NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Adalimumab for the treatment of adults with psoriasis

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide clarification on the trial populations, the indirect treatment comparison, and the cost-effectiveness data.

Information that was submitted to the National Institute for Health and Clinical Excellence in confidence has been removed from this version of the report. Black bars in the text indicate where this has occurred.

Abbreviations

Anti-TNF	Anti-tumour necrosis factor
BAD	British Association of Dermatologists
BNF	British national formulary
BSA	Body surface area
BSR	British Society for Rheumatology
CI	Confidence interval
DLQI	Dermatology life quality index
EMEA	European Medicines Agency
EOW	Every other week
EQ-5D	Euro quality of life questionnaire
ERG	Evidence Review Group
ICER	Incremental cost-effectiveness ratio
MS	Manufacturer's submission
PASI	Psoriasis area and severity index
PGA	Physician's global assessment
PSSRU	Personal Social Services Research Unit
PUVA	Psoralen and long-wave ultraviolet radiation
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SF-36	Short form (version 36)
SHTAC	Southampton Health Technology Assessment Centre
TA	Technology appraisal

Anticipated licensed indication

The anticipated indication for adalimumab (Humira, Abbott Laboratories Limited) is as follows:

Adalimumab is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or psoralen and long-wave ultraviolet radiation (PUVA).

The European Medicines Agency (EMEA) has issued a positive opinion for adalimumab for the above indication.

Key issues for consideration

- When comparing adalimumab with etanercept, is it more appropriate to consider etanercept given intermittently or continuously? What are the most appropriate assumptions for intermittent etanercept with regards to dose and disutility?
- What are the most appropriate estimates to be assigned to key parameters in the model, including length of hospital stay for non-responders, estimates of inpatient costs and utility values, as compared with those used in previous appraisals of biologic therapies (etanercept, efalizumab and infliximab)?
- What are the implications of the concerns raised about the limited information presented on the included comparison trials and the methodological assumptions used in the mixed treatment comparison?
- Is improvement in psoriasis area and severity index (PASI) score (the outcome measure used in the economic analysis) an appropriate measure for treatment response?
- How should potential short and long-term adverse events associated with adalimumab be dealt with? The manufacturer's model does not include adverse events.
- Does the Committee consider adalimumab to be:
  - a replacement for etanercept (as recommended in current NICE guidance TA103)
  - an alternative, equivalent treatment option to etanercept
  - an alternative only when etanercept cannot be used because of intolerance or contraindications?
- Does the Committee consider adalimumab to be more appropriate for use in certain subgroups? If so, are there any equality issues that need to be taken into consideration?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	The manufacturer states that the submission will address the clinical and cost effectiveness of treatment with adalimumab in accordance with the licensed indication. The population in the marketing authorisation is expected to be adults with moderate to severe chronic 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.
Intervention	Adalimumab (it is expected that dosing will be an 80 mg loading dose at baseline then 40 mg every other week (EOW) from week 1).
Comparators	All standard and biologic therapies were considered for inclusion in the evidence synthesis, which is used to inform the cost-effectiveness modelling (acitretin, ciclosporin, hydroxycarbamide, methotrexate, photo[chemo]therapy [PUVA], etanercept, efalizumab and infliximab). As per the York Assessment Group model previously developed for technology appraisal (TA) 103 for etanercept and efalizumab for the treatment of psoriasis, it was not possible to include acitretin, hydroxycarbamide and PUVA, as the appropriate data were not available.
Outcomes	A range of outcomes to assess the impact of treatment with adalimumab on psoriasis will be considered, including the following. PASI response (50/75/90/100). Physician's global assessment of disease activity. Patient's global assessment of disease activity. Health-related quality of life (dermatology life quality index [DLQI], short form version 36 [SF-36] and Euro quality of life questionnaire [EQ-5D]). Pain associated with psoriatic plaques and psoriatic arthritis (PsA) (where applicable) and pruritus related to psoriasis will be assessed using visual analogue scales. Safety of adalimumab (analysis of adverse events). Quality-adjusted life years (QALYs) is the primary outcome measure used in the economic model (cost−utility analysis). The QALY gain is determined by the level of PASI response.
Economic evaluation	The cost effectiveness of treatment is assessed in terms of incremental cost per quality-adjusted life year. The model considers the use of standard and biologic therapies over time as in the York Assessment Group model developed for TA103 for etanercept and efalizumab for the treatment of psoriasis. Costs are considered from an NHS perspective in the base-case economic model analysis. Absenteeism from work will be included in the economic model in a sensitivity analysis.

Previous NICE guidance

- 'Etanercept and efalizumab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 103, July 2006).

  Key points of guidance:

  1.1 Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met.

  • The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more **and** a Dermatology Life Quality Index (DLQI) of more than 10.

  • The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments.

  1.2 Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these patients. An adequate response is defined as either:

  • a 75% reduction in the PASI score from when treatment started (PASI 75) or

  • a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from when treatment started.

  1.3 Efalizumab, within its licensed indications, is recommended for the treatment of adults with plaque psoriasis under the circumstances detailed in section 1.1 only if their psoriasis has failed to respond to etanercept or they are shown to be intolerant of, or have contraindications to, treatment with etanercept.

- 'Infliximab for the treatment of adults with psoriasis' (NICE technology appraisal currently in development).

  Key points of guidance (taken from FAD, November 2007. Final guidance awaiting publication):

  1.1 Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met.

  • The disease is very severe as defined by a total Psoriasis Area Severity Index (PASI) of 20 or more **and** a Dermatology Life Quality Index (DLQI) of more than 18.

  • The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate **or** PUVA (psoralen and long-wave ultraviolet radiation), **or** the person is intolerant to or has a contraindication to these treatments.

  1.2 Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks. An adequate response is defined as either:

  • a 75% reduction in the PASI score from when treatment started (PASI 75) **or**

  • a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI from when treatment started.

  1.3 When using the DLQI healthcare professionals should take care to ensure that they take account of a patient's disabilities (such as physical impairments) or linguistic or other communication difficulties, in reaching conclusions on the severity of plaque psoriasis. In such cases healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure. The same

approach should apply in the context of a decision about whether to continue the use of the drug in accordance with section 1.2.

1.2 Evidence Review Group comments

1.2.1 Population

The Evidence Review Group (ERG) noted that the patient group in the manufacturer's submission (MS) decision problem was a more tightly defined group than that stated in the final scope for the appraisal.

1.3 Statements from professional/patient groups and nominated experts

The clinical specialist stated that the PASI 75 responses observed in study M02-528 (Gordon et al. 2006) for people fulfilling the British Association of Dermatologists (BAD) guidelines criteria for initiating a biological therapy confirm that the results are generalisable to UK clinical practice. The clinical specialist added that adalimumab also provides a useful alternative for treating people whose psoriasis has failed to respond to, or become refractory to, other anti-TNF alpha treatments. It was also noted that facilities in dermatology for the delivery and monitoring of other biologics are developing but are not fully established. The specialist also suggested that it may be appropriate for people with more severe skin disease to be registered in the BAD Biologics Register so that the long-term safety and efficacy of adalimumab could be determined.

The patient group experts stated that this technology will increase the choice and treatment options available for people with psoriasis, particularly if previous treatments have failed. Current standard therapies are not always appropriate: emollients and topical treatments can be smelly, messy and difficult to apply, ultraviolet (UV) treatment requires frequent hospital visits, and inpatient treatment for severe psoriasis involves a lengthy stay in hospital. Adalimumab may reduce the need for other topical or systemic treatments. The patient group experts also highlighted the impact that adalimumab could have on psoriatic arthritis and other comorbidities. The patient group experts

request the Committee to consider the availability of this treatment based on individual choice and clinical need, and to consider careful monitoring of people receiving this treatment.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer presented data from five trials that it described as forming the evidence base for the efficacy of adalimumab in the treatment of adults with moderate to severe chronic plaque psoriasis. Three of these studies were randomised controlled trial (RCTs) (M02-528, REVEAL and CHAMPION) lasting between 12 and 52 weeks, and two were continuation trials (M02-529 and M02-658) lasting 48 weeks and 2 years, respectively (the 2-year study is ongoing and data are available from an interim efficacy analysis only) (table 1). All of the RCTs compared adalimumab with placebo and one also compared adalimumab with methotrexate.

A further two RCTs (M02-538 and M03-596) were presented by the manufacturer because they provide data on time to relapse in people who had a dose reduction or treatment withdrawal, and data on re-treatment with adalimumab in people who had relapsed following dose reduction or treatment withdrawal. However, these studies had a different treatment regimen to the five trials above and were not included in the MS to the EMEA to demonstrate the efficacy of adalimumab. The results of these latter two studies are not presented here but can be found on pages 64 to 65 and pages 72 to 73 of the MS.

Summary details of the seven studies are presented in table 1.

Table 1 Summary of adalimumab trials, taken from MS table 5.2.1

Trial name	Design/ duration	Participants	Intervention/ comparator	Primary outcome
M02-528 (n = 147)	12-week, phase II RCT USA, Canada	Moderate to severe chronic plaque psoriasis (≥ 5% BSA). Inadequate response to topical therapy	Adalimumab 40 mg or placebo EOW sc Adalimumab 40 mg or placebo weekly sc	% people with ≥ PASI 75 at week 12
M03-656 (REVEAL) (n = 1212)	52-week, phase III RCT USA, Canada Period A: 16-week placebo-controlled Period B: 17-week open-label Period C: 19-week placebo-controlled	Moderate to severe chronic plaque psoriasis (≥ 10% BSA, PASI ≥ 12, PGA of at least moderate disease)	Period A: adalimumab 40 mg or placebo EOW sc Period B: adalimumab 40 mg EOW sc Period C: adalimumab 40 mg or placebo EOW sc	% people with ≥ PASI 75 at week 16 % people losing an adequate response after re-randomisation to placebo at week 33 and on or before week 52
M04-716 (CHAMPION) (n = 271)	16-week, phase III RCT Europe, Canada	Moderate to severe chronic plaque psoriasis (≥ 10% BSA, PASI ≥ 10, PGA of at least moderate disease)	Adalimumab 40 mg EOW sc Methotrexate 7.5 mg EOW sc Placebo EOW sc and weekly	% people with ≥ PASI 75 at week 16
M02-529 (n = 137)	48-week, phase II extension study (12 weeks double-blind, 36 weeks open-label) USA, Canada	Moderate to severe chronic plaque psoriasis. Completion of lead-in study M02-528	12-week double-blind period: previously assigned M02-528 dose of adalimumab. People who received placebo in M02-528: 80 mg adalimumab on week 0 and 40 mg EOW from week 1	% people with PASI 75 at week 12
M02-658 [redacted]	2-year, phase III, ongoing open-label extension study USA, Europe, Canada	People who participated in study M02-529, M02-538, M03-596, M03-656 or M04-716 and remained eligible	Adalimumab 40 mg EOW sc	Number and % people with PASI 50/75/90 every 12 weeks Number and % people with PGA of 'clear' or 'minimal' every 12 weeks

M02-538 (n = 148)	76-week, phase II RCT (12 weeks open-label, 12 weeks double-blind, 52 weeks follow-up) USA, Canada	Moderate to severe chronic plaque psoriasis (≥ 5% BSA)	12-week open-label period: adalimumab 80 mg at weeks 0 and 1; adalimumab 40 mg weekly sc 12-week double-blind period: treatment withdrawal (placebo); dose decrease (adalimumab 40 mg EOW sc) 52 weeks follow-up: no treatment	Time to relapse after week 12 to week 24 for people who had a week 12 ≥ PASI 50 response
M03-596 (n = 32)	24-week, phase II extension study (12 weeks open-label, 12 weeks double-blind) USA, Canada	Moderate to severe chronic plaque psoriasis. People randomised into study M02-538 who had < PASI 50 response after week 12 and on or before week 24	12-week open-label period: adalimumab 80 mg at weeks 0 and 1; adalimumab 40 mg weekly sc 12-week double-blind period: people with ≥ PASI 50 continued double-blind treatment arms from M02-538	% of people with clinical response, defined as ≥ PASI 50 response relative to week 0 PASI, in the lead-in study M02-538

BSA, body surface area; EOW, every other week; MS, manufacturer's submission; PASI, psoriasis area and severity index; PGA, physician global assessment of disease; sc, subcutaneously.

A significantly larger proportion of people treated with adalimumab had a primary endpoint response of greater than or equal to PASI 75 relative to baseline PASI score compared with people given placebo or methotrexate (see table 2).

Table 2 Proportion of people (%) with ≥ PASI 75 relative to baseline

	Adalimumab EOW	Adalimumab weekly	Placebo	Methotrexate
M02-528* (week 12)	53	80	4	–
REVEAL* (week 16)	70.9	–	6.5	–
CHAMPION* (week 16)	80	–	19	36
M02-529** (week 12)	64 (55)[a]	72	–	–
M02-658** (week 48)	[redacted]	–	–	–

* p < 0.001 for adalimumab versus placebo/methotrexate; ** p value not given.

[a] 64% for people who received adalimumab EOW in both lead-in study (M02-528) and extension study M02-529; 55% for people who received placebo in lead-in study (M02-528) and then adalimumab EOW in M02-529.

EOW, every other week; PASI, psoriasis area and severity index.

Longer term data from the pivotal phase III trial, REVEAL, show that PASI response is maintained and continues to favour adalimumab over placebo. During the open-label period of the trial (period B – see table 1), 89% of people originally randomised to adalimumab had at least a PASI 75 response at week 33, and PASI 90 response rates increased in people originally randomised to placebo. In period C of the trial (week 33 to week 52), the proportion of people for whom an adequate response was lost (a primary outcome of the trial) was statistically significantly higher for people re-randomised to placebo (28.4%) compared with people re-randomised to adalimumab (4.9%, [between treatment group difference of 23.5%, 95% CI 16.9 to 30.2]). In addition, there are longer term data from an interim analysis of 49 people from trial M02-658, showing that PASI responses were maintained up to week 120 of adalimumab therapy.

For secondary outcomes recorded in the trials, there were statistically significant differences between adalimumab and placebo/methotrexate in physician's global assessment (PGA) score, DLQI score and health-related quality of life scores.

Adalimumab was generally safe and well tolerated. Data from the placebo-controlled study set (n = 1469 [see pages 85–86 of the MS for details]) show that the incidence of adverse events that might be related to the study drug was statistically significantly higher in the adalimumab treatment group than in the placebo treatment group. The most commonly reported adverse effects in people treated with adalimumab were nasopharyngitis, upper respiratory tract infection and headache. The incidence of severe adverse events was low and comparable in the adalimumab and placebo treatment groups.

The manufacturer carried out an indirect comparison of adalimumab with etanercept, efalizumab, infliximab, ciclosporin and methotrexate, using a mixed treatment comparison approach within a Bayesian evidence synthesis framework. This approach links each treatment together by a link to placebo, either by means of direct comparison or through comparison with any other active agent compared with placebo.

The manufacturer included four RCTs comparing etanercept with placebo, four comparing infliximab with placebo, five comparing efalizumab with placebo, one comparing ciclosporin with placebo and one comparing methotrexate with ciclosporin. The PASI 75 response results of this analysis, taken from the MS, are presented in table 3 (for PASI 50 and PASI 90 results see page 83 of the MS).

Table 3 Results of mixed treatment comparison (PASI 75 response)

Treatment	Probability of a response 95% CI			Relative risks 95% CI		
	Mean	Lower	Upper	Mean	Lower	Upper
PASI 75 response						
Supportive care	5%	4%	6%	1.00	1.00	1.00
Etanercept 50 mg BIW	52%	43%	60%	11.60	9.16	14.78
Etanercept 25 mg BIW	38%	29%	47%	8.47	6.36	11.07
Efalizumab 1 mg/kg	29%	24%	35%	6.56	5.20	8.27
Infliximab 5 mg/kg	81%	75%	87%	18.21	14.38	23.12
Methotrexate	37%	22%	55%	8.25	4.68	13.27
Ciclosporin 5 mg/kg/day	55%	29%	79%	12.29	6.07	19.49
Ciclosporin 3 mg/kg/day	34%	18%	53%	7.64	3.78	12.64
Adalimumab 40 mg EOW	67%	57%	74%	14.91	11.68	18.62

BIW, twice weekly; CI, confidence interval; EOW, every other week; PASI, psoriasis area and severity index; RR, relative risk.

The PASI 50 response for adalimumab was 86% (CI 80%, 90%) with a relative risk of 5.93 (CI 4.98, 6.95) compared with supportive care. The PASI 90 response for adalimumab was 37% (CI 28%, 45%) with a relative risk of 54.4 (CI 37.92, 75.43) compared with supportive care.

The manufacturer concluded that the probability of PASI response is statistically significantly higher for both adalimumab and infliximab compared with etanercept.

2.2 Evidence Review Group comments

Overall, the ERG considered that the manufacturer provided an unbiased estimate of treatment efficacy for adalimumab based on the results of placebo-controlled trials. However, the ERG identified a number of limitations with other aspects of the clinical effectiveness data provided as follows.

- Only one of the adalimumab trials compared adalimumab with an active comparator (methotrexate).
- No explanation was presented by the manufacturer as to why a standard meta-analysis was not conducted. Therefore, the overall treatment effect of adalimumab achieved across the trials is unknown and the only indication

of overall efficacy comes from the results of the mixed treatment comparison.

- The ERG is uncertain about the appropriateness of the mixed treatment comparison because the MS does not discuss the issue of possible heterogeneity across the trials.
- The ERG noted that very limited descriptions of the comparator trials and the methodological assumptions used in the mixed treatment comparison were provided by the manufacturer. However, the results for most of the included treatments are broadly similar to those published by the York Assessment Group in their analysis of etanercept (TA103).
- The MS did not provide a definition of moderate to severe chronic plaque psoriasis and did not use disease severity as a criterion for including studies in the systematic review.
- It is uncertain to what extent the trial populations included in the adalimumab and comparator trials match the population specified in the decision problem, in terms of prior treatment with systemic therapy.

2.3 Statements from professional/patient groups and nominated experts

The clinical specialist stated that although comparative trials have not been performed, the efficacy results presented by Gordon et al. 2006 (study M02-528) are as good as the most effective licensed therapy (infliximab) and are better than those found with etanercept or efalizumab. The clinical specialist added that because adalimumab is a fully human anti-TNF alpha agent it is likely to have advantages over currently available agents: it is administered subcutaneously, it has acceptable results following administration every other week, and greatly reduces the risk of immunological reactions (anaphylactic, vasculitic, neutralising antibodies or induction of auto-antibodies). The clinical specialist noted that the exposure in person years in other indications is less than that with existing anti-TNF alpha agents, and this could be a disadvantage.

The patient/carer group experts highlighted how effective treatments for psoriasis can lead to improvements in quality of life and the impact on daily lives, including symptoms, mental health, general health, employment and family/carer impact. Possible disadvantages noted by the patient/carer group experts included lack of long-term data on efficacy and safety, and also that administering the treatment by self-injection may not be suitable for everyone. However, self-injection may make a person feel more in control of their medication.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer's cost-effectiveness analysis was based on a previous analysis undertaken by Woolacott et al. 2006 (referred to here as the York report or model) which assessed the use of etanercept and efalizumab for the treatment of psoriasis. The York model was further developed to incorporate additional evidence, particularly for the clinical efficacy of adalimumab. The manufacturer states that the model included only treatments and doses that are licensed and recommended for use in people with psoriasis in the UK.

The manufacturer's base-case analysis considers people with moderate to severe psoriasis and the model follows a continuation rule set out by the BAD Guideline and NICE guidance. Each treatment undergoes a trial period, after which the person will only continue therapy if a predetermined improvement in their disease severity is achieved. In the manufacturer's base case, this is defined as achieving a PASI 75 response (the DLQI was not used in the analysis as an indication of response). The manufacturer states that people whose condition does not have this level of response (non-responders) move on to trial the next available treatment in the sequence (page 101 of the MS). The time at which response is measured is defined in the respective European marketing authorisations (where available) or the primary endpoint of the respective RCTs, and varies between 12 weeks (etanercept, efalizumab and low-dose ciclosporin), 14 weeks (infliximab) and 16 weeks (adalimumab

and methotrexate). The treatment period for each therapy (following a response) was taken from the York report, calculated using a Markov model with an annual cycle, and assumed a drop-out rate of 20% for all patients. The manufacturer states that the model examines all potential systemic treatments for this patient group both simultaneously and compared with supportive care, rather than analysing each combination of treatments separately. The expected costs and benefits for patients are estimated for the time spent on each therapy. Each treatment is ranked in terms of its incremental cost-effectiveness ratio (ICER) to supportive care, which determines the most cost-effective treatment sequence at a set of ICER threshold values. The manufacturer's model is stated to consider drug treatment sequences over the lifetime of patients.

As in the York model, the manufacturer's model did not include adverse events associated with the treatments because the manufacturer states that biologic agents have been proven to be relatively safe, with very little toxicity seen in clinical trials or clinical practice. The manufacturer argues that not including adverse events is unlikely to affect the ICERs, except perhaps for reducing the relative cost effectiveness of methotrexate and ciclosporin.

3.1.1 Resource use and utilities

The cost and resource use data were taken from the York report, NHS Reference Costs and National Tariff and the 'British national formulary' (BNF 53, 2007). The Personal Social Services Research Unit (PSSRU) inflation index was used to update costs to 2005−06, if current costs were not available. The cost of administration of the biologics was calculated by assuming that educating people to self-inject would involve three 1-hour sessions of nurse time during the trial period (adalimumab, etanercept and efalizumab) and infliximab infusion costs were based on the British Society for Rheumatology (BSR) standard guidelines. The number of days of hospitalisation for non-responders per year was assumed to be 21 days, taken from the York report. The manufacturer conducted a search for other

sources of evidence for this parameter (page 114 of the MS), but found other estimates were based on non-UK data.

The utilities in the model were calculated from the evidence collected in two of the adalimumab studies/trials (M04-716 [CHAMPION] and M02-528). The baseline utility and psoriasis severity values are shown in table 4.

Table 4 Baseline utility and psoriasis severity values

Baseline variables	Trial M02-528				Trial M04-716 (CHAMPION)			
	Baseline DLQI ≤ 10 (n = 62)		Baseline DLQI > 10 (n = 82)		Baseline DLQI ≤ 10 (n = 132)		Baseline DLQI > 10 (n = 119)	
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
EQ-5D	0.794	0.159	0.563	0.307	0.810	0.159	0.647	0.266
PASI	13.679	6.775	17.290	7.513	18.759	6.651	19.943	7.526
DLQI	6.323	2.715	17.720	5.430	5.796	2.615	16.017	3.895

Note: Only people with baseline EQ-5D measures were included in the analysis.

DLQI, dermatology life quality index; EQ-5D, Euro quality of life questionnaire; PASI, psoriasis area and severity index.

In these studies, the responsiveness of changes in EQ-5D scores by PASI response was assessed over 16 weeks. A mixed model with repeated measures of analysis of covariance was used to assess the relationship between changes in EQ-5D and clinical response. The results show that the responsiveness of changes in EQ-5D was significantly different between people with a baseline DLQI greater than 10 and those with a baseline DLQI of 10 or less ($p = 0.01$; table 5).

Table 5 Changes of EQ-5D by PASI response and baseline DLQI

Baseline DLQI	PASI response	Δ EQ-5D[a]	SE	P values[b]	
				Versus PASI 50–90	Versus PASI 50–
≤ 10 (n = 194)	PASI 90+	0.130	0.031	0.982	0.436
	PASI 50–90	0.102	0.022	N/A	0.605
	PASI 50–	0.045	0.024	0.605	N/A
> 10 (n = 201)	PASI 90+	0.308	0.027	0.008	< 0.001
	PASI 50–90	0.178	0.023	N/A	0.014
	PASI 50–	0.063	0.025	0.014	N/A

[a] p = 0.01 for test of overall PASI response categories by baseline DLQI interaction from a mixed model with repeated measures analysis of covariance.

[b] Pairwise comparisons between means were performed using Scheffe's test adjusting for multiple comparisons.

DLQI, dermatology life quality index; EQ-5D, Euro quality of life questionnaire; N/A, not applicable; PASI, psoriasis area and severity index.

The PASI response estimates for each treatment from the mixed treatment comparison evidence synthesis were linked to the utility estimates, providing the QALYs for each therapy.

The utilities used in the base-case analysis were taken from people with severe psoriasis (baseline DLQI > 10). Sensitivity analyses were carried out for utility values from people with a DLQI of 10 or less at baseline, from all patients, and from the York model for all patients (PASI response < 50%: 0.05; ≥ 50% and < 75%: 0.17; ≥ 75% and < 90%; 0.19; ≥ 90%: 0.21).

The manufacturer incorporated a disutility assumption into the model to account for the difference in utility between continuous and intermittent therapy, reflecting that the re-commencement and effect of treatment is not instantaneous.

3.1.2 Results

The manufacturer's base-case results demonstrated that adalimumab was the most cost-effective biologic strategy, with additional costs of £4993, resulting in an ICER of £30,500 per QALY gained compared with supportive care. Infliximab had the highest incremental costs of £7736, resulting in an ICER of £42,000 per QALY gained compared with supportive care, with the other

biologic treatments giving ICERS between £37,000 and £40,000 per QALY gained. Both methotrexate and ciclosporin were found to be cost-saving (table 6).

Table 6 Manufacturer's base-case results (annualised)[a]

	Mean QALY (95% CI)	Mean cost (£) (95% CI)	ICER versus biologics only[b]	ICER versus supportive care
Methotrexate	0.129	–3844	−	–29,759
Ciclosporin	0.079	–1987	−	–25,135
Supportive care	0	0	–	–
Etanercept intermittent[c]	0.110	4114	Extended domination[d]	37,284
Etanercept high intermittent[c]	0.123	4699	Extended domination	38,358
Efalizumab	0.124	4942	Extended domination	39,948
Adalimumab	0.164	4993	30,538	30,538
Etanercept	0.134	5058	Dominated[e]	37,676
Infliximab	0.182	7736	147,906	42,492

[a] See section 6.2.3 of the MS for details of drug dosages and frequency.

[b] Only biologics and supportive care compared. This excludes methotrexate and ciclosporin from the analysis.

[c] Denotes intermittent use, where use is stopped upon remission and restarted upon relapse.

[d] Extended domination refers to cases where the ICER is higher than that of another drug even though one of either costs or QALYs is more favourable.

[e] A treatment is dominated if an alternative has lower costs and higher effectiveness.

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

The manufacturer's cost-effectiveness acceptability curve for the biologics is presented on page 122 of the MS. The manufacturer states that as the threshold increases, adalimumab has the highest probability of being cost effective in comparison with supportive care. The manufacturer presents a table indicating the most cost-effective ordering of therapies as a function of cost-effectiveness threshold (see page 125 of the MS). This shows that below a value of £30,500 per QALY gained, the treatment sequence should be methotrexate followed by ciclosporin, followed by supportive care. No other treatments are determined to be cost effective below this threshold. Above this, adalimumab should be incorporated into the sequence instead of supportive care.

The results of the sensitivity analysis have been reproduced in table 7 (page 127 of the MS). The analysis identified one of the key drivers of cost effectiveness to be the number of days hospitalised because of non-response to treatment: 0 days, 16 days and 39 days giving ICERs for adalimumab compared with supportive care of £60,629, £37,718 and £4782 per QALY gained, respectively.

Table 7 ICERs from sensitivity analyses changing key parameters (£ per QALY compared with supportive care)

	Etanercept intermittent	Efalizumab	Adalimumab	Etanercept 25 mg continuous	Infliximab
Base case[a]	*37,284*	*39,948*	*30,538*	*37,676*	*42,492*
Hospitalisation days = 16	47,322	48,506	37,718	45,912	45,063
Hospitalisation days = 39	1,374	9,253	4,782	8,138	18,790
Hospitalisation days = 0	79,281	75,813	60,629	72,190	70,184
No disutility on intermittent therapy	30,660	39,948	30,538	37,676	42,492
High doses of ciclosporin	37,284	39,948	30,538	37,676	42,492
Continuous ciclosporin use	37,284	39,948	30,538	37,676	42,492
Etanercept dose 74% of continuous	27,585	39,948	30,538	37,676	42,492
Alternative utility values	41,844	43,264	38,679	42,304	57,946
PASI response assessed using PASI 50	42,308	43,103	35,243	42,838	46,836
Utility values of people with DLQI ≤ 10	91,389	95,920	80,124	92,387	116,073
Utility values of all patients	52,770	56,209	44,005	53,330	61,911
People with high weight (assume 90 kg)	37,284	39,948	30,538	37,676	59,118
People with low weight (assume 60 kg)	37,284	39,948	30,538	37,676	25,866
Include lost productivity while hospitalised	24,736	29,223	21,540	27,356	34,211
Only 40% of non-responders hospitalised (49 days in hospital)	40,119	42,362	32,562	40,000	44,355
Adalimumab phase II trial excluded	37,671	39,856	29,399	37,970	42,644

Note: Breakdown of costs and QALYs can be found in tables 6.3.3.2 and 6.3.3.3 of the MS.

[a] Base-case parameters: hospitalisation 21 days, intermittent etanercept dose is a percentage 88% of continuous dose, PASI response assessed using PASI 75.

DLQI, dermatology life quality index; ICER, incremental cost-effectiveness ratio; PASI, psoriasis area and severity index; QALY, quality-adjusted life year.

Using alternative utility values from the York model (Woolacott et al. 2006) increases the ICER for adalimumab compared with supportive care (to

£38,679 per QALY gained), as does applying utility values from all patients (to £44,005 per QALY gained) and including patients with less severe psoriasis with a baseline DLQI of 10 or less (to £80,124 per QALY gained). When it is assumed that there is no disutility on intermittent therapy, the ICER for intermittent etanercept compared with supportive care is reduced to £30,660 per QALY gained.

Assuming only 40% of non-responders are hospitalised, but for 49 days, marginally increases the ICERs (£32,562 per QALY gained for adalimumab).

3.2 Evidence Review Group comments

The ERG considered that the economic model presented by the manufacturer used an appropriate approach for the disease area given the available data. However, the ERG identified that the clinical pathway for the model presented in the MS in figure 6.2.6.1 (page 102 of the MS) did not appear to represent the model structure. The diagram suggests people switch between treatments if they do not respond to a particular treatment but the model does not provide this option.

Responders (defined as people with PASI response equal to or greater than 75 or 90 after the trial period) continue with treatment during the treatment period and are assumed to stay at this level of improvement for a period of time and then become a non-responder. The average duration of treatment is estimated using an annual drop-out rate of 20%, with an estimated average treatment duration of 186 weeks. Non-responders receive supportive care after the trial period.

The ERG highlighted a number of important issues relating to the uncertainty surrounding parameters in the model. These included the following.

- Few details were given of the regression model used to relate changes in PASI scores to EQ-5D data, therefore the ERG could not be sure of the appropriateness of the approach taken.

- The manufacturer's base-case analysis includes people with a DLQI greater than 10. Depending on the baseline PASI scores, this group is likely to be categorised as having severe psoriasis. The results from the scenario analysis show that changes in the DLQI group used have large effects on the cost-effectiveness estimates. For example, if the group with DLQI less than 10 is used then the cost per QALY gained for adalimumab increases to more than £80,000 per QALY gained. The ERG comments that the characteristics of the people who receive care are very important in determining results.
- Uncertainty exists about the correct way to model key comparators with adalimumab, in particular intermittent etanercept. The ERG noted that it is unclear how widely intermittent etanercept is used in clinical practice and the degree to which costs are avoided with intermittent therapy. It is also unclear as to how much utility is lost owing to psoriasis flare ups. The ERG commented that the assumptions made regarding the cost of intermittent etanercept, relating to the proportion of continuous cost incurred by intermittent therapy, affect the comparative cost of intermittent etanercept compared with adalimumab.
- The ERG noted an apparent lack of data regarding the need for inpatient stays and costs for non-responders. The assumption in the manufacturer's model was that non-responders to treatment receive 21 inpatient days per year whereas those who respond to treatment (are on treatment) receive no inpatient stays. Changes in this value (length and cost) have large effects on the cost-effectiveness estimates for the biological drugs.
- The data used to estimate effectiveness and also drop-out from treatment have been taken mainly from short-term trials. The ERG commented that it is therefore unclear about what would happen over the longer term.

3.2.1 Exploratory Evidence Review Group analyses

The ERG carried out some exploratory sensitivity analyses estimating the effect of varying parameter values on the ICER for adalimumab compared with supportive care. The ERG used the confidence intervals for the parameters as ranges in the sensitivity analyses. If these were not available,

an arbitrary range was used. These results are presented in table 8. The ERG noted that the results were generally robust to changes in the model parameters, and the results were most sensitive to changes in cost of adalimumab, cost of inpatient stay and the annual length of inpatient stays for non-responders.

Table 8 ERG one-way sensitivity analyses on the effect of changing parameter values on ICER for adalimumab compared with supportive care

Variable	Base case	Inputs		ICER		Difference
		Low	High	Low	High	
Utility gain, e.g. PASI ≥ 90%[a]	0.31	0.256	0.36	£30,526	£30,098	£428
Annual drop out rates	20%	10%	30%	£28,747	£32,414	£3667
Treatment response rate, e.g. PASI ≥ 90%[ab]	37%	28%	45%	£32,293	£29,312	£2981
Inpatient stay for non-responders, days/year	21	16	25	£37,421	£24,622	£12,799
Cost of inpatient stay (+/−20%)	£256	£204	£307	£36,283	£24,338	£11,945
Cost of adalimumab per vial (+/−20%)	£358	£286	£429	£18,276	£42,346	£24,070

[a] Ranges for sensitivity taken from lower and upper 95% confidence limits for all response categories.

[b] Treatment response rate varied for both placebo and adalimumab together.

ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PASI, psoriasis area and severity index.

The ERG also ran a number of scenario analyses to test certain assumptions in the model. When running the model with the same dosage for intermittent etanercept as for the York report, the ICER for intermittent etanercept compared with supportive care was £27,256 per QALY gained. The ICER for adalimumab compared with intermittent etanercept was £36,671 per QALY gained (table 9).

Table 9 ERG scenario analysis: dosage for intermittent etanercept is the same as used in the York report

	Incremental cost	Incremental QALY	ICER compared with supportive care	ICER
Supportive care	£0.00	0.000	−	−
Etanercept 25 mg BIW	£3033	0.111	£27,256	£27,256
Efalizumab 1 mg/kg	£4936	0.125	£39,612	Extended dominance[a]
Adalimumab 40 mg EOW	£4993	0.165	£30,311	£36,671
Etanercept 25 mg continuous	£5051	0.135	£37,304	Extended dominance
Infliximab 5 mg/kg	£7737	0.183	£42,245	£149,037
Etanercept 50 mg BIW	£9910	0.123	£80,288	Dominated[b]

[a] Extended domination refers to cases where the ICER is higher than that of another drug even though one of either costs or QALYs is more favourable.

[b] A treatment is dominated if an alternative has lower costs and higher effectiveness.

BIW, twice weekly; EOW, every other week; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

The ERG also reduced the cost of intermittent etanercept in line with the length of the treatment (68%) and off-treatment periods, which reduced the ICER for intermittent etanercept versus supportive care to £22,689 per QALY gained. In this case, the ICER for adalimumab compared with intermittent etanercept was £46,122 per QALY gained. Reducing the length of inpatient stays for non-responders to 40% of 21 days (8.4 days) increased the ICER for adalimumab to £48,229 per QALY gained.

The ERG also investigated the effect of using individual point estimates for the utility gain associated with PASI responses for the base-case model (DLQI > 10). This involved using values of 0.167 for the PASI 75−90 group and 0.189 for the PASI 50−75 group instead of a value of 0.178 for both groups. The effect was comparatively small, changing the ICER for adalimumab compared with supportive care from £30,311 to £31,291 per QALY gained.

The ERG ran a probabilistic sensitivity analysis (PSA) using alternative assumptions to the manufacturer: firstly, three infusions for infliximab in the

trial period (instead of four); and secondly, the cost of intermittent etanercept was the same as used in the York report (74% of the continuous etanercept costs). The results are shown in table 10, and on page 73 of the ERG report.

Table 10 Results for the ERG's probabilistic sensitivity analysis

Drug	Mean QALY	Mean cost	ICER	ICER versus supportive care
Supportive care	0.000	£0.00	0	–
Etanercept 25 mg BIW	0.111	£3042.56	£27,450	£27,450
Efalizumab 1 mg/kg	0.124	£4941.15	Extended dominance[a]	£39,757.09
Adalimumab 40 mg EOW	0.164	£4991.39	£36,770	£30,373.81
Etanercept 25 mg continuous	0.135	£5056.84	Dominated[b]	£37,492.97
Infliximab 5 mg/kg	0.183	£7177.66	£115,067	£39,268.48
Etanercept 50 mg BIW	0.123	£9912.53	Dominated	£80,527.60

[a] Extended domination refers to cases where the ICER is higher than that of another drug even though one of either costs or QALYs is more favourable.

[b] A treatment is dominated if an alternative has lower costs and higher effectiveness.

BIW, twice weekly; EOW, every other week; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Using the ERG assumptions alters the results, and reduces the probability that adalimumab is the most cost-effective strategy at £30,000 per QALY gained from 46% to 16%.

4 Authors

Helen Knight, Zoe Charles and Elisabeth George, with input from the Lead Team (Professor Stirling Bryan and Dr Rosalind Ramsay).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The evidence review group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessments Centre (SHTAC), University of Southampton:

- Turner D, Picot J, Cooper K et al. Adalimumab for the treatment of psoriasis, November 2007

B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope and assessment report. Organisations listed in I were invited to make written submissions. Organisations listed in II gave their expert views on adalimumab for the treatment of psoriasis by providing a written statement to the Committee.

I Manufacturer/sponsor:

- Abbott Laboratories Limited

II Professional/specialist and patient/carer groups:

Patient / Carer Groups

- Age Concern England
- Changing Faces
- Counsel and Care
- Help the Aged
- Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
- Psoriasis Association
- Skin Care Campaign
- Specialised Healthcare Alliance

Professional Groups

- British Association for Services to the Elderly
- British Association of Dermatologists
- British Dermatological Nursing Group
- British Skin Foundation
- British Society of Rehabilitation Medicine

- Community Practitioners' & Health Visitors Association
- National Association of Primary Care
- Primary Care Dermatology Society
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Physicians
- Royal Pharmaceutical Society
- Royal Society of Medicine - Forum on Intellectual Disabilities
- United Kingdom Clinical Pharmacy Association

Others

- Department of Health
- Kirklees PCT
- Nottinghamshire County PCT
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- Age Concern Cymru
- Board of Community Health Councils in Wales
- British National Formulary
- Department of Health, Social Services and Public Safety for Northern Ireland
- Medicines and Healthcare products Regulatory Agency (MHRA)
- National Public Health Service for Wales
- NHS Confederation
- NHS Purchasing and Supply Agency
- NHS Quality Improvement Scotland
- Scottish Medicines Consortium

Possible comparator manufacturer(s)

- Bristol-Myers Squibb (hydroxycarbamide)
- Crawford Pharmaceuticals (psoralen)
- Mayne Pharma Plc (methotrexate)
- Medac GmBH (hydroxycarbamide)
- Novartis Pharmaceuticals UK Ltd (ciclosporin)
- Pfizer Ltd (methotrexate)
- Roche Products Ltd (acitretin)
- Schering-Plough Ltd (infliximab)
- MerckSerono Ltd (efalizumab)
- Wockhardt UK Ltd (methotrexate)
- Wyeth Pharmaceuticals (etanercept, methotrexate)

Relevant research groups

- British Epidermo-Epidemiology Society

- Cochrane Skin Group - Centre of Evidence-based Dermatology, University of Nottingham
- MRC Clinical Trials Unit
- Skin Research Centre, University of Leeds
- Skin Treatment and Research Trust (START)

C Additional references used:

NICE technology appraisal guidance 103 (2003) Etanercept and efalizumab for the treatment of adults with psoriasis. TA103. www.nice.org.uk/TA103

NICE technology appraisal (FAD currently in appeal stage) Infliximab for the treatment of adults with psoriasis. www.nice.org.uk

Woolacott N, Hawkins N, Kainth A et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. Health Tech Assess 2006; 10(46)