renal dysfunction or abnormal white blood cell count were excluded.</p> <p>Stage 2: Participants who had received efalizumab 1 mg or 2 mg dose in stage 1. Stage 3: all patients continuing in study after Stage 2.</p> <p>Number randomised and treated Stage 1: 597 Stage 2: 434</p> <p>Age <i>Mean age (SD)</i> Total: 46 yrs (not stated)</p> <p>Gender Total: male 65%</p> <p>Psoriasis history <i>Duration of psoriasis (Mean (SD))</i> Total: 19 yrs (not stated)</p> <p><i>Prior systemic therapy</i> Total: 67%</p> <p>PASI score at baseline(Mean (SD)) Total: 20.0 (not stated)</p>	<p>Stage 1</p> <p>Intervention Efalizumab Dose regimen: 1 mg/kg SC once a wk Length of treatment: 12 wks No. randomised: 232 No. completed: 211</p> <p>Intervention Efalizumab Dose regimen: 2 mg/kg SC once a wk Length of treatment: 12 wks No. randomised: 243 No. completed: 227</p> <p>Comparator Placebo Dose regimen: Equivalent Length of treatment: 12 wk No. randomised: 122 No. completed: 111</p> <p>Stage 2:</p> <p>Intervention Efalizumab Patients with PASI ≥ 50 end Stage 1 were re-randomised to two different dose frequencies.</p> <p>Dose regimen: efalizumab SC 2 mg/kg once a wk Length of treatment: 12 wk No. randomised: 86 No. completed: 78</p> <p>Dose regimen: efalizumab SC 2 mg/kg once every 2 wks. Length of treatment: 12 wk No. randomised: 85 No. completed: 80</p> <p>Patients with PASI ≤ 50 at end of Stage 1 were re-randomised to: Dose regimen: efalizumab SC</p>	<p>Stage 1</p> <p>PASI 75 Efalizumab 1 mg 12 wks: 52/232 (22%); efalizumab 2 mg 12 wks: 69/243 (28%); placebo 12 wks: 6/122 (5%); p<0.001 for placebo vs. both efalizumab doses</p> <p>PASI 50 Efalizumab 1 mg 12 wks: 120/232 (52%); efalizumab 2 mg 12 wks: 138/243 (57%); placebo 12 wks: 19/122 (16%); p<0.001 for placebo vs. both efalizumab doses</p> <p>PASI 90 Efalizumab 1 mg 12 wks: 10/232 (4%); efalizumab 2 mg 12 wks: 15/243 (6%); placebo 12 wks: 1/122 (>1%); p=NS placebo vs. both efalizumab doses</p> <p>DLQI (Mean % improvement) Efalizumab 1 mg 12 wks: 45.4%; placebo 12 wks: 12.3%; p<0.001</p> <p>PSA frequency (Mean % improvement) Efalizumab 1 mg 12 wks: 41.9%; placebo 12 wks: 9.0%; p<0.001</p> <p>PSA severity (Mean % improvement) Efalizumab 1 mg 12 wks: 45.1%; placebo 12 wks: 8.1%; p<0.001</p> <p>Itching scores (Mean % improvement) Efalizumab 1 mg 12 wks: 43.3%; placebo 12 wks: 12.9%; p<0.001</p> <p>Stage 2</p> <p>Patients with PASI 75 at wk 12:</p> <p>PASI 75 Efalizumab 1 mg 24 wks: 30/39 (77%); efalizumab 2 mg 24 wks: 31/40 (78%); placebo 24 wks: 8/40 (20%); p<0.001 for placebo vs. both efalizumab doses</p> <p>PASI 50 Efalizumab 1 mg 24 wks: 35/39 (90%); efalizumab 2 mg 24 wks: 38/40 (95%); placebo 24 wks: 16/40 (40%); p=NS placebo vs. both efalizumab doses</p> <p>PASI 90 Efalizumab 1 mg 24 wks: 12/39 (31%); efalizumab 2 mg 24 wks: 13/40 (32%); placebo 24 wks: 1/40 (2%); p=NS placebo vs. both efalizumab doses</p> <p>Patients with PASI 50-74 at wk 12:</p> <p>PASI 75 Efalizumab 1 mg 24 wks: 25/47 (53%); efalizumab 2 mg 24 wks: 13/45 (29%); placebo 24</p>

<p>Concurrent therapies All patients were permitted to use Eucerin cream, tar or salicylic acid preparations for psoriasis of the scalp, limited application of low-potency corticosteroids, and oral antipruritic agents.</p> <p>Comments</p>	<p>4 mg/kg once a wk. Length of treatment: 12 wks No. randomised: 118 No. completed: 101</p> <p>Comparator Placebo Dose regimen: Equivalent Length of treatment: 12 wk No. randomised: 145 No. completed: 96</p> <p>Stage 3: No study treatment</p> <p>Primary Outcome PASI 75 at 12 wks</p> <p>Sample size calculation Planned sample size was 500 patients, based on assumption of 25% response rate on efalizumab and 2% on placebo, giving 95% power at the 0.025% level</p> <p>Statistical analyses Fisher's exact test and two-sample t-test. Analysis of Stage 2 data was stratified by treatment response in Stage 1</p> <p>ITT analysis Yes. Analysis included all patients randomised</p> <p>Comments</p>	<p>wks: 2/46 (4%); p<0.001 for placebo vs. both efalizumab doses</p> <p>PASI 50 Efalizumab 1 mg 24 wks: 35/47 (74%); efalizumab 2 mg 24 wks: 30/45 (67%); placebo 24 wks: 5/46 (11%); p=NS placebo vs. both efalizumab doses</p> <p>PASI 90 Efalizumab 1 mg 24 wks: 1/47 (2%); efalizumab 2 mg 24 wks: 3/45 (7%); placebo 24 wks: 0 (0%); p=NS placebo vs. both efalizumab doses</p> <p>Patients with PASI <50 at wk 12:</p> <p>PASI 75 Efalizumab 4 mg 24 wks: 15/118 (15%); placebo 24 wks: 1/59 (2%); p<0.001 for placebo vs. both efalizumab doses</p> <p>PASI 50 Efalizumab 4 mg 24 wks: 47/118 (40%); placebo 24 wks: 9/59 (15%); p<0.001 for placebo vs. both efalizumab doses</p> <p>PASI 90 Efalizumab 4 mg 24 wks: 5/118 (4%); placebo 24 wks: 1/59 (2%); p<0.001 for placebo vs. both efalizumab doses</p> <p>Stage 3 For wks 24-36 mean time to relapse (loss of more than 50% of improvement achieved in PASI score at Wk 24) in those who had achieved \geq PASI50 was 84 days. At wk 36 approximately one third of patients who had received continuous efalizumab had not relapsed.</p> <p>Adverse events <i>Stage 1</i> Adverse events reported by \geq 5% patients in any treatment group during Stage 1</p> <table border="1"> <tr> <td></td> <td>Efalizumab 1 mg (n=232)</td> <td>Efalizumab 2 mg (n=243)</td> </tr> <tr> <td>Any</td> <td>91 (75%)</td> <td>207 (85%)</td> </tr> <tr> <td>Drug-exposure related</td> <td>49 (40%)</td> <td>117 (50%)</td> </tr> </table> <p>Non-infectious adverse events</p> <table border="1"> <tr> <td></td> <td>Efalizumab 1 mg (n=232)</td> <td>Efalizumab 2 mg (n=243)</td> </tr> <tr> <td>Headache</td> <td>29 (24%)</td> <td>71 (31%)</td> </tr> <tr> <td>Nausea</td> <td>11 (9%)</td> <td>34 (15%)</td> </tr> <tr> <td>Chills</td> <td>3 (2%)</td> <td>38 (16%)</td> </tr> <tr> <td>Pain</td> <td>4 (3%)</td> <td>35 (15%)</td> </tr> <tr> <td>Fever</td> <td>6 (5%)</td> <td>26 (11%)</td> </tr> <tr> <td>Asthenia</td> <td>7 (6%)</td> <td>17 (7%)</td> </tr> <tr> <td>Myalgia</td> <td>5 (4%)</td> <td>16 (7%)</td> </tr> </table>		Efalizumab 1 mg (n=232)	Efalizumab 2 mg (n=243)	Any	91 (75%)	207 (85%)	Drug-exposure related	49 (40%)	117 (50%)		Efalizumab 1 mg (n=232)	Efalizumab 2 mg (n=243)	Headache	29 (24%)	71 (31%)	Nausea	11 (9%)	34 (15%)	Chills	3 (2%)	38 (16%)	Pain	4 (3%)	35 (15%)	Fever	6 (5%)	26 (11%)	Asthenia	7 (6%)	17 (7%)	Myalgia	5 (4%)	16 (7%)
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			<p>Not stated</p> <p>Withdrawals due to adverse events Adverse events leading to withdrawal were more common in patients receiving placebo.</p> <p>Stage 3 For treatment-free follow-up (wks 24-36) adverse events in all patients were: infection (13%); worsening psoriasis (9%); pruritis (6%); arthritis (5%); 5 efalizumab treated patients developed anti-efalizumab antibodies; the safety profile of these patients was not different to that of the other patients.</p> <p>Serious adverse events 13 patients (3%) had a serious AE (5 non-fatal infections and 3 psoriasis-related events). <i>Withdrawals due to adverse events</i> Not stated</p> <p>Comments In the industry submission, adverse events experienced by >2% patients, I have not extracted these. Also severe AEs experienced by >1% patients are reported (p65), I have not extracted these here. Not sure if these are the same as 'serious' adverse events. I think not, comparing the serious adverse event data taken from Lebwohl and Gordon against the 'severe' adverse events reported in the industry submission (p65)</p>
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Study details and design	Participant details	Intervention/Comparator details	Results/Comments																								
<p>Papp, 2001,⁷⁷ USA and Canada</p> <p>Type of publication Full publication</p> <p>Other publications/reports None</p> <p>Funding XOMA; Genentech Inc.</p> <p>Study design Double-blind RCT, parallel Monotherapy</p> <p>Setting Outpatient (not stated)</p> <p>Duration of follow-up 20 wks</p> <p>Frequency of follow-up Not clear. Assessment of efficacy at wk 8 (one week after last infusion)</p>	<p>Inclusion/exclusion criteria Chronic moderate to severe plaque psoriasis, with a minimum PASI of 12 and affecting $\geq 10\%$ body surface. Psoriasis diagnosed for ≥ 6 months and stable for ≥ 3 months. Aged 18 to 70 yrs and weighed 120 kg or less. Systemic (including UVB and PUVA) therapies stopped ≥ 28 days before trial and topical therapy stopped ≥ 14 days before trial. Patients with guttate, pustular or erythrodermic psoriasis were excluded.</p> <p>Number randomised and treated 145</p> <p>Age <i>Mean age (SD)</i> Efalizumab 0.1 mg: 43.2 yrs (14.6 yrs) Efalizumab 0.3 mg: 44.5 yrs (12.9 yrs) Placebo: 42.3 yrs (12.3 yrs)</p> <p><i>Median (range)</i> Efalizumab 0.1 mg: 42 yrs (21-72 yrs); Efalizumab 0.3 mg: 44 yrs (21-69 yrs); Placebo: 42 yrs (21-66 yrs)</p> <p>Gender Efalizumab 0.1 mg: male 73%; Efalizumab 0.3 mg: male 63% Placebo: male 67%</p> <p>Psoriasis History <i>Duration of psoriasis (mean (SD))</i> Efalizumab 0.1 mg: 19.2 yrs (10.4 yrs); Efalizumab 0.3 mg: 22.8 yrs (12.6 yrs); Placebo: 17.8 yrs (10.0 yrs)</p> <p>Prior systemic therapy Efalizumab 0.1 mg: 77%; Efalizumab 0.3 mg: 81%; Placebo: 85%</p>	<p>Intervention Efalizumab Dose regimen: 0.1 mg/kg IV infusion once a wk; Length of treatment: 8 wk No. randomised: 22; No. completed: 18</p> <p>Intervention Efalizumab Dose regimen: 0.3 mg/kg IV infusion once a wk. Length of treatment: 8 wk No. randomised: 75 No. completed: 71</p> <p>Comparator Placebo Dose regimen: Equivalent Length of treatment: 8 wk No. randomised: 48 (47 treated) No. completed: 41</p> <p>Primary outcome Proportion achieving change in Physician GA to \geq 'fair' indicating a 25% improvement at day 56 (one week after final IV infusion).</p> <p>Sample size calculation Not stated</p> <p>Statistical analysis Fisher Exact test (two sided) Wilcoxon rank sum test</p> <p>ITT analysis Yes. All patients randomised included in analysis.</p> <p>Comments</p>	<p>No. (%) with at least 'Fair' improvement in PGA Efalizumab 0.1 mg: 11/22 (50%) Efalizumab 0.3 mg: 53/75 (71%) (p:0.0004 vs. placebo) Placebo: 18/48 (38%)</p> <p>No. (%) with at least 'Good' improvement in PGA Efalizumab 0.1 mg: 5/22 (23%) Efalizumab 0.3 mg: 38/75 (51%) (p:0.002 vs. placebo) Placebo: 7/48 (15%)</p> <p>No. (%) with 'excellent' improvement in Physician GA Efalizumab 0.1 mg: 1/22 (5%) Efalizumab 0.3 mg: 19/75 (25%); p:0.0003 vs. placebo Placebo: 1/48 (2%)</p> <p>No. (%) with clearance No patients on any treatment achieved clearance of their psoriasis.</p> <p>Mean (SD) PASI score at Day 56 Efalizumab 0.1 mg: 14.2 (8.9) Efalizumab 0.3 mg: 10.9 (8.4); p<0.0001 vs. placebo Placebo: 13.9 (7.5)</p> <p>Median change in PASI score from baseline to Day 56 Efalizumab 0.1 mg: not stated Efalizumab 0.3 mg: -7.1; p<0.0001 vs. placebo Placebo: -1.8</p> <p>Adverse events AEs reported by $\geq 10\%$ patients in any group</p> <table border="0"> <tr> <td>Efalizumab 0.1 mg/kg (n:22)</td> <td>Efalizumab 0.3 mg/kg (n:75)</td> <td>Placebo (n:47)</td> </tr> <tr> <td>Headache</td> <td>31 (41%)</td> <td>15 (32%)</td> </tr> <tr> <td>Fever</td> <td>4 (18%)</td> <td>8 (17%)</td> </tr> <tr> <td>Chills</td> <td>2 (9%)</td> <td>2 (4%)</td> </tr> <tr> <td>Asthenia</td> <td>3 (14%)</td> <td>8 (17%)</td> </tr> <tr> <td>Nausea</td> <td>4 (18%)</td> <td>7 (15%)</td> </tr> <tr> <td>Vomiting</td> <td>0 (0%)</td> <td>8 (11%)</td> </tr> <tr> <td>Dizziness</td> <td>3 (14%)</td> <td>4 (9%)</td> </tr> </table>	Efalizumab 0.1 mg/kg (n:22)	Efalizumab 0.3 mg/kg (n:75)	Placebo (n:47)	Headache	31 (41%)	15 (32%)	Fever	4 (18%)	8 (17%)	Chills	2 (9%)	2 (4%)	Asthenia	3 (14%)	8 (17%)	Nausea	4 (18%)	7 (15%)	Vomiting	0 (0%)	8 (11%)	Dizziness	3 (14%)	4 (9%)
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	<p>Note in this study systemic included ciclosporin, methotrexate, UVB and PUVA.</p> <p>PASI score at baseline (mean (SD)) Efalizumab 0.1 mg: 18.2 (6.7); Efalizumab 0.3 mg: 19.1 (7.3); Placebo: 16.2 (4.4).</p> <p>Concurrent therapies Not stated</p> <p>Comments</p>	<p>Urinary abnormality 3 (14%) 4 (5%) 5 (11%)</p> <p>Infectious adverse events including any serious infections Any infection NR NR Serious infection: not reported</p> <p>Cancer One efalizumab 0.1 mg/kg patient developed breast cancer 9 months after treatment; not considered study drug related.</p> <p>Other non-infectious serious adverse events Ten serious adverse events reported overall: breakdown by treatment group not reported. Most not related to study drug. One patient on efalizumab 0.3 mg/kg reported unilateral hearing loss that resolved 140 days after start of treatment: not considered drug related.</p> <p>Deaths None</p> <p>Withdrawals due to adverse events None</p> <p>Positive test for anti-efalizumab antibody 1/19 (5%) patients treated with 0.1 mg/kg; 10/70 (14%) patients treated with 0.3 mg/kg; none on placebo.</p> <p>Other important adverse event results Adverse events more common in the efalizumab 0.3 mg/kg group compared to placebo were: headache, fever, psoriasis, chills, nausea, infection, pain, vomiting, pharyngitis, flu syndrome, and back pain; most were mild.</p>
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<p>ACD2058g, 2004,⁷⁴</p> <p>Type of publication Industry submission (based on clinical trial data on file with Serono)</p> <p>Other publications/ reports Menter, 2004,¹⁵⁸ Full publication Gordon, 2002,¹⁶¹ Abstract</p> <p>Funding Serono</p> <p>Study design Double-blind RCT, parallel Monotherapy</p> <p>The study was in 2 stages: Stage 1: RCT Stage 2: Continued treatment or re-treatment following relapse for non-responders</p> <p>Setting Not stated</p> <p>Duration of follow-up Stage 1: 12 wks Stage 2: 12 wks</p> <p>Frequency of follow-up Assessment at 12 wks</p> <p>Extracted by: Anita Checked by: NW</p>	<p>Inclusion/exclusion criteria Adults with moderate to severe plaque psoriasis who had had prior systemic therapy or were candidates for systemic therapy. Patients had to have a minimum PASI score of 12 and \geq 10% BSA. Patients had to have been diagnosed \geq 6 months and have been clinically stable for \geq 3 months</p> <p>Number randomised and treated 498</p> <p>Age <i>Mean age</i> Efalizumab: 45.5 yrs Placebo: 41.7 yrs</p> <p>Gender Not stated</p> <p>Psoriasis history Not stated</p> <p><i>Prior systemic therapy</i> Not stated</p> <p><i>Other</i> Not stated</p> <p>Concurrent therapies Not stated</p> <p>Comments</p>	<p>Intervention Efalizumab Dose regimen: 1 mg/kg SC once a wk Length of treatment: 12 wks No. randomised: 162 No. completed: 149</p> <p>Intervention Efalizumab Dose regimen: 2 mg/kg SC once a wk Length of treatment: 12 wks No. randomised: 166 No. completed: 145</p> <p>Comparator Placebo Dose regimen: Not stated Length of treatment: 12 wks No. randomised: 170 No. completed: 151</p> <p>Primary Outcome Not stated</p> <p>Sample size calculation Not stated</p> <p>Statistical analyses Not stated</p> <p>ITT analysis Yes. Included all patients randomised</p> <p>Comments</p>	<p>PASI 50 Efalizumab 1 mg 12 wks: 99/162 (61%); placebo 12 wks: 25/170 (14.7%); p<0.001</p> <p>DLQI (Mean % improvement) Efalizumab 1 mg 12 wks: 47.0%; placebo 12 wks: 16.1%; p<0.001</p> <p>PSA frequency (Mean % improvement) Efalizumab 1 mg 12 wks: 43.4%; placebo 12 wks: 13.5%; p<0.001</p> <p>PSA severity (Mean % improvement) Efalizumab 1 mg 12 wks: 45.2%; placebo 12 wks: 14.1%; p<0.001</p> <p>Itching scores (Mean % improvement) Efalizumab 1 mg 12 wks: 45.3%; placebo 12 wks: 8.5%; p<0.001</p> <p>Adverse events <i>Stage 1</i> Adverse events reported by \geq 5% of patients treated with efalizumab</p> <table border="0"> <tr> <td>At least 1 adverse event</td> <td>Efalizumab 1 mg (n=162)</td> <td>Placebo (n=170)</td> </tr> <tr> <td>Drug-exposure related</td> <td>135 (83%)</td> <td>130 (77%)</td> </tr> <tr> <td></td> <td>75 (46%)</td> <td>58 (34%)</td> </tr> </table> <p>Non-infectious adverse events</p> <table border="0"> <tr> <td>Headache</td> <td>57 (35%)</td> <td>51 (30%)</td> </tr> <tr> <td>Chills</td> <td>20 (12%)</td> <td>10 (6%)</td> </tr> <tr> <td>Fever</td> <td>12 (7%)</td> <td>9 (5%)</td> </tr> <tr> <td>Pain</td> <td>21 (13%)</td> <td>16 (9%)</td> </tr> <tr> <td>Accidental injury</td> <td>17 (11%)</td> <td>6 (4%)</td> </tr> <tr> <td>Asthenia</td> <td>16 (10%)</td> <td>17 (10%)</td> </tr> <tr> <td>Nausea</td> <td>14 (9%)</td> <td>16 (9%)</td> </tr> <tr> <td>Diarrhoea</td> <td>12 (7%)</td> <td>12 (7%)</td> </tr> <tr> <td>Myalgia</td> <td>13 (8%)</td> <td>8 (5%)</td> </tr> <tr> <td>Sinusitis</td> <td>12 (7%)</td> <td>6 (4%)</td> </tr> <tr> <td>Rhinitis</td> <td>13 (8%)</td> <td>14 (8%)</td> </tr> <tr> <td>Pruritis</td> <td>8 (5%)</td> <td>11 (7%)</td> </tr> <tr> <td>Peripheral oedema</td> <td>9 (6%)</td> <td>5 (3%)</td> </tr> <tr> <td>Back pain</td> <td>10 (6%)</td> <td>5 (3%)</td> </tr> <tr> <td>Cough increased</td> <td>5 (3%)</td> <td>8 (5%)</td> </tr> <tr> <td>Worsening psoriasis</td> <td>8 (5%)</td> <td>4 (2%)</td> </tr> <tr> <td>Dizziness</td> <td>11 (7%)</td> <td>8 (5%)</td> </tr> <tr> <td>Hearing loss</td> <td>12 (7%)</td> <td>5 (3%)</td> </tr> </table>	At least 1 adverse event	Efalizumab 1 mg (n=162)	Placebo (n=170)	Drug-exposure related	135 (83%)	130 (77%)		75 (46%)	58 (34%)	Headache	57 (35%)	51 (30%)	Chills	20 (12%)	10 (6%)	Fever	12 (7%)	9 (5%)	Pain	21 (13%)	16 (9%)	Accidental injury	17 (11%)	6 (4%)	Asthenia	16 (10%)	17 (10%)	Nausea	14 (9%)	16 (9%)	Diarrhoea	12 (7%)	12 (7%)	Myalgia	13 (8%)	8 (5%)	Sinusitis	12 (7%)	6 (4%)	Rhinitis	13 (8%)	14 (8%)	Pruritis	8 (5%)	11 (7%)	Peripheral oedema	9 (6%)	5 (3%)	Back pain	10 (6%)	5 (3%)	Cough increased	5 (3%)	8 (5%)	Worsening psoriasis	8 (5%)	4 (2%)	Dizziness	11 (7%)	8 (5%)	Hearing loss	12 (7%)	5 (3%)
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Study details and design	Participant details	Intervention/outcome/analyses details	Results
<p>ACD2600g, 2004,⁷⁵</p> <p>Type of publication Industry submission (based on clinical trial data on file with Serono)</p> <p>Other publications/ reports FDA website and SPC</p> <p>Funding Not stated</p> <p>Study design Double-blind RCT, parallel Monotherapy</p> <p>Setting Not stated</p> <p>Duration of follow-up 12 wks</p> <p>Frequency of follow-up Assessment at 12 wks</p> <p>Extracted by: Anita Checked by: NW</p>	<p>Inclusion/exclusion criteria Adults with moderate to severe plaque psoriasis who had had prior systemic therapy or were candidates for systemic therapy. (CiC information removed)</p> <p>Number randomised and treated 686</p> <p>Age <i>Mean age</i> Efalizumab: 45.6 yrs Placebo: 46.4 yrs</p> <p>Gender Not stated</p> <p>Psoriasis history Not stated</p> <p><i>Prior systemic therapy</i> Not stated</p> <p><i>Other</i> Not stated</p> <p>Concurrent therapies Not stated</p> <p>Comments</p>	<p>Intervention Efalizumab Dose regimen: 1 mg/kg SC once a wk Length of treatment: 12 wks No. randomised: 450 No. completed: 421</p> <p>Comparator Placebo Dose regimen: Not stated Length of treatment: 12 wks No. randomised: 236 No. completed: 218</p> <p>Primary Outcome Not stated</p> <p>Sample size calculation Not stated</p> <p>Statistical analyses Not stated</p> <p>ITT analysis Yes. Included all patients randomised</p> <p>Comments</p>	<p>PASI 50 Efalizumab 12 wks: 234/450 (52%); placebo 12 wks: 33/263 (12.5%); p<0.001 (CiC removed)</p> <p>Adverse events (CiC removed)</p> <p>Infectious adverse events including any serious infections (CiC removed)</p> <p>Cancer (CiC removed)</p> <p>Other non-infectious serious adverse events (CiC removed)</p> <p>Deaths (CiC removed)</p> <p>Withdrawals due to adverse events (CiC removed)</p> <p>Positive test for anti-efalizumab antibodies (CiC removed)</p> <p>Other important adverse event results (CiC removed)</p> <p>Comments (CiC removed)</p>

Study details and design	Participant details	Intervention/outcome/analyses details	Results
<p>IMP24011, 2004,⁷⁶</p> <p>Type of publication Industry submission (based on clinical trial data on file with Serono)</p> <p>Other publications/ reports SPC</p> <p>Funding Serono</p> <p>Study design Double-blind RCT, parallel Monotherapy</p> <p>Setting Not stated</p> <p>Duration of follow-up 12 wks</p> <p>Frequency of follow-up Extracted by: Anita Checked by: NW</p>	<p>Inclusion/exclusion criteria Adults with moderate to severe plaque psoriasis who had had prior systemic therapy or were candidates for systemic therapy. (CiC removed)</p> <p>Number randomised and treated 793</p> <p>Age (CiC removed)</p> <p>Gender (CiC removed)</p> <p>Psoriasis history (CiC removed)</p> <p><i>Prior systemic therapy</i> (CiC removed)</p> <p><i>Other</i> (CiC removed)</p> <p>Concurrent therapies (CiC removed)</p> <p>Comments</p>	<p>Intervention Efalizumab Dose regimen: 1 mg/kg SC once a wk Length of treatment: 12 wks No. randomised: 529 No. completed: (CiC removed)</p> <p>Comparator: Placebo Dose regimen: Not stated Length of treatment: 12 wks No. randomised: 264 No. completed: (CiC removed)</p> <p>Primary Outcome Not stated</p> <p>Sample size calculation (CiC removed)</p> <p>Statistical analyses (CiC removed)</p> <p>ITT analysis (CiC removed)</p> <p>Comments PASI 75 was reported to be a trial outcome, but no data was reported for this.</p>	<p>PASI 50 (CiC removed)</p> <p>(CiC removed)</p> <p>Adverse events (CiC removed)</p> <p>Cancer (CiC removed)</p> <p>Other non-infectious serious adverse events (CiC removed)</p> <p>Deaths (CiC removed)</p> <p>Withdrawals due to adverse events (CiC removed)</p> <p>Positive test for anti-efalizumab antibodies (CiC removed)</p> <p>Other important adverse event results (CiC removed)</p> <p>Comments (CiC removed)</p>

10.5 Data extraction tables: intervention adverse events

10.5.1 Data extraction tables: intervention adverse events - etanercept

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
<p>Bathon, 2000,⁷⁶ USA Genovese, 2002,¹⁶³ USA</p>	<p>Indication Early rheumatoid arthritis</p>	<p>Intervention Etanercept Dose regimen: 10mg SC twice a wk</p>	<p>STAGE 1 (MTHS 0-12) Non-infectious adverse events</p>

<p>Type of publication Full publication</p> <p>Other publications/ reports Bathon, 2003,¹⁶⁴ Full publication</p> <p>Funding Immunex</p> <p>Study design Stage 1: Double-blind RCT Stage 2: Open label follow-up</p> <p>Duration of follow-up Stage 1: 12 mths Stage 2: 12 mths</p> <p>Study objective To compare the efficacy and safety of etanercept and methotrexate in patients with early rheumatoid arthritis.</p> <p>Extracted by: Anita Checked by: NFW</p>	<p>Inclusion criteria Patients ≥ 18 yrs of age who had had rheumatoid arthritis for no more than three yrs, had not been treated with methotrexate, and had no other important concurrent illness. Patients were required to have positive rheumatoid factor or at least 3 bone erosions of the hand, wrists or feet; at least 10 swollen joints; and at least 12 tender or painful joints. DMARDs were discontinued at least 4 weeks before the study began.</p> <p>Total no. of participants Stage 1: 632 Stage 2: 512</p> <p>Age Etanercept 10mg: mean 50.0 yrs (SD 13, range 19-84) Etanercept 25mg: mean 51.0 yrs (SD 13, range 21-82)</p> <p>Gender Etanercept 10mg: male 25% Etanercept 25mg: male 26%</p> <p>Concurrent therapies All patients received 1mg folic acid per day. Other drugs permitted were stable doses of NSAIDs, prednisone (≤10mg a day), glucocorticoids</p> <p>Comments</p>	<p>Duration/frequency of treatment: 24 mths No. of participants: stage 1: 208; stage 2: 166</p> <p>Intervention Etanercept Dose regimen: 25mg SC twice a wk Duration/frequency of treatment: 12 mths No. of participants: stage 1: 207; stage 2: 177</p> <p>Comparators Methotrexate (stage 1 n=217; stage 2 n=169): 2.5mg oral three times a wk titrated to 2.5mg oral eight times a wk after 8 wks</p> <p>Assessment Adverse events were graded on a scale derived from the Common Toxicity Criteria for the National Cancer Institute. Patients were assessed every 3 mths for adverse events</p> <p>Comments Patients who discontinued either study drug received standard care and continued to be evaluated for the duration of the study.</p>	<p>occurring in ≥10% patients in any etanercept group (no. of patients)</p> <table border="1"> <thead> <tr> <th></th> <th>Etanercept 10mg n=208</th> <th>Etanercept 25mg n=207</th> </tr> </thead> <tbody> <tr> <td>Low peripheral lymphocyte count</td> <td>63 (30%)</td> <td>Not reported</td> </tr> <tr> <td>Injection site reaction</td> <td>52 (25%)</td> <td>77 (37%)</td> </tr> <tr> <td>Headache</td> <td>29 (14%)</td> <td>46 (22%)</td> </tr> <tr> <td>Nausea</td> <td>Not reported</td> <td>35 (17%)</td> </tr> <tr> <td>Sporadic neutropenia</td> <td>36 (17%)</td> <td>(16%)</td> </tr> <tr> <td>Rhinitis</td> <td>30 (14%)</td> <td>31 (15%)</td> </tr> <tr> <td>Diarrhoea</td> <td>29 (14%)</td> <td>30 (14%)</td> </tr> <tr> <td>Bleeding at injection site</td> <td>19 (9%)</td> <td>29 (14%)</td> </tr> <tr> <td>Asthenia</td> <td>26 (13%)</td> <td>27 (13%)</td> </tr> <tr> <td>Influenza-like syndrome</td> <td>33 (16%)</td> <td>26 (13%)</td> </tr> <tr> <td>Rash</td> <td>21 (10%)</td> <td>25 (12%)</td> </tr> <tr> <td>Dyspepsia</td> <td>10 (5%)</td> <td>24 (12%)</td> </tr> <tr> <td>Dizziness</td> <td>12 (6%)</td> <td>22 (11%)</td> </tr> <tr> <td>Back pain</td> <td>23 (11%)</td> <td>20 (10%)</td> </tr> <tr> <td>Abdominal pain</td> <td>28 (13%)</td> <td>20 (10%)</td> </tr> <tr> <td>Sinusitis</td> <td></td> <td></td> </tr> </tbody> </table> <p>Other non-infectious adverse events (no. of patients) Etanercept 10mg: Grade 3 neutropenia 1 Etanercept 25mg: Grade 3 neutropenia 2</p> <p>Infectious adverse events including any serious infections occurring in ≥10% patients in any etanercept group (no. of patients)</p> <table border="1"> <thead> <tr> <th></th> <th>Etanercept 10mg 57 (27%)</th> <th>Etanercept 25mg 72 (35%)</th> </tr> </thead> <tbody> <tr> <td>Upper respiratory tract infection</td> <td>22 (11%)</td> <td>28 (14%)</td> </tr> <tr> <td>Skin infection</td> <td></td> <td></td> </tr> </tbody> </table> <p>All types of infection occurred at a rate of 1.5 events per patient yr across the two etanercept groups</p> <p>Infection requiring hospitalisation or IV antibiotics occurred in < 3% of patients</p> <p>There were no opportunistic infections</p> <p>The rate of serious infections was similar to that in mths 13-24</p> <p>Cancer (no. of patients)</p> <table border="1"> <thead> <tr> <th></th> <th>Etanercept 10mg</th> <th>Etanercept 25mg</th> </tr> </thead> <tbody> <tr> <td>Breast cancer</td> <td>1</td> <td>0</td> </tr> <tr> <td>Lung cancer</td> <td>1</td> <td>0</td> </tr> <tr> <td>Carcinoid lung cancer</td> <td>0</td> <td>1</td> </tr> <tr> <td>Hodgkin's disease</td> <td>0</td> <td>1</td> </tr> </tbody> </table>		Etanercept 10mg n=208	Etanercept 25mg n=207	Low peripheral lymphocyte count	63 (30%)	Not reported	Injection site reaction	52 (25%)	77 (37%)	Headache	29 (14%)	46 (22%)	Nausea	Not reported	35 (17%)	Sporadic neutropenia	36 (17%)	(16%)	Rhinitis	30 (14%)	31 (15%)	Diarrhoea	29 (14%)	30 (14%)	Bleeding at injection site	19 (9%)	29 (14%)	Asthenia	26 (13%)	27 (13%)	Influenza-like syndrome	33 (16%)	26 (13%)	Rash	21 (10%)	25 (12%)	Dyspepsia	10 (5%)	24 (12%)	Dizziness	12 (6%)	22 (11%)	Back pain	23 (11%)	20 (10%)	Abdominal pain	28 (13%)	20 (10%)	Sinusitis				Etanercept 10mg 57 (27%)	Etanercept 25mg 72 (35%)	Upper respiratory tract infection	22 (11%)	28 (14%)	Skin infection				Etanercept 10mg	Etanercept 25mg	Breast cancer	1	0	Lung cancer	1	0	Carcinoid lung cancer	0	1	Hodgkin's disease	0	1
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Prostate cancer	0		1
Other non-infectious serious adverse events			
Not reported			
Deaths (no.)			
Metastatic lung cancer	Etanercept 10mg	1	Etanercept 25mg
Non-infectious complications from dissection of pre-existing aortic aneurysm	0		1
Withdrawals due to adverse events (no.)			
Etanercept 10mg: 2 (10.6%)	Etanercept 25mg: 5 (4.8%)		
Positive test for anti-etanercept antibody			
< 3% of etanercept patients were positive. The positives tests were not associated with adverse events			
Other important adverse event results			
Not reported			
STAGE 2 (MTHS 13-24)			
Non-infectious adverse events			
Not reported			
Infectious adverse events including any serious infections			
(no. of patients)	Etanercept 10mg	n=166	Etanercept 25mg
Celutitis	1	1	1
Bronchitis	1	1	0
Pneumonia	1	1	0
Cystitis	0	0	2
There were no tuberculosis infections			
Cancer (no. of patients)			
Etanercept 10mg: 1	Etanercept 25mg: 1		
Other non-infectious serious adverse events (no. of patients)			
Not reported			
Deaths			
There were no deaths			

		<p>Withdrawals due to adverse events (no. of patients) Etanercept 10mg: 2 Etanercept 25mg: 5</p> <p>Positive test for anti-etanercept antibody Not reported</p> <p>Other important adverse event results Not reported</p> <p>STAGE 1 AND 2 COMBINED (MTHS 0-24)</p> <p>Non-infectious adverse events occurring in $\geq 10\%$ patients in any group (no. of patients)</p> <table border="1"> <thead> <tr> <th></th> <th>Etanercept 10mg n=208</th> <th>Etanercept 25mg n=207</th> </tr> </thead> <tbody> <tr> <td>Low peripheral lymphocyte count</td> <td>Not reported</td> <td>Not reported</td> </tr> <tr> <td>Injection site reaction</td> <td>66 (32%)</td> <td>81 (39%)</td> </tr> <tr> <td>Headache</td> <td>56 (27%)</td> <td>51 (25%)</td> </tr> <tr> <td>Nausea</td> <td>30 (14%)</td> <td>42 (20%)</td> </tr> <tr> <td>Rash</td> <td>40 (19%)</td> <td>37 (18%)</td> </tr> <tr> <td>Rhinitis</td> <td>41 (20%)</td> <td>37 (18%)</td> </tr> <tr> <td>Diarrhoea</td> <td>28 (14%)</td> <td>35 (17%)</td> </tr> <tr> <td>Asthenia</td> <td>25 (12%)</td> <td>33 (16%)</td> </tr> <tr> <td>Bleeding at injection site</td> <td>31 (15%)</td> <td>32 (16%)</td> </tr> <tr> <td>Sporadic neutropenia</td> <td>Not reported</td> <td>Not reported</td> </tr> <tr> <td>Dyspepsia</td> <td>33 (16%)</td> <td>31 (15%)</td> </tr> <tr> <td>Dizziness</td> <td>15 (7%)</td> <td>30 (15%)</td> </tr> <tr> <td>Abdominal pain</td> <td>26 (13%)</td> <td>26 (13%)</td> </tr> <tr> <td>Back pain</td> <td>17 (8%)</td> <td>25 (12%)</td> </tr> <tr> <td>Accidental injury</td> <td>24 (12%)</td> <td>23 (11%)</td> </tr> <tr> <td>Pain</td> <td>17 (8%)</td> <td>22 (11%)</td> </tr> <tr> <td>Ecchymosis</td> <td>19 (9%)</td> <td>23 (11%)</td> </tr> <tr> <td>Vomiting</td> <td>7 (3%)</td> <td>20 (10%)</td> </tr> <tr> <td>Hypertension</td> <td>23 (11%)</td> <td>18 (9%)</td> </tr> <tr> <td>Peripheral oedema</td> <td>23 (11%)</td> <td>14 (7%)</td> </tr> </tbody> </table> <p>Infectious adverse events including any serious infections occurring in $\geq 10\%$ patients in any etanercept group (no. of patients): Not reported</p> <p>There were no opportunistic infections</p> <p>Infection requiring hospitalisation or IV antibiotics (no. of patients) Etanercept 10mg: 5 (2.4%) Etanercept 25mg: 7 (3.4%)</p>		Etanercept 10mg n=208	Etanercept 25mg n=207	Low peripheral lymphocyte count	Not reported	Not reported	Injection site reaction	66 (32%)	81 (39%)	Headache	56 (27%)	51 (25%)	Nausea	30 (14%)	42 (20%)	Rash	40 (19%)	37 (18%)	Rhinitis	41 (20%)	37 (18%)	Diarrhoea	28 (14%)	35 (17%)	Asthenia	25 (12%)	33 (16%)	Bleeding at injection site	31 (15%)	32 (16%)	Sporadic neutropenia	Not reported	Not reported	Dyspepsia	33 (16%)	31 (15%)	Dizziness	15 (7%)	30 (15%)	Abdominal pain	26 (13%)	26 (13%)	Back pain	17 (8%)	25 (12%)	Accidental injury	24 (12%)	23 (11%)	Pain	17 (8%)	22 (11%)	Ecchymosis	19 (9%)	23 (11%)	Vomiting	7 (3%)	20 (10%)	Hypertension	23 (11%)	18 (9%)	Peripheral oedema	23 (11%)	14 (7%)
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		<p>Cancer (no. of patients) Etanercept 10mg: 3 Etanercept 25mg: 4</p> <p>Other serious non-infectious adverse events Not reported</p> <p>Deaths (no.) See stage 1 (mths 0-12) data</p> <p>Withdrawals due to adverse events (no.) Etanercept 10mg: 11 (6.6%) Etanercept 25mg: 15 (7.3%)</p> <p>Positive test for anti-etanercept antibody 14 (3.5%) etanercept patients were positive: etanercept 10mg: 6 (2.9%) patients; etanercept 25mg: 8 (3.9%) patients. The positives tests were not associated with adverse events</p> <p>Other important adverse event results Not reported</p> <p>Comments Withdrawal data reported for stage 1 and 2 combined (mths 0-24) do not tally with withdrawal data reported for stage 1 (mths 0-12). Using stage 1 data (mths 0-12) and stage 2 data (mths 13-24), withdrawal figures tally to Etanercept 10mg: 24 (11.5%) Etanercept 25mg: 15 (7.2%)</p> <p>The reporting of infection and serious adverse events across the different time periods and different publications was inconsistent</p>
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Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results																																																												
<p>Davis, 2003,⁹⁰ USA, Canada and Europe</p> <p>Type of publication Full publication</p> <p>Other publications/ reports None</p> <p>Funding Immunex Corp.</p> <p>Study design Double-blind placebo-controlled RCT</p> <p>Duration of follow-up 24 wks</p> <p>Study objective To determine the safety and efficacy of etanercept in adults with moderate to severe ankylosing spondylitis</p> <p>Extracted by: AK Checked by: NFW</p>	<p>Indication Ankylosing spondylitis</p> <p>Inclusion criteria Patients aged between 18 to 70 years with ankylosing spondylitis. Patients were excluded if they had complete ankylosis (fusion) of the spine, had previously received TNF inhibitor therapy, had serious infection within 4 wks of starting the study, were pregnant, or received DMARDs (except for hydroxychloroquine, sulfasalazine, or methotrexate) within 4 wks of starting.</p> <p>Total no. of participants 277</p> <p>Age Etanercept: mean 42.1 yrs (range 24-70) Placebo: mean 41.9 yrs (range 16-65)</p> <p>Gender Etanercept: male 76% (n=105) Placebo: male 76% (n=105)</p> <p>Concurrent therapies Hydroxychloroquine, sulfasalazine, methotrexate, NSAIDs and prednisone, analgesics were permitted.</p> <p>Comments</p>	<p>Intervention Etanercept Dose regimen: 25mg SC twice a wk Duration/frequency of treatment: 24 wks No. of participants: 138</p> <p>Comparators Placebo (n=139): equivalent</p> <p>Assessment All patients who were randomised and received at least one dose of study drug were evaluated for adverse events, which were graded on a scale derived from derived from the Common Toxicity Criteria for the National Cancer Institute. Patient diaries were used to record any adverse events. Study staff reviewed the diary with the patient at each visit.</p> <p>Comments</p>	<p>Non-infectious adverse events occurring in $\geq 5\%$ patients (no. of patients)</p> <table border="0"> <tr> <td>Injection site reaction</td> <td>Placebo 13 (9%)</td> <td>Etanercept 41 (30%)</td> </tr> <tr> <td>Injection site bruising</td> <td>23 (17%)</td> <td>29 (21%)</td> </tr> <tr> <td>Headache</td> <td>16 (12%)</td> <td>19 (14%)</td> </tr> <tr> <td>Accidental injury</td> <td>6 (4%)</td> <td>17 (12%)</td> </tr> <tr> <td>Diarrhoea</td> <td>13 (9%)</td> <td>11 (8%)</td> </tr> <tr> <td>Rash</td> <td>9 (6%)</td> <td>11 (8%)</td> </tr> <tr> <td>Rhinitis</td> <td>9 (6%)</td> <td>8 (6%)</td> </tr> <tr> <td>Abdominal pain</td> <td>7 (5%)</td> <td>8 (6%)</td> </tr> <tr> <td>Dizziness</td> <td>3 (2%)</td> <td>8 (6%)</td> </tr> <tr> <td>Flu syndrome</td> <td>10 (7%)</td> <td>5 (4%)</td> </tr> </table> <p>Infectious adverse events including any serious infections occurring in $\geq 5\%$ patients (no. of patients)</p> <table border="0"> <tr> <td>Upper respiratory tract infection</td> <td>Placebo 16 (12%)</td> <td>Etanercept 28 (20%)</td> </tr> </table> <p>There were no opportunistic or tuberculosis infections</p> <p>Serious infections (no. of patients): Etanercept: wound infection after cat bite 1 Placebo: Viral infection 1</p> <p>Cancer Not reported</p> <p>Other non-infectious serious adverse events (no. of patients)</p> <table border="0"> <tr> <td>Chest pain</td> <td>Placebo 1</td> <td>Etanercept 1</td> </tr> <tr> <td>Accidental injury</td> <td>2</td> <td></td> </tr> <tr> <td>Suicide attempt</td> <td>1</td> <td></td> </tr> <tr> <td>Lymphadenopathy</td> <td></td> <td>1</td> </tr> <tr> <td>Staphylococcal cellulitis after spider bite</td> <td></td> <td>1</td> </tr> <tr> <td>Fever with injection site reaction</td> <td></td> <td>1</td> </tr> <tr> <td>Ulcerative colitis</td> <td></td> <td>1</td> </tr> <tr> <td>Intestinal obstruction due to adhesions</td> <td></td> <td>1</td> </tr> <tr> <td>Bone fracture after trauma</td> <td></td> <td>3</td> </tr> </table>	Injection site reaction	Placebo 13 (9%)	Etanercept 41 (30%)	Injection site bruising	23 (17%)	29 (21%)	Headache	16 (12%)	19 (14%)	Accidental injury	6 (4%)	17 (12%)	Diarrhoea	13 (9%)	11 (8%)	Rash	9 (6%)	11 (8%)	Rhinitis	9 (6%)	8 (6%)	Abdominal pain	7 (5%)	8 (6%)	Dizziness	3 (2%)	8 (6%)	Flu syndrome	10 (7%)	5 (4%)	Upper respiratory tract infection	Placebo 16 (12%)	Etanercept 28 (20%)	Chest pain	Placebo 1	Etanercept 1	Accidental injury	2		Suicide attempt	1		Lymphadenopathy		1	Staphylococcal cellulitis after spider bite		1	Fever with injection site reaction		1	Ulcerative colitis		1	Intestinal obstruction due to adhesions		1	Bone fracture after trauma		3
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Ileitis secondary to Crohn's disease		1																								

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
<p>Geborek, 2002,³⁴ Sweden</p> <p>Type of publication Full publication</p> <p>Other publications/ reports None</p> <p>Funding Not stated</p> <p>Study design Prospective study</p> <p>Duration of follow-up 2 yrs</p> <p>Study objective To apply a clinical protocol adapted to monitor new treatments in RA to evaluate tolerability and efficacy of etanercept, infliximab, and leflunomide under post-marketing conditions.</p> <p>Extracted by: AK Checked by: NW</p>	<p>Indication Rheumatoid arthritis</p> <p>Inclusion criteria Patients who had failed on at least two DMARDs, including methotrexate, who started on treatment with etanercept, infliximab or leflunomide.</p> <p>Total no. of participants 369</p> <p>Age Etanercept: mean 54.0 yrs</p> <p>Gender Etanercept: male 22%</p> <p>Concurrent therapies Prednisolone, systemic glucocorticoid, DMARDs</p> <p>Comments</p>	<p>Intervention Etanercept Dose regimen: 25mg SC twice a wk Duration/frequency of treatment: No. of participants: 166</p> <p>Comparators Infliximab (n=135): 3mg/kg infusion at start, wks 2, 6, 12 and thereafter every 8th wk. Later the dose could be individually tailored and increased. Leflunomide (n=103): 100 mg oral days 1-3 and thereafter 20mg a day.</p> <p>Assessment For assessment, the patient was included in the new treatment group when starting on a new regimen. If restarted on one treatment after a pause, the patient was considered to have continued to receive the original therapeutic regimen.</p> <p>Comments All adverse events were recorded using WHO terminology. Patients were allowed to switch between etanercept, infliximab, and leflunomide if withdrawn from any of the three treatments. 33 patients tried two treatments, and one tried all three.</p>	<p>Non-infectious adverse events Not reported</p> <p>Infectious adverse events including any serious infections Not reported</p> <p>Serious infections (no.): Etanercept: Bacterial infection 3 (days 130, 150, 270)</p> <p>Cancer Not reported</p> <p>Other non-infectious serious adverse events (no.) Etanercept Myocardial infarction 4, days 41, 63, 130, 501 Uterine cervical carcinoma 2, days 160, 413 Acute myeloid leukaemia 1, day 440 General malaise 1, day 350 Leucopenia 1, day 91 Bell's paralysis 1, day 130 Cutaneous vasculitis 1, day 368 Discoid lupus 1, day 69</p> <p>Deaths (no.) Etanercept 1, day 180 Immunocytoma of breast 1, day 220 Myocardial infarction 1, day 413</p> <p>Withdrawals due to adverse events Etanercept: Adverse reactions were the main cause of withdrawal throughout the study.</p> <p>Positive test for anti-etanercept antibody Not reported</p> <p>Other important adverse event results The total no. of observational yrs for etanercept was 232.8</p> <p><i>Graded side effects per 100 yrs (no.)</i> Etanercept 1.3 (n=3) Fatal</p>

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
<p>Klareskog, 2004,⁹¹ Europe, Australia, UK and USA</p> <p>Type of publication Full publication</p> <p>Other publications/ reports Industry submission (TEMPO trial), 2004,⁶⁷</p> <p>Funding Wyeth Research</p> <p>Study design Double-blind RCT</p> <p>Duration of follow-up 52 weeks</p> <p>Study objective To assess combination treatment with etanercept and methotrexate versus the monotherapies in patients with rheumatoid arthritis.</p> <p>Extracted by: AK Checked by: NW</p>	<p>Indication Rheumatoid arthritis</p> <p>Inclusion criteria Patients aged ≥ 18 years with disease duration of 6 months to 20 years with active adult-onset rheumatoid arthritis (defined as ≥ 10 swollen and ≥ 12 painful joints). Patients had to have had a less than satisfactory response to \geq one DMARD other than methotrexate. Patients previously treated with methotrexate were included provided that they had not had clinically important toxic effects or lack of response and had not been treated with methotrexate within 6 months of enrolment.</p> <p>Total no. of participants 682</p> <p>Age Etanercept: mean 53.2 yrs (SD 13.8)</p> <p>Gender Etanercept: male 23%</p> <p>Concurrent therapies NSAIDs, corticosteroids. All patients received 5mg folic acid supplement twice a week</p> <p>Comments</p>	<p>Intervention Etanercept Dose regimen: 25mg SC twice a wk and oral placebo once a wk Duration/frequency of treatment: 52 wks No. of participants: 223</p> <p>Comparators Methotrexate (n=228): 7.5 escalated to 20mg oral once a wk and placebo SC twice a wk Combination (n=231): Etanercept 25mg SC twice a wk combined with methotrexate oral once a wk</p> <p>Assessment Treatment-emergent adverse events were defined as either an adverse event that was not present at baseline or an event present at baseline that worsened during the study. A serious infection was defined as need for treatment with parenteral antibiotics or admission.</p> <p>Comments</p>	<p>Non-infectious adverse events Treatment-emergent adverse events occurring in $\geq 10\%$ patients Etanercept 192 (86%) 26 (12%) 19 (9%) 23 (10%) 28 (13%) 14 (6%) 23 (10%) 34 (15%) 46 (21%) 22 (10%) 16 (7%) 7 (3%)</p> <p>Any adverse event Abdominal pain Accidental injury Asthenia Back pain Cough increased Diarrhoea Headache Injection site reaction Nausea Rash Vomiting</p> <p>Infectious adverse events including any serious infections Etanercept: All infections 131 (59%); Serious infections 10 (4%)</p> <p>Cancer Etanercept: Basal cell carcinoma 1; Breast cancer 1; Rectal cancer 1; Melanoma 1</p> <p>Other non-infectious serious adverse events (no. of patients) Etanercept: Total 25 (11%)</p> <p>Deaths (no.) Etanercept: Heart failure and suspected sepsis 1</p> <p>Withdrawals due to adverse events Etanercept: 25</p> <p>Positive test for anti-etanercept antibody Not reported</p> <p>Other important adverse event results Not reported</p> <p>Comments</p>

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results																																								
<p>Mease, 2004,⁹² USA</p> <p>Type of publication Full publication</p> <p>Other publications/ reports Baumgartner, 2001,¹⁶⁵ Industry trial report Baumgartner, 2003,¹⁶⁶ Industry trial report Klareskog, 2003,¹⁶⁷ Industry expert report Ory, 2002,¹⁶⁸ Abstract</p> <p>Funding Immunex Corporation</p> <p>Study design Stage 1: Double-blind placebo controlled RCT Stage 2: Maintenance period (blinded) Stage 3: Open label follow-up</p> <p>Duration of follow-up Stage 1: 24 wks Stage 2: <24 wks Stage 3: 48 wks</p> <p>Study objective To evaluate the safety, efficacy, and effect on radiographic progression of etanercept in patients with psoriatic arthritis.</p> <p>Extracted by: Anita Checked by: NW</p>	<p>Indication Psoriatic arthritis</p> <p>Inclusion criteria Patients between 18 and 70 yrs of age with active psoriatic arthritis and stable plaque psoriasis (target lesion >2cm diameter) with >3 swollen joints and >3 painful/tender points with at least one of the following sub-types of psoriatic arthritis: DIP involvement; polyarticular arthritis; arthritis mutilans; asymmetric peripheral arthritis; or ankylosing spondylitis-like. Arthritis had to have demonstrated an inadequate response to NSAID therapy</p> <p>Total no. of participants Stage 1: 205 (CiC removed) Stage 3: 168</p> <p>Age Stage 1: Total: mean (CiC removed) (range 18-76) Etanercept: mean 47.6 (range 18-76) Placebo: mean 47.3 (range 21-73)</p> <p>Gender Stage 1: Etanercept: male 57% (n=58) Placebo: male 45% (n=47)</p> <p>Concurrent therapies Methotrexate, NSAIDs,</p>	<p>Intervention Etanercept Stage 1: Dose regimen: 25mg SC twice a wk Duration/frequency of treatment: 24 wks No. of participants: 101</p> <p>Stage 2: After completing stage 1, patients could chose to continue on their blinded study treatment in this maintenance period until all patients had completed 24 wks of study treatment and the database was locked Dose regimen: 25mg SC twice a wk Duration/frequency of treatment: <u>CiC removed</u></p> <p>Stage 3: After the database was locked all patients who completed 12 wks of study drug in stage 1 (CiC removed) were eligible to enter a 48-week open label extension. Dose regimen: 25mg SC twice a wk Duration/frequency of treatment: 48 wks No. of participants: 168 (87 previously on etanercept; 81 stage 1 previously on placebo) <u>CiC removed</u></p> <p>Comparators Stage 1: Placebo (n=104): Equivalent</p> <p>Stage 2: Placebo (CiC removed), Equivalent</p> <p>Assessment All patients who were randomised and received at least one dose of study drug were evaluated for adverse events. <u>CiC removed</u></p> <p>Comments</p>	<p>STAGE 1 (24WK DOUBLE-BLIND RCT) Non-infectious adverse events occurring in >5% patients in any group (no. of patients)</p> <table border="0"> <tr> <td>Placebo</td> <td>Etanercept</td> </tr> <tr> <td>69 (66%)</td> <td>65 (64%)</td> </tr> <tr> <td>9 (9%)</td> <td>36 (36%)</td> </tr> <tr> <td>11 (11%)</td> <td>12 (12%)</td> </tr> <tr> <td>5 (5%)</td> <td>8 (8%)</td> </tr> <tr> <td>5 (5%)</td> <td>8 (8%)</td> </tr> <tr> <td>8 (8%)</td> <td>6 (6%)</td> </tr> <tr> <td>7 (7%)</td> <td>5 (5%)</td> </tr> <tr> <td>6 (6%)</td> <td>4 (4%)</td> </tr> <tr> <td>5 (5%)</td> <td>4 (4%)</td> </tr> <tr> <td>7 (7%)</td> <td>2 (2%)</td> </tr> <tr> <td>7 (7%)</td> <td>1 (1%)</td> </tr> <tr> <td>6 (6%)</td> <td>1 (1%)</td> </tr> <tr> <td>6 (6%)</td> <td>1 (1%)</td> </tr> <tr> <td>6 (6%)</td> <td>0 (0%)</td> </tr> <tr> <td>5 (5%)</td> <td>1 (1%)</td> </tr> </table> <p>Any adverse event Injection site reaction Injection site ecchymosis Accidental injury Headache Simusitis Rash Cough increase Dizziness Nausea Rhinitis Diarrhoea Dyspepsia Immunisation reaction Pruritus</p> <p>Infectious adverse events including any serious infections occurring in >5% patients in any group (no. of patients)</p> <table border="0"> <tr> <td>Placebo</td> <td>Etanercept</td> </tr> <tr> <td>45 (43%)</td> <td>40 (40%)</td> </tr> <tr> <td>24 (23%)</td> <td>21 (21%)</td> </tr> <tr> <td>6 (6%)</td> <td>6 (6%)</td> </tr> </table> <p>Any infection Upper respiratory infection Urinary tract infection</p> <p>Infections that required hospitalisation or use of intravenous antibiotics (no. of patients) Etanercept: 0 Placebo: Gastroenteritis 1</p> <p>Cancer None</p> <p>Other non-infectious serious adverse events Etanercept: Total 4 (4 patients); Chest pain 1; Renal calculus 1; Multiple sclerosis 1; Synscope 1 Placebo: Total 8 (4 patients); Angina pectoris 1; Gastroenteritis 1; Gastritis 1; Atrial fibrillation 1; GI haemorrhage; Heart failure 1; Perforated large intestine 1; Surgery complications for perforated bowel (intraoperative haemorrhage 1</p> <p>Deaths Etanercept: 0</p>	Placebo	Etanercept	69 (66%)	65 (64%)	9 (9%)	36 (36%)	11 (11%)	12 (12%)	5 (5%)	8 (8%)	5 (5%)	8 (8%)	8 (8%)	6 (6%)	7 (7%)	5 (5%)	6 (6%)	4 (4%)	5 (5%)	4 (4%)	7 (7%)	2 (2%)	7 (7%)	1 (1%)	6 (6%)	1 (1%)	6 (6%)	1 (1%)	6 (6%)	0 (0%)	5 (5%)	1 (1%)	Placebo	Etanercept	45 (43%)	40 (40%)	24 (23%)	21 (21%)	6 (6%)	6 (6%)
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<p>corticosteroids, topical preparations (for scalp, axilla, or groin only).</p> <p>Comments</p>		<p>Placebo: Total 1; Surgery complications for perforated bowel (intraperitoneal haemorrhage) 1</p> <p>Withdrawals due to adverse events</p> <p>Etanercept: Total 1; Elevated liver enzymes 1</p> <p>Placebo: Total 1; Increased psoriasis 1</p> <p>Positive test for anti-etanercept antibody</p> <p>All samples were negative for anti-etanercept antibodies</p> <p>Other important adverse event results</p> <p>CiC removed</p> <p>STAGE 2 (<24WKS MAINTENANCE PERIOD)</p> <p>Non-infectious adverse events</p> <p>CiC removed</p> <p>Infectious adverse events including any serious infections</p> <p>CiC removed</p> <p>Cancer</p> <p>CiC removed</p> <p>Other non-infectious serious adverse events</p> <p>CiC removed</p> <p>Deaths (CiC removed)</p> <p>Withdrawals due to adverse events (no. of patients)</p> <p>CiC removed</p> <p>Positive test for anti-etanercept antibody</p> <p>CiC removed</p> <p>Other important adverse event results</p> <p>CiC removed</p> <p>STAGE 3 (48 WK OPEN-LABEL FOLLOW-UP)</p> <p>Non-infectious adverse events</p> <p>CiC removed</p> <p>Infectious adverse events including any serious infections</p> <p>CiC removed</p> <p>Cancer</p>
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			<p>CiC removed</p> <p>Other non-infectious serious adverse events CiC removed</p> <p>Deaths <i>(CiC information removed)</i></p> <p>Withdrawals due to adverse events (no.) CiC removed</p> <p>Positive test for anti-etanercept antibody CiC removed</p> <p>Other important adverse event results CiC removed</p> <p>STAGE 2 AND STAGE 3 COMBINED Non-infectious adverse events CiC removed</p> <p>Infectious adverse events including any serious infections CiC removed</p> <p>Cancer CiC removed</p> <p>Other non-infectious serious adverse events CiC removed</p> <p>Deaths CiC removed</p> <p>Withdrawals due to adverse events (no.) (CiC removed)</p> <p>Positive test for anti-etanercept antibody (CiC removed)</p> <p>Other important adverse event results (CiC removed)</p> <p>Comments CiC removed</p>
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Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results																																
<p>Moreland, 1999³⁵ USA</p> <p>Type of publication Full publication</p> <p>Other publications/ reports None</p> <p>Funding Immunex Corp.</p> <p>Study design Double-blind RCT</p> <p>Duration of follow-up 26 wks</p> <p>Study objective To establish the benefit of etanercept in the treatment of rheumatoid arthritis over time with simplified dosing.</p> <p>Extracted by: ZK Checked by: NFW</p>	<p>Indication Rheumatoid arthritis</p> <p>Inclusion criteria Patients were adults aged ≥ 18 yrs with active rheumatoid arthritis that had an inadequate response to one of any four DMARDs. Use of DMARDs stopped at least 4 wks prior to study.</p> <p>Total no. of participants 234</p> <p>Age Etanercept (10mg): mean 53 yrs Etanercept (25mg): mean 53 yrs Placebo: mean 51 yrs</p> <p>Gender Etanercept (10mg): male 16% Etanercept (25mg): male 26% Placebo: male 24%</p> <p>Concurrent therapies Oral corticosteroids, NSAIDs, and analgesics (except 24 hrs before joint examinations) were permitted.</p> <p>Comments</p>	<p>Intervention Etanercept Dose regimen: 10mg SC twice a wk Duration/frequency of treatment: 26 wks No. of participants: 76</p> <p>Intervention Etanercept Dose regimen: 25mg SC twice a wk Duration/frequency of treatment: 26 wks No. of participants: 78</p> <p>Comparators Placebo (n=80): equivalent</p> <p>Assessment Not reported</p> <p>Comments</p>	<p>Non-infectious adverse events (no. of events per patient-yr) Occurring in ≥ 10% of patients</p> <table border="1"> <thead> <tr> <th></th> <th>Placebo</th> <th>Etanercept 10mg</th> <th>Etanercept 25mg</th> </tr> </thead> <tbody> <tr> <td>Injection-site reaction</td> <td>0.79 (13%)</td> <td>7.39 (43%)</td> <td>11.76 (49%)</td> </tr> <tr> <td>Headache</td> <td>0.65 (10%)</td> <td>0.81 (20%)</td> <td>0.46 (14%)</td> </tr> <tr> <td>Sinusitis</td> <td>0.42 (11%)</td> <td>0.26 (11%)</td> <td>0.34 (12%)</td> </tr> <tr> <td>Rhinitis</td> <td>0.54 (11%)</td> <td>0.36 (12%)</td> <td>0.37 (10%)</td> </tr> <tr> <td>Diarrhea</td> <td>0.28 (6%)</td> <td>0.33 (11%)</td> <td>0.18 (5%)</td> </tr> </tbody> </table> <p>Infectious adverse events including any serious adverse events (no.) Occurring in ≥ 10% of patients</p> <table border="1"> <thead> <tr> <th></th> <th>Placebo</th> <th>Etanercept 10mg</th> <th>Etanercept 25mg</th> </tr> </thead> <tbody> <tr> <td>Upper respiratory tract infection</td> <td>0.93 (16%)</td> <td>0.85 (29%)</td> <td>1.11 (33%)</td> </tr> </tbody> </table> <p>Cancer Not reported</p> <p>Other non-infectious serious adverse events Not reported</p> <p>Deaths Not reported</p> <p>Withdrawals due to adverse events (no.) Etanercept 10 mg: Injection-site reactions 1 Etanercept 25 mg: Total 0</p> <p>Positive test for anti-etanercept antibody 1 etanercept 10mg patient tested positive for non-neutralising anti-etanercept antibodies at 3 and 4 months</p> <p>Other important adverse events Not reported</p> <p>Comments</p>		Placebo	Etanercept 10mg	Etanercept 25mg	Injection-site reaction	0.79 (13%)	7.39 (43%)	11.76 (49%)	Headache	0.65 (10%)	0.81 (20%)	0.46 (14%)	Sinusitis	0.42 (11%)	0.26 (11%)	0.34 (12%)	Rhinitis	0.54 (11%)	0.36 (12%)	0.37 (10%)	Diarrhea	0.28 (6%)	0.33 (11%)	0.18 (5%)		Placebo	Etanercept 10mg	Etanercept 25mg	Upper respiratory tract infection	0.93 (16%)	0.85 (29%)	1.11 (33%)
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Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
<p>Phillips, 2002,³⁸</p> <p>Type of publication Full publication</p> <p>Other publications/ reports None</p> <p>Funding National Institute of Health (NIH) grants and Arthritis Foundation Investigator Award</p> <p>Study design Retrospective review of medical records</p> <p>Duration of follow-up 6 mths</p> <p>Study objective To investigate the long-term safety and tolerability of etanercept in patients with systemic rheumatic diseases.</p> <p>Extracted by: ZK Checked by: NFW</p>	<p>Indication Rheumatic diseases Rheumatoid arthritis 49 (66%) Juvenile rheumatoid arthritis 25 (14%) Psoriatic arthritis 17 (9%) Ankylosing spondylitis 4 (2%) Dermatomyositis, Still's disease or undifferentiated inflammatory arthritis (9%)</p> <p>Inclusion criteria Patients receiving 25mg etanercept twice weekly</p> <p>Total no. of participants 168</p> <p>Age mean 52.8 yrs (SD 15.6)</p> <p>Gender Etanercept: male 19%</p> <p>Concurrent therapies Methotrexate (56%) Other DMARDs (8%) Corticosteroids (62%)</p> <p>Comments</p>	<p>Intervention Etanercept Dose regimen: 25mg twice a wk Duration of treatment: median 10 mths (range 1-19) No. of participants: 180</p> <p>Assessment Not reported</p> <p>Comments Medically important or serious adverse events defined as those requiring IV antibiotics or hospitalisation. The records of 180 patients were reviewed but as 12 patients were lost to follow-up during the time period of the study, only 168 patients were included in the final calculations.</p>	<p>Non-infectious adverse events Minor adverse events (no. of patients) Injection site reactions 6 Chest pain 5 Skin rash 14 Depression 5</p> <p>Infectious adverse events including any serious infections Upper respiratory infection/cough/sinusitis: 16 patients</p> <p>Serious infections (no of patients) Acute cholecystitis 1 Septic wrist 1 Arthroplastic hip infection 1 Bacteremia 1 Psoas abscess/internal perforation 1</p> <p>Cancer None</p> <p>Other non-infectious serious adverse events 5 (2.9%) patients experienced serious adverse events</p> <p>Deaths (no.) Total 2 (both infection related)</p> <p>Withdrawals due to adverse events (no.) Total 10; minor adverse event 6; serious infection 4</p> <p>Positive test for anti-etanercept antibody Not reported</p> <p>Other important adverse event results 91 (54%) of patients experienced an adverse event; 86 (51%) patients experienced a minor adverse event</p> <p>Comments</p>

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
<p>Willis, 2001,⁹⁷ Europe</p> <p>Type of publication Abstract (interim analysis)</p> <p>Other publications/ reports Wajidula, 2000,¹⁶⁹ Abstract</p> <p>Funding Wyeth-Ayerst.</p> <p>Study design Open-label study</p> <p>Duration of follow-up 1-2 yrs</p> <p>Study objective To evaluate the long-term safety and efficacy of etanercept in patients who completed prior double-blind studies comparing etanercept to placebo</p> <p>Extracted by: AK Checked by: NFW</p>	<p>Indication Rheumatoid arthritis</p> <p>Inclusion criteria Patients with inadequate responses to DMARDs</p> <p>Total no. of participants 549</p> <p>Age Not stated</p> <p>Gender Not stated</p> <p>Concurrent therapies Not stated</p> <p>Comments</p>	<p>Intervention Etanercept Dose regimen: 25mg SC twice a wk Duration/frequency of treatment: 1-2 yrs No. of participants: 549 (479 (87%) completed 1 year follow-up, 94 (17%) completed 2 year follow-up))</p> <p>Comparators None</p> <p>Assessment Not stated</p> <p>Comments</p>	<p>Non-infectious adverse events The most frequent adverse events were injection site reactions</p> <p>Infectious adverse events including any serious infections The most frequent adverse events were upper respiratory infections Rate of serious infections have remained unchanged over the course of the study</p> <p>Cancer Rate of malignancies have remained unchanged over the course of the study</p> <p>Other non-infectious serious adverse events Not stated</p> <p>Deaths Not stated</p> <p>Withdrawals due to adverse events The rate of withdrawal for tolerance-related reasons was 8%</p> <p>Positive test for anti-etanercept antibody Not stated</p> <p>Other important adverse event results Not stated</p> <p>Comments</p>

10.5.2 Data extraction tables: intervention adverse events – efalizumab

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
<p>Gottlieb, 2004,⁹⁵ USA</p> <p>Type of publication Conference poster</p> <p>Other publications/ reports Gottlieb, 2003,¹⁷⁰ Abstract Gottlieb, 2002,¹⁷¹ Abstract ACD2243g, 2004,¹⁷² Industry submission</p> <p>Funding Genentech, Inc.</p> <p>Study design Open label study of efalizumab. All patients received efalizumab. For first 12 weeks patients were randomised to receive concomitant corticosteroids or not.</p> <p>Duration of follow-up 36 mths</p> <p>Study objective To evaluate the efficacy, safety and tolerability of long-term continuous efalizumab therapy in patients who respond to an initial 12 wk course of efalizumab.</p> <p>NOTE: No data available for this study except for the long-term adverse events data extracted here. No data on relative efficacy or AE with or without corticosteroids</p> <p>Extracted by: NW Checked by: AK</p>	<p>Indication Moderate to severe plaque psoriasis</p> <p>Inclusion criteria Patients with moderate to severe plaque psoriasis were entered into a 12 week period of efalizumab treatment. Those who achieved at least PASI 50 or Physician’s global assessment of mild, minimal or clear were entered into long-term treatment with efalizumab.</p> <p>Total no. of participants 339</p> <p>Age Efalizumab: mean 43.6 yrs (range 19-73)</p> <p>Gender Efalizumab: male 64.9% (n=220)</p> <p>Concurrent therapies During the initial 12 wks half the patients were randomised to receive concomitant topical steroids. During the long term follow-up patients were permitted to receive topical therapy or UVB therapy.</p>	<p>Intervention Efalizumab Dose regimen: Initial 3 mths 2mg/kg/wk SC; subsequent 33 mths 1mg/kg/wk SC</p> <p>Duration/frequency of treatment: 36 mths No. of participants: 339 initial 3 mths; 290 subsequent 33 mths</p> <p>Comparators None</p> <p>Assessment Not reported.</p> <p>Comments Safety analyses were conducted on the as treated population (i.e., only patients remaining in the study)</p>	<p>Non-infectious adverse events Non-infectious adverse events that occurred in at least 5% of patients during any 12 week period of the follow-up phase included: accidental injury, increased cough, rhinitis and sinusitis.</p> <p>Infectious adverse events including any serious infections Infectious adverse events that occurred in at least 5% of patients during any 12 week period of the follow-up phase included: non-specific infections, mostly colds and URI. The average frequency of non-specific infection per 3 mth period over the 30 mth follow-up ranged from 8.8% to 15.9% of patients. That for infection related adverse events ranged from 18.0% to 30.1% of patients</p> <p>Cancer The average frequency of skin cancer per 3 mth period over the 30 mth follow-up ranged from 0 to 3.3% of patients.</p> <p>Other non-infectious serious adverse events The average frequency of serious adverse events per 3 mth period over the 30 mth follow-up ranged from 1.0% to 5.5% of patients.</p> <p>Deaths Not reported</p> <p>Withdrawals due to adverse events The average frequency of withdrawals due to adverse events per 3 mth period over the 30 mth follow-up was 3.1% of patients or less.</p> <p>Positive test for anti-etanercept antibody Not reported</p> <p>Other important adverse event results Clinically significant, including serious, adverse events remained generally stable between each 3 month period</p>

10.6 Adverse effects

10.6.1 Adverse Effects of Etanercept

10.6.1.1 Information from standard reference texts

The adverse effects of etanercept summarised from standard reference sources^{62, 64, 78, 79} are listed below.

Adverse events that are frequent and requiring medical attention are infection, respiratory tract infection, varicella infection. Adverse events that are frequent but only require medical attention if they continue or are bothersome, are abdominal pain, headache, injection site reaction, nausea and vomiting, pharyngitis, rhinitis, and sinusitis. Adverse events that are less frequent but requiring medical attention are abdominal abscess, septic arthritis, bronchitis, cellulitis, cholecystitis, hypertension, hypotension, pneumonia, pyelonephritis, sepsis, and development of new positive antinuclear antibodies (ANA) or anti-double-stranded DNA antibodies. Adverse events that are rare but requiring medical attention are aplastic anaemia, generalised anaemia, CNS effects suggestive of MS, transverse myelitis or other demyelinating conditions, leukopenia, optic neuritis, pancytopenia, neutropenia, seizures, thrombocytopenia, and tuberculosis. Adverse events that are less frequent or rare and only require medical attention if they continue or are bothersome are anorexia, asthenia, cough, cutaneous vasculitis, diarrhoea, dry eyes, dry mouth, dyspepsia, fatigue, foot abscess, joint pain, leg ulcer, ocular inflammation, generalised pain, skin rash, and subcutaneous nodules.

Serious adverse events reported with etanercept include malignancies, asthma, infections, heart failure, myocardial infarction, myocardial ischaemia, chest pain, syncope, cerebral ischaemia, hypertension, hypotension, cholecystitis, pancreatitis, gastrointestinal haemorrhage, bursitis, confusion, depression, dyspnoea, abnormal healing, renal insufficiency, kidney calculus, deep vein thrombosis, pulmonary embolism, membranous glomerulonephropathy, polymyositis, thrombophlebitis, liver damage, leucopenia, paresis, paresthesia, vertigo, allergic alveolitis, angioedema, scleritis, bone fracture, lymphadenopathy, ulcerative colitis and intestinal obstruction.

Other side-effects include hypersensitivity reactions (including angioedema, bronchospasm, urticaria, and anaphylaxis), worsening heart failure, fever, depression, lupus erythematosus-like syndrome, pruritus. Other effects reported for etanercept are: oesophagitis, pancreatitis, gastro-intestinal haemorrhage, myocardial or cerebral ischaemia, venous thromboembolism, dyspnoea, bone fracture, renal impairment, polymyositis, bursitis, lymphadenopathy

This list of adverse effects appears very comprehensive but provides only limited information on the significance and frequency of individual events.

10.6.1.2 Information from existing reviews of etanercept

In addition to the standard reference texts, there have been a large number of articles and reviews published regarding the adverse effects of etanercept.⁸⁰⁻⁸⁹ To date the main areas of concern relate to the potential of etanercept to increase the risk of

infections, malignancy, heart failure, conditions secondary to the development of autoimmune antibodies, haematological disorders and demyelinating disease.

Infections

Like other treatments for RA, psoriasis or psoriatic arthritis etanercept is immunosuppressant and all carry a risk of rendering the patient susceptible to infection. The most frequently occurring infections associated with etanercept and other anti-TNF are upper respiratory tract infections. These are generally not serious i.e do not require hospitalisation or IV antibiotics. The FDA review in August 2001¹⁷³ reported that of an estimated 82000 patients treated worldwide with etanercept there had been 13,000 MedWatch reports, 2782 (21%) of which were of infections.

Mycobacterium tuberculosis infection (TB) is a major concern with anti-TNF agents. This is because tumour necrosis factor is important for controlling *M. tuberculosis* infection within the body. Ninety-five percent of those infected will contain the organism via an effective cell-mediated immune response. Exposure to anti-TNF agents may enable reactivation of latent infection. The number of cases with infliximab has been estimated as 24.4 cases/100 000 compared to a rate of 6.2 cases/100 000 in patients with rheumatoid arthritis. Data reviewed by the FDA in August 2001¹⁷³ indicated that the risk of TB with etanercept seems lower than with infliximab. However differences in incidences may reflect different background prevalence and there may be other confounding factors; the relative risk of TB with infliximab and etanercept is difficult to quantify. The review concluded that testing for TB prior to etanercept therapy was not warranted but that caution was required and physicians need to be alert to the possibility of TB infections in patients treated with etanercept.

Other infections which may be of significance are:

Listeria monocytogenes, *Streptococcus pneumoniae*, *Aspergillus fumigatus*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Pneumocystis jirovecii (carinii)*, *Coccidioides immitis* and opportunistic infections.

Congestive heart failure

The pharmacology of anti-TNFs suggested the possibility that these agents would have beneficial effects in patients with congestive heart failure (CHF). Two fairly large randomised double-blind placebo controlled trials found no evidence of efficacy for etanercept. However, one trial found a trend towards a higher mortality with etanercept and this appeared to be dose related. These findings were not substantiated by the second trial and therefore the risk of increased mortality in patients with CHF from etanercept cannot be considered definitive.

Malignancy

There is no real indication that etanercept is associated with an increase in solid tumours over the background rate. There is some concern regarding the incidence of lymphoma, which has been reported for etanercept. Lymphomas are more common in patients with rheumatoid arthritis (RA) and there is uncertainty whether this is related to the disorder or to the treatments used for RA. Most commonly associated with anti-TNF therapy is Hodgkin's lymphoma, with an apparent time to onset of 10-21

months. It is not known if this is worse than the incidence associated with other disease modifying anti-rheumatic drugs (DMARDs).

Development of antibodies

Treatment with etanercept has been associated the development of antibodies in some patients: non-neutralising antibodies, anti-nuclear antibodies and anti- double strand DNA antibodies. Generally the development of these antibodies has not been found to be clinically significant but there have been some reports of symptoms consistent with lupus-like syndrome.

Lupus-like syndromes

Reports of a lupus-like rash associated with positive antibodies appear to represent a real but very rare side-effect of etanercept therapy. None of the cases were associated with systemic features of systemic lupus erythematosus (SLE) or with a definite diagnosis of SLE.

Demyelinating disease

Concerns were established after several spontaneous reports of demyelinating disease associated with etanercept: some of new cases of multiple sclerosis (MS) and others of exacerbations of existing multiple sclerosis. The pharmacology of anti-TNFs suggests a possible therapeutic role in MS, however a randomised controlled trial of an anti-TNF drug (not etanercept) found an adverse effect of therapy. This finding was reflected in the experience of two patients with MS treated with infliximab. The FDA review¹⁷³ concluded that although the evidence is not conclusive “TNF agents as a class, may worsen MS in some patients. Caution is clearly warranted in treating patients with pre-existing demyelinating syndromes or in continuing etanercept therapy in patients who develop a demyelinating syndrome.”

Seizures

There have been reports of seizures or convulsions in patients treated with etanercept. However the association with etanercept therapy is not clear: the condition of some patients with pre-existing seizures was not exacerbated by etanercept therapy.

Haematological adverse effects

There have been rare reports of aplastic anaemia and cases of pancytopenia. Although the cases of aplastic anaemia represent a rare event the rate is higher than would have been expected. This increased rate may reflect the higher prevalence in patients with RA. All the cases of pancytopenia were confounded by other factors and the association with etanercept is very unclear.

Intestinal perforation

There have been several cases of intestinal perforation reported for etanercept. The FDA review¹⁷³ concluded that the incidence did not appear to be in excess of the background incidence and that evidence for an association with etanercept was not strong.

Against this background information on the adverse effects profile of etanercept we reviewed systematically all long-term (greater than 24 weeks) studies of at least 100 patients for further information on the adverse effects of etanercept.

10.6.1.3 Adverse Events for Etanercept: data from included studies

From the selection of trials for inclusion in the efficacy evaluation of etanercept three RCTs of etanercept in psoriasis provided data on the adverse effects of etanercept in psoriasis.⁶⁹⁻⁷¹ Although these trials do not meet the selection criteria for studies to be included in the adverse effects part of the review they are included in order that the data on both the harms as well as the benefits reported in the trials of efficacy are considered in this review.

In addition to the RCTs of efficacy a total of nine clinical studies that provided data on the adverse events of etanercept were identified.⁹⁰⁻⁹⁸ Details of all studies are presented in the data extraction tables (Appendix 10.5.1). Each of these nine studies had included at least 100 patients and provided at least 24 weeks data. Five of these studies were of patients treated with etanercept for rheumatoid arthritis; one was of patients with psoriasis, one was of patients with psoriatic arthritis, one study was of patients with ankylosing spondylitis and the last was of patients with either rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis.

Overall there are data available on the adverse effects of etanercept over 12 weeks, 24 wks (6 months), one year and 2 years or more.

Adverse effects of etanercept over 12 weeks

(Note because one of the selection criterion for studies to be included in the evaluation of adverse effects was that trials should be at least 24 weeks long, only the data from the trials of efficacy in psoriasis are included in this summary of 12 week data.)

Two RCTs of etanercept in psoriasis^{69, 70} provided data on the adverse effects of etanercept over a 12 week period (Table 10.6.1). Both trials compared etanercept 25 mg twice weekly and etanercept 50 mg twice weekly with placebo. One trial contained approximately 160 patients per arm whilst the other contained approximately 190 patients per arm, giving patient totals of 358 for etanercept 25 mg, 358 for etanercept 50 mg and 359 for placebo.

Withdrawals due to adverse events occurred in 1 to 3% of patients on etanercept and 1 to 2% of patients on placebo. Neither trial reported the total number of patients reporting an adverse event: non-infectious and infectious adverse events were reported separately. In both trials the proportion of patients that reported any non-infectious adverse event was around (*CiC removed*) in both etanercept dose groups and in the placebo group. (*CiC removed*). Headache was commonly reported in all groups at a rate of around (*CiC removed*). Similarly, in these two trials the rate of injection site ecchymosis was (*CiC removed*).

The reported rate of infections was around (*CiC removed*) to 30% in all treatment groups (*CiC removed*). This finding was similar for upper respiratory tract infections

which occurred in 5% to (*CiC removed*) of all patients. (*CiC removed*). Other non-serious infections were reported by less than (*CiC removed*) of all etanercept patients.

(*CiC removed*).

Adverse effects of etanercept over 24 weeks (6 months)

Six studies provided data on the adverse effects of etanercept given for a period of 24 weeks (6 months) (table 10.6.2).^{69, 71, 90, 92, 95, 98} Two were of patients with psoriasis and there was one each of patients with psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis and any rheumatic disease. Four of these studies were placebo-controlled double-blind RCTs and one was also a double-blind RCT but provided no placebo data. The sixth study was an uncontrolled retrospective case series.

The total number of patients reporting an adverse event was not reported in any of the studies. Patients with psoriasis were studied in one placebo-controlled double-blind RCT⁷¹ and one double-blind RCT but with no placebo data.⁶⁹ (*CiC information removed*) In the one double-blind RCT of patients treated for psoriatic arthritis non-infectious adverse events occurred in 64% of patients treated with etanercept 25 mg twice weekly compared with 66% treated with placebo.⁹²

Individual adverse events reported by 5% or more of etanercept-treated patients in at least one of the studies are listed in Table 4.2.2. (*CiC information removed*). This was seen in all indications: in the placebo-controlled RCTs injection site reaction was reported in 9% to 49% of etanercept treated patients compared to 0% to 13% of placebo treated patients. In the placebo controlled trial of psoriasis patients sinusitis was more common in etanercept patients than placebo patients.

The proportion of patients suffering an infection during treatment with etanercept 25 mg was reported in three double-blind RCTs: two placebo controlled and one in which the control was etanercept 50 mg. It ranged from (*CiC removed*). The placebo-controlled trial in psoriasis patients found a (*CiC removed*) of infection with treatment (*CiC removed* compared with *CiC removed* on placebo), whereas the trial in psoriatic arthritis found the rate on active treatment and placebo to be the same (40% and 43%). The rate reported in the one psoriasis study where data covered only weeks 13 to 24 of treatment was (*CiC removed*).⁶⁹ Upper respiratory tract infections appeared to be more common in etanercept treated patients than in placebo-treated patients. Of the four trials that reported placebo-controlled data only the one in psoriatic arthritis did not report a higher rate in the active treatment group. Individual studies reported urinary tract infection, herpes simplex infection and bronchitis as occurring in (*CiC removed*) of patients respectively.

Serious infections were reported by fewer than 1% of patients in any group in the controlled trials. The case series of 149 patients reported a rate of 3%.

Serious adverse events were uncommon and reported approximately equally on active and placebo treatments. The case series reported the highest rate (3%).(*CiC removed*).

Withdrawals due to adverse events were not consistently higher in etanercept treated patients compared with placebo; the highest rate reported was 5.6% in the uncontrolled case series.

(CiC removed)

In the one study that reported it the proportion of patients developing anti-etanercept antibodies by 24 weeks was 2%.

The RCT comparison between etanercept 25 mg and etanercept 50 mg twice weekly found no increase in adverse events associated with the higher dose.⁶⁹

Adverse effects of etanercept over 12 months (1 year)

Data from two double-blind RCTs of patients suffering from rheumatoid arthritis were available for the adverse events of etanercept 25mg over 12 months of treatment^{91, 96}. Unfortunately in both of these RCTs the control was methotrexate and therefore comparative placebo data were not available. The most common adverse events (those reported by $\geq 10\%$ of patients in at least one of these trials) are listed in Table 10.6.3. One study reported the proportion of patients experiencing any adverse event (86%),⁹¹ and the same study reported a rate of 59% for any infection. Injection site reaction was the most commonly reported adverse event in both trials. Neutropenia was reported in one of these long-term trials; this adverse effect has not been seen in trials of shorter duration. Upper respiratory tract infection was common (35% reported in one trial⁹⁶) and skin infections were reported in 14% of patients.⁹⁶ These findings are reflected by an uncontrolled open-label follow-up study of etanercept in patients with rheumatoid arthritis.⁹⁷ Serious infections occurred in 4% of patients in one RCT⁹¹ and in 3% in the other RCT.⁹⁶ Opportunistic infections were not reported for any of the studies. Cases of cancer were reported at rates of < 1% to 2% across these studies; one of the uncontrolled open-label follow-up studies reported that the rate of malignancy had not changed over the course of the study.⁹⁷

Other serious adverse events, reported in one of the RCTs occurred at a rate of 11%. The rate of withdrawals reported by these three one year studies in RA varied: 11% and 2% in the two RCTs^{91, 96} and 8% in the uncontrolled open-label follow-up study.⁹⁷ Two studies reported the proportion of patients developing anti-etanercept antibodies; 3% and 6% respectively.

One year data for etanercept in psoriasis patients were available from one uncontrolled follow-up study.⁷⁰ *(CiC removed)*.

Adverse effects of etanercept over 2 years or more

Three studies provided data on the adverse effects of etanercept over a period of two years or more.^{92, 94, 96} Of these, two were open-label follow-up of RCTs and one was an uncontrolled observational study. Two were of patients with rheumatoid arthritis and one was of patients with psoriatic arthritis. The results from these studies are summarised in Table 10.6.4.

The long-term data in psoriatic arthritis patients comes from an extension of an RCT.⁹² (*CiC removed*). Unfortunately data on serious adverse effects were not reported for this study.

Even with these long-term data the information relating to serious adverse events, particularly serious infections and cancer are sparse. Serious infection and opportunistic infections are not reported.

Two year data from two studies, one in patients with rheumatoid arthritis and one in patients with psoriatic arthritis,^{92, 96} indicate a (*CiC removed*) rate of adverse events in rheumatoid arthritis patients. Injection site reaction is the most common non-infectious adverse event in both trials but the rate reported was (*CiC removed*) in the rheumatoid arthritis population: 39% compared with (*CiC removed*). Other adverse events such as headache, nausea, rash, diarrhoea, and rhinitis occurred at a (*CiC removed*) frequency in the rheumatoid arthritis trial than in the psoriatic arthritis trial. These differences may reflect differences in the underlying disease or the concomitant medication taken by the two populations.

In the one study that reported it the proportion of patients developing anti-etanercept antibodies was 3.9%.

10.6.1.4 Summary of adverse events data for etanercept

Data were available for 2 years or more of etanercept treatment but most of the long-term data are from patients with RA. Furthermore published long-term data are poorly reported and thus of limited value. For patients with psoriasis data are only available for up to six months. From the clinical trial data reviewed it can be seen that the most common adverse effect of etanercept is injection site reaction; this includes ecchymosis, bruising or bleeding at the injection site. The rate of infections with etanercept is high but not necessarily higher than that on placebo. With longer term use neurological adverse events are reported and haematological effects such as neutropaenia appear. However, it is unclear how treatment related such affects are. Data regarding anti-etanercept antibodies are also scarce, with few studies reporting them. The rates reported indicated that up to 6% of patients might develop antibodies. As identified from earlier reviews, the main areas of concern relate to the potential of etanercept to increase the risk of serious infections, malignancy, heart failure, conditions secondary to the development of autoimmune antibodies, haematological disorders and demyelinating disease. These serious events are uncommon and not readily identified from the published reports of clinical trials.

Table 10.6.1: Pooled adverse events data – Etanercept 12 weeks follow-up

	Leonardi 2004 ⁶⁹ (DB-RCT in psoriasis – 12 week data)		Elewski ⁷⁰ (DB-RCT in psoriasis – 12 week data)	
	Etanercept 25 mg N=162	Etanercept 50 mg N=164	Placebo N=166	Etanercept 25 mg N=196
Non-infectious adverse events				
Occurring in	≥ 5% patients	≥ 5% patients		> 5%
Any non-infectious	CiC removed	CiC removed	CiC removed	CiC removed
Injection site reaction	28 (17%)	22 (13%)	12 (7%)	35 (18%)
Headache	19 (12%)	11 (7%)	11 (7%)	CiC removed
Inject site ecchymosis	4 (2%)	8 (5%)	6 (4%)	CiC removed
Accidental injury	5 (3%)	7 (4%)	7 (4%)	CiC removed
Infectious adverse events including any serious infections				
Any infections	CiC removed	CiC removed	CiC removed	56 (29%)
U. resp infection	15 (9%)	9 (5%)	19 (11%)	CiC removed
CiC removed	CiC removed	CiC removed	CiC removed	CiC removed
Serious infections (no.):	(CiC removed)	(CiC removed)	(CiC removed)	0
Cancer	(CiC removed)	(CiC removed)	(CiC removed)	(CiC removed)
Other non-infectious serious adverse events (no.)	(CiC removed)	(CiC removed)	(CiC removed)	1
Deaths (no.)	(CiC removed)	(CiC removed)	(CiC removed)	0
Withdrawals due to adverse events	(CiC removed)	(CiC removed)	(CiC removed)	3
Positive test for anti-etanercept antibody	NA	NA	NA	2 (1%)
Other important adverse event results				(CiC removed)
				NA
				2 (1%)
				(CiC removed)
				NA
				1
				(CiC removed)
				1
				0
				2 (1%)
				NA

* Where rate is given as <3%, <5% or <10% the data were derived from a publication that reported adverse events that had occurred at or above the given percentage rate. The listed adverse event was not specified in the report for that study and it has been assumed that it occurred at a rate below the cut off level.

Table 10.6.2: Pooled adverse events data - Etanercept 24 weeks (6 months) follow-up

	Davis 2003 (DB-RCT ankylosing spondylitis – 24 wks)		Gottlieb 2003 (DB-RCT psoriasis – 24 wks)		Mease 2004 (DB-RCT psoriatic arthritis – 24 wks)		Moreland 1999 (DB-RCT rheumatoid arthritis – 26 wks)		Phillips 2002 uncontrolled case series rheumatoid disease - 6 mths)		Leonardi 2004 (DB-RCT psoriasis – 13-24 wks)	
	Etanercept 25mg n=138	Placebo (n=139)	Etanercept 25mg n=57	Placebo (n=55)	Etanercept 25mg n=101	Placebo n=139	Etanercept 25mg n=78	Placebo n=80	Etanercept 25mg n=180	Etanercept 25mg n=149	Etanercept 50mg n=159	
Non-infectious adverse events (no. of patients) occurring in	No. (%)	No. (%)	No. pts (%)	No. pts (%)	No. pts (%)	No. pts (%)	No. events/pt yr	No. pts (%)	No. pts (%)			
	>5% patients		> 5% of patients		>5% patients		≥ 10% of patients					>5% patients
Any non-infectious AE	NR	NR	(CiC removed)	(CiC removed)	65 (64%)	69 (66%)	NR	NR	NR	(CiC removed)	(CiC removed)	(CiC removed)
Abdominal pain	8 (6%)	7 (5%)	(CiC removed)	(CiC removed)	<5%	<5%	<10%	<10%	NR	(CiC removed)	(CiC removed)	(CiC removed)
Accidental injury	17 (12%)	6 (4%)	4 (7%)	2 (4%)	8 (8%)	5 (5%)	<10%	<10%	NR	<3%	<3%	<3%
Asthenia	<5%	<5%	(CiC removed)	(CiC removed)	<5%	<5%	<10%	<10%	NR	7 (5%)	2 (1%)	2 (1%)
Cellulitis	<5%	<5%	(CiC removed)	(CiC removed)	<5%	<5%	<10%	<10%	NR	(CiC removed)	(CiC removed)	(CiC removed)
Diarrhoea	11 (8%)	13 (9%)	(CiC removed)	(CiC removed)	1 (1%)	6 (6%)	0.18 (5%)	0.28 (6%)	NR	(CiC removed)	(CiC removed)	(CiC removed)
Dizziness	8 (6%)	3 (2%)	(CiC removed)	(CiC removed)	4 (4%)	5 (5%)	<10%	<10%	NR	(CiC removed)	(CiC removed)	(CiC removed)
Headache	19 (14%)	16 (12%)	9 (16%)	7 (13%)	8 (8%)	5 (5%)	0.46 (14%)	0.65 (10%)	NR	8 (5%)	4 (3%)	4 (3%)
Hypertension	<5%	<5%	4 (7%)	2 (4%)	<5%	<5%	<10%	<10%	NR	(CiC removed)	(CiC removed)	(CiC removed)
Injection site reaction	41 (30%)	13 (9%)	5 (9%)	0 (0%)	36 (36%)	9 (9%)	11.76 (49%)	0.79 (13%)	6 (3.6%)	<3%	<3%	<3%
Injection site bruising / ecchymosis	29 (21%)	23 (17%)	6 (11%) (CiC removed)	5 (9%) (CiC removed)	12 (12%)	11 (11%)	<10%	<10%	NR	(CiC removed)	(CiC removed)	(CiC removed)
Pain	<5%	<5%	4 (7%)	4 (7%)	<5%	<5%	<10%	<10%	NR	(CiC removed)	(CiC removed)	(CiC removed)
Psoriasis	<5%	<5%	(CiC removed)	(CiC removed)	<5%	<5%	<10%	<10%	NR	(CiC removed)	(CiC removed)	(CiC removed)

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Rash	11 (8%)	9 (6%)	(CiC removed)	(CiC removed)	5 (5%)	7 (7%)	<10%	<10%	14 (8.3%)	<3%	<3%
Rhinitis	8 (6%)	9 (6%)	(CiC removed)	(CiC removed)	1 (1%)	7 (7%)	0.37 (10%)	0.54 (11%)	NR	(CiC removed)	(CiC removed)
Sinusitis	<5%	<5%	8 (14%)	4 (4%)	6 (6%)	8 (8%)	0.34 (12%)	0.42 (11%)	NR	<3%	<3%
Infectious adverse events including any serious infections (no. of patients) occurring in >5% patients											
Any infectious AE	NR	NR	(CiC removed)	(CiC removed)	40 (40%)	45 (43%)	NR	NR	NR	(CiC removed)	(CiC removed)
Upper respiratory tract infection	28 (20%)	16 (12%)	20 (35%)	11 (20%)	21 (21%)	24 (23%)	1.11 (33%)	0.93 (16%)	16 (9.5%)	9 (6%)	11 (7%)
Urinary tract infection	<5%	<5%	(CiC removed)	(CiC removed)	6 (6%)	6 (6%)	<10%	<10%	NR	(CiC removed)	(CiC removed)
Herpes simplex	<5%	<5%	(CiC removed)	(CiC removed)	<5%	<5%	<10%	<10%	NR	(CiC removed)	(CiC removed)
Bronchitis	<5%	<5%	(CiC removed)	(CiC removed)	<5%	<5%	<10%	<10%	NR	(CiC removed)	(CiC removed)
Opportunistic or tuberculous infections (no. of patients):	0	0	NR	NR	NR	NR	NR	NR	NR	<3%	<3%
Serious infections (no. of patients):	1	1	1	1	0	1	NR	NR	5 (3.0%)	(CiC removed)	(CiC removed)
Cancer	NR	NR	NR	NR	0	0	NR	NR	0	(CiC removed)	(CiC removed)
Other non-infectious serious AEs (no. of patients)	8	4	1	2	(CiC removed)	(CiC removed)	NR	NR	5 (3.0%)	(CiC removed)	(CiC removed)
Deaths	NR	NR	0	0	0	1	NR	NR	2 (1.2%)	NR	NR
Withdrawals due to adverse events (no. of patients)	7 (5%)	1 (1%)	2 (3.5%)	6 (11%)	1 (1%)	1 (1%)	0	0	10 (5.6%)	(CiC removed)	(CiC removed)

Table 10.6.3: Pooled adverse events data – Etanercept 1 year follow-up

	Klarskog (Rheumatoid arthritis DB-RCT - 52 weeks) Etanercept 25 mg N=223	Bathson (Rheumatoid arthritis DB-RCT 1 yr - 52 weeks) Etanercept 25 mg n=207	Elewski (Psoriasis Open-label follow-up - 48 wks) Etanercept 25mg (177 on placebo and 190 on 50 mg dose for first 12 wks) N=557 (CiC removed)	Willis (Rheumatoid arthritis Open-label follow-up – approx. 1 yr) Etanercept 25 mg N=549
Any adverse event	192 (86%)			
Non-infectious adverse events				
Occurring in	≥ 5%	in ≥ 10% patients		
Any non-infectious adverse event	NR	NR	(CiC removed)	The most frequent adverse events were injection site reactions
Abdominal pain	26 (12%)	20 (10%)		
Accidental injury	19 (9%)	<10%	(CiC removed)	
Asthenia	23 (10%)	27 (13%)		
Back pain	28 (13%)	22 (11%)		
Cough increased	14 (6%)	<10%		
Diarrhoea	23 (10%)	30 (14%)		
Dizziness	<5%	24 (12%)		
Dyspepsia	<5%	25 (12%)		
Headache	34 (15%)	46 (22%)	(CiC removed)	
Influenza-like syndrome	<5%	26 (13%)		
Injection site reaction	46 (21%)	77 (37%)		
Injection site ecchymosis	<5%	29 (14%)	(CiC removed)	
Low peripheral lymphocyte count	<5%	NR (56% for lower dose)		
Migraine			(CiC removed)	
Nausea	22 (10%)	35 (17%)		
Neutropenia Sporadic	<5%	(16%)		
Rhinitis	<5%	31 (15%)		
Rash	16 (7%)	25 (12%)		
Sinusitis	<5%	20 (10%)		
Infectious adverse events including any serious infections				
Occurring in	≥ 10%	≥ 10%		
Any infection;	131 (59%)	NR	(CiC removed)	The most frequent adverse events were upper respiratory infections
Upper respiratory tract infection		72 (35%)		
Skin infection		28 (14%)		

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Serious infections	10 (4%)	< 3%	(CiC removed)	Rate of serious infections remained unchanged over the course of the study
Opportunistic infections	NR	0		NR
Cancer	4	3	(CiC removed)	Rate of malignancies have remained unchanged over the course of the study
Other non-infectious serious adverse events (no. of patients)	25 (11%)	NR	(CiC removed)	NR
Deaths (no.)	1	1	(CiC removed)	NR
Withdrawals due to adverse events	25	5	(CiC removed)	The rate of withdrawal for tolerance-related reasons was 8%
Positive test for anti-etanercept antibody	NR	< 3%	(CiC removed)	NR
Other important adverse event results		All types of infection occurred at a rate of 1.5 events per patient yr. The rate of serious infections was similar to that in mths 13-24		NR

* Where rate is given as <3%, <5% or <10% the data were derived from a publication that reported adverse events that had occurred at or above the given percentage rate. The listed adverse event was not specified in the report for that study and it has been assumed that it occurred at a rate below the cut off level.

Table 10.6.4: Pooled adverse events data – Etanercept 2 years or more follow-up

	Bathson (rheumatoid arthritis, open-label follow-up - 2 yrs) n=207	Mease (psoriatic arthritis, open-label follow-up - 96 weeks) Etanercept 25 mg (CiC removed)	Geborek 2002 (rheumatoid arthritis, open-label follow-up - 2 yrs) Etanercept 25 mg N=166
Non-infectious adverse events occurring in	>10%	CiC Removed	NR
Any non-infectious AE	NR	CiC Removed	
Injection site reaction	81 (39%)	CiC Removed	
Echymosis (injection site)	23 (11%)	CiC Removed	
Bleeding at injection site	32 (16%)	CiC Removed	
Accidental injury	23 (11%)	CiC Removed	
Headache	51 (25%)	CiC Removed	
Back pain	25 (12%)	CiC Removed	
Hypertension	<10%	CiC Removed	
Nausea	42 (20%)	CiC Removed	
Rash	37 (18%)	CiC Removed	
Rhinitis	37 (18%)	CiC Removed	
Diarrhoea	35 (17%)	CiC Removed	
Asthenia	33 (16%)	CiC Removed	
Sporadic neutropenia	>10%	CiC Removed	
Dyspepsia	31 (15%)	CiC Removed	
Dizziness	30 (15%)	CiC Removed	
Abdominal pain	26 (13%)	CiC Removed	
Pain	22 (11%)	CiC Removed	
Vomiting	20 (10%)	CiC Removed	
Low peripheral lymphocyte count	≥10%	CiC Removed	
Infectious adverse events including any serious infections occurring in	≥10%	CiC Removed	NR
Any infection	NR	CiC Removed	
Upper respiratory infection	NR	CiC Removed	
Flu syndrome	NR	CiC Removed	
Sinusitis	NR	CiC Removed	
Pharyngitis	NR	CiC Removed	
Serious infection	7 (3.4%)	CiC Removed	3
Opportunistic infections	0		NR

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Cancer (no. of patients)	4	<i>CiC Removed</i>	NR (at least one)
Other serious non-infectious adverse events	Not reported	<i>CiC Removed</i>	8
Deaths (no.)	1	<i>CiC Removed</i>	3
Withdrawals due to adverse events (no.)	15 (7.3%)	<i>CiC Removed</i>	
Positive test for anti-etanercept antibody	8 (3.9%)	<i>CiC Removed</i>	NR
Other important adverse event results		<i>CiC Removed</i>	The total no. of observational yrs for etanercept was 232.8 Graded side effects per 100 yrs (no.) Fatal 1.3 (n=3) (included above) Life-threatening 0 (n=0) Serious 7 (n=15) Moderate 16 (n=36) Mild 27 (n=61) Not graded 2 (n=5)

* Where rate is given as <3%, <5% or <10% the data were derived from a publication that reported adverse events that had occurred at or above the given percentage rate. The listed adverse event was not specified in the report for that study and it has been assumed that it occurred at a rate below the cut off level.

10.6.2 Adverse Effects of Efalizumab

10.6.2.1 Information from standard reference texts

The information included in the Summary of Product Characteristics for efalizumab (Raptiva) is summarised below.

The most frequent symptomatic adverse events reported during efalizumab therapy were mild to moderate dose-related acute flu-like symptoms including headache, fever, chills, nausea and myalgia. In large placebo-controlled clinical studies, these reactions were observed in approximately 41% of efalizumab-treated patients and 24% in placebo-treated patients over 12 weeks of treatment. After initiation of therapy, these reactions were generally less frequent and occurred at similar rates to that seen in the placebo group from the third and subsequent weekly injections. Antibodies to efalizumab were detected in only 6% of patients. In this small number of patients no differences were observed in pharmacokinetics, pharmacodynamics, clinically noteworthy adverse events or clinical efficacy.

Those adverse events that were very common (i.e. occurred in more than 1 in 10 patients) in the total population studied clinically with efalizumab were leukocytosis and lymphocytosis, and flu-like symptoms (fever, headaches, chills, nausea and myalgia). Common adverse events (i.e. occurred in between 1 in 10 and 1 in 100 patients) were psoriasis, arthralgia, psoriatic arthritis (exacerbation/flare), hypersensitivity reactions, back pain, asthenia, elevation of alkaline phosphatase, and elevation of ALT. Uncommon adverse events (i.e. occurred in between 1 in 100 and 1 in 1000 patients) were thrombocytopenia, urticaria, and injection site reactions. No rare (between 1 in 1000 and 1 in 10,000 patients) or very rare less than 1 in 10,000 reactions were reported.

Infections were common in efalizumab treated patients, however in placebo controlled trials this rate was not higher than with placebo treatment.

Analysis following long-term use in a cohort of 158 patients with moderate to severe psoriasis receiving efalizumab 1 mg/kg/week for 108 weeks did not show any noteworthy differences in frequency of adverse events as compared to 12 weeks of exposure to efalizumab. Safety data beyond 12 weeks in the target population were not yet available.

Therapies affecting the immune system have been associated with an increased rate of malignancies. In placebo controlled clinical trials, the overall incidences of malignancy (the majority of which were non-melanoma skin cancers) were similar in efalizumab-treated patients and in placebo-treated patients. In addition, the incidences of specific tumours in efalizumab patients were in line with those observed in control psoriasis populations. Among psoriasis patients who received efalizumab at any dose, the overall incidence of malignancies of any kind was 1.7 per 100 patient-years for efalizumab-treated patients compared with 1.6 per 100 patient-years for placebo-treated patients. Experience with efalizumab has not shown evidence of risk of developing malignancy exceeding that expected in the psoriasis population.

10.6.2.2 Information from existing reviews of efalizumab

Little has been published on the adverse effects of efalizumab. Two overviews^{99, 100} summarise the clinical trials data. These data are evaluated as part of the systematic review below and are therefore not discussed further here.

10.6.2.3 Adverse events for efalizumab: data from included studies

In addition to the five trials already identified for the assessment of the efficacy of efalizumab,⁷²⁻⁷⁶ there was one long-term follow-up study⁹³ that provided information on the adverse effects of efalizumab sub-cutaneous injection. One trial of an intravenous formulation of efalizumab was also found.⁷⁷ Details of all studies are presented in the data extraction tables (Appendix 10.5.2). All studies of efalizumab were in psoriasis patients; no data from studies of other indications met the inclusion criteria.

The five trials were all double-blind placebo-controlled RCTs conducted in patients with plaque psoriasis. All five trials evaluated efalizumab at a dose of 1mg/kg administered sub-cutaneously once a week. One trial also evaluated a higher dose of 2 mg/kg, administered once a week.⁷² All five trials provided adverse events data for a 12-week treatment period, with a total number of (*CiC removed*) patients treated with efalizumab 1 mg/kg once a week, (*CiC removed*) treated with efalizumab 2 mg once a week, and (*CiC removed*) treated with placebo. In addition, two trials^{72, 74} provided data for a further 12 weeks in selected patients (number not reported) and one of these trials⁷² provided data for a treatment free follow-up period of 12 weeks (171 with efalizumab and 158 with placebo).

Adverse effects of efalizumab over 12 weeks

These data are summarised in Table 10.6.5. Across the trials the proportion of patients reporting at least one adverse event during treatment with efalizumab 1 mg/kg was high (range (*CiC removed*) to 86%). However the rate on placebo was also high ranging from (*CiC removed*) to 77% of patients. Headache was the most commonly reported non-infectious adverse event in all five trials with the proportion of patients reporting headache with efalizumab 1 mg/kg ranging from (*CiC removed*) to 35%. In all five trials the proportion of patients reporting headache in the placebo group was lower ranging from (*CiC removed*) to 30%. Chills was the next most common adverse event (*CiC removed*) to 16% of patients) and in all but one trial the rate in the efalizumab group was double that in the placebo group (range 2% to 6%). Nausea, myalgia, pain and fever were reported by at least (*CiC removed*) of patients in all or almost all trials and the rates were generally higher in the groups who received active rather than placebo treatment. Rhinitis, asthenia, diarrhoea, and accidental injury were also reported commonly but the rates in the placebo treated groups were approximately equal to those in the efalizumab groups.

Infection was reported in around (*CiC removed*) of patients on efalizumab compared to around (*CiC removed*) on placebo. No specific infection was reported more commonly with efalizumab than with placebo. Unfortunately the rate of serious infections was not reported so whether or not there is any tendency for efalizumab to increase these relatively rare events cannot be discerned from these trial data.

The rate of serious adverse events with efalizumab was low at around 2%, but again data are sparse with only two trials reporting them.^{72, 73} There were no deaths associated with 12 weeks of efalizumab treatment and most trials did not report cancer data.

Withdrawals due to adverse events were at a rate of around 4% on efalizumab compared to around 2% on placebo.

Rates of around 1% to (CiC removed) for patients who developed anti-efalizumab antibodies were reported.

The adverse events reported for the 2 mg/kg dose of efalizumab over 12 weeks reflect those reported with the 1 mg/kg dose and do not appear to occur with any greater frequency.⁷² However some data were not reported and it may be found that rates of infection or serious adverse effects may be higher with the higher dose.

Adverse effects of efalizumab over 24 weeks

Two trials^{72, 74} evaluated 24 weeks of efalizumab treatment but for both the level of detail available from the available reports is very limited and these are not presented in a table. These trials reported that adverse events were similar or less than for the initial 12 week period and one trial⁷² reported adverse events leading to withdrawal were more common in patients receiving placebo. Unfortunately, one of these trials evaluated only the higher dose of efalizumab for the second 12 weeks,⁷² and in the other it is unclear which dose was studied.⁷⁴ Furthermore, the total number of patients treated with efalizumab was only 171 in one trial⁷² and not reported in the other.⁷⁴ (CiC removed).

For treatment-free follow-up (weeks 24-36) adverse events in all patients were: infection (13%); worsening psoriasis (9%); pruritis (6%); arthritis (5%). Five efalizumab treated patients developed anti-efalizumab antibodies; the safety profile of these patients was not different to that of the other patients. Thirteen patients (3%) had a serious adverse event (5 non-fatal infections and 3 psoriasis-related events).

One trial of an intravenous formulation of efalizumab in which 97 patients were randomised to 0.1 mg/kg or 0.3 mg/kg efalizumab and 45 were randomised to placebo followed-patients for 20 weeks. The findings of this trials reflected those for the sub-cutaneous formulation.⁷⁷ Details can be found in the data extraction tables (Appendix 10.5.2)

Adverse effects of efalizumab over 1 year or more

One long-term study provided data on 339 patients who had responded to efalizumab and who were then followed for up to three years.⁹³ This study reported the data in terms of 12 week periods during the whole follow-up period. The results are summarised in Table 4.2.6. These data indicated that the clinically significant adverse events were non-specific infections (mostly colds and upper respiratory tract), accidental injury, increased cough, rhinitis and sinusitis.

The rate of serious adverse events per 3 month period ranged from 1% to 5.5% over the whole study period. The average frequency of skin cancer per 3 month period

ranged from 0 to 3.3%: the higher figure representing one month's atypical high rate. Withdrawals during any period of the follow-up were at a rate of 3.4% or less. The authors state that 'Clinically significant including serious adverse vents remained generally stable between each 3 month period'.

(CiC removed)

10.6.2.4 Summary of adverse events data for efalizumab

The available data for 12 weeks of treatment with efalizumab demonstrate a very high rate of adverse events but this rate is not higher than that reported on placebo. The events which are more commonly reported with efalizumab than with placebo are headache, chills, and in some trials but at a lower rate, nausea, myalgia, pain and fever. The rate of infection is also high, but again, the rate is no higher than on placebo. Unfortunately data for serious infections are not reported and therefore the relative incidence of these cannot be evaluated. Similarly, few data on serious adverse events with efalizumab are available. Overall withdrawal rates due to adverse events are low at 4%, compared to around 2% on placebo. One to *(CiC removed)* of patients treated with efalizumab for 12 weeks developed anti-bodies, but this did not appear to be associated with any increased risk of adverse events. The rate of adverse events on a higher dose of efalizumab (2 mg/kg) did not appear to be higher than that on the 1 mg/kg dose, but this higher dose was tested in only one trial and so firm conclusions cannot be drawn. The available published reports of the efalizumab trials did not reveal leukocytosis and lymphocytosis as common adverse consequences of therapy.

Longer-term data for efalizumab are not readily available; those trials that were conducted have been reported in summary form only. Overall the adverse events over longer periods up to three years appear to reflect those over 12 weeks and to remain stable.

In summary, the publicly available information for efalizumab indicates that the drug is well tolerated over a 12 week period, however, few data for any longer-term treatment are available for evaluation.

Table 10.6.5: Pooled adverse events data – Efalizumab 12 weeks follow-up

	Gordon 2003 ⁷³ DB-RCT, Psoriasis 12 wks		IMP24011 ⁷⁶ CiC removed		ACD2600 ⁷⁵ CiC removed		ACD2058 ⁷⁴ DB-RCT, Psoriasis 12 weeks		Lebwohl 2003 ⁷² DB-RCT, Psoriasis 12 weeks		
	Efalizumab 1mg(n=368)	Placebo (n=187)	CiC removed	CiC removed	CiC removed	CiC removed	Efalizumab 1 mg (n=162)	Placebo (n=170)	Efalizumab 1 mg(n=232)	Efalizumab 2 mg(n=243)	Placebo (n=122)
Adverse events occurring in	≥ 5% of all patients		CiC removed		CiC removed		≥ 5% of efalizumab patients		≥ 5% patients in any treatment group		
Total	296 (80%)	133 (71%)	CiC removed	CiC removed	CiC removed	CiC removed	135 (83%)	130 (77%)	199 (86%)	207 (85%)	91 (75%)
Drug-exposure related	163 (44%)	47 (25%)	CiC removed	CiC removed	CiC removed	CiC removed	75 (46%)	58 (34%)	117 (50%)	NR	49 (40%)
Non-infectious adverse events											
Headache	123 (33%)	39 (21%)	CiC removed	CiC removed	CiC removed	CiC removed	57 (35%)	51 (30%)	71 (31%)	93 (38%)	29 (24%)
Chills	44 (12%)	10 (5%)	CiC removed	CiC removed	CiC removed	CiC removed	20 (12%)	10 (6%)	38 (16%)	31 (13%)	3 (2%)
Nausea	39 (11%)	13 (7%)	CiC removed	CiC removed	CiC removed	CiC removed	14 (9%)	16 (9%)	34 (15%)	35 (14%)	11 (9%)
Myalgia	38 (10%)	8 (4%)	CiC removed	CiC removed	CiC removed	CiC removed	13 (8%)	8 (5%)	16 (7%)	22 (9%)	5 (4%)
Pain	37 (10%)	9 (5%)	CiC removed	CiC removed	CiC removed	CiC removed	21 (13%)	16 (9%)	35 (15%)	29 (12%)	4 (3%)
Fever	25 (7%)	3 (2%)	CiC removed	CiC removed	CiC removed	CiC removed	12 (7%)	9 (5%)	26 (11%)	29 (12%)	6 (5%)
Rhinitis	23 (6%)	11 (6%)	CiC removed	CiC removed	CiC removed	CiC removed	13 (8%)	14 (8%)	18 (8%)	13 (5%)	8 (7%)
Asthenia	22 (6%)	9 (5%)	CiC removed	CiC removed	CiC removed	CiC removed	16 (10%)	17 (10%)	17 (7%)	27 (11%)	7 (6%)
Diarrhoea	20 (5%)	10 (5%)	CiC removed	CiC removed	CiC removed	CiC removed	12 (7%)	12 (7%)	16 (7%)		11 (9%)
Accidental injury	17 (5%)	19 (10%)	CiC removed	CiC removed	CiC removed	CiC removed	17 (11%)	6 (4%)	11 (5%)		9 (7%)
Sinusitis	<5%	<5%	CiC removed	CiC removed	CiC removed	CiC removed	12 (7%)	6 (4%)	<5%	<5%	
Pruritis	<5%	<5%	CiC removed	CiC removed	CiC removed	CiC removed	8 (5%)	11 (7%)	<5%	<5%	
Peripheral oedema	<5%	<5%	CiC removed	CiC removed	CiC removed	CiC removed	9 (6%)	5 (3%)	14 (6%)	12 (5%)	5 (4%)
Back pain	<5%	<5%	CiC removed	CiC removed	CiC removed	CiC removed	10 (6%)	5 (3%)	10 (4%)	16 (7%)	1 (1%)

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Cough increased	<5%		<5%	CiC removed	removed CiC removed	CiC removed	removed CiC removed	5 (3%)	8 (5%)	8 (3%)	13 (5%)	5 (4%)
Worsening psoriasis	<5%		<5%	CiC removed	removed CiC removed	CiC removed	removed CiC removed	8 (5%)	4 (2%)	12 (5%)	8 (3%)	2 (2%)
Dizziness	<5%		<5%	CiC removed	removed CiC removed	CiC removed	removed CiC removed	11 (7%)	8 (5%)	9 (4%)		6 (5%)
Hearing loss	<5%		<5%	CiC removed	removed CiC removed	CiC removed	removed CiC removed	12 (7%)	5 (3%)	24 (10%)	12 (5%)	6 (5%)
Anthralgia	<5%		NR	CiC removed	removed CiC removed	CiC removed	removed CiC removed	<5%	NR	12 (5%)	10 (4%)	2 (2%)
Vomiting	<5%		NR	CiC removed	removed CiC removed	CiC removed	removed CiC removed	<5%	NR	14 (6%)	6 (2%)	1 (1%)
Acne	<5%		NR	CiC removed	removed CiC removed	CiC removed	removed CiC removed	<5%	NR			
Infectious adverse events including any serious infections												
Any infection	27%		23%	CiC removed	removed CiC removed	CiC removed	removed CiC removed	27%	23%	22%	NR	25%
Infection not specified	46 (13%)		23 (12%)	CiC removed	removed CiC removed	CiC removed	removed CiC removed	23 (14%)	23 (14%)	27 (12%)	43 (18%)	19 (16%)
Pharyngitis	27 (7%)		10 (5%)	CiC removed	removed CiC removed	CiC removed	removed CiC removed	9 (6%)	14 (8%)	14 (6%)	22 (9%)	6 (5%)
Flu-like syndrome	27 (7%)		7 (4%)	CiC removed	removed CiC removed	CiC removed	removed CiC removed	<5%	NR	<5%	<5%	<5%
Herpes simplex	17 (5%)		7 (4%)	CiC removed	removed CiC removed	CiC removed	removed CiC removed	10 (6%)	10 (6%)	5 (4%)	8 (3%)	14 (6%)
Gastroenteritis	5 (1%)		10 (5%)	CiC removed	removed CiC removed	CiC removed	removed CiC removed	<5%	NR	<5%	<5%	<5%
Serious infections	0.5%		0.5%	CiC removed	removed CiC removed	CiC removed	removed CiC removed	NR	NR	NR	NR	NR
Cancer	2		0	CiC removed	removed CiC removed	CiC removed	removed CiC removed	NR	NR	NR	NR	NR
Other non-infectious serious adverse events	2% (9/368)		1% (1/187)	CiC removed	removed CiC removed	CiC removed	removed CiC removed	NR	NR	4 (2%)	7 (3%)	1 (1%)
Deaths	0		0	CiC removed	removed CiC removed	CiC removed	removed CiC removed	0	0			

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Withdrawals due to adverse events	12 (3%)	2 (1%)	CiC removed	CiC removed	CiC removed	CiC removed	6 (3.7%)	6 (3.5%)	9 (4%)	7 (3%)	2 (2%)
Positive test for anti-efalizumab antibody	8 (2%)	0	CiC removed	CiC removed	CiC removed	CiC removed	2/314 (0.6%)	NR	3/456 (0.7%)		

DB-RCT – double blind randomised control trial

Table 10.6.6: Pooled adverse events data – Efalizumab 1 year or more follow-up

	Gottlieb 2004 (psoriasis, open-label follow-up - 3 yrs)
	Etanercept 25 mg N=339
Non-infectious adverse events	Non-infectious adverse events that occurred in at least 5% of patients during any 12 week period of the follow-up phase included: accidental injury, increased cough, rhinitis and sinusitis.
Any non-infectious AE	
Injection site reaction	
Ecchymosis (injection site)	
Bleeding at injection site	
Accidental injury	
Headache	
Back pain	
Hypertension	
Nausea	
Rash	
Rhinitis	
Diarrhoea	
Asthenia	
Sporadic neutropenia	
Dyspepsia	
Dizziness	
Abdominal pain	
Pain	
Vomiting	
Low peripheral lymphocyte count	
Infectious adverse events including any serious infections	Infectious adverse events that occurred in at least 5% of patients during any 12 week period of the follow-up phase included: non-specific infections, mostly colds and URI. The average frequency of non-specific infection per 3 mth period over the 30 mth follow-up ranged from 8.8% to 15.9% of patients. That for infection related adverse events ranged from 18.0% to 30.1% of patients
<i>occurring in</i>	
Any infection	
Upper respiratory infection	
Flu syndrome	
Sinusitis	
Pharyngitis	
Serious infection	
Opportunistic infections	NR
Cancer (no. of patients)	The average frequency of skin cancer per 3 mth period over the 30 mth follow-up ranged from 0 to 3.3% of patients.
Other serious non-infectious adverse events	The average frequency of serious adverse events per 3 mth period over the 30 mth follow-up ranged from 1.0% to 5.5% of patients.
Deaths (no.)	NR
Withdrawals due to adverse events (no.)	The average frequency of withdrawals due to adverse events per 3 mth period over the 30 mth follow-up was 3.1% of patients or less.
Positive test for anti-etanercept antibody	NR
Other important adverse event results	Clinically significant, including serious, adverse events remained generally stable between each 3 month period

* Where rate is given as <3%, <5% or <10% the data were derived from a publication that reported adverse events that had occurred at or above the given percentage rate. The listed adverse event was not specified in the report for that study and it has been assumed that it occurred at a rate below the cut off level.

10.7 Data extraction tables: efficacy of other treatments for moderate to severe psoriasis

10.7.1 Included studies of other treatments for moderate to severe psoriasis

Study details	Participants	Treatment	Outcomes and results
Reference Ellis 1991 ¹⁰²	Psoriasis type Plaque	Treatment Ciclosporin 3 mg/kg/day n=25 Ciclosporin 5 mg/kg/day n=20 Ciclosporin 7.5 mg/kg/day n=15	% clear/almost clear Ciclosporin 3 mg/kg/day 36%; Ciclosporin 5 mg/kg/day 65%; Ciclosporin 7 mg/kg/day 80%; Placebo 0%
Study design RCT Whole body	Resistant to topicals/require systemics? Yes Minimum BSA included >25% Minimum PASI included NS Adult? Yes Number of participants n=85	Comparator Placebo equivalent Number of patients n=25 Duration of treatment 8 wks Outcome measure % clear/almost clear Mean PASI (from graph) Physician GA	mean PASI (from graph) Ciclosporin 3 mg/kg/day 6.2 (range 4-7); Ciclosporin 5 mg/kg/day 6.5 (range 5-7); Ciclosporin 7 mg/kg/day 6.5 (range 6-7); Placebo 6.1 (range 5-7) Physician GA Ciclosporin 3 mg/kg/day (wk 0) mean 6.2; (wk 8) mean 3.8 (SE 0.4) Ciclosporin 5 mg/kg/day (wk 0) mean 6.5; (wk 8) mean 2.7 (SE 0.3) Ciclosporin 7 mg/kg/day (wk 0) mean 6.5; (wk 8) mean 1.9 (SE 0.2) Placebo (wk 0) mean 6.1; (wk 8) mean 5.9 (SE 0.2)

Study details	Participants	Treatment	Outcomes and results
Reference Guenther 1991 ¹⁰³	Psoriasis type Plaque	Treatment Ciclosporin 5 mg/kg/day Number of patients n= 12	PASI 50/ PSI 50 Ciclosporin wk4: 9/12; Placebo: 0/11 Ciclosporin wk6: 11/12; Placebo 0/11 Ciclosporin wk10: 12/12; Placebo 1/11
Study design RCT	Resistant to topicals/ require systemics? NS	Comparator Placebo equivalent Number of patients n= 11	Mean PASI Ciclosporin wk0: 23 (n=12); Placebo 21 (n=11) Ciclosporin wk10: 2 (n=11); Placebo 16 (n=3)
Whole body	Minimum BSA included ≥ 25	Duration of treatment 10 wks	
	Minimum PASI included ≥ 12	Outcome measure PASI 50 Mean PASI score	
	Adult? Yes		
	Number of participants n= 23		

Study details	Participants	Treatment	Outcomes and results
<p>Reference Meffert 1997¹⁰⁴</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? Yes</p> <p>Minimum BSA included NS</p> <p>Minimum PASI included 8-25</p> <p>Adult? Yes</p> <p>Number of participants n= 128</p>	<p>Treatment Ciclosporin 1.25 mg/kg/day Number of patients n=41 Ciclosporin 2.5 mg/kg/day Number of patients n= 44</p> <p>Comparator Placebo equivalent n=43</p> <p>Duration of treatment 10 wks</p> <p>Outcome measure PASI 75 PASI 50 Mean PASI Reduction in PASI (from graph)</p>	<p>PASI 75 Ciclosporin 1.25 mg/kg/day (n=41): 10% Ciclosporin 2.5 mg/kg/day (n=44): 29%; Placebo mg/kg/day (n=43): 5%</p> <p>PASI 50 Ciclosporin 1.25 mg/kg/day (n=41): 21% Ciclosporin 2.5 mg/kg/day (n=44): 58%; Placebo mg/kg/day (n=43): 10%</p> <p>Mean PASI Ciclosporin 1.25 mg/kg/day wk0 (n=40): mean 16.7 (5.7 SD) Ciclosporin 1.25 mg/kg/day wk10 (n=40): mean 11.8 (6.8 SD) Ciclosporin 2.5 mg/kg/day wk0 (n=41): mean 15.1 (5.0 SD) Ciclosporin 2.5 mg/kg/day wk10 (n=41): mean 7.6 (6.2 SD) Placebo wk0 (n=39): mean 15.6 (5.1 SD) Placebo wk10 (n=39): mean 14.9 (7.9 SD)</p> <p>Reduction in PASI Ciclosporin 1.25 mg/kg/day wk1 (n=41): mean 4.3 (9.8 SD) Ciclosporin 1.25 mg/kg/day wk3 (n=41): mean 11.7 (22.3 SD) Ciclosporin 1.25 mg/kg/day wk6 (n=41): mean 22.1 (29 SD) Ciclosporin 1.25 mg/kg/day wk10 (n=41): mean 27.2 (34.6 SD)</p> <p>Ciclosporin 2.5 mg/kg/day wk1 (n=44): mean 10.2 (15.3 SD) Ciclosporin 2.5 mg/kg/day wk3 (n=44): mean 22.9 (26.3 SD) Ciclosporin 2.5 mg/kg/day wk6 (n=44): mean 39.3 (28.8 SD) Ciclosporin 2.5 mg/kg/day wk10 (n=44): mean 51 (30.9 SD)</p> <p>Placebo wk1 (n=43): mean 3.2 (6.5 SD) Placebo wk3 (n=43): mean 7.3 (19.2 SD) Placebo wk6 (n=43): mean 11 (28 SD) Placebo wk10 (n=43): mean 5.9 (36.1 SD)</p>

Study details	Participants	Treatment	Outcomes and results
Reference van Joost 1988 ¹⁰⁵	Psoriasis type Plaque	Treatment Ciclosporin 5.5 mg/kg/day (mean dose) Number of patients n=10	PASI 75 Ciclosporin: 7/10 Placebo: 0/10
Study design RCT	Resistant to topicals/ require systemics? Yes	Comparator Placebo equivalent Number of patients n=10	PASI 50/ PSI 50 Ciclosporin: 9/10 Placebo: 0/10
Whole body	Minimum BSA included NS	Duration of treatment 4 wks	Reduction in PASI Ciclosporin (n=10): mean 72% Placebo (n=10): mean 3%
	Minimum PASI included > 20	Outcome measure PASI 75 PASI 50 (from graph) Reduction in PASI	
	Adult? Yes		
	Number of participants n= 20		

Study details	Participants	Treatment	Outcomes and results
<p>Reference Dogan 1999¹⁴</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type NS</p> <p>Resistant to topicals/ require systemics? Yes</p> <p>Minimum BSA included ≥15%</p> <p>Minimum PASI included Pre-treatment PASI mean 12</p> <p>Adult? Yes</p> <p>Number of participants n=50</p>	<p>Treatment Acitretin (50mg/day for 15 days, 25mg/day thereafter plus PUV A (oral psoralen) 3/wk.</p> <p>Note: the average UVA dose was 52.4 j/cm and the average number of UVA sessions was 13) Number of patients n=20</p> <p>Comparator PUVA 3/wk (10 patients used oral psoralen (average UVA dose 187.7 j/cm and average number of UVA sessions 31), 20 used bath psoralen (average UVA dose 44.6 j/cm and average number of UVA sessions 20.4)). Number of patients n=30</p> <p>Note: varied between</p> <p>Duration of treatment Maximum of 3 mths (or until clearance of psoriasis)</p> <p>Outcome measure PASI 50/ PSI 50 % clear/almost clear</p>	<p>PASI 50/ PSI 50 Acitretin plus PUV A 20/20 (100%) PUVA 29/30 (97%) (Note: bath PUV A 20/20 (100%) but oral PUV A 9/10 (90%)</p> <p>% clear/almost clear (defined as 80-100% improvement in PASI) Acitretin plus PUV A 6/20 (30%) PUVA 25/30 (83%) (Note: bath PUV A 19/20 (95%) but oral PUV A 6/10 (60%)</p>

Study details	Participants	Treatment	Outcomes and results
Reference Goldfarb 1988 ¹⁰⁸ Study design RCT Whole body	Psoriasis type NS Resistant to topicals/ require systemics? NS Minimum BSA included >10% Minimum PASI included NS Adult? Yes Number of participants n=38	Treatment Acitretin 10 mg Acitretin 25 mg Acitretin 50 mg Acitretin 75 mg Number of patients n=26 Comparator <i>Placebo equivalent</i> Number of patients n=12 Duration of treatment 8 wks Outcome measure Physician global score (0-6) 0=absent or clear, 6=severe Physician improvement ratings (worse, unchanged, fair, good, excellent)	Physician GA Acitretin 10 mg (n=5): mean 0 (0 SE) Acitretin 25 mg (n=5): mean 1 (0.3 SE) Acitretin 50 mg (n=11): mean 1.6 (0.04 SE) Acitretin 75 mg (n=5): mean 3 (0.8 SE) Placebo (n=12): mean 0.5 (0.3 SE) Improvement Acitretin 10 mg (n=5): 2 worse, 3 unchanged Acitretin 25 mg (n=5): 1 worse, 4 fair Acitretin 50 mg (n=11): 6 fair, 3 good, 2 excellent Acitretin 75 mg (n=5): 1 fair, 2 good, 2 excellent Placebo (n=12): 5 worse, 1 unchanged, 5 fair, 1 excellent
Study details Reference Lassus 1987 ¹⁰⁹ Study design RCT Whole body	Psoriasis type Plaque, erythrodermic, pustular Resistant to topicals/ require systemics? NS Minimum BSA included NS Minimum PASI included NS Adult? NS Number of participants n=80	Treatment Acitretin 10 mg Acitretin 25 mg Acitretin 50 mg Number of patients n=60 Comparator Placebo equivalent Number of patients n=20 Duration of treatment 8 wks Outcome measure Need for topicals % reduction in PASI (data not extractable from graph)	Need for topicals Acitretin 10 mg (n=20): 6 Acitretin 25 mg (n=20): 7 Acitretin 50 mg (n=20): 4 Placebo (n=20): 12

Study details	Participants	Treatment	Outcomes and results
<p>Reference Saurat 1988¹¹</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque, erythrodermic</p> <p>Resistant to topicals/ require systemics? NS</p> <p>Minimum BSA included >20%</p> <p>Minimum PASI included NS</p> <p>Adult? NS</p> <p>Number of participants n=58</p>	<p>Treatment Acitretin 50 mg/day + PUVA Etretnate 50 mg/day + PUVA Number of patients n=38</p> <p>Comparator PUVA + placebo Number of patients n=20</p> <p>Duration of treatment 12 wks</p> <p>Outcome measure Remission (equal to PASI 90), days to clear (mean)</p>	<p>PASI 90 Acitretin (n=20): 17 Placebo (n=22): 16</p> <p>Clearance Acitretin wk6 (n=18):8 Acitretin wk8 (n=18):16 Acitretin wk10 (n=18):17 Acitretin wk12 (n=18):17 Etretnate wk 6 (n=20):5 Etretnate wk 8 (n=20):11 Etretnate wk 10 (n=20):13 Etretnate wk 12 (n=20):16 Placebo wk 6 (n=20):3 Placebo wk 8 (n=20):7 Placebo wk 10 (n=20):13 Placebo wk 12 (n=20):16</p> <p>Days to clearance Acitretin wk6 (n=18): mean 47.8 (2.3 SE) Etretnate wk 6 (n=20): mean 57.8 (4.4 SE) Placebo wk6 (n=20): mean 65.4 (4.1 SE)</p>

Study details	Participants	Treatment	Outcomes and results
Reference Sommerburg 1993 ¹¹² Study design RCT Whole body	Psoriasis type Plaque, guttate or nummularis Resistant to topicals/ require systemics? NS Minimum BSA included NS Minimum PASI included NS Adult? Yes Number of participants n=88	Treatment Acitretin 25 mg/day + PUVA (3 to 5/wk) Number of patients n=44 Comparator PUVA (3 to 5/wk) + placebo Number of patients n=44 Duration of treatment 8 wks Outcome measure Physician assessment (complete remission, marked improvement, slight improvement, no change, exacerbation) ≥75% decrease in PSI Reduction in PSI (score points/%)	Clearance Acitretin + PUVA (n=44): 28 Placebo (n=44): 19 Improvement Acitretin + PUVA (n=44): 9 marked improvement, 1 slight improvement, 1 no change, 1 exacerbation Placebo (n=44): 11 marked improvement, 7 slight improvement, 2 no change, 4 exacerbation >75% decrease in PSI Acitretin + PUVA (n=44): 34 Placebo (n=44): 26 Reduction in PSI Acitretin + PUVA (n=44): median 24 Placebo (n=44): median 21

Study details	Participants	Treatment	Outcomes and results
Reference Tanew 1991 ¹¹³ Study design RCT Whole body	Psoriasis type Plaque, guttate or erythrodermic Resistant to topicals/ require systemics? NS Minimum BSA included >20% Minimum PASI included NS Adult? Yes Number of participants n=42	Treatment PUVA 4/wk+ Acitretin 1 mg/kg a day Number of patients n=22 Comparator PUVA 4/wk+ placebo Number of patients n=20 Duration of treatment 11 wks or until complete clearing Outcome measure 90% clearance	Clearance PUVA + Acitretin (n=30): 22 Placebo (n=30): 20

Study details	Participants	Treatment	Outcomes and results
<p>Reference van de Kerkhof 1998¹¹⁵</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? Yes</p> <p>Minimum BSA included NS</p> <p>Minimum PASI included NS (mean (SD): irtmt 17.8 (8.9), ctrl 17.4 (SD 8.6))</p> <p>Adult? Yes</p> <p>Number of participants n=135</p>	<p>Treatment Acitretin 20 to 70mg/day + calcipotriol 2/day Number of patients n=76</p> <p>Comparator Acitretin 20 to 70mg/day + placebo Number of patients n=59</p> <p>Duration of treatment 12 wks</p> <p>Outcome measure Reduction in PASI score (from graph) Investigator/patient assessment (clear or marked improvement, moderate or slight improvement, unchanged or worse)</p>	<p>Reduction in PASI Acitretin + calcipotriol (n=76): mean 13.2 Acitretin + placebo (n=59): mean 8.8</p> <p>Mean PASI <i>Acitretin + calcipotriol: (0 wks) mean 17.8 (8.9 SE); (12 wks) mean 3.75</i> Acitretin + placebo: (0 wks) mean 17.4 (8.6 SE); (12 wks) mean 6.25</p> <p>Degree of improvement <i>Acitretin + calcipotriol (n=76): 51 Clear or marked improvement; 25 moderate or slight improvement; 26 unchanged or worse.</i> Acitretin + placebo (n=59): 24 Clear or marked improvement; 33 moderate or slight improvement, 29 unchanged or worse</p>

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Study details	Participants	Treatment	Outcomes and results
<p>Reference Altmeier 1994¹²⁴</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque, guttate or erythrodermic</p> <p>Resistant to topicals/ require systemics? NS</p> <p>Minimum BSA included >10%</p> <p>Minimum PASI included NS</p> <p>Adult? Yes</p> <p>Number of participants n=100</p>	<p>Treatment Fumaderm 105 escalating to 1290mg/day Number of patients n=49</p> <p>Comparator Placebo equivalent Number of patients n=51</p> <p>Duration of treatment 16 wks</p> <p>Outcome measure Physician's assessment: complete remission (PASI 95), good improvement (PASI 70-95%), moderate improvement (PASI 30-69%), slight improvement (PASI <30%), no change (PASI 0%), deterioration (PASI <0%); Mean PASI (from graph)</p>	<p>Mean PASI Fumaderm (16 wks): 10.77 Placebo (16 wks): 23</p> <p>Physician's assessment Fumaderm (16 wks): 12 complete remission, 15 good improvement, 3 moderate improvement, 5 slight change, 9 no change, 5 deterioration Placebo (16 wks): 1 complete remission, 3 good improvement, 2 moderate improvement, 3 slight change, 25 no change, 17 deterioration</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Nieboer 1989¹⁷⁴</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? NS</p> <p>Minimum BSA included >10%</p> <p>Minimum PASI included NS</p> <p>Adult? Yes</p> <p>Number of participants n=80</p>	<p>Treatment MEFAE-Na 240 mg/day Number of patients n=19 DMFAE 240 mg/day Number of patients n=22</p> <p>Comparator Placebo equivalent Number of patients n=19, n=20</p> <p>Duration of treatment 4 months</p> <p>Outcome measure Improvement measured by psoriasis severity score (0-17) including PSI 50</p> <p>Psoriasis severity score (0=absence of symptom, 5=>50% BSA involved)</p>	<p>PSI 50 MEFAE-Na: 1/19; placebo: 2/19 DMFAE: 6/22; placebo: 0/20</p> <p>Improvement MEFAE-Na: 1 > 50% improvement, 6 25-50% improvement, 9 <25% improvement Placebo: 2 > 50% improvement, 5 25-50% improvement, 8 <25% improvement DMFAE: 6 > 50% improvement, 6 25-50% improvement, 4 <25% improvement Placebo: 0 > 50% improvement, 1 25-50% improvement, 12 <25% improvement</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Nugteren Huying 1990¹²⁵</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type NS</p> <p>Resistant to topicals/ require systemics? NS</p> <p>Minimum BSA included >10 %</p> <p>Minimum PASI included NS</p> <p>Adult? Yes</p> <p>Number of participants n=32</p>	<p>Treatment DMFAE – 120 mg, MEFAE-Ca 87mg MEFAE-Mg 5mg MEFAE-Zn 3mg Number of patients n=12</p> <p>OHFAE 284mg; MEFAE-Mg 5mg; MEFAE-Zn 3mg Number of patients n=10</p> <p>Comparator Placebo Number of patients n=10</p> <p>Duration of treatment 16 wks</p> <p>Outcome measure Clearance %BSA (no data)</p>	<p>Clearance DMFAE, MEFAE-Ca MEFAE-Mg MEFAE-Zn: 6 clear, 3 improved OHFAE; MEFAE-Mg; MEFAE-Zn: 0 clear, 0 improved Placebo: 0 clear, 0 improved</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Nieboer 1990¹⁷⁵</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque, macular or guttate</p> <p>Resistant to topicals/ require systemics? NS</p> <p>Minimum BSA included >10%</p> <p>Minimum PASI included NS</p> <p>Adult? Yes</p> <p>Number of participants n=45</p>	<p>Treatment DMFAE-EC 120 to 480 mg <i>Number of patients n=22</i></p> <p>Comparator FAC-EC 120mg 1-4 tablets/day <i>Number of patients n=23</i></p> <p>Duration of treatment 4 months</p> <p>Outcome measure Improvement measured by psoriasis severity score (0-17; % of baseline score calculated to find proportion with 50% improvement)</p>	<p>PASI 50/ PSI 50 DMFAE-EC: 10/22 (45%) FAC-EC: 12/23 (52%)</p> <p>Clearance DMFAE-EC: 4/22 FAC-EC: 4/23</p> <p>Failure DMFAE-EC: 5/22 (22%) FAC-EC: 1/23 (4%)</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Chaudari 2001¹²²</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? Yes</p> <p>Minimum BSA included >5%</p> <p>Minimum PASI included NS (mean baseline PASI: trtmt 5mg/kg 22.1; mean trtmt 10mg/kg 26.6; ctrl 20.3</p> <p>Adult? Yes</p> <p>Number of participants n=33</p>	<p>Treatment Infliximab 5mg/kg Number of patients n=11 Infliximab 10mg/kg Number of patients n=11</p> <p>Comparator Placebo Number of patients n=11</p> <p>Duration of treatment 10 wks</p> <p>Outcome measure PASI 75 Mean PASI Physician GA (Good=50-74% clearing with moderate improvement, Excellent=75-90% clearing with striking improvement, Clear=100% clearing, Fair=25-49% clearing with slight improvement, Poor=0-24% clearing with little or no change, Worse);</p>	<p>PASI 75 Infliximab 5mg/kg: 9/11 (82%) Infliximab 10mg/kg: 8/11 (73%) Placebo: 2/11 (18%)</p> <p>PASI 50/PSI 50 Infliximab 5mg/kg: 9/11 Infliximab 10mg/kg: 10/11 Placebo: 2/11</p> <p>Mean PASI Infliximab 5mg/kg (wk 0): 22.1; (wk 10) 3.8 Infliximab 10mg/kg (wk 0): 26.6; (wk 10) 5.9 Placebo (wk 0): 20.3; (wk 10) 17.5</p> <p>Improvement Infliximab 5mg/kg: 9 clear or excellent, 0 good Infliximab 10mg/kg: 7 clear or excellent, 3 good; 91% Placebo: 1 clear or excellent, 1 good; 18%</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Gottlieb 2004²³</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? Yes</p> <p>Minimum BSA included ≥10%</p> <p>Minimum PASI included ≥12%</p> <p>Adult? Yes</p> <p>Number of participants n=249</p>	<p>Treatment Infliximab 3 mg/kg at wks 0, 2 and 6 Number of patients n=99 Infliximab 5 mg/kg at wks 0, 2 and 6 Number of patients n=99</p> <p>Comparator Placebo Number of patients n=51</p> <p>Duration of treatment Assessment at 10 wks</p> <p>Outcome measure PASI 90 PASI 75 PASI 50 Physician GA assessment of scaling, erythema, and induration based on a 6-point scale (0=not present, 1=minimally present, 2=mild, 3=moderate, 4=marked, 5=severe); Median change from baseline in DLQI; median DLQI scores</p>	<p>PASI 90 Infliximab 3 mg/kg: 45 (45.5%) Infliximab 5 mg/kg: 57 (57.6%) Placebo: 1 (2%)</p> <p>PASI 75 Infliximab 3 mg/kg: 71 (71.7%) Infliximab 5 mg/kg: 87 (87.9%) Placebo: 3 (5.9%)</p> <p>PASI 50 Infliximab 3 mg/kg: 83 (83.8%) Infliximab 5 mg/kg: 96 (97%) Placebo: 11 (21.6%)</p> <p>Improvement Infliximab 3 mg/kg: 71 (71.7%) minimal or cleared; 87 (87.9%) mild, minimal, or cleared Infliximab 5 mg/kg: 89 (89.9%) minimal or cleared; 97 (98.0%) mild, minimal, or cleared Placebo: 5 (9.8%) minimal or cleared; 23 (45.1%) mild, minimal, or cleared</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Sandhu 2003¹⁰⁶</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque and erythrodermic</p> <p>Resistant to topicals/ require systemics? NS</p> <p>Minimum BSA included >40%</p> <p>Minimum PASI included NS (mean baseline PASI: trtmt 29.6, ctrl 27.6)</p> <p>Adult? Yes</p> <p>Number of participants n=30</p>	<p>Treatment Methotrexate 0.5 mg/kg/day (approx 35mg/wk) Number of patients n=15</p> <p>Comparator Ciclosporin 3-4 mg/kg/day Number of patients n=15</p> <p>Duration of treatment 12 wks</p> <p>Outcome measure PASI 75 PASI 50 Mean PASI Reduction in PASI Clearance</p>	<p>PASI 75 Methotrexate: 15 Ciclosporin: 14</p> <p>PASI 50 Methotrexate: 15 Ciclosporin: 15</p> <p>Mean PASI Methotrexate (wk 0): 27.6 (2.3 SE); (wk 12) 0.4 (0.2 SE) Ciclosporin (wk 0): 29.6 (2.1 SE); (wk 12) 4.3 (1.7 SE)</p> <p>Reduction in PASI Methotrexate (wk 2): 35%; (wk12) 98.5% Ciclosporin (wk2): 15%; (wk12) 85.6%</p> <p>Clearance Methotrexate: 13/15 Ciclosporin: 6/15</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Heydendael 2003¹⁰⁷</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? Yes</p> <p>Minimum BSA included NS</p> <p>Minimum PASI included >8</p> <p>Adult? Yes</p> <p>Number of participants n=85</p>	<p>Treatment Methotrexate 15-22.5 mg/wk Number of patients n=43</p> <p>Comparator Ciclosporin 3-5 mg/kg/day Number of patients n=42</p> <p>Duration of treatment 16 wks</p> <p>Outcome measure PASI 90 PASI 75 mean PASI Physician GA (score 0-10, 0=worst, 10=clearance) F-36</p>	<p>PASI 09 Methotrexate: 17/43 Ciclosporin: 14/42</p> <p>PASI 75 Methotrexate: 26/43 Ciclosporin: 30/42</p> <p>Mean PASI Methotrexate (wk 0): 13.4 (3.2 SD); (wk 16) 5 (0.7 SD) Ciclosporin (wk 0): 14 (6.6 SD); (wk 16) 3.8 (0.5 SD)</p> <p>Reduction in PASI Methotrexate: 64% Ciclosporin: 74%</p> <p>Physician GA Methotrexate: mean 7 (0.38 SE) Ciclosporin: mean 4.8 (0.29 SE)</p> <p>SF 36 Methotrexate: physical mean 52 (1.7 SE), mental mean 51 (1.4 SE) Ciclosporin: physical mean 53 (1.4 SE), mental mean 51 (1.4 SE)</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Rim 2003^{1,6}</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? NS</p> <p>Minimum BSA included >5%</p> <p>Minimum PASI included NS (mean baseline PASI: trtm 21.6, ctrl 24.3)</p> <p>Adult? Yes</p> <p>Number of participants n=60</p>	<p>Treatment Acitretin 10-40 mg/day + calcipotriol 50 mg/twice daily Number of patients n=40</p> <p>Comparator Acitretin 10-40 mg/day Number of patients n=20</p> <p>Duration of treatment 12 wks (and 52 wks)</p> <p>Outcome measure Clearance Improvement Failure. Definitions unclear</p>	<p>Clearance Acitretin + calcipotriol (12 wks): 16/40 (40%); (52 wks) 24/40 Acitretin (12 wks): 3/20 (15%); (52 wks) 8/20</p> <p>Improvement Acitretin + calcipotriol: 15/40 (38%) Acitretin: 13/20 (65%)</p> <p>Failure Acitretin + calcipotriol: 9/40 (22.5%) Acitretin: 4/20 (20%)</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Gordon 1999^{1,8}</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? Yes</p> <p>Minimum BSA included NS</p> <p>Minimum PASI included NS</p> <p>Adult? Yes</p> <p>Number of participants n=100</p>	<p>Treatment PUVA (oral) 2/wk Number of patients n=49</p> <p>Comparator NBUBV 2/wk Number of patients n=51</p> <p>Duration of treatment Until clearance of plaques of psoriasis at all sites above the knee</p> <p>Outcome measure Clearance No. exposures to clearance Still clear after 3 and 6 mths</p>	<p>Clearance PUVA: 41/49; (6 months) 17/49 NBUBV: 32/51; (6 months) 7/51</p> <p>No. exposures to clearance PUVA: median 16.7 NBUBV: median 25.3 (95% CI 1.24, 1.86)</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Markham 2003¹¹⁹</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? NS</p> <p>Minimum BSA included >8%</p> <p>Minimum PASI included Baseline range 11 to 19</p> <p>Adult? Yes</p> <p>Number of participants n=54</p>	<p>Treatment NBUVB 3/wk <i>Number of patients n=29</i></p> <p>Comparator PUVA (oral 8-MOP) 2/wk <i>Number of patients n=25</i></p> <p>Duration of treatment Until patients were completely clear</p> <p>Outcome measure No. of treatments to clear Days to clear Duration of remission (days) Remission</p>	<p>Clearance NBUVB (3 mths): 23/29; (6 mths) 16/29; (9 mths) 23/29; (12 mths) 7/29 PUVA (3 mths): 18/25; (9 mths) 18/25; (12 mths) 10/25</p> <p>Days to clear NBUVB (n=24): median 67 (95% CI 47.9, 81.7) PUVA (n=21): median 66 (95% CI 52.0, 92.6)</p> <p>No. exposures to clearance NBUVB (n=24): median 25.5 (95% CI 18.0, 32.5) PUVA (n=21): median 19 (14.6, 25.0)</p> <p>Duration of remission (days) NBUVB (n=24): median 288.5 (95% CI 170.6, 365.0) PUVA (n=21): median 231 (95% CI 162.7, 365.0)</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Caca-Biljanovska 2002¹⁰</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? NS</p> <p>Minimum BSA included NS (>30%)</p> <p>Minimum PASI included NS (mean baseline PASI: trtm 24.06 (SD 3.62); ctrl 24.56 (SD 3.40))</p> <p>Adult? Yes</p> <p>Number of participants n=40</p>	<p>Treatment PUVA 4/wk for 6 wks + 2/wk for 2 wks Number of patients n=20</p> <p>Comparator Acitretin 30 mg/day as an initial dose Number of patients n=20</p> <p>Duration of treatment 8 wks</p> <p>Outcome measure Mean PASI scores at 2, 4, 6, and 8 weeks Clearing</p>	<p>Mean PASI PUVA (wk 0): mean 24.06 (SE 3.62); (wk 8) mean 1.69 (SE 1.55) Acitretin (wk 0): mean 24.56 (SE 3.5); (wk 8) mean 0.9 (SE 1.07)</p> <p>Clearance PUVA: 7/20 Acitretin: 10/20</p> <p>Improvement PUVA: 7 clear; 3 moderate; 10 considerable Acitretin: 10 clear; 2 moderate; 8 considerable</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Dawe 2003^{1,20}</p> <p>Study design RCT Half body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? Yes</p> <p>Minimum BSA included NS</p> <p>Minimum PASI included NS</p> <p>Adult? Yes</p> <p>Number of participants n=56</p>	<p>Treatment NBUVB 3/wk Number of patients n=28</p> <p>Comparator PUVA (bath/TMP) 2/wk Number of patients n=28</p> <p>Duration of treatment Until clearance/MRA, or a max. of 30 trtmts</p> <p>Outcome measure Clearance/MRA Time to clearance/MRA (values not given) No. exposures to clearance/MRA Median decrease in psoriasis severity score (scaling, erythema, induration)</p>	<p>Reduction in PASI NBUVB: mean 20 PUVA: mean 17.5</p> <p>Clearance NBUVB: 18/28 PUVA: 15/28</p> <p>Days to clear NBUVB (n=18): median 62 PUVA (n=18): median 74</p> <p>No. exposures to clearance NBUVB (n=18): median 24.5 PUVA (n=18): median 19; (95% CI 1.5, 5.5)</p>

10.7.2 Excluded studies of other treatments for moderate to severe psoriasis

Study details	Participants	Treatment	Outcomes and results
Reference Engst 1989 ¹⁷⁶ Study design RCT Whole body	Psoriasis type Plaque Resistant to topicals/ require systemics? Yes Minimum BSA included NS Minimum PASI included >20 Adult? NS Number of participants n=12	Treatment <i>Ciclosporin 5 mg/kg/day.</i> <i>Number of patients n= 6</i> Comparator Placebo equivalent Number of patients n=6 Duration of treatment 4 wks Outcome measure PASI 75	PASI 75 Ciclosporin (n=6): 3 Placebo (n=6): 1

Study details	Participants	Treatment	Outcomes and results
<p>Reference Kingston 1987¹⁷⁷</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? NS</p> <p>Minimum BSA included >20%</p> <p>Minimum PASI included NS</p> <p>Adult? Yes</p> <p>Number of participants n=NS</p>	<p>Treatment Acitretin 10 mg Acitretin 50 mg Acitretin 75 mg Number of patients n=NS</p> <p>Comparator Placebo Number of patients n=NS</p> <p>Duration of treatment 8 wks</p> <p>Outcome measure Excellent (>75% clearance), good (50-75%), minimal (<50%). No placebo data</p>	<p>NS</p>

Study details	Participants	Treatment	Outcomes and results
Reference Madhok 1987 ¹⁷⁸	Psoriasis type Plaque, pustular	Treatment Acitretin 25 mg Acitretin 50 mg <i>Number of patients n=NS</i>	NS
Study design RCT	Resistant to topicals/ require systemics? NS	Comparator Placebo equivalent Number of patients n=NS	
Whole body	Minimum BSA included >15%	Duration of treatment 8 wks	
	Minimum PASI included NS	Outcome measure NS	
	Adult? Yes		
	Number of participants n=NS		

Study details	Participants	Treatment	Outcomes and results
<p>Reference Olsen 1989¹⁷⁹</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? NS</p> <p>Minimum BSA included >10%</p> <p>Minimum PASI included NS</p> <p>Adult? Yes</p> <p>Number of participants n=NS</p>	<p>Treatment Acitretin 25 mg Acitretin 50 mg <i>Number of patients n=NS</i></p> <p>Comparator Placebo Number of patients n=NS</p> <p>Duration of treatment 8 wks</p> <p>Outcome measure Assessment of severity of erythema, thickness and pustules, but no placebo data</p>	<p>NS</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Van Weelden 1990¹⁷</p> <p>Study design RCT</p> <p>Half body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/require systemics? NS</p> <p>Minimum BSA included NS</p> <p>Minimum PASI included NS</p> <p>Adult? Yes</p> <p>Number of participants n=NS</p>	<p>Treatment PUVA 2/wk Number of patients n=NS</p> <p>Comparator NBUVB 2/wk n=NS</p> <p>Duration of treatment 4 wks or until the comparisons of the symmetrical body sides gave the same difference two times in a row</p> <p>Outcome measure Overall impression (not extractable)</p>	<p>Overall impression (not extractable)</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Storbeck 1993¹²¹</p> <p>Study design RCT</p> <p>Half body</p>	<p>Psoriasis type Plaque, guttate or erythroderma</p> <p>Resistant to topicals/require systemics? NS</p> <p>Minimum BSA included NS</p> <p>Minimum PASI included NS</p> <p>Adult? Yes (17 to 66 years)</p> <p>Number of participants n=NS</p>	<p>Treatment NBUVB 3-5/wk + dithranol or BBUVB 3-5/wk + dithranol <i>Number of patients n=NS</i></p> <p>Comparator NBUVB 3-5/wk or BBUVB 3-5/wk <i>Number of patients n=NS</i></p> <p>Duration of treatment Treatment continued until patient stopped complying</p> <p>Outcome measure PASI (not extractable)</p>	<p>PASI (not extractable)</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Williams 1985¹⁸⁰</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? NS</p> <p>Minimum BSA included >30</p> <p>Minimum PASI included NS</p> <p>Adult? Yes</p> <p>Number of participants n=NS</p>	<p>Treatment PUVA 2/wk Number of patients n=NS</p> <p>Comparator UVB + tar (4/day) 5/wk (Goeckerman) Number of patients n=NS</p> <p>Duration of treatment NS</p> <p>Outcome measure Considerable improvement/clear on 6 pt scale % reduction of percentage body coverage by psoriasis (no data) No. of treatments to achieve 90% improvement (no data)</p>	<p>NS</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Leavell 1970¹⁸¹</p> <p>Study design RCT</p> <p>Whole body Cross-over trial</p>	<p>Psoriasis type Severe recalcitrant psoriasis</p> <p>Resistant to topicals/require systemics? NS</p> <p>Minimum BSA included NS</p> <p>Minimum PASI included NS</p> <p>Adult? Yes</p> <p>Number of participants n=24</p>	<p>Treatment Hydroxycarbamide 0.5g 2/day <i>Number of patients n=12</i></p> <p>Comparator Placebo equivalent Number of patients n=12</p> <p>Duration of treatment 8 wks</p> <p>Outcome measure Physician and patient subjective impression of improvement on 3 point scale (progression of disease, no change, improvement)</p>	<p>Improvement Hydroxycarbamide (n=12): Physician: 7 improvement, 3 no change; Patient: 9 improvement, 1 increased disease Placebo (n=12): Physician: 1 improvement, 7 no change, 2 increased disease; Patient: 1 improvement, 5 no change, 4 increased disease</p>

Study details	Participants	Treatment	Outcomes and results
<p>Reference Ellis 1986⁸²</p> <p>Study design RCT</p> <p>Whole body</p>	<p>Psoriasis type Plaque</p> <p>Resistant to topicals/ require systemics? Yes</p> <p>Minimum BSA included >20%</p> <p>Minimum PASI included NS</p> <p>Adult? Yes</p> <p>Number of participants n=21</p>	<p>Treatment Ciclosporin 14 mg/kg/day Number of patients n= 11</p> <p>Comparator Placebo equivalent Number of patients n= 10</p> <p>Duration of treatment 4 wks</p> <p>Outcome measure Physician GA of improvement (clear=100%; marked improvement=51-99% better; moderate improvement=11-50% better; minimal/no change=0-10% better; worse)</p>	<p>PASI 50/PSI 50 Ciclosporin: 8/11 Placebo: 0/10</p> <p>Clearance Ciclosporin: 2/11 Placebo: 0/10</p> <p>Improvement Ciclosporin: 2 clearance, 6 marked improvement, 1 minimal Placebo: 10 minimal or no change</p>

10.8 Code used for evidence synthesis and economic modelling

All code is in WinBUGS and R.

Random EFFECTS MODEL

```
model
{
  # this just has to be large enough to ensure all phi[j]'s > 0
  C <- 1

  #random effect baseline, equates to placebo/PASI50 endpoint
  for (s in 1:nStudies)
    {
      mu[s]~dnorm(muMean,muTau)
    }

  #define mean treatment effects - beta[Tx]
  #define random treatment effect variates - randBeta[ Tx]
  for (t in 2:nTx)
    {
      beta[t] ~ dnorm(0,.001)
      for (s in 1:nStudies)
        {
          randBeta[s,t]~dnorm(beta[t],txTau)
        }
    }

  #treatment effect (and variance) is zero for placebo.
  beta[1] <- 0
  for (s in 1:nStudies)
    {
      randBeta[s,1]<-0
    }

  #Model data
  for (j in 1:nObs)
    {
      #study baseline and treatment effect -random treatment effects model
      base[j] <- mu[study[j]] + randBeta[study[j],Tx[j]]

      #fixed treatment effects version
      #base[j] <- mu[study[j]] + beta[Tx[j]]

      #probability of <50 percent reduction in PASI
      pOutcome[1,j] <- phi(base[j])

      #probability of 50-75 percent reduction in PASI
```

```
pOutcome[2,j] <- phi(base[j]+c75) - phi(base[j])

#probability of 75-90 percent reduction in PASI
pOutcome[3,j] <- phi(base[j]+ c90) - phi(base[j]+c75)

#probability of >=90 percent reduction in PASI
pOutcome[4,j] <- 1-phi(base[j]+c90)

#probability of >=75 percent reduction in PASI
pOutcome[5,j] <- 1-phi(base[j]+c75)

#probability of >=50 percent reduction in PASI
pOutcome[6,j] <- 1-phi(base[j])

#probability of <75 (clearance) percent reduction in PASI
pOutcome[7,j] <- phi(base[j]+c75)

#probability of >=75 (clearance) percent reduction in PASI
pOutcome[8,j] <- 1-phi(base[j]+c75)

#probability of <75 percent reduction in PASI
pOutcome[9,j] <- phi(base[j]+c75)

#Likelihood function, probability of endpoint to the power of number of observations
L[j]<- pow(pOutcome[outcome[j],j],n[j])

#use zeroes trick as described in winbugs manual
logL[j]<- log(L[j])
zeros[j] <- 0
phi[j] <- -logL[j] + C
zeros[j] ~ dpois(phi[j])

predictedP[j] <- pOutcome[outcome[j],j]
}

#predicted treatment effects in terms of absolute probabilities and Relative Risks
for (t in 1:nTx)
{
  predictedTX50[t] <- 1-phi(muMean + beta[t])
  rr50[t] <- predictedTX50[t] /predictedTX50[1]

  predictedTX75[t] <- 1-phi(muMean + c75 + beta[t])
  rr75[t] <- predictedTX75[t] /predictedTX75[1]

  predictedTX90[t] <- 1-phi(muMean + c90 + beta[t])
  rr90[t] <- predictedTX90[t] /predictedTX90[1]
}

#priors for ordered probit cut points
```



```
{
sims <- bugs(
  data=data,
  inits=inits,
  parameters.to.save=parameters.to.save,
  model.file=bugs.file,
  n.chains=1,
  debug=winDebug,
  n.iter = n.iter,
  n.burnin = n.burnin,
  n.thin=n.thin
)

return(sims)
}

#select valid comparators from excel sheet
comparators <- comparators[comparators!=""]

#select valid lambda values
ceRange <- ceRange[1:which.max(ceRange)]

#coerce ce labels into matrix
ceLabels <- cbind(numeric(),ceRange)

#number of valid datapoints
nObs <- sum(outcome>0)

#select valid outcome codes
outcome <- outcome[1:nObs]

#select valid studies
study <- Study[1:nObs]

#select valid treatments
Tx <- Tx[1:nObs]

#select valid n's
n <- n[1:nObs]

#generate list of study names
studyNames <-as.character(unique(study))

#generate list of study codes
studyCodeList <- 1:length(studyNames)

#number of unique studies
nStudies <- length(studyCodeList)

#code studies
```

```
studyCode <- studyCodeList[match(study,studyNames)]

#list of unique treatments
txNames <-as.character(unique(Tx))

#generate list of tx codes
txCodeList <- 1:length(txNames)

#number of unique treatments
nTx <- length(txCodeList)

#code treatments
txCode <- txCodeList[match(Tx,txNames)]

#only run winbugs code is flag is set
if (runWin==1)
  {
    #run winbugs
    probInits <- list(list(mu=rep(0,nStudies),beta=c(NA,rep(0,(nTx-1))),c75=0.5,c90inc=1))
    probBugsData <- list(study=studyCode,Tx=txCode,outcome=outcome,n=n,nObs=nObs,nTx=nTx,nStudies=nStudies)
    probParameters.to.save <-
c("predictedP","predictedTX50","predictedTX75","predictedTX90","rr50","rr75","rr90","beta","txSd","sd","c75","c90")
    probX <-
genSamps(probBugsData,init=probInits,n.iter=nThin*(nSims+nBurnin),n.burnin=nBurnin*nThin,n.thin=nThin,bugs.file=
probWinSource,parameters.to.save=probParameters.to.save,winDebug=winDebug)

    #extract predicted probabilities,mean and CI
    probPredictedP <- cbind(probX$summary[1:nObs,1],NA)
    probPredictedTX50 <- probX$summary[(nObs+1):(nObs+nTx),c(1,3,7)]
    probPredictedTX75 <- probX$summary[(nObs+nTx+1):(nObs+nTx*2),c(1,3,7)]
    probPredictedTX90 <- probX$summary[(nObs+nTx*2+1):(nObs+nTx*3),c(1,3,7)]

    #extract relative risks
    rrTX50 <- probX$summary[(nObs+nTx*3+1):(nObs+nTx*4),c(1,3,7)]
    rrTX75 <- probX$summary[(nObs+nTx*4+1):(nObs+nTx*5),c(1,3,7)]
    rrTX90 <- probX$summary[(nObs+nTx*5+1):(nObs+nTx*6),c(1,3,7)]

    #extract DIC and deviance
    probDeviance <- probX$summary[length(probX$summary[,1]),1]
    probDIC <- probX$DIC

    #extract simulates from simulated posterior distribution
    prob50Resp =probX$sims.array[,1,(nObs+1):(nObs+nTx)]
    prob75Resp =probX$sims.array[,1,(nObs+nTx+1):(nObs+2*nTx)]
    prob90Resp =probX$sims.array[,1,(nObs+2*nTx+1):(nObs+3*nTx)]

    #label simulates
    dimnames(prob50Resp)[[2]] <- txNames
    dimnames(prob75Resp)[[2]] <- txNames
    dimnames(prob90Resp)[[2]] <- txNames
```

```
#duplicate etanercept sims for continuous etan option
etan25 <- (1:length(txNames))[txNames=="Etanercept 25mg"]

#add duplicates
prob50Resp <- cbind(prob50Resp,prob50Resp[,etan25])
prob75Resp <- cbind(prob75Resp,prob75Resp[,etan25])
prob90Resp <- cbind(prob90Resp,prob90Resp[,etan25])

#add names and label for continuous etan
txNames <- c(txNames,"Etanercept 25mg Continuous")
txLabels <- cbind("",txNames)

#relabel
dimnames(prob50Resp)[[2]] <- txNames
dimnames(prob75Resp)[[2]] <- txNames
dimnames(prob90Resp)[[2]] <- txNames
}

#generate utility vector

#generate DLQI distribution for different PASI levels
D00DLQI <- rnorm(nSims,D00Mean,D00SD/sqrt(D00N))
D50DLQI <- rnorm(nSims,D50Mean,D50SD/sqrt(D50N))
D75DLQI <- rnorm(nSims,D75Mean,D75SD/sqrt(D75N))
D90DLQI <- rnorm(nSims,D90Mean,D90SD/sqrt(D90N))

#generate EQ5D DLQI co-efficient distribution
EQ5DBeta <- rnorm(nSims,EQ5DBetaMean,EQ5DBetaSE)

#generate utility distributions for different PASI levels
D00Utility <- EQ5DBeta*D00DLQI
D50Utility <- EQ5DBeta*D50DLQI
D75Utility <- EQ5DBeta*D75DLQI
D90Utility <- EQ5DBeta*D90DLQI

#estimate mean and se utility for different PASI levels
D00UtilityMean <- mean(D00Utility)
D00UtilitySE <- sd(D00Utility)
D50UtilityMean <- mean(D50Utility)
D50UtilitySE <- sd(D50Utility)
D75UtilityMean <- mean(D75Utility)
D75UtilitySE <- sd(D75Utility)
D90UtilityMean <- mean(D90Utility)
D90UtilitySE <- sd(D90Utility)

#label cost variables
names(drugInitCost) <- drugTX
names(drugMinCost) <- drugTX
names(drugMaxCost) <- drugTX
```

```
#convert durations to years
periodResp <- periodRespWk/(365.25/7)
periodRespEffect <- periodRespEffectWk/(365.25/7)
periodRespCost <- periodRespCostWk/(365.25/7)
periodTrial <- periodTrialWk/(365.25/7)

#label duration variables
names(periodTrial) <- periodTX
names(periodTrial) <- periodTX
names(periodResp) <- periodTX
names(periodRespEffect) <- periodTX
names(periodRespCost) <- periodTX

#extract placebo response probs
plcb50Resp<-prob50Resp[, "Supportive Care"]
plcb75Resp<-prob75Resp[, "Supportive Care"]
plcb90Resp<-prob90Resp[, "Supportive Care"]
uPlacebo <- D00Utility*(1-plcb50Resp)+D50Utility*(plcb50Resp-plcb75Resp)+D75Utility*(plcb75Resp-
plcb90Resp)+D90Utility*plcb90Resp

#derive placebo cost
if (pasiCut==50)
  {
    placeboCost <- nonRespHospCost*(1-prob50Resp[, "Supportive Care"])
  }

if (pasiCut==75)
  {
    placeboCost <- nonRespHospCost*(1-prob75Resp[, "Supportive Care"])
  }

#define decision model
psorModel <-
function(uPlacebo,placeboCost,prob50Resp,prob75Resp,prob90Resp,D00Utility,D50Utility,D75Utility,D90Utility,periodTrial,p
eriodRespEffect,periodRespCost,periodResp,
      drugInitCost,drugMinCost,drugMaxCost,nonRespHospCost,nSims)
  {

    uAll <- D00Utility*(1-prob50Resp)+D50Utility*(prob50Resp-prob75Resp)+D75Utility*(prob75Resp-
prob90Resp)+D90Utility*prob90Resp

    if (pasiCut==50)
      {
        pResp <- prob50Resp
        uResp<- (D50Utility*(prob50Resp-prob75Resp)+D75Utility*(prob75Resp-
prob90Resp)+D90Utility*prob90Resp)/pResp
```

```
    }

    if (pasiCut==75)
    {
      pResp <- prob75Resp
      uResp<- (D75Utility*(prob75Resp-prob90Resp)+D90Utility*prob90Resp)/pResp
    }

    drugCost <- gamma(nSims,drugMinCost,drugMaxCost)

    totalCost = drugInitCost + pResp*periodRespCost*drugCost+(1-pResp)*nonRespHospCost*periodTrial -
    (periodTrial+pResp*periodRespCost)*placeboCost
    cost <- totalCost/(periodTrial+pResp*periodRespCost)

    totalEffect = periodTrial*(uAll-uPlacebo)+pResp*periodRespEffect*(uResp-uPlacebo)
    effect <- totalEffect/(periodTrial+pResp*periodRespEffect)

    return(list(cost=cost,qaly=effect))
  }

#run decision model for each treatment option

cost <- numeric()
qaly <- numeric()

for (drug in comparators)
{
  x <- psorModel (
    uPlacebo=uPlacebo,
    placeboCost=placeboCost,
    prob50Resp=prob50Resp[,drug],
    prob75Resp=prob75Resp[,drug],
    prob90Resp=prob90Resp[,drug],
    D00Utility=D00Utility,
    D50Utility=D50Utility,
    D75Utility=D75Utility,
    D90Utility=D90Utility,
    periodTrial=periodTrial[drug],
    periodRespEffect=periodRespEffect[drug],
    periodRespCost=periodRespCost[drug],
    periodResp=periodResp[drug],
    drugInitCost=drugInitCost[drug],
    drugMinCost=drugMinCost[drug],
    drugMaxCost=drugMaxCost[drug],
    nonRespHospCost=nonRespHospCost,
    nSims=nSims
  )
}
```

```
cost <- cbind(cost,x$cost)
qaly <- cbind(qaly,x$qaly)
}

row.names(cost) <- character()
dimnames(cost)[[2]] <- comparators
dimnames(qaly)[[2]] <- comparators

qalyMean <- apply(qaly,2,mean)
costMean <- apply(cost,2,mean)
costTiles <- apply(cost,2,quantile,c(0.025,0.975))
qalyTiles <- apply(qaly,2,quantile,c(0.025,0.975))
options <- cbind(qalyMean,qalyCI=t(qalyTiles),costMean,costCI=t(costTiles))

index<-order(options[,"costMean"])
options<-options[index,]

drugs <- attributes(options)$dimnames[[1]]
retain <-options

icerChar <-""
domFlag <- TRUE

#tells function when to stop looking for dominated options
while (domFlag == TRUE)
{

l <- length(retain[,"qalyMean"])

qalyDiff <- retain[,"qalyMean"][2:l] > retain[,"qalyMean"][1:(l-1)]
nonDom <- TRUE

if(l>2)
{
nonDom <- qalyDiff >0
icerChar[!nonDom[drugs]] <- "Dominated"
retain<-retain[c(TRUE,nonDom),]
}

if (sum(nonDom==FALSE)==0) domFlag<-FALSE
}

#exclude dominated options
exDomFlag <-TRUE
while (exDomFlag ==TRUE)
{
```

```
#sort the data frame

l <- length(retain[,"costMean"])
icer <- (retain[,"costMean"][2:l]-retain[,"costMean"][1:(l-1)])/(retain[,"qalyMean"][2:l]-retain[,"qalyMean"][1:(l-1)])

#include first, last and options where ICER is less than next costlier option
i <- length(icer)
nonExDom <- TRUE

if (i>1)
  {
    nonExDom <- icer[1:(i-1)]<icer[2:i]
    icerChar[!nonExDom[drugs]] <- "Extended Domination"
    retain<-retain[c(TRUE,nonExDom,TRUE),]
  }

if (sum(nonExDom==FALSE)==0) exDomFlag<-FALSE
}

names(icerChar) <- drugs

icerChar[names(icer)] <- as.numeric(trunc(icer))

supplIcer <-trunc(options[,4]/options[,1])

options[,1:3] <- round(options[,1:3],3)
options[,4:6] <- trunc(options[,4:6])

icerResults <- cbind(options,icerChar,supplIcer)

icerTitles <- rbind(c("QALYs","", "", "Costs", "", "", "", ""),c("Mean", "2.5% CI", "97.5% CI", "Mean", "2.5% CI", "97.5% CI", "ICER", "ICER against Supportive Care"))
icerLabels <- cbind("",drugs)

#cost-effectiveness acceptability

optSeq <- character()

for (ce in ceRange)
  {

    netBenMean <- qalyMean*ce - costMean
    s <- comparators[order(netBenMean,decreasing=TRUE)]

    #Remove options which offer less net-benefit than supportive care
    s[netBenMean[order(netBenMean,decreasing=TRUE)]<0]==""

    optSeq <- rbind(optSeq,s)
```



```

}

#cost-effectiveness acceptability

probOptLabels <- rbind(character(),c("QALY WTP",comparators))
probFeasLabels <- rbind(character(),c("QALY WTP",comparators))

probOpt <- numeric()
probFeas <- numeric()

for (ce in ceRange)
{

  netBen <- qaly*ce - cost
  optimum <- netBen
  optimum[] <- 0

  optimum[cbind(1:length(netBen[,1]),max.col(netBen))] <- 1
  feasible <- netBen >= netBen[,"Supportive Care"]

  probOpt <- rbind(probOpt,c(ce,apply(optimum,2,mean)))
  probFeas <-rbind(probFeas,c(ce,apply(feasible,2,mean)))

}

```

10.9 Findings from the economic evaluations

10.9.1 Data extraction table

Primary Source	Feldman, S. R., Garton, R., Averett, W., Balkrishnan, R. and Vallee, J. (2003) "Strategy to manage the treatment of severe psoriasis: considerations of efficacy, safety and cost." Expert Opinion on Pharmacotherapy, 4, 9: 1525-1533.
Author	Feldman
Date	2003
Type of economic evaluation	Cost effectiveness analysis
Currency used	US dollars
Year to which costs apply	2002
Perspective used	Third party payer Authors state that indirect costs have been estimated, but these are not reported and it is unclear whether they are included in the cost effectiveness analysis.
Timeframe	12 months
Comparators	UVB PUVA, 40 mg / 30 treatments Methotrexate, 15 mg Acitretin, 25 mg / day Ciclosporin, 3 mg/kg/day (= 240 mg/day) Ciclosporin, 5 mg/kg/day (= 400 mg/day) Alefacept 15 mg intramuscular (18 injections annually) Alefacept 7.5 mg intravenous (18 injections annually)

York Technology Assessment Group
Efalizumab And Etanercept For The Treatment Of Psoriasis

	Infliximab 5 mg/kg/day (6 infusions annually) Infliximab 10 mg/kg/day (6 infusions annually) Etanercept, 25 mg/kg twice weekly Etanercept, 50 mg/kg twice weekly																				
Source(s) of effectiveness data	Literature review: existing systematic reviews and supplementary review of recently published papers (for biologics). Expert opinion																				
Source(s) of resource use data	Published clinical guidelines (dosage, dosing frequency, duration of treatment, laboratory tests). Manufacturers' guidelines (dosage, dosing frequency, duration of treatment). Expert opinion (physician office visits, duration of treatment for infliximab and etanercept).																				
Source(s) of unit cost data	Medicare fee schedules, national, median reimbursement value (provider costs, laboratory tests, intravenous infusion, UVB). Medicare fee schedules, local, median reimbursement value (liver biopsy). Drug Topics Red Book (drug acquisition costs).																				
Modelling approach used	Simple decision tree																				
Summary of effectiveness results	Treatment success rate, measured as percentage of patients achieving a 75% improvement in PASI score from baseline (PASI75). <table style="width: 100%; border: none;"> <tr><td>UVB</td><td style="text-align: right;">70%</td></tr> <tr><td>PUVA</td><td style="text-align: right;">80%</td></tr> <tr><td>Methotrexate (15 mg)</td><td style="text-align: right;">30%</td></tr> <tr><td>Acitretin</td><td style="text-align: right;">30%</td></tr> <tr><td>Ciclosporin</td><td style="text-align: right;">70%</td></tr> <tr><td>Alefacept</td><td style="text-align: right;">40%</td></tr> <tr><td>Infliximab</td><td style="text-align: right;">80%</td></tr> <tr><td>Etanercept</td><td style="text-align: right;">47%</td></tr> </table>	UVB	70%	PUVA	80%	Methotrexate (15 mg)	30%	Acitretin	30%	Ciclosporin	70%	Alefacept	40%	Infliximab	80%	Etanercept	47%				
UVB	70%																				
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Methotrexate (15 mg)	30%																				
Acitretin	30%																				
Ciclosporin	70%																				
Alefacept	40%																				
Infliximab	80%																				
Etanercept	47%																				
Summary of cost results (annual)	<table style="width: 100%; border: none;"> <tr><td>UVB</td><td style="text-align: right;">US\$3600</td></tr> <tr><td>PUVA</td><td style="text-align: right;">US\$4600</td></tr> <tr><td>Methotrexate (15 mg)</td><td style="text-align: right;">US\$1600</td></tr> <tr><td>Acitretin (25 mg/day)</td><td style="text-align: right;">US\$5200</td></tr> <tr><td>Ciclosporin (3 mg/kg/day)</td><td style="text-align: right;">US\$6500</td></tr> <tr><td>Ciclosporin (5 mg/kg/day)</td><td style="text-align: right;">US\$10,000</td></tr> <tr><td>Alefacept (i.v.)</td><td style="text-align: right;">US\$16,000 (to \$20,000)</td></tr> <tr><td>Infliximab (5 mg/kg)</td><td style="text-align: right;">US\$18,000</td></tr> <tr><td>Etanercept (25 mg/kg, twice weekly)</td><td style="text-align: right;">US\$16,900</td></tr> <tr><td>Etanercept (50 mg/kg, twice weekly)</td><td style="text-align: right;">US\$33,000</td></tr> </table>	UVB	US\$3600	PUVA	US\$4600	Methotrexate (15 mg)	US\$1600	Acitretin (25 mg/day)	US\$5200	Ciclosporin (3 mg/kg/day)	US\$6500	Ciclosporin (5 mg/kg/day)	US\$10,000	Alefacept (i.v.)	US\$16,000 (to \$20,000)	Infliximab (5 mg/kg)	US\$18,000	Etanercept (25 mg/kg, twice weekly)	US\$16,900	Etanercept (50 mg/kg, twice weekly)	US\$33,000
UVB	US\$3600																				
PUVA	US\$4600																				
Methotrexate (15 mg)	US\$1600																				
Acitretin (25 mg/day)	US\$5200																				
Ciclosporin (3 mg/kg/day)	US\$6500																				
Ciclosporin (5 mg/kg/day)	US\$10,000																				
Alefacept (i.v.)	US\$16,000 (to \$20,000)																				
Infliximab (5 mg/kg)	US\$18,000																				
Etanercept (25 mg/kg, twice weekly)	US\$16,900																				
Etanercept (50 mg/kg, twice weekly)	US\$33,000																				

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Summary of cost-effectiveness results	Annual cost per treatment success (US\$)	
	UVB	US\$5100
	PUVA	US\$5700
	Methotrexate (15 mg)	US\$5400
	Acitretin (25 mg/day)	US\$17,300
	Ciclosporin (3 mg/kg/day)	US\$6500
	Ciclosporin (5 mg/kg/day)	US\$14,200
	Alefacept (i.v.)	US\$40,600
	Infliximab (5 mg/kg)	US\$22,500
	Etanercept (25 mg/kg, twice weekly)	US\$35,900
Etanercept (50 mg/kg, twice weekly)	US\$33,000	
Sensitivity analysis	Variables investigated by deterministic sensitivity analysis include dose (ciclosporin, methotrexate, infliximab, and etanercept), delivery method (alefacept) and efficacy (all treatments). Under all analyses, phototherapy (UVB or PUVA) was the most cost effective treatment, with methotrexate the most cost-effective <i>systemic</i> option.	
Main Conclusions	UVB phototherapy is the least costly and probably the safest way to manage psoriasis, but it may be inconvenient for patients. PUVA, methotrexate, alefacept, infliximab and etanercept all appear to be appropriate second-line choices for psoriasis, each with advantages and disadvantages, and considerable patient and physician judgement is required in deciding which of these agents to prescribe in which order. Ciclosporin is an appropriate therapy for short-term treatment of disease flare before transitioning to a safer long-term treatment.	

10.9.2 Quality assessment table

All items are graded as either yes (item adequately addressed), no (item not adequately addressed), ? unclear or not enough information, NA not applicable or NS not stated.

Study question		Comments
1. Costs and effects examined	<input type="checkbox"/>	
2. Alternatives compared	<input type="checkbox"/>	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	<input checked="" type="checkbox"/>	The authors report that indirect costs have been measured, but these do not appear to have been included in the cost analysis.
Selection of alternatives		
4. All relevant alternatives are compared (including doing nothing if applicable)	<input type="checkbox"/>	The authors have excluded combination therapy 'for simplicity'.
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	<input type="checkbox"/>	
6. The rationale for choosing the alternative programmes or interventions compared is stated	<input type="checkbox"/>	The comparators represent clinical practice in the US.
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	<input type="checkbox"/>	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	<input type="checkbox"/>	
10. Effectiveness data from RCT or review of RCTs	<input type="checkbox"/>	
11. Potential biases identified (especially if data not from RCTs)	<input type="checkbox"/>	The absence of head-to-head trial data was acknowledged to be a shortcoming of the analysis.
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	<input type="checkbox"/>	Baseline estimates of effectiveness were chosen by consensus, but details of this process are not reported. Effectiveness estimates were unadjusted against placebo.
Costs		
13. All the important and relevant resource use included	<input type="checkbox"/>	
14. All the important and relevant resource use measured accurately (with methodology)	<input type="checkbox"/>	In the absence of trial or observational data, expert opinion formed the basis for several estimates of resource use.
15. Appropriate unit costs estimated (with methodology)	<input type="checkbox"/>	Median fee schedule values were used.
16. Unit costs reported separately from resource use data	<input type="checkbox"/>	
17. Productivity costs treated separately from other costs	NA	Productivity costs are not reported.
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	<input type="checkbox"/>	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life years, QALYs, etc.)	<input type="checkbox"/>	
20. Methods to value health states and other benefits are stated (e.g. time trade off)	NA	
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, health care professionals etc.)	NA	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	<input checked="" type="checkbox"/>	The model appears to be a simple decision tree, although this is not explicitly stated.

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23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	?	The choice of model is not discussed. Details of most of the important input parameters are reported, but some are not.
24. All model outputs described adequately.	?	Cost per treatment success is reported for most treatments, although not all (especially where more than one dose for a particular therapy was explored).
Discounting		
25. Discount rate used for both costs and benefits	NA	
26. Do discount rates accord with NHS guidance (1.5%-2% for benefits; 6% for costs)?	NA	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	×	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	×	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	×	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	×	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	NA	
32. Are the probability distributions adequately detailed and appropriate?	NA	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	×	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	×	
35. The choice of variables for sensitivity analysis is justified	?	
36. The ranges over which the variables are varied are stated	×	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	×	
38. Major outcomes are presented in a disaggregated as well as aggregated form	□	
39. Applicable to the NHS setting	?	The comparators chosen, the type and frequency of laboratory tests and the unit costs reflect US clinical practice. For these reasons, findings may not be generalisable to the NHS.

10.10 Data extraction and quality assessment tables for economic evaluations submitted by manufacturers

10.10.1 Cost-effectiveness model submitted by Wyeth – data extraction

Primary Source	Company submission.
Author	Wyeth Pharmaceuticals UK.
Date	16 th July 2004.
Type of economic evaluation	Cost effectiveness analysis; health effects in terms of QALYs; NHS cost perspective.
Currency used	£ Sterling.
Year to which costs apply	Drug costs: BNF – year not specified. Costs of adverse events: NHS Reference Costs – year not specified.
Perspective used	NHS
Timeframe	Results presented at 12 weeks (trial analysis) and 96 weeks (extrapolated analysis).
Comparators	For the 12-week trial analysis, the model compares the following options (i) etanercept 25mg twice weekly; (ii) etanercept 50mg twice weekly; (iii) no systemic treatment. For the 96 week extrapolated model there are two sets of comparisons. Firstly: (i) continuous etanercept lower dose; (ii) continuous etanercept higher dose; (iii) no systemic therapy. Secondly: (i) intermittent etanercept lower dose; and (ii) no systemic therapy.
Source(s) of effectiveness data	All effectiveness evidence is taken from the three etanercept registration studies performed by Wyeth and Amgen: Studies 20021632; 20021639; 20021642. These studies provide information on baseline PASI and quality of life (in terms of DLQI); change in DLQI and PASI over time (up to 24 weeks), adverse drug events related to the therapy. Sub-group analysis is undertaken by baseline DLQI and PASI. In order to express effectiveness in terms of quality-adjusted life-years (QALYs), DLQI (primary analysis) and PASI (secondary analysis) are ‘mapped’ to EQ-5D utility. This is based on an observational study of patients with psoriasis in Cardiff. For the evaluation of the continuous and intermittent strategies, treatment starting and stopping rules (using PASI changes measured in the trials) are based on clinical opinion.
Source(s) of resource use data	Dosage drugs: the trial evidence. Monitoring and administration assumptions: clinical opinion. Adverse events of drug: the trial evidence.
Source of mortality data	No mortality data are included in the analysis.
Sources of utility data	The ‘mapping’ of quality of life (DLQI) and PASI to utility was based on a survey undertaken in Cardiff. This included all patients identified from hospital records as having been treated at a single acute NHS hospital for psoriasis over a 2-year period. Patients were asked to complete the DLQI and the EQ5D. PASI data were taken from clinical notes (i.e. past data). A regression model was developed to predict (EQ-5D-based) utility from DLQI. The analysis found a statistically significant association between these measures and estimated each one-point increase in the DLQI to be associated with a fall of 0.0248 in patient utility. Patients’ DLQI scores at each visit were converted into utility scores using the algorithm: $EQ5D \text{ utility score} = 0.956 - [0.0248 \times (DLQI \text{ total score})]$
Source(s) of unit cost data	Drug costs: British National Formulary. Costs for purposes of costing adverse events: NHS Reference Costs.
Modelling approach used	The short-term (12 week) analysis is based on patient-level data pooled across the registration trials, so no formal modelling is involved. The longer-term extrapolation (for continuous and intermittent etanercept) is based on model over a time horizon of 96 weeks. For <i>continuous therapy</i> , the model followed a simplified Markov process. It was based on 8 treatment periods of 12 weeks (total time horizon of 96 weeks). Patients start the model receiving treatment with one of the three strategies (see above). At the end of the initial (12 week) treatment period the model reflects the probability of three events: (i) an improvement of at least 75 % in PASI over baseline (PASI 75); (ii) an improvement of between 50-75% in PASI over baseline; (iii) treatment failure (PASI response <50). Patients experiencing an improvement of PASI 50 or better are assumed to continue treatment; those who do not are assumed to cease treatment. By the end of a second period (24 weeks post-randomisation), those patients who continue therapy and achieve a PASI 75 response to therapy are assumed to stay on treatment. By the end of the second period, some of the patients who withdraw from therapy are assumed to achieve spontaneous response. In subsequent periods, patients are assumed to remain in their existing health state, except those who are removed from treatment but progressively achieve PASI 75 response at the rate observed in the no treatment group of the clinical trials (i.e. spontaneous remission). A similar extrapolation model is used to evaluate <i>intermittent</i> etanercept therapy. After 12

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	<p>weeks, response is assessed and etanercept withdrawn from all patients. Patients who do not achieve a PASI50 response or better receive no further therapy. Patients who achieve a response of PASI 50 or better are eligible for re-treatment. The patients receive a further course of 12 weeks treatment once response has been lost.</p>
Summary of effectiveness results	<p>The short-term (12 analysis) indicates incremental QALYs of 0.018 (etanercept 25mg compared to no systemic therapy), 0.020 (etanercept 50mg compared to no systemic therapy) and 0.002 (etanercept 50mg compared to etanercept 25mg). For the 96 week model for continuous therapy these estimates are, respectively, 0.152, 0.180 and 0.028, for all patients, and 0.312, 0.276 and -0.036 for patients with baseline PASI>20 and baseline DLQI>15.</p> <p>For the 96-week model of intermittent 25mg (twice per week) etanercept, incremental QALYs were 0.127 (compared to no systemic therapy) in all patients, and 0.194 in patients with baseline PASI>10 and baseline DLQI>15.</p>
Summary of cost results	<p>The cost of adverse events were found to be low and similar between the etanercept and placebo arms of the 3 registration trials.</p> <p>For the 12 week analysis based on trial data, the costs were estimated as £2043 (drug), £76 (initial visit), £218 (follow-up visits), 15 (adverse events) and £2352 (total) with etanercept 25mg. These costs were £4160, £76, £218, £9 and £4464, respectively, with etanercept 50mg. They were £0, £0, £55, £18 and £72 with placebo (no systemic therapy). These costs were then used in the extrapolation models.</p>
Summary of cost-effectiveness results	<p>The short-term (12 analysis) indicates incremental costs per QALY gained of £124,732 (etanercept 25mg compared to no systemic therapy), £219,996 (etanercept 50mg compared to no systemic therapy) and £1,255,840 (etanercept 50mg compared to etanercept 25mg). For the 96 week model for continuous therapy these estimates are, respectively, £53,056, £64,559 and £127,464 for all patients, and £25,926, £37,320 and 25mg etanercept dominating for patients with baseline PASI>20 and baseline DLQI>15.</p> <p>For the 96-week model of intermittent 25mg (twice per week) etanercept, incremental costs per QALY gained were £37,199 (compared to no systemic therapy) in all patients, and £24,229 in patients with baseline PASI>10 and baseline DLQI>15.</p>
Sensitivity analysis	<p>A range of scenario analyses were undertaken to assess how the cost per QALY gained varied with baseline PASI and DLQI. These showed that the ICERs were lower in patients with worse baseline quality of life and clinical severity. No other sensitivity analyses were reported.</p>
Main Conclusions	<p>The estimated costs per QALY gained of etanercept were high if the time horizon is set equal to the follow-up in the registration trials (12 weeks).</p> <p>The use of an extrapolation model to estimate cost-effectiveness over 96 weeks suggests lower ICERs for continuous and intermittent therapy, particularly in patients with relatively poor baseline PASI and DLQI.</p>

10.10.2 Cost-effectiveness model submitted by Wyeth – quality assessment

All items will be graded as either √ (item adequately addressed), ✗ no (item not adequately addressed), ? unclear or not enough information, NA not applicable or NS not stated.

Wyeth Pharmaceuticals submission

Study question		Comments
1. Costs and effects examined	?	Costs of hospitalisation for severe patients were not included.
2. Alternatives compared	?	No comparison with other biological therapy (i.e. efalizumab) or other licensed systemic therapies (e.g. methotrexate). Comparison of etanercept at different doses with option of no systemic therapy, under different configurations regarding when the biological is used continuously or intermittently.
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	√	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✗	No comparison with other biological therapy (i.e. efalizumab) or other licensed systemic therapies (e.g. methotrexate). Also no direct comparison of continuous and intermittent use of etanercept.
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	√	
6. The rationale for choosing the alternative programmes or interventions compared is stated	√	This is based partly on what was done in the registration trials, and partly on clinical advice regarding the continuous and intermittent strategies.
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	√	Cost-effectiveness/utility analysis; effects in terms of QALYs.
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	√	
10. Effectiveness data from RCT or review of RCTs	√	Patient-level data from 3 registration trials which have been pooled for analysis.
11. Potential biases identified (especially if data not from RCTs)	N/A	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✗	In pooling the data across the 3 trials, there is no apparent consideration of heterogeneity.
Costs		
13. All the important and relevant resource use included	?	No consideration of hospitalisation costs.
14. All the important and relevant resource use measured accurately (with methodology)	?	Little detail about costing of adverse events. No price year.
15. Appropriate unit costs estimated (with methodology)	?	Little detail.
16. Unit costs reported separately from resource use data	√	
17. Productivity costs treated separately from other costs	N.A.	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✗	Country stated (UK); year not stated.
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life years, QALYs etc.)	√	QALYs
20. Methods to value health states and other benefits are stated (e.g. time trade off)	√	Mapping from DLQI and based on EQ5D.

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21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, health care professionals etc.)	NA	Based on EQ-5D index.
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	√	Simple Markov model.
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	√	
24. All model outputs described adequately.	√	
Discounting		
25. Discount rate used for both costs and benefits	√	Apparently no discounting used. Longest time horizon is 96 weeks, so this absence is not crucial.
26. Do discount rates accord with NHS guidance (1.5%-2% for benefits; 6% for costs)?	NA	
Allowance for uncertainty		
Stochastic analysis of patient-level data	✗	
27. Details of statistical tests and confidence intervals are given for stochastic data	NA	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	NA	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	NA	
Probabilistic analysis of decision models	✗	
30. Are all appropriate input parameters included with uncertainty?	NA	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	NA	
32. Are the probability distributions adequately detailed and appropriate?	NA	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	NA	
Deterministic analysis	✗	No clear analysis of uncertainty. Variability in cost-effectiveness according to baseline disease severity and quality of life is assessed using scenario analysis.
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	NA	
35. The choice of variables for sensitivity analysis is justified	NA	
36. The ranges over which the variables are varied are stated	NA	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	√	
38. Major outcomes are presented in a disaggregated as well as aggregated form	?	Only cost per QALY estimates presented for many of the subgroup analyses (by baseline severity and quality of life).
39. Applicable to the NHS setting	√	

10.10.3 Cost-effectiveness model submitted by Serono – data extraction

Primary Source	Company submission.
Author	Serono Ltd.
Date	16 th July 2004.
Type of economic evaluation	Cost effectiveness analysis; health effects in terms of QALYs; NHS cost perspective.
Currency used	£ Sterling.
Year to which costs apply	Drug costs: 2003. Hospital resource use: 2001 to 2003.
Perspective used	NHS
Timeframe	Base-case of 10 years (alternatives for costs of 5 years and 1 year).
Comparators	Model compares alternative strategies, in moderate to severe psoriasis, of starting therapy with efalizumab or with (more potent) topical creams: calcipotriol or bethamethasone.
Source(s) of effectiveness data	Response rates (using a PASI 50 threshold) at 12 weeks for efalizumab are taken from 5 placebo-controlled registration trials: ACD2058g, ACD2059g, ACD2390g, ACD2600g and IMP24011. PASI 50 response data for topical therapy were taken from the placebo arms of those trials. Adverse event data (which were attributed costs and, if serious, led to treatment discontinuation, were also taken from the active (efalizumab) and placebo (topicals) arms of the registration trials. Discontinuation rates for reasons other than non-response or adverse events were taken from the registration trials (for efalizumab), a review of calcipotriol and bethamethasone trials (for topicals).
Source(s) of resource use data	Efalizumab dosages, administration and monitoring: Summary of Product Characteristics and assumptions. Topical therapies: assumption of 27.7% use of calcipotriol and 40.7% bethamethasone plus assumptions about clinician visits. No costs for emollient therapy, but some clinician visits assumed. Resource use associated with adverse events were apparently taken from the registration trials.
Source of mortality data	No mortality data are included in the analysis.
Sources of utility data	Study by Zug <i>et al</i> ²⁶ based on a survey of 87 patients with psoriasis who responded to various utility instruments (the time trade-off was used in the model). Patients who fail to respond at 12 weeks (in terms of PASI 50) were assumed to have a utility of 0.59 based on the 'severe psoriasis' state valued by Zug <i>et al</i> . Those who responded were assumed to have a utility of 0.945 which was derived as the mean of the estimated utility for 'mild psoriasis' (0.89) and good health (1).
Source(s) of unit cost data	Drug costs: BNF 2003. Hospital resource use: PSSRU 2002/3, NHS Reference Costs 2003, Leeds Teaching Hospital NHS Trust provider-provider tariff 2001/2.
Modelling approach used	The model takes the form of a decision tree. Patients start therapy with either efalizumab or topicals. The decision tree models the probability of continuation beyond 12 weeks of therapy based on treatment response (PASI 50) and adverse events. Patients responding at 12 weeks maintain the QALY gain of a responder until the end of the model (for 10 years) unless there is discontinuation of therapy after 12 weeks for reasons other than lack of efficacy or adverse events. Patients who discontinue with efalizumab are assumed to move to topicals, and those who discontinue with topicals are assumed to move to emollients for symptom relief (i.e. cannot achieve a PASI 50 response). After discontinuation, patients are assumed to accumulate QALYs based on the utility of severe psoriasis once the efficacy has worn off (based on relapse rates from the trials).
Summary of effectiveness results	Over a 10-year time horizon, the number of successfully-treated years (i.e. defined base on PASI 50 response) are 3.92 with efalizumab and 1.01 with topicals. The number of quality-adjusted life-years are 1.39 with efalizumab and 0.36 with topicals.
Summary of cost results	The cost of efalizumab is £27,032, £18,488 and £5,611 over 10, 5 and 1 year respectively. The equivalent costs for topicals are £453, £303 and £123, respectively.
Summary of cost-effectiveness results	The incremental cost per successfully treated year with efalizumab is £9,082. The incremental cost per additional QALY with efalizumab is £25,582.
Sensitivity analysis	Probabilistic sensitivity analyses and expected costs and effects were taken from this, but no presentation of parameter uncertainty was undertaken (e.g. with cost-effectiveness planes or cost-effectiveness acceptability curves). A range of sensitivity analyses were undertaken. The most important of these (in terms of variation in the ICER) was a two-way sensitivity analysis of the utility values given to responders and non-responders. Over the range of variation in these inputs, the incremental cost per additional QALY ranged from £15,237 (utilities of 1.00 for a responder and 0.40 for a non-responder) to £92,001 (utilities of 0.80 for a responder and 0.70 for a non-responder).
Main Conclusions	The results from the economic model show that the treatment cost with efalizumab for one year of treatment success (50% reduction in PASI score) is between £9,082 and £9,144 per patient. The cost/QALY results from the deterministic and probabilistic analyses were £25,759 and £25,582, respectively. Sensitivity analyses showed that the main driver of cost-effectiveness is the utility difference between a responder and a non-responder.

10.10.4 Cost-effectiveness model submitted by Serono – quality assessment

All items will be graded as either √ (item adequately addressed), ✗ no (item not adequately addressed), ? unclear or not enough information, NA not applicable or NS not stated.

Wyeth Pharmaceuticals submission

Study question		Comments
1. Costs and effects examined	√	
2. Alternatives compared	?	No comparison with other biological therapy (i.e. etanercept) or other licensed systemic therapies (e.g. methotrexate).
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	√	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✗	No comparison with other biological therapy (i.e. etanercept) or other licensed systemic therapies (e.g. methotrexate).
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	√	
6. The rationale for choosing the alternative programmes or interventions compared is stated	√	This is based partly on what was done in the registration trials, and partly on assumptions about how therapies would be used in practice.
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	√	Cost-effectiveness/utility analysis; effects in terms of successfully-treated years (based on PASI 50) and QALYs.
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion).	√	
10. Effectiveness data from RCT or review of RCTs	√	From 5 registration trials and a review of RCTs for topical therapies (calcipotriol and bethamethasone).
11. Potential biases identified (especially if data not from RCTs)	NA	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	
Costs		
13. All the important and relevant resource use included	√	
14. All the important and relevant resource use measured accurately (with methodology)	√	
15. Appropriate unit costs estimated (with methodology)	√	
16. Unit costs reported separately from resource use data	√	
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	√	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life years, QALYs etc.)	√	QALYs
20. Methods to value health states and other benefits are stated (e.g. time trade off)	√	Clearly described but potential weakness of study (see main text).
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, health care professionals etc.)	√	Derived directly from patients using the EQ5D.
Decision modelling		

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22. Details of any decision model used are given (e.g. decision tree, Markov model)	√	Decision tree.
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	?	The assumption of continued utility gains for responding patients (with the exception of a small number of discontinuers for reasons other than lack of efficacy and adverse events) is strong and not well justified.
24. All model outputs described adequately.	?	Costs are not disaggregated and there is a lack of clarity about the time horizons being used.
Discounting		
25. Discount rate used for both costs and benefits	√	
26. Do discount rates accord with NHS guidance (1.5%-2% for benefits; 6% for costs)?	√	
Allowance for uncertainty		
Stochastic analysis of patient-level data	×	
27. Details of statistical tests and confidence intervals are given for stochastic data	NA	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	NA	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	NA	
Probabilistic analysis of decision models	√	But methods and results not presented.
30. Are all appropriate input parameters included with uncertainty?	NS	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	NS	
32. Are the probability distributions adequately detailed and appropriate?	NS	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	NS	
Deterministic analysis	√	Range of one-way (and one two-way) sensitivity analyses.
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	√	
35. The choice of variables for sensitivity analysis is justified	×	
36. The ranges over which the variables are varied are stated	?	Yes, but not justified.
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	√	
38. Major outcomes are presented in a disaggregated as well as aggregated form	×	
39. Applicable to the NHS setting	√	

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10.11.1 Treatment with Fumaderm

Fumaderm is normally introduced slowly during the first six weeks of treatment. There are two strengths of tablet, Fumaderm Initial being about one quarter the strength of Fumaderm. Treatment is started with Fumaderm Initial and the dose is gradually increased. It is important to follow the instructions carefully to keep the risk of side effects to a minimum.

Week		Tablet		
		Breakfast	Lunch	Dinner
1	Fumaderm Initial	-	-	1
2	Fumaderm Initial	1	-	1
3	Fumaderm Initial	1	1	1
4	Fumaderm	-	-	1
5	Fumaderm	1	-	1
6	Fumaderm	1	1	1

The normal final dose required is one Fumaderm tablet three times daily. Occasionally higher doses may be required.

Week		Tablet		
		Breakfast	Lunch	Dinner
7	Fumaderm	1	1	2
8	Fumaderm	2	1	2
9	Fumaderm	2	2	2

Two tablets of Fumaderm three times daily is the maximum dose.

The most common side-effects from Fumaderm[®] are flushing of the face and a feeling of warmth. These symptoms are usually harmless and tend to get better during treatment. The tablets can sometimes cause indigestion, stomach cramps or diarrhoea. These can be unpleasant but tend to improve during continued treatment. If they cause problems the daily dose should be reduced by one tablet. To avoid getting these side-effects it is best to take Fumaderm[®] at meal times with plenty of liquid. If indigestion or diarrhoea occur then milk products and yoghurt can be helpful.

10.11.2 Contraindications

Severe peptic ulceration, liver disease, renal impairment; pregnancy and lactation; abnormal white cell or platelet counts; other systemic medication for psoriasis.

10.11.3 Monitoring

FBC and differential, biochemical profile: before commencement, then fortnightly to three months, then monthly.

Discontinue FUMADERM immediately

- if WBC falls below $3000 \times 10^9/l$
- if creatinine rises above normal range

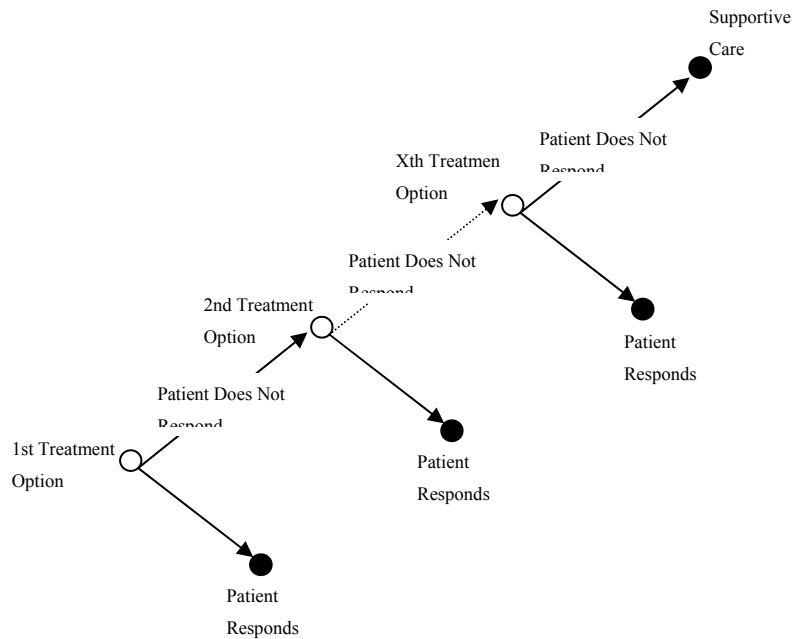
RJGC: 17th April 2003

10.12 Methods details of the cost-effectiveness modelling for treatments of chronic disease

Model Structure:

Plaque Psoriasis is a chronic non-progressive disease with a number of treatment options, if an individual patient does not respond to or tolerate a particular treatment option an alternate one may be tried. If an effective treatment is not found, then a patient will receive supportive care. This process is illustrated in Figure 1.

Figure 1: Treatment of a chronic disease

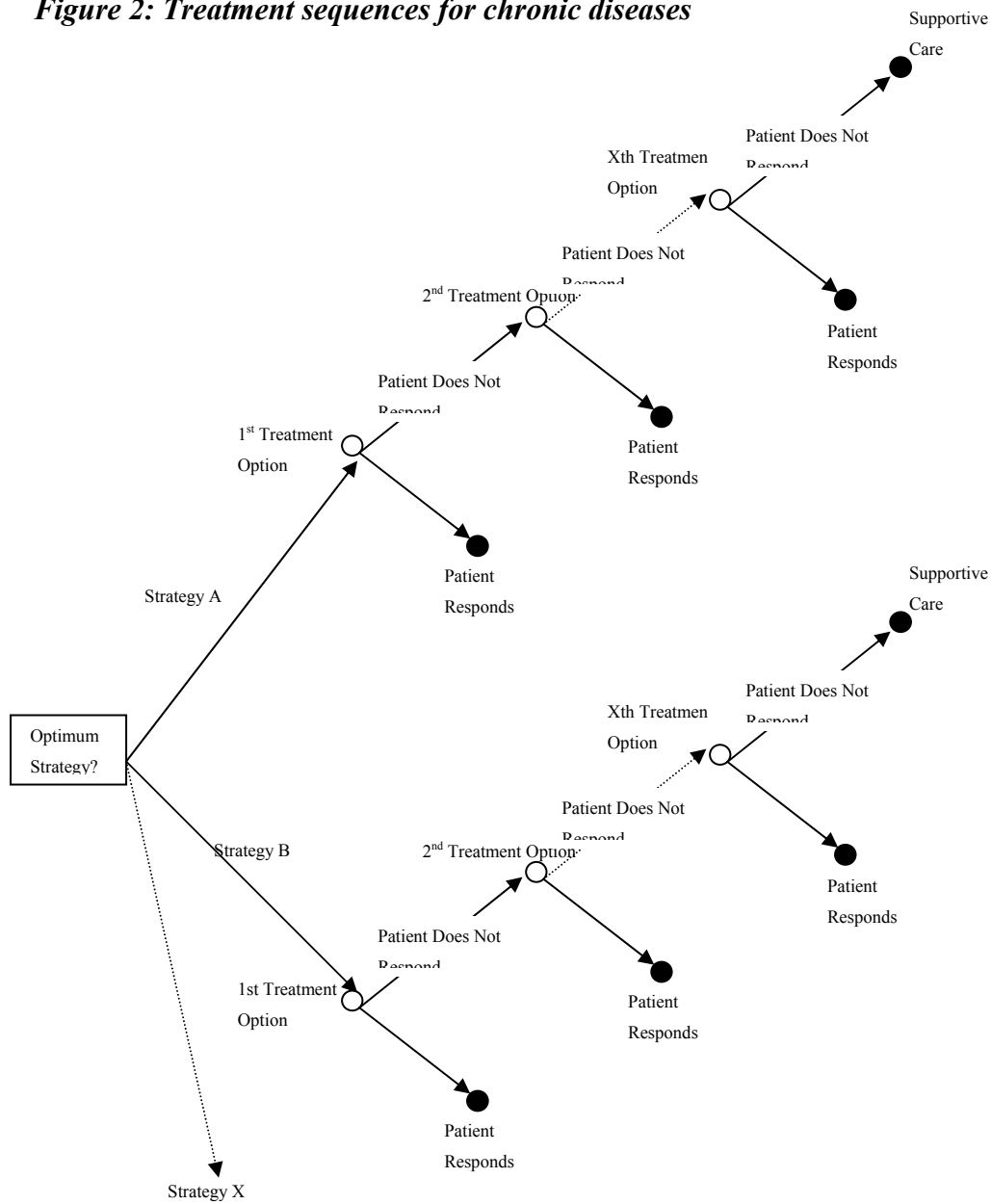


To identify the most cost-effective treatment, we need to estimate the expected costs and benefits for all relevant comparators. We can see from Figure 1 that, to estimate the expected costs and benefits associated with a specific treatment option, we need to estimate three items :

- 1) For patients who respond to the specific treatment, the costs and benefits over the treatment lifetime.
- 2) For patients who do not respond to the specific treatment, the cost and benefits over the period that the treatment was trialled.
- 3) For patients who do not respond to the specific treatment: costs and benefits of the future treatments. This will require estimates of items 1 & 2 for each of the subsequent treatment options.

Therefore, we need to consider the cost-effectiveness of different treatment *strategies*, each consisting of a sequence of treatment options to be trialled for a patient, rather than the cost-effectiveness of individual treatments. This is illustrated in Figure 2.

Figure 2: Treatment sequences for chronic diseases



The primary decision problem is to identify, for an individual patient, the optimum treatment strategy. In addition, we may wish to consider the definition of treatment success which leads to a patient being maintained on a particular treatment.

Specific Challenges

There are a number of specific challenges associated with the cost-effectiveness analysis for treatments of chronic diseases.

1) The number of potential treatment strategies:

Each potential treatment strategy should be regarded as a separate comparator. With 4 treatment options, there are [(perm 4 from 4)+ (perm 3 from 4)+(perm 2 from 4)+(perm 1 from 4)] or $24 + 24 + 12 + 4 = 64$ potential treatment strategies. If we include the option to use treatment options in combination, there are even more possible sequences. Table 4 shows that, as the number of treatment options increase, the number of potential strategies increase geometrically. As the number of treatment options increase, the cost-effectiveness analysis may not be tractable and the meaningful presentation of results including all potential strategies is difficult.

Table 1: Number of treatment strategies

<i>Number of treatments options</i>	<i>Number of distinct treatment sequences</i>
1	1
2	4
3	15
4	64
5	325
6	1956
7	13699

One option is to narrow the range of strategies based on existing opinion. However, existing expert opinions are likely to vary and the analysis may simply reinforce rather than potentially modify existing opinion. An alternative option is to limit the number of treatment options included in the treatment strategy but this may lead to an analysis which does not really address the decision problem and be unable to modify existing opinion.

2) The absence of data regarding treatment response conditional on prior treatment:

It is likely that the probability that a patient will respond to a treatment will vary according to his/her treatment history. For example, if a patient has failed to respond to a particular treatment option, he/she may be less likely to respond to further treatments from the same pharmacological class.

3) The need to select the optimum treatments for individual patients:

If our analysis identifies a single treatment strategy as being the most cost-effective, this particular strategy may not be suitable for all (or any) individuals as:

- A particular treatment option in the strategy may be contra-indicated for an individual patient.
- A particular treatment option in the strategy may have already been tried by an individual and found not to be tolerated or effective
- The acceptability of known side effects associated with a treatment option may vary between individuals. For instance, the teratogenic risk associated with the anti-epileptic drug valproate may be acceptable to a female epileptic of reproductive age whereas the risk of hirsutism associated with phenytoin may be acceptable to a young male.
- A treatment option in the sequence may not be available, for example due to the lack of the specialist facilities.
- The strategy may not correspond to accepted clinical practice, such as the requirement to try treatment options from a different therapeutic class following treatment failure. There will often be a lack of empirical evidence supporting these and they may vary between locations.

If the single strategy we have identified as being most cost-effective is not suitable for a group of individuals our analysis will leave the decision-maker without useful information. This suggests that, in addition to the requirement to consider a wide variety of treatment strategies, we may also need to consider different sets of treatment options for different groups of individuals.

4) Extrapolation from short-term clinical trial data:

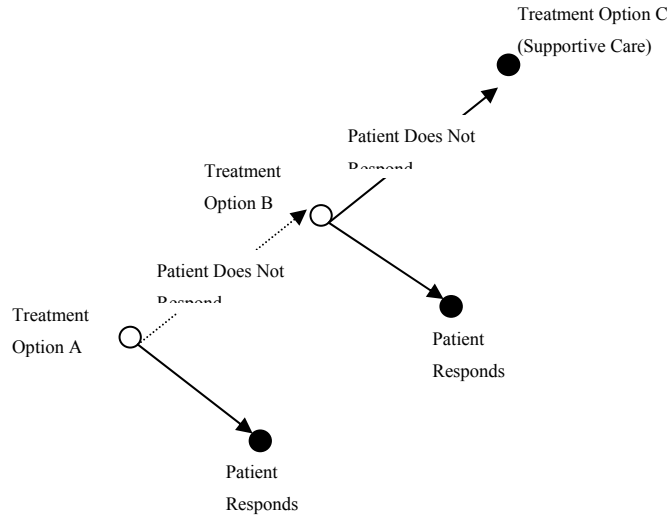
Our cost-effectiveness analysis will usually need to consider a longer treatment horizon than that observed in the available comparative clinical trials. If we expect the benefits or disbenefits of treatment to extend beyond the treatment period we may need to consider this in our model. For example, for progressive diseases such as rheumatoid arthritis or Parkinson's disease, we need to consider the extent to which a treatment may provide symptomatic relief, a benefit restricted to the treatment period, and may retard the disease process and provide benefit beyond the treatment period.

The rheumatoid arthritis model developed by Brennan *et al.*¹⁸³ was a simple decision tree model which incorporated the treatment effect as increasing utility only during the period of treatment, this corresponds to the treatment solely providing symptomatic relief and increasing expected utility only during the period of treatment. In contrast, the base-case model developed by Kobelt *et al.*¹⁸⁴ incorporated the relative treatment effect as a change in the Markov-Model transition matrix during the period of treatment, this corresponds to the treatment solely acting by retarding the disease process and not providing any symptomatic relief and will lead to the increase in expected utility from the treatment being maintained long after the treatment has finished. These differing approaches in modelling the treatment effect may lead to quite different estimates of cost-effectiveness. It is important that we are clear about the implications of different model structures and that our choice of model structure reflects decision-makers' beliefs regarding the natural history of the disease and treatment rather than analytical convenience.

Model Structure

In light of the considerations outlined above, the following analytical structure is proposed for the York model for psoriasis.

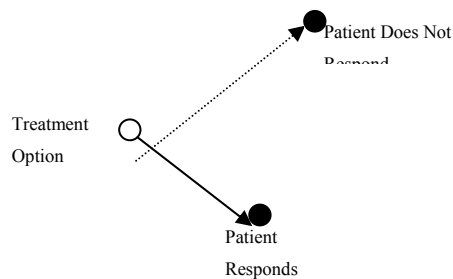
Figure 3: Structure of York psoriasis model



Let us consider a single treatment strategy illustrated in Figure 3 consisting of 3 treatment options; A,B, and C, with treatment option C being supportive care.

Let NB_A be the expected net benefit per unit time for a patient during the period that they are treated with treatment A, the *treatment period net-benefit*. This is the weighted average of the expected net-benefit benefit over the treatment lifetime for those patients who respond to treatment and the expected net-benefit over the treatment trial period for those who do not respond, Figure 4.

Figure 4.



Similarly NB_B is the expected treatment period net-benefit per unit time for the patients treated with treatment B and NB_C is the expected treatment-period net benefit for the patients treated with treatment C. If P_A is the probability of responding to treatment A and P_B is the probability of responding to treatment B, the expected overall net benefit per unit time of the strategy will be :

$$NB_A + (1-P_A)NB_B + (1-P_A)(1-P_B) NB_C$$

As we established earlier, the decision problem is to identify the optimum strategy which will result in the greatest expected net-benefit per unit time. The earlier in the strategy a treatment options is tried, the greater the proportion of patients who will receive and respond to an option. Therefore, to maximise the expected total net-benefit per unit time for the treatment strategy the options should be tried in order of decreasing expected treatment period net-benefit per unit time. If we can estimate the treatment period net-benefit for each individual treatment, the optimum strategy, based on the treatment options suitable for an individual patient, can be determined. We can also identify those treatment options that offer a lower expected net-benefit than supportive care and should not be used. This analysis is only suitable for treatments where we do not believe there is an effect on disease progression and we do not wish to condition efficacy on previous treatment as the treatment period net-benefit estimates for the various treatment options are regarded as independent

Using this analytic approach, we can present the results as a table showing the optimum ordering of treatment options as a function of the monetary value of treatment benefit.

Threshold WTP for a unit of effect	0	10	100
Optimal Sequence (Those options below supportive care should not be used)	AAA	BBB	CCC
	BBB	AAA	BBB
	CCC	CCC	AAA
	DDD	DDD	DDD

In addition, we can present probabilistic results; for example:

Treatment	Probability Treatment should be first line ($\lambda=100$)	Probability treatment is cost-effective compared to supportive care ($\lambda=100$)
AAA	0.3	0.8
BBB	0.5	0.7
CCC	0.1	0.1
DDD	0.1	0.05

To estimate the net-benefit for a treatment we need to consider the following parameters:

- Probability that a patient responds
- For those patients who respond:
 - Expected treatment lifetime
 - Treatment acquisition cost per unit time
 - Utility for a responding patient, where possible, this should be treatment specific and accounting for the disutility associated with tolerable side effects
- For those patients who do not respond:
 - Expected trial period
 - Treatment acquisition cost per unit time

Utility for a non-responding patient, where possible, this should be treatment specific and accounting for the disutility associated with tolerable side effects