Efalizumab and etanercept for psoriasis – consultee/commentator comments on the appraisal consultation document
26 September 2005 – 17 October 2005

National Institute for Health and Clinical Excellence

Consultee/ Commentator	**Section**	**Comment**	Response
NHS-QIS* (1)	General	This is a comprehensive review of the treatment of psoriasis and the effectiveness of two of the newer biological agents. I am not aware of any other evidence not considered, and consider the conclusions reached to be entirely sensible and logical. They form a proper basis at present for prescribing advice to the NHS in Scotland, and if unchanged in the final document, will not require any modification for use in Scotland.	No action required.
Royal College of Paediatrics and Child Health	General – specify that it refers to adults	I would encourage them to add "in adults" in the title since they have only appraised it for this age range. Since they have not appraised the drugs' use for children and young people, we would be keen for them to state this and to recommend research in their use for the younger patient. We would also request that they state that there is no recommendation from the institute on the use for the paediatric age, rather than people believing that it has been rejected. Clearly, the decisions on use in paediatric practice will have to be made on an individual patient basis.	Adults added to the title. Etanercept and efalizumab are not licensed for use in children. NICE can only issue guidance within the licensed indications.
Royal College of Paediatrics and Child Health	General & 5.1.2– specify that it refers to adults; future appraisal to include children	I have read through this document. I agree entirely with XX's views above. I think it important to flag up that it specifically excludes children, although I had though that they agreed to look at children when I attended the London meeting prior to the production of this document. I am sure that biologics will be used in children when clinicians consider it necessary and I think we should ask the British Society for Paediatric Dermatology and the British Paediatric Rheumatological Society to collect data on their use in the form of a register. I presume that the companies will eventually have data on clinical trials in children and publish them but this could be some time away. Perhaps when NICE revisit this in perhaps 2 years time they can update it to include children, if feasible.	Comment noted. Adults added to the title. Etanercept and efalizumab were licensed during the appraisal and the indications did not include the treatment of children with psoriasis. NICE can only issue guidance within the licensed indications.

Psoriatic Arthropathy Alliance	General	Physician treatment of choice should not be impaired by non NICE approval, recommendations or non inclusion in current appraisal process The PAA recognises that there are economical constraints on prescribing but would like to hope that patients will also take a responsible role in the prescribing of these newer therapies.	Comment noted.
Royal College of Physicians and the British Association of Dermatologists	Remit – plaque psoriasis	The remit of the Appraisal Committee is set out in the preamble to the Appraisal Consultation Document (ACD): The Department of Health and the National Assembly for Wales have asked the National Institute for Health and Clinical Excellence (NICE or the Institute) to conduct an appraisal of efalizumab and etanercept for the treatment of psoriasis and provide guidance on its use to the NHS in England and Wales. This does not restrict it to plaque psoriasis and this seems to have crept into the title, recommendations and audit criteria (Appendix C) without justification in the ACD. Section 2 (Clinical Need and Practice), by contrast, refers only to psoriasis, not to plaque psoriasis.	Etanercept and efalizumab were licensed during the appraisal and are indicated for plaque psoriasis only. NICE can only issue guidance within the licensed indications. ”Plaque” has been removed from the title.
NHS-QIS* (2)	Remit - infliximab	It seems likely that infliximab may be licensed for psoriasis before NICE guidance is available for these 2 agents which will confuse the guidance.	Comment noted and infliximab has subsequently been licensed. The timing was, however, too late to allow inclusion with etanercept and efaluzimab.

Psoriatic Arthropathy Alliance	1 – Choice of treatments; appropriate therapies	The PAA would like to emphasize that a wide choice of potential treatments should be available regardless of cost Those most in need should be offered the most appropriate therapies, this does not necessarily mean that these patients would only qualify based on physician examination, but also include quality of life aspects that may prohibit other 'first line' therapies	Quality of life has been added as a treatment criterion.
Wyeth Pharmaceuticals	1 – Eligibility criteria / Quality of life	In our original submission of 16th July 2004 Wyeth established that there is a much stronger correlation between use of NHS resource and patients' actual quality of life index score, as defined by the Dermatology Life Quality Index (DLQI), than with clinical outcome measures as defined by PASI. Thus these relationships were used as the basis of our economic modelling strategy, a different approach than that taken by the York Evaluation Team, who used a PASI matrix approach. Whilst determination of the economic value of these agents is driven by patient quality of life, Wyeth recognise that a single measure of quality of life is unlikely to be sufficient criteria for use of etanercept, but this combined with an appropriate clinical outcome measure would define suitable patients much more effectively. Only using a PASI score of ≥ 20 is an inappropriate criterion upon which to identify the subgroup of patients the appraisal committee concluded are likely to receive cost effective treatment with etanercept; i.e. patients who have very poor quality of life and who are likely to require hospital admission for treatment. A PASI score of ≥ 20 will exclude a number of patients that have a high impact on NHS resource consumption. A PASI score of > 10 combined with a DLQI score > 10, as identified by the British Association of Dermatologists (BAD) in their recently produced guideline on the use of biological interventions in psoriasis, is a more appropriate rule for identifying such severe patients[i, ii]. The originators of the PASI index identified that a patient with a PASI score above 10 (not 20) would be considered for hospitalisation[iii].	The eligibility criteria have been amended to: "The disease is severe as defined by a total Psoriasis Area Severity Index [PASI] ≥ 10 and a Dermatology Life Quality Index [DLQI] >10."

Wyeth Pharmaceuticals	1 & 4.2.3 – Eligibility criteria / Quality of life/ revised Wyeth economic model	The Wyeth economic model has been revised to both incorporate parameters adopted by the York Technology Assessment Group; (i.e. to extend the time horizon to 10 years and to incorporate the cost of 21 days hospitalisation) and to extend the initial treatment period from 12 to 24 weeks in patients who achieve a PASI of ≥ 50 but < 75 at 12 weeks. The incremental cost per quality adjusted life year (QALY) for etanercept 25 mg biw intermittent therapy over supportive care in patients with a baseline PASI of > 10 and baseline DLQI > 10 was £6,168 confirming that etanercept therapy is cost effective in such patients (Appendix 2). The Wyeth model indicates that the cost effectiveness of treating patients with a PASI ≥ 10 and DLQI ≥ 10 (£6,168) is similar to the cost effectiveness of treating patients with a PASI > 20 (£ 3,795).	The eligibility criteria have been amended to: "The disease is severe as defined by a total Psoriasis Area Severity Index [PASI] ≥ 10 and a Dermatology Life Quality Index [DLQI] >10."
Royal College of Physicians and the British Association of Dermatologists	1 – Eligibility criteria / Quality of life	**Eligibility criteria and assessment of disease response must include a quality of life indicator** in addition to the PASI score given the nature of psoriasis, and to achieve parity with NICE guidance in other disease areas. The correlation of PASI with impact on quality of life is poor and it is as important to consider how psoriasis affects the individual psychosocially as it is merely to consider extent of disease Some patients will be severely disadvantaged and denied treatment if the entrance requirement is set at this level and no allowance for other factors is considered. Highly visible (face, hands) or symptomatic psoriasis (hands, feet, flexures and genitalia) may have an impact which is poorly reflected in the PASI score and for which quality of life scores offer a much better surrogate. Involvement of face and hands can profoundly affect the patient emotionally, functionally and economically.	The eligibility criteria have been amended to: "The disease is severe as defined by a total Psoriasis Area Severity Index [PASI] ≥ 10 and a Dermatology Life Quality Index [DLQI] >10."

Royal College of Physicians and the British Association of Dermatologists	1 – Eligibility criteria / PASI	**We question the evidence to support a PASI score of more than 20 for eligibility**. This we feel is inappropriate. Work by Professor Finlay [1] has demonstrated that patients with a PASI score of greater than 10 are likely to be suffering severe impairment of quality of life and to be considered for drugs such as methotrexate and ciclosporin or for hospital admission. Clinical trials on which the evidence for efficacy of these agents were based had a lower inclusion criterion e.g. PASI of >10 or >12. In section 4.2.3.2, the ICERs are based on patients with PASI> 10 DLQI>15. The advice therefore seems to be divergent from the evidence put forward for this assessment. Feldman suggested PASI > 11 or >10% Body Surface Area (BSA) as indicating severe disease (Journal of Investigative Dermatology 1996; 106: 183-186). A BSA > 10% has also been defined as having severe disease in the National Psoriasis Foundation. Facts on Psoriasis: Disease severity (2004). To stop treatment in order to achieve the suggested PASI threshold of >20 would risk acute severe disease relapse with a consequent need for urgent hospitalisation. Rigid application of the >20 rule would disadvantage and possibly endanger such patients and risk increasing their overall management costs.	The eligibility criteria have been amended to: "The disease is severe as defined by a total Psoriasis Area Severity Index [PASI] ≥ 10 and a Dermatology Life Quality Index [DLQI] >10."

[1] (Finlay AY. Current severe psoriasis and the Rule of Tens. *Br J Dermatol* 2005;**152**:861-867 and Hongbo Y, Thomas C L. Harrison M A, Salek M S, Finlay A Y. Translating the science of quality of life into practice: What do Dermatology Life Quality Index (DLQI) scores mean? JID 2005 (In press – available on request from Professor Finlay, Cardiff)

NHS-QIS* (2)	1 – Eligibility criteria / PASI	It is not clear from the document how the eligibility criterion of PASI>20 is arrived at. Most of the trial data reviewed involved patients with PASI>10-12. The BAD guidelines (in press) acknowledge this by suggesting PASI>10 but also requiring a measure of quality of life impairment (DLQ>10), which seems preferable as it relates more to the patients needs rather than a single static measure of disease extent.	The eligibility criteria have been amended to: "The disease is severe as defined by a total Psoriasis Area Severity Index [PASI] ≥ 10 and a Dermatology Life Quality Index [DLQI] >10."
Royal College of Physicians and the British Association of Dermatologists	1.1 – allowable dose	**We feel there will be advantages to having the facility to utilise a higher dose** (50mg twice weekly) of etanercept in some situations where greater efficacy is required. New data in the Papp study[2] shows a clear advantage of the 50mg dose of etanercept and we feel this should be available to for those patients who only respond suboptimally to the 25mg dose - particularly as your current recommendation would class these as treatment failures and may lead onto switching agents, repeating screening, risking a flaring of the psoriasis and further time taken to assess whether it is going to work. We feel it appropriate to restrict the higher dose but not to put it out of bounds.	The Papp results were included in the assessment report (trial referenced as Elewski 2003). In the economic analysis, etanercept 50 mg was less cost effective than intermittent etanercept 25 mg in all scenarios. Further explanation is provided in section 4.3.7 of the FAD. The licensed indications for etanercept do not allow for recommendations for 50 mg to be used after 25 mg. NICE can only issue guidance in accordance with the licensed indications.

[2] Papp KA, Tyring SK, Lahfa M *et al*. A global phase III randomised controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 2005; **In press**.

Wyeth Pharmaceuticals	1.1 – allowable dose	The option to dose with etanercept 50mg twice weekly for 12 weeks should be made available for those patients with severe psoriasis requiring rapid relief of symptoms and control of their disease. Patients with very active psoriasis and with particularly poor quality of life, such as those with flare or rebound following failure or abrupt discontinuation of systemic or other biological agents, require particularly rapid control of their disease in order to prevent hospitalisation. An analysis of the most severe quartile of patients (PASI ≥ 22) has demonstrated that these patients have a greater response to etanercept 50 mg twice weekly compared with placebo than the total study population (PASI 75 response at 12 weeks; 63% vs 5% compared to 49% vs 4% for the most severe quartile and total population respectively)[iv]. 49% of patients receiving etanercept 50 mg twice weekly achieved a PASI 75 response at 12 weeks, compared with 34% of patients receiving etanercept 25mg twice weekly in both phase III randomised controlled trials comparing the two doses (p = 0.005 and 0.002) [v, vi]. There was a statistically significant difference from the placebo group in the proportion of patients with such improvements by 4 weeks in the 50 mg twice-weekly group compared with 8 weeks in the 25 mg twice-weekly group in both trials. A pooled analysis of the 3 randomised controlled trials containing the 50mg twice weekly dose demonstrated a significantly greater mean percentage improvement in PASI score and DLQI score as early as the first week of treatment[vii]. The revised Wyeth economic model indicates that the incremental cost per QALY for etanercept 50mg compared with supportive care in patients with PASI ≥ 25 and a DLQI ≥ 10 is £7,122 (Appendix 2). Furthermore the incremental cost per QALY for etanercept 50mg compared with etanercept 25mg in this group of patients is just £9,364, suggesting that such treatment is cost effective in those patients for whom it is clinically necessary.	In the economic analysis, etanercept 50 mg was less cost effective than intermittent etanercept 25 mg in all scenarios. Further explanation is provided in section 4.3.7 of the FAD. The 12 week assessment criteria have been amended to: 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 5-point reduction in DLQI from when treatment started.
Royal College of Physicians and the British Association of Dermatologists	1.2 – sequencing of the interventions	**Dictating the sequence in which the agents should be used is not appropriate**. There is no evidence of significant differences in efficacy between the two agents and this is further supported by recent data. If this is the first instance in which NICE has prescribed the order in which drugs have to be used, there needs to be a better evidence base than that presented in this assessment.	In the economic analysis intermittent etanercept 25 mg dominated efalizumab in all scenarios.

NHS-QIS* (2).	1.2 – sequencing of the interventions	In the group who fail etanercept 25mg, the recommendation suggests treatment with efalizumab. I know of no evidence for the effectiveness of efalizumab in this setting. It would be nice to have additional option of a trial of etanercept 50mg in this setting, bearing in mind that these are severely affected patients who are otherwise out of treatment options.	The licensed indications for etanercept do not allow for recommendations for 50 mg to be used after 25 mg. NICE can only issue guidance in accordance with the licensed indications. In all scenarios of the economic analysis, etanercept 50 mg was less cost effective than intermittent etanercept 25 mg. Efalizumab was dominated by intermittent etanercept 25 mg in all scenarios. However, due to the different mechanisms of action, the Committee felt it appropriate to allow efalizumab for sub-groups of individuals for whom etanercept had failed.
Serono Ltd	1.2 – sequencing of the interventions	On the basis of all the data available to-date, a sequential approach for the use of etanercept and efalizumab is neither reasonable nor justifiable. Despite being unable to access the Appraisal Committee model, we anticipate that, if all relevant data are properly considered, efalizumab will be shown to be more cost effective than etanercept 25mg continuous, positioning efalizumab at some point between modelled 25mg intermittent and 25mg continuous. In other words, efalizumab will be shown to be as cost effective as etanercept "pragmatic use" suggested by the Appraisal Committee. The final guidance should recommend the use of efalizumab interchangeably with etanercept for patients who have failed to respond to other systemic therapies in routine use or if they are intolerant of, or contraindicated to, these treatments.	All data submitted were taken into account. In all scenarios of the economic analysis, etanercept 50 mg was less cost effective than intermittent etanercept 25mg and efalizumab was dominated by intermittent etanercept 25 mg. However, due to the different mechanisms of action the Committee felt it appropriate to allow efalizumab for sub-groups of individuals for whom etanercept had failed. The assessment group economic model was unavailable to consultees and commentators because it contains information designated as confidential by consultees.

Wyeth Pharmaceuticals	1.3 – achievement of PASI-75 at 12 weeks	PASI 75 is an inappropriately high definition of treatment response at 12 weeks, which would deny a quarter of the patients treated with etanercept who achieve this response by 24 weeks the opportunity to do so. PASI 50 at 12 weeks has been recognized as the most appropriate definition of a treatment responder at this time point. Nearly half of patients achieving a PASI response of ≥ 50 but < 75 at 12 weeks with etanercept 25 mg twice weekly go on to achieve a PASI 75 response at 24 weeks with continued treatment. Whilst a 75% reduction in PASI score (PASI 75) is the current benchmark of primary endpoints for recent clinical trials of psoriasis, an analysis of the PASI 50 response has shown it to equate to a clinically meaningfully improvement in psoriasis and as such it represents a more discerning endpoint in clinical practice . Evidence for this comes from the fact that: (1) The PASI score is not linearly reflective of psoriasis severity. A 95% reduction in area of psoriasis, without a change in redness, scaliness and induration, translates to only a 66% reduction in PASI. Conversely a drop in erythema, scale and induration from an average score of 3 to 1 would similarly only lead to a two-thirds reduction in PASI. Thus a PASI 50 represents far greater than a 50% improvement in psoriasis. (2) Patients who achieve a PASI 50 response obtain a large proportion of the utility gain of individuals who achieve PASI 75. Table A1 within Appendix 1 contains the relevant figures from the etanercept pooled phase III study dataset, which shows that for all patients the utility gain over placebo is 0.14 for PASI 50 responders and 0.16 for PASI 75 responders. Therefore PASI 50 responders acquire 87% of the utility gain achieved by PASI 75 responders. Even for patients with the worse quality of life at baseline, i.e. highest DLQI quartile, PASI 50 responders achieve two-thirds the utility of PASI 75 responders (0.19 vs 0.30). (3) Patients with a PASI 75 response frequently defer restarting treatment until their PASI response falls to well below 50, implying than their perceived health gain is maintained at PASI 50. (4) Effective, meaningful therapies are consistently differentiated from placebo at PASI 50, as evidenced by histologic and photographic evidence. The BAD in their Guidelines on the use of Biological Interventions in Psoriasis define PASI 50 as an adequate therapeutic response and therefore define a PASI < 50 as an inadequate response to treatment. An analysis of the fate of patients in the etanercept phase III studies reveals that 41/150 (27%) of patients who did not achieve a PASI 75 response at 12 weeks did so with continued treatment by 24 weeks, an opportunity which would be denied those patients if the current definition of treatment response was to remain (See Appendix 1). However 32/67 (48%) of patients who achieve a PASI 50, but not a PASI 75, response at 12 weeks go on to reach a PASI 75 response with a further 12 weeks of therapy. Thus the likelihood of a	The 12-week assessment criteria have been amended to: 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 5-point reduction in DLQI from when treatment started.

Royal College of Physicians and the British Association of Dermatologists	1.3 – achievement of PASI-75 at 12 weeks	The requirement for a PASI improvement of 75% at 12 weeks will deny treatment to a significant group of patients with a worthwhile response who go on improving over time. A PASI improvement of 50% at 12 weeks is considered a better target. As it is now well established that maximal improvement from both drugs may not be achieved by 12 weeks, the stipulation that PASI-75 must be achieved by 12 weeks is potentially wasting resources by forcing a treatment which will later be successful, to be abandoned inappropriately. Longer-term data in the recently reported studies (above) confirm this. Improvement in PASI may fall short of 75% but the benefits on quality of life may still be significant and not achievable with other agents. We agree that patients who fail to achieve a reduction in PASI of 50% should discontinue treatment at the 12 week stage. The advice you give to use PASI 75 was taken from the rheumatologists' guidelines for joint disease. These were written a few years ago for a different patient group. Our guidelines are more recent and considered the effects of these drugs on the skin rather than the joints and were formulated with the help of rheumatologists who were involved in producing the BSR guidelines. We considered the published evidence that a PASI improvement of 50% was seen by patients and physicians as a worthwhile response for patients with severe disease (Carlin CS, Feldman SR, Krueger JG et al. 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; 859-66). We have also suggested that a PASI improvement of 50% be used prospectively to define failure of other agents. If the response criterion recommended by the Appraisal Committee were applied to standard drugs such as methotrexate and ciclosporin, then the number of patients eligible for biologicals might paradoxically increase.	The 12- week assessment criteria have been amended to: 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 5-point reduction in DLQI from when treatment started.

NHS-QIS (2)	1.3 – achievement of PASI-75 at 12 weeks	There is evidence that PASI-50 is acceptable to patients and correlates with a meaningful improvement in quality of life. This may be more appropriate as a marker of disease response in a clinical setting that PASI-75.	The 12-week assessment criteria have been amended to: 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 5-point reduction in DLQI from when treatment started.
Wyeth Pharmaceuticals	1.3 and 4.3.6 - achievement of PASI-75 at 12 weeks	We concur with the clinical experts who suggest that 12 weeks is a sufficient period of time in which to determine whether a patient is likely to respond to treatment with etanercept or efalizumab. We also agree with the British Association of Dermatologists (BAD) who, in their guidelines on the use of biological interventions in psoriasis, recommend that the PASI 50 is the most appropriate measure to determine whether a patient is likely to respond to treatment.	The 12-week assessment criteria have been amended to: 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 5-point reduction in DLQI from when treatment started.
NHS-QIS* (2)	1.3 – Assessment of efficacy at 12 weeks	The evidence base shows continuing improvement beyond 12 weeks of treatment, and therefore requiring an assessment of efficacy at 12 weeks seems unreasonable.	The SmPC specifies that 12 weeks; treatment should be stopped if there is no response. A 12-week assessment is therefore required. The 12-week assessment criteria have been amended to: 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 5-point reduction in DLQI from when treatment started.
Psoriatic Arthropathy Alliance	1.3 – non responders	Failure or non-responders are offered other therapies or alternate treatments and not excluded from other licensed biological treatments.	Due to the different mechanisms of action the Committee felt it appropriate to allow efalizumab for sub-groups of individuals for whom etanercept had failed.

Psoriatic Arthropathy Alliance r	1.4 – Collaboration between specialists	Assessment and treatment should include other related conditions (such as psoriatic arthritis) and how these should be managed in consultation with the appropriate speciality and patient. The response/improvement in relation to other disease aspects, therefore, should be taken in consideration before withdrawal.	NICE can only issue guidance according to the licensed indications. Efalizumab is not licensed for psoriatic arthritis. Psoriatic arthritis guidance examines the use of etanercept. The guidance, however, makes specific note for people with co-existing psoriasis and psoriatic arthritis to be managed by collaboration between dermatologists and rheumatologists.
Wyeth Pharmaceuticals	1.4 – efalizumab and psoriatic arthritis	Taken together the two sentences in this section give the impression that either etanercept or efalizumab may be used for the treatment of psoriatic arthritis. However the evidence for a beneficial effect of efalizumab on the joint component of psoriatic arthritis is lacking and consequently the product is not licensed for such use. To avoid confusion this should be clarified.	Comment noted. No amendment made.
Royal College of Physicians and the British Association of Dermatologists	2.2	In section 2.2 (page 3), drugs should be included as an aggravating cause of psoriasis.	"Some medications may also cause exacerbations" added.
Wyeth Pharmaceuticals	2.3 – proportion of patients with joint involvement	Whilst the proportion of the entire psoriasis population who also have joint involvement is estimated to be 5 – 7%, as the Appraisal Consultation Document for etanercept and infliximab for the treatment of psoriatic arthritis correctly identifies, this rises to approximately 40% of patients with severe skin disease, such as those considered within the scope of the current appraisal. Clinicians are encouraged to check for joint involvement to address concerns regarding the under reporting of psoriatic arthritis. Clinicians are more likely to routinely check for a diagnosis with a 40% prevalence than they are with a 5 – 7% prevalence. Thus inclusion of the 40% estimate will be more relevant to the population under consideration and help to encourage the appropriate assessment of potential joint involvement in psoriatic disease.	Sentence amended to: "It is estimated that 5–7% of all people with psoriasis, and approximately 40% of those with extensive skin disease, develop joint inflammation, which is known as psoriatic arthritis."

Wyeth Pharmaceuticals	2.7 & 2.8 & 1 – limitations of the PASI	The PASI score has been demonstrated to be a poor predictor of quality of life[viii, ix]. There are several reasons for this: (1) The PASI score measures the extent of disease and does not discriminate between the site of involvement. However, as the appraisal committee have acknowledged, the effect of psoriasis on quality of life is dependent on the area of the body affected. Thus a relatively small patch of psoriasis on visible areas of skin, particularly the face or extremities, can be perceived as disproportionately disfiguring compared with a larger area of involvement on the trunk. As a consequence a patient with a PASI score much lower than 20 can have significant impairment in their quality of life[x, xi]. (2) The PASI score does not take into account skin symptoms such as itching, bleeding or burning which have a major impact on patient quality of life, morbidity and perception of severity. Furthermore such symptoms are most troublesome and often restricted to flexural surfaces such as elbows, knees and groin. Thus despite the fact that scores of skin symptoms are measures of clinical severity like the PASI, there is a strikingly poor correlation between the two[5]. The severity of skin symptoms does however correlate with measures of quality of life. (3) Impact of clinical severity of psoriasis on quality of life is mediated through the ability of individual patients to cope with their disease[xii]. The ability to cope with psoriasis is not necessarily correlated to the extent or clinical characteristics of the disease as considered by PASI[5]. Indeed it has been identified that patients who are more reactive to the ever present underlying stress of dealing with psoriasis are more at risk in terms of their mental health independent of the clinical severity or anatomical location of their psoriasis. Furthermore this form of stress contributes significantly more to the variance in patients' disability in everyday life than any other medical or health status variable. In the absence of a correlation between PASI and quality of life measures, it is proposed that they be considered separately and measured in parallel.	The eligibility criteria have been amended to: "The disease is severe as defined by a total Psoriasis Area Severity Index [PASI] ≥ 10 and a Dermatology Life Quality Index [DLQI] >10". The 12-week assessment criteria have also been amended to include quality of life.

Wyeth Pharmaceuticals	2.8 - DLQI	The DLQI has been identified elsewhere in the appraisal consultation document as a validated health related quality of life measure. A DLQI score of > 10 represents a skin disease having a very large effect on a patient's life.	The eligibility criteria have been amended to: "The disease is severe as defined by a total Psoriasis Area Severity Index [PASI] ≥ 10 and a Dermatology Life Quality Index [DLQI] >10". The 12-week assessment criteria have also been amended to include quality of life. Section 2.8 of the FAD has been amended to state "A score of greater than 10 is considered to correlate with a substantial effect on an individual's HRQoL".
Serono Ltd	3.1.3 – Efalizumab and thrombocytopenia	With respect to thrombocytopenia, the company would like to highlight that platelet counts are not "required" by EMEA as mentioned in the ACD, but rather "recommended".3 Indeed, the same adverse event of thrombocytopenia is reported for both efalizumab and etanercept at the same frequency in both product labels (uncommon - 0.1%-1%).	'Required' amended to 'recommended'. SmPC for etanercept does not make any recommendations with respect to platelet counts.
Serono Ltd	3.1.4, 4.2.4 – Cost of efalizumab	The manufacturer's submission deadline was 3 weeks after the license was received for efalizumab. Consequently, the listed price has now been established and is slightly lower than that used in the submission. The price is now £169.2 per vial (MIMS July 05), which equates to £8,798.4 for 52 weeks, rather than £8,828.61 currently used.	£169.20 is the cost quoted in the ACD and used in the Assessment Group's modelling.
Wyeth Pharmaceuticals	3.2.1 - Licence	The etanercept license as quoted is incorrect. The end of the relevant sentence should be amended to: 'or are intolerant to other systemic therapy including cyclosporine, methotrexate **or** PUVA'.	'And' amended to 'or'.

[3] Raptiva Annex 1: summary of product characteristics. 4.4 Special warnings and special precautions for use p.3 EMEA 18/11/04 Raptiva-H-542-N-01-PI http://www.emea.eu.int/humandocs/Humans/EPAR/raptiva/raptiva.htm

Serono Ltd	4.1 and 4.2.4 – efalizumab efficacy in a 'high need' group	To our knowledge the trial IMP 24011 randomised double blind placebo controlled study is the only one that prospectively recruited high-need patients and that prospectively demonstrates efficacy of efalizumab in such a difficult to treat population. Of the new therapies either approved or in development for the treatment of psoriasis, none have demonstrated so clearly, clinical efficacy and safety in such a well defined population of patients who have failed on, are contraindicated or intolerant to current systemic treatments (described in the protocol of study IMP 24011 as "High Need"). It would be highly speculative therefore, to retrospectively extrapolate efficacy and safety from moderate to severe psoriasis patients to this clearly defined population. To be eligible for the study, patients were required to have a minimum PASI score of 12.0 at screening and either a) a history of previous systemic therapy for psoriasis or b) in the Investigator's judgment, candidacy for systemic therapy for psoriasis with no previous history of such treatment. To be eligible for "high need" (HN) categorisation, patients were required to be unsuitable for therapy with at least two currently available systemic therapies because of lack of efficacy, intolerance or contraindication. Overall, a total of 793 patients were randomised (264 assigned to placebo and 529 to efalizumab); 526 of these patients were classified as HN (184 assigned to placebo and 342 to efalizumab), leaving 267 in the non-HN category (80 assigned to placebo and 187 to efalizumab). In the HN group, 29.5% (CI 24.7%-34.7%) of efalizumab treated patients achieved PASI-75 at week 12 compared to 2.7% of those on placebo. In the non-HN group, 34.8% (CI 28.0%-42.1%) of efalizumab treated patients achieved PASI-75 at week 12 compared to 7.5% on placebo. The treatment effect is the same in both groups (26.8% in HN group compared to 27.3% in non-HN group), thus demonstrating that efalizumab has equivalent efficacy in high need patients compared to the overall moderate-severe psoriasis population. On the basis of the eligible group of patients defined by the ACD, this "High Need" group is the only patient population that should be taken into consideration in the HTA model for the 12-week time point. Estimating efficacy and safety by pooling different patient population outcomes, i.e. from moderate to severe psoriasis patients together with those patients who have failed on, are contraindicated or intolerant to current systemic therapies, would substantially bias the final Guidance to the NHS.	The committee considered the results of the IMP24011 study. See FAD Section 4.3.2. However, the Committee agreed that the overall baseline characteristics of the patients included in the trials indicated that they were a population with relatively severe psoriasis. It also heard from the clinical experts that, in clinical practice, these drugs were used as per the licensed indications and were as effective for people who had not responded to other available treatments as for those who were treatment naïve.

Wyeth Pharmaceuticals	3.2.3	Given that any causal relationship between the uncommon but serious adverse events and etanercept remains unclear a more accurate statement would be that they **may** be related to the immunomodulatory activity.	Sentence amended to "that may be related to"
Royal College of Physicians and the British Association of Dermatologists	4.1.1.1 – dose that efalizumab was studied	In section 7. 4.1.1.1 (page 9), doses of 1-2 mg/kg/wk used in studies by Leonardi 2005 and Lebwohl 2003. (There being no significant difference between the doses)	NICE can only issue guidance within the licensed indications. Efalizumab is licensed at a dose of 1.0 mg/kg body weight weekly. The 2-mg results were presented separately in the assessment report and not taken into account by the Committee.
Serono Ltd	4.1.1.2 – efficacy of efalizumab – pooled results	Since Trial ACD2058 was only recently published[4] and not considered in table 4.2.14 (ACD page 73) of the original evaluation report, this trial could not be included in the evidence synthesis for efalizumab. This was a phase III, randomised, double-blind trial, whereby 498 patients received subcutaneous 1 or 2 mg/kg/wk efalizumab or placebo for 12 weeks. Efalizumab-treated patients who achieved <PASI 75 were re-randomized to a second 12-week course of treatment. At week 12, 38.9% of 1mg/kg efalizumab-treated patients achieved the primary endpoint of the study, PASI 75 (vs. placebo 2.4%; P<.001). At week 24 (extension study 2058), an additional 21.1% of 1mg/kg efalizumab-treated patients achieved PASI-75 (vs. placebo 6.7%, P = .018). Efalizumab was well tolerated throughout the whole study period. The published report of this trial is included with this response. If Table 4.2.14 is thus updated to include results from this trial, the mean PASI 75 rate would be higher (29.3 vs. 27% currently assumed. Inclusion of these data would have produced a rate comparable to that used for etanercept for the same time point.	This trial was included in the assessment report and taken into account. However, only the PASI 50 results were available. The newly available PASI 75 results were considered by the Committee (Section 4.1.1.2). Previous (RR 6.3; CI: 4.3 to 9.4) New (RR 7.4; CI: 5.2 to 10.7)

[4] Leonardi, C., K. Papp, K. Gordon, A. Menter, S. Feldman, I. Caro, P. Walicke, P. Compton, and A. Gottlieb. "Extended Efalizumab Therapy Improves Chronic Plaque Psoriasis: Results from a Randomised Phase Iii Trial." *Journal American Academy Dermatology* (2005) 52 (3 pt 1): 425 - 33

Serono Ltd	4.1.1.4, 4.1.1.5 – long term follow-up of efalizumab	Shortfall [in longer term data] can now be redressed by the following three studies: Trial ACD 2391 (24 weeks) Twenty-four week data were recently published for efalizumab from a study of similar design to that of etanercept . Trial ACD2391 is an open label extension to trial ACD2390 (Gordon et al, 2003), which was included in the evidence synthesis for the ACD, as shown in Table 2. By the end of 24 weeks of continuous 1mg/kg per week s/c efalizumab treatment, 43.8% of subjects (161 of 368) achieved a PASI-75 response. Recently published data for etanercept indicate that 42% of patients achieve a PASI-75 after 24-week therapy. Taken together, these recently published data are suggestive that efalizumab may have superior, or at least equivalent, efficacy compared to etanercept over longer treatment periods. Trial IMP 24011 (24 weeks) Trial IMP 24011 has previously been discussed in relation to the provision of data for "high-need" patients (HN), a population that closely matches that of the target population stated by the ACD (see subsection a. above). This trial also provides data up to 24 weeks, demonstrating that 58 of the 118 (47.5%) patients who were partial responders at week 12, achieved PASI-75 at week 24. The results were similar for HN patients (46.8%; 33/77) and non-HN patients (48.8%; 20/41) at this time point. As mentioned, the full study report for this trial is included with this response together with the peer-reviewed manuscript and related referees' comments. Study ACD 2243g (60 weeks) ACD2243g is an open-label phase III study that evaluated 12 weeks of subcutaneously administered efalizumab and up to 132 additional weeks continued therapy. This long-term trial included 339 subjects in a 12-week induction treatment period with 2mg/kg. Those patients who achieved a clinical benefit (PASI 50 or more, or static physician's global assessment (sPGA) of cleared, minimal or mild) were permitted to enter the maintenance period of up to three years where they received efalizumab administered at 1 mg/kg per week s/c. The initial 15 months of this study have been published in a peer reviewed journal (Gottlieb et al, 2004) and demonstrate that the initial response to therapy is maintained and improved over the long term. In summary, it is our contention that all of the above studies, summarised in Table 3 [of the Serono comments], demonstrate the longer term safety and efficacy of 1mg/kg per week s/c efalizumab and should be taken into consideration in the same way as the demonstration provided by the etanercept trials.	None of the efalizumab RCTs extended beyond 12 weeks. The extension data were considered by the Committee, as noted in FAD Section 4.1.1.4.

Wyeth Pharmaceuticals	4.1.1.5 – efalizumab and rebound	There is data confirming the existence of rebound in psoriasis after discontinuation of efalizumab and therefore the statement to the contrary should be removed. The efalizumab SmPC contains the following special warning and special precautions for use: 'Abrupt discontinuation of treatment may cause a recurrence or exacerbation of plaque psoriasis including erthrodermic 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 necessary'. Gaylor and Duvic[xiii] reviewed the psoriasis adverse events following withdrawal of efalizumab submitted to the US regulatory agency, which included recurrence (rebound) of plaque psoriasis, unusual morphology, guttate psoriasis, psoriatic erthroderma, pustular psoriasis and inverse psoriasis in 6.3, 3.6, 2.1, 0.7, 0.6 and 0.2% of patients respectively. Guidelines on the management of psoriasis with efalizumab, recently published in collaboration with the manufacturer, state that rebound following treatment discontinuation has been observed in 6.65% of responding or partially responding patients discontinuing efalizumab[xiv]. Results from a company sponsored, phase IV, open-label investigational study (IMP25180) into the approach for managing rebound in efalizumab patients indicate that in the majority of cases (78%) the recurrence was inflammatory in nature[xv].	Comments noted. Sentence stating that the Assessment Group did not identify any data removed.

Serono Ltd	4.1.1.6 – Safety of efalizumab	Efalizumab works by a highly specific mode of action (Jullien et al, 2004[5]), that avoids many of the safety concerns associated with anti-TNF therapy, which include MS-like syndromes, congestive heart failure, malignancies (lymphoma), pancytopenia, lupus-like syndromes and severe and sometimes fatal infections (tuberculosis). The most frequently observed adverse events in all efalizumab treatment periods were transient acute adverse events. In placebo controlled clinical trials, infection rates in efalizumab-treated patients were approximately 27.3% versus 24.0% in placebo-treated patients. These rates do not appear to increase with continued therapy up to 15 months (Gottlieb et al, 2004). Safety data from the same study similarly do not indicate any increase with time in serious adverse events, malignancy, events leading to withdrawal or those that are psoriasis-related. In placebo controlled clinical trials, the overall incidence of malignancy (the majority of which were non-melanoma skin cancers) was similar in efalizumab-treated patients compared to those treated with placebo. Efalizumab is supported by the largest evidence based data in psoriasis, including long term published data up to 15 months. Etanercept, on the other hand, has been widely used in arthritic conditions, from whence the bulk of the evidence supporting its safety is derived (section 4.3 of evaluation report). This group of patients is very different to psoriasis patients. In summary, the safety profile of efalizumab, taken together with the similar short-term efficacy of etanercept and efalizumab, support the fact that efalizumab is interchangeable with etanercept.	Comments noted. In the economic analysis, efalizumab was dominated by intermittent etanercept 25 mg in all scenarios. However, due to the different mechanisms of action the Committee felt it appropriate to allow efalizumab for subgroups of individuals for whom etanercept had failed.

[5] Jullien D, Prinz JC, Langley RG, Caro I, Dummer W, Joshi A, Dedrick R, Natta P. T-cell modulation for the treatment of chronic plaque psoriasis with efalizumab (Raptiva): mechanisms of action. Dermatology. 2004;208(4):297-306.

Wyeth Pharmaceuticals	4.1.2.3 – deterioration in mean PASI score	The correct change in mean PASI score of patients who had their 50 mg twice weekly dose halved at 12 weeks to 25 mg twice week for the subsequent 12 weeks was 0.1. This negligible change is neither statistically or clinically significant and therefore represents a maintenance of response over time and not a statistically significant deterioration as claimed in the ACD. In their Assessment Report the Health Technology Assessment Group appear to have combined the reduction in mean PASI score from week 12 to week 24 occurring in the group who continued to receive etanercept 25 mg twice weekly (-2.0) with the slight increase in mean PASI score (0.1) occurring in the group who had their 50mg twice weekly dose halved to 25mg twice weekly at the 12 week time point, and then inappropriately attributed the sum of the difference to just one of the groups i.e. the dose reduction group. This approach is illogical and methodologically flawed. Due to the faster speed of response obtained with 50 mg twice weekly, the mean PASI score at 12 weeks was lower than that seen with 25 mg twice weekly (5.5 vs 7.7). Despite a dose reduction this response was maintained over the subsequent 12 weeks in patients initially receiving 50 mg twice weekly, resulting in a mean PASI score of 5.6 at 24 weeks. Mean PASI scores continued to improve in the patients initially receiving 25 mg twice weekly who continued on this dose for a further 12 weeks, resulting in a mean PASI score at 24 weeks of 5.8. The mean PASI scores at 24 weeks were similar but numerically superior (i.e. lower) in the group starting on 50 mg and reducing to 25mg twice weekly than in the group the received 25 mg twice weekly throughout (5.6 vs 5.8 respectively). Confirmation of the maintenance of the response from 12 to 24 weeks in patients undergoing a reduction in dose from 50 mg to 25 mg twice weekly is obtained from the proportion of patients achieving a PASI 75 response. A higher proportion of patients achieved PASI 75 at 24 weeks (54%) than at 12 weeks (49%) despite the reduction in dose. Once again the proportion of patients achieving this response was higher in the group who underwent dose reduction than the group maintained on 25 mg twice weekly (54% vs 45% respectively). The patients who had their dose halved did not have a statistically significant deterioration in their mean PASI. The statement to this effect is incorrect and misleading and should therefore be removed.	Comment noted and sentence removed.

Wyeth Pharmaceuticals	4.1.2.6 - Infliximab	Infliximab was excluded from the scope of the appraisal on the grounds that it is unlicensed and therefore it should not be referred to the final guidance. The suggestion that infliximab is more effective than the two biologic therapies currently under assessment, along with subsequence comments on its cost effectiveness in a US setting provides misleading advice on the likely cost effectiveness within the UK NHS. To refer to the product, which has not undergone the same rigorous evaluation as efalizumab or etanercept, would result in a deviation from the institute's published procedure.	Infliximab has now received a marketing authorisation. This guidance does not however make recommendations on the use of infliximab for psoriasis as it was not licensed in time to allow it to be appraised.
Psoriatic Arthropathy Alliance	4.2 – Economic models	Appropriate prescribing should not be just based on an economical model.	Comment noted and other considerations were taken into account.
Wyeth Pharmaceuticals	4.2.1.1 – referring to infliximab	Inclusion of the results of the US based cost-effectiveness analysis suggesting that infliximab is more cost effective than etanercept is misleading and should be removed. Reference to the existence of the analysis and its limited usefulness for decision making in the UK would however be appropriate. As the Appraisal Consultation Document acknowledges a cost effectiveness analysis based on the costs derived from the US health care system is not applicable in the UK. Further work undertaken by the Technology Assessment Group (Section 6.5.3 of the Assessment Report), conducted above and beyond the scope of the appraisal, indicates that infliximab therapy is likely to be less cost effective than either etanercept or efalizumab within the UK NHS. Infliximab was excluded from the scope of the appraisal on the grounds that it is unlicensed and therefore it should not be referred to the final guidance.	The paragraph is reporting the results in the publication and these issues were noted. Infliximab has now received a marketing authorisation. This guidance does not however make recommendations on the use of infliximab for psoriasis as it was not licensed in time to allow it to be appraised
Wyeth Pharmaceuticals	4.2.3.1	Number and cost of adverse events were included in the Wyeth model see section 5.3.6 page 51. The duration of the model has been extended and so appropriate discounting on costs and effects have been applied to the revised model (Appendix 2).	Comment noted – revised analysis considered.

Serono Ltd	4.2.4, 4.3.4 & 4.3.5 – intermittent versus continuous therapy with etanercept; retreatment	We would like to bring to the attention of the Appraisal Committee the need for careful interpretation of etanercept's re-treatment rates in order to obtain a robust and reliable health economic model. Indeed, the majority of patients who are retreated with etanercept 25mg twice per week do not re-establish disease control in terms of PASI 75, suggesting attenuation of efficacy with re-treatment courses (see detailed comments in Appendix A [of the Serono comments on the ACD]).	Comment noted. Response will also be required to be monitored should the patient receive subsequent cycles of therapy.
NHS-QIS* (2)	4.2.4, 4.3.4 & 4.3.5 – intermittent versus continuous therapy with etanercept	I am a little concerned about the dominating effect of intermittent etanercept in the modeling. Many patients will also have psoriatic arthritis which may make it preferable to have continuous therapy. It is also acknowledged in the report that the length of remission when etanercept is discontinued may be relatively short in this group of severely affected patients, implying that intermittent therapy may be not very different that continuous therapy. If this is the case in practice, the difference in cost effectiveness between the two agents is relatively small.	The licensed indications for etanercept do not allow for continuous therapy. The maximum duration of therapy is 24 weeks. NICE can only issue guidance within the licensed indications.
Royal College of Physicians and the British Association of Dermatologists	4.2.4, 4.3.4 & 4.3.5 – intermittent versus continuous therapy with etanercept	It is not clear whether the ICER model took account of the less constant control that would occur with intermittent treatment. It is reasonable to assume that among high need patients the disease would undergo repeated exacerbations and these would each take 12-24 weeks to respond - a less costly but also less effective scenario over 1 year. Sensitivity analysis of the economic models should factor in the possibility that intermittent treatment over 12 months might produce only 50% of the qualy that continuous treatment might. In 4.3.5 you state " efalizumab and etanercept continuous were dominated by intermittent etanercept". We are not convinced that it is fair to compare continuous and intermittent treatment. A cost comparison of continuous efalizumab against continuous etanercept needs to be quoted but has been missed in this evaluation. Likewise the ICERS for efalizumab in patients with severe disease at risk of admission are not given in section 4.2.4.2, so it is not possible for the reader to evaluate any basis for the economic conclusions.	The licensed indications for etanercept do not allow for continuous therapy. The maximum duration of therapy is 24 weeks. NICE can only issue guidance within the licensed indications. The economic modelling conducted by the assessment group considered this scenario. Under all scenarios efalizumab was dominated.

Wyeth Pharmaceuticals	4.3.2 – efficacy in patients failing systemic therapy	A post hoc analysis of one of the phase III randomised controlled trials of etanercept[11] confirms expert testimony that it is as effective for people who had not responded to other available treatments as for those who were treatment naïve. 64% of patients had failed at least one prior systemic therapy; cyclosporine, tacrolimus, methotrexate, azathioprine, cyclophosphamide, thioguanine, oral retinoids, hydroxyurea, fumarates, systemic steroids or phototherapy; PUVA or UVB. In patients receiving etanercept 25 mg twice weekly for 12 weeks a PASI 75 response was observed in 37% of patients who had failed at least one of the above-mentioned therapies compared with 28% in patients who had not failed prior therapy and 34% overall[xvi]. Similarly for patients receiving etanercept 50 mg twice weekly for 12 weeks a PASI 75 response was observed in 51% of patients who had failed at least one of the above-mentioned therapies compared with 40% in patients who had not failed prior therapy and 49% overall. [See Wyeth's response to the ACD for relevant graph].	Comments noted.
Wyeth Pharmaceuticals	4.3.3 – etanercept 50 mg	As noted above, the revised Wyeth model indicates that in patients with poor quality of life and very active psoriasis (i.e. PASI ≥ 22 and DLQI ≥ 10) the incremental cost per QALY for etanercept 50mg compared with supportive care is £7,122 (Appendix 2). Furthermore the incremental cost per QALY for etanercept 50mg compared with etanercept 25mg in this group of patients is just £9,364, suggesting that such treatment is cost effective in those patients for whom it is clinically necessary.	In all scenarios of the economic analysis etanercept 50 mg was less cost effective than intermittent etanercept 25 mg. The Committee was, however, not persuaded that this very severe subgroup had been sufficiently defined (in terms of PASI score or DLQI at baseline) or that their potential for an enhanced response was supported by trial data.
Wyeth Pharmaceuticals	4.3.4 – intermittent etanercept	The Wyeth model, utilising patient level data, replicates the pattern of relapse seen with intermittent therapy including the fact that a percentage of patients relapse within weeks of discontinued therapy. Indeed a comparison between the intermittent model and the study data suggest that the model is conservative and overestimates the number of patients who relapse quickly (Appendix 1, Figure A1) [See Wyeth's response to the ACD for further details]	Comment noted.

Royal College of Physicians and the British Association of Dermatologists	4.3.5 & 7.3.2 – failure to respond/intolerance	Section 4.3.5 gives the criteria for efalizumab as "failed to respond to or … intolerant of etanercept" while section 7.3.2 has "or has a contra-indication to etanercept". There is a difference between being **intolerant** and **having a contra-indication.** These sections should be consistent, if etanercept were to remain the favoured agent after the considerations above.	Amendment made to ensure consistency.
Royal College of Physicians and the British Association of Dermatologists	5 and General – Children and further research	Although not licensed in children there is concern that we will be able to continue to use etanercept when appropriate in children with psoriasis. Etanercept is used by rheumatologists for children with Juvenile RA and has been used at Great Ormond Street in very occasional children with severe psoriasis unresponsive to methotrexate. These cases are rare but we feel it would be reasonable to advise that (1) etanercept is the favoured product at this stage as there is greater experience with it in children in general and (2) the drug be initiated by special centres with experience of treatment of children. Alternatively it could be acknowledged that the use in children was out-with the scope of this appraisal and that recommendations were not made perhaps making the case for more clinical trials in children on which to base recommendations.	Etanercept is licensed for adults only. NICE can only issue guidance within the licensed indications. Adults added to the title of the appraisal.
NHS-QIS* (2)	5 and General – Children and further research	No mention of use of these agents in children, which may occasionally be necessary.	Etanercept is licensed for adults only. NICE can only issue guidance within the licensed indications.
Royal College of Paediatrics and Child Health	5.1.2 – registries; children	There is also the national register held by the British Society of Paediatric and Adolescent Rheumatology that collects data on patients whose disease started in childhood and who have received biological agents for arthritis. Some children will receive Etanercept for psoriatic arthritis as this is included in the NICE technology appraisal guidance no.35. This national biological register has a different format from that produced by the BSR.	Comment noted, however etanercept is licensed for adults only. NICE can only issue guidance within the licensed indications.
Royal College of Physicians and the British Association of Dermatologists	6 – Resource impact	In section 6. 2.12 (page 6) in assessing the costs of alternative therapies you may find useful information from a poster presented at the EADV, Prague 2002 by Piercy et al. 'Estimating the cost of moderate to severe chronic plaque psoriasis in the UK.'. Briefly, annual cost of systemic treatment: acitretin £411,545; cyclosporin £10,151,526; methotrexate £1,485,007; phototherapy (UVB/PUVA) £14,956,500; inpatient £8,983,200.	Comment noted.

Royal College of Physicians and the British Association of Dermatologists	Appendix C – audit/ definition of standard therapy	The wording in Section 1.a of Appendix C (audit criteria), if interpreted as written, is extremely restrictive. As it stands a patient would have had to have tried and failed "all other systemic therapy in routine use" or to be intolerant or have a contraindication to "all other systemic therapy in routine use". As worded, a patient who had a contraindication to one systemic therapy but had failed all the others would not qualify. The second "all" does not appear in sections 1.1 and 1.2. The definition of standard therapy and of its failure or contra-indication is covered on page 5 of our guideline with greater clarity. The drugs that must have been used require much clearer instructions. "All other systemic therapy in routine use including ciclosporin, methotrexate and PUVA" is confusing as there are many agents that are non-standard or not licensed such as hydroxycarbamide and fumarates. Specifically, in our guideline, we define standard treatment as acitretin, ciclosporin, methotrexate, narrow band UVB and psoralen photochemotherapy (PUVA).	Amended. Cyclosporin, methotrexate and/or PUVA are specified in the marketing authorisations.
Wyeth Pharmaceuticals	Appendix C – additional criterion (Register)	In order to ensure that information on long-term outcomes is collected consideration should be given to including entry into the national register as an audit criteria e.g. 'The person who is prescribed etanercept or efalizumab is enrolled in the BAD Biological Interventions Register (BADBIR).	The Institute is aware of the proposed BADBIR register and the Committee strongly encouraged its establishment.

* Commentators (no right to appeal)

1. Comments from the web

Commentator	Section	Comment	Proposed Action/Response
Individual respondent 1	General – conflict of interest	Our department has been one of the centres involved in multicentre clinical trials for evaluation of medications for treatment of psoriasis, one of which currently involves efalizumab and is funded by Serono. We have many patients in our department who receive treatment with systemic medications for psoriasis, and a number of these patients have failed to respond to certain systemic treatments and/or have developed adverse effects as a result of systemic therapies and/or have contraindications to certain systemic therapies. In keeping with my role, I have read in detail the publications in the dermatology and scientific literature on the treatment of psoriasis by the new biologics.	Comment noted. No action required.

Individual respondent 2	1 – Fumarates and infliximab	Should not fumaric acid esters be also included as a systemic treatment to be tried before the biologicals? - better efficacy/side effect profile and cheaper. Infliximab was generally considered to be the most effective biological in the comparative studies presented at the March 2005 American Academy of Dermatology meeting. This seemed to be accepted by the majority of speakers and delegates, despite being bombarded by marketing from the products you"ve evaluated. It seems a potential waste of resources to not even consider infliximab when there is some evidence indicating that it is better than etanercept or efaluzimab, perhaps by up to 30%. To my mind the question should be. Does the need to give infliximab as a day patient infusion and its poorer safety profile outweigh the evidence of increased efficacy compared with etanercept and efaluzimab? Thanks for considering these comments. And keep up the good work producing dermatology guidelines!	Thank you for your comments. The standard systemic therapies mentioned in the guidance are those that are specified in the marketing authorisations. NICE can only issue guidance within the licensed indications. Infliximab had not received marketing authorisation in sufficient time to be included in this appraisal.
Individual respondent 3	1 – Eligibility/PASI>=20	I think the requirement for PASI=20 is too stringent. A person can have severe disabling psoriasis yet not reach this level e.g. someone with 50% involvement of the entire skin with marked erythema (3) and scaling (3) but no induration will have a PASI of 18. Someone with psoriasis of the feet severe enough to prevent them walking will have a PASI of <10. The effect on QoL should be taken into account. There has to be a cut-off but 20 is too high….. Incorporate QoL into requirements (e.g. DLQI<10) with lower PASI.	The eligibility criteria have been amended: “The disease is severe as defined by a total Psoriasis Area Severity Index [PASI] ≥ 10 and a Dermatology Life Quality Index [DLQI] >10”
Individual respondent 1	1 – Eligibility/PASI>=20	Why do the guidelines state that the disease should be severe as measured by a total Psoriasis Area Severity Index [PASI] = 20? Is it not appropriate to base the guidelines on data from clinical trials (which contained patients with PASIs greater than 10 or 12)? Why designate a PASI = 20 when it has been shown that quality of life can be significantly impaired at PASI"s lower than 20? Why deny someone with psoriasis who has not responded to other appropriate therapy the chance to receive etanercept or efalizumab which could dramatically alter their life (including employment aspects, ability to socialise, etc)?	The eligibility criteria have been amended: “The disease is severe as defined by a total Psoriasis Area Severity Index [PASI] ≥ 10 and a Dermatology Life Quality Index [DLQI] >10”
Individual respondent 1	1 – failure to respond to other therapy	The wording ""psoriasis has failed to respond to all other systemic therapy in routine use "" is confusing and needs clarification. Are you recommending that dermatologists use non-licensed systemic medications for psoriasis before they can use these licensed medications? Please clarify this.	Clarification made: “The psoriasis has failed to respond to standard systemic therapies”
Individual respondent 1	1 – Sequencing of interventions	Why is efalizumab recommended only when etanercept has failed? The trials show that efalizumab works for moderate to severe psoriasis. There have been no trials to show it works in those failing etanercept and no studies have compared efalizumab with etanercept.	In the cost-effectiveness analysis, efalizumab was dominated by intermittent etanercept 25 mg. However due to the different mechanisms of action the

			Committee felt it appropriate to allow efalizumab for subgroups of individuals for whom etanercept had failed.
Individual respondent 4	1 – Sequencing of interventions	I am surprised at the recommendation of the ACD to use etanercept ahead of efalizumab. Recent published data I have seen shows efalizumab to be effective in the difficult to treat prosiatic patients (Sterry) and that this efficacy continues over a 36 month period (Gottlieb)	In the cost-effectiveness analysis, efalizumab was dominated by intermittent etanercept 25 mg. The guidance allows for the use in individuals who are contra-indicated to or have not responded to etanercept.
Individual respondent 5	1 & 4 – Sequencing of interventions	It is completely unclear why the committee feels it can or should recommend that Etanercept be used first when there is really no comparative evidence. Both drugs are simply stunning in their effectiveness against some of the worst cases of psoriasis imaginable. The clinician considering patients likely to require treatment with these agents ought to retain freedom to make the clinical judgement and decision about which order they are used in. It is likely that Efalizumab may be regarded as preferred in many cases as it is not limited to 12 weeks or any form of intermittent use. These patients will certainly relapse on a fairly short time scale when treatment is stopped, so being able to continue therapy will be a very important consideration.	In the cost-effectiveness analysis, efalizumab was dominated by intermittent etanercept 25 mg. The guidance allows for the use in individuals who are contra-indicated to or have not responded to etanercept.
Individual respondent 6	1 – Sequencing of interventions	There should not be a stepped approach for efalizumab which is as effective as etanercept as shown in the phase 3 raptiva (clear) trial by sterry, dubertret, papp, chimenti & larsen	In the cost-effectiveness analysis, efalizumab was dominated by intermittent etanercept 25 mg. The guidance allows for the use in individuals who are intolerant, contra-indicated to or have not responded to etanercept.
Individual respondent 7	1 & 3 – Sequencing of treatments	I have prescribed efalizumab and have a number of further patients to treat. I am surprised at the advice from NICE to use etanercept ahead of efalizumab, given that there is considerably more data available that reviewed in this ACD. Leonardi (J AM ACAD Derm 2005) shows a PASI75 response of 39% at 12 weeks, greater than the data for etanercept. I also am aware of data up to 36 months that shows an improving effect in PASI 75 patients. With safety in mind, I note the BAD guidance recommends efalizumab ahead of etanercept in patients with CHF, risk of TB and patients may develop demyelination with etanercept. I sincerely hope that the judgement is amended to reflect this data.	In the cost-effectiveness analysis, efalizumab was dominated by intermittent etanercept 25 mg. The guidance allows for the use in individuals who are intolerant, contra-indicated to or have not responded to etanercept. These data were all taken into account.

Individual respondent 8	1 – Sequencing of interventions	These drugs have different modes of actions. The data on efficacy and safety and cost/benefit are still emerging. It is prejudicial and counterproductive (for patients and clinicians) to have one agent recommended ahead of another at this stage.	In the cost-effectiveness analysis, efalizumab was dominated by intermittent etanercept 25 mg. The guidance allows for the use in individuals who are intolerant, contra-indicated to or have not responded to etanercept.
Individual respondent 1	1.3 – Achievement of PASI-75 at 12 weeks	While it is good if a patient can get a response of PASI 75 at 12 weeks, the evidence suggests that a number of subjects who receive efalizumab may only have a PASI 50 improvement at week 12 but will go on to reach PASI 75 at a later stage. Despite that it takes these patient longer to reach PASI 75, the end point is still the same and denying these patients long term therapy with this drug when it is effective is wrong. In addition, the patients who are suitable for the new biologics will have already have received most if not all other available systemic therapies for their psoriasis, so it is inappropriate at this stage to stop them receiving treatment with a drug that improves their psoriasis by 50% (whether etanercept or efalizumab). I accept that the guidance could change to PASI 75 in the future when a greater number of therapies (including biologics) are available in the UK, but at the present time we as dermatologists need to be able to offer these patients some form of treatment for their psoriasis.	The 12-week response criteria have been amended to: 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 5-point reduction in DLQI from when treatment started.
Individual respondent 9	1.3 – PASI-75	These drugs have additional valuable role as an alternative rotational therapy for those patients who have developed hepatotoxicity or nephrotoxicity from methotrexate or ciclosporin. Time spent on these biological therapies will allow recovery of organ toxicity. In this case the achievement of a pasi75 is not essential. as rotation back onto conventional therapy may be facilitated	The 12-week response criteria have been amended to: 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 5-point reduction in DLQI from when treatment started.
Individual respondent 5	1.3 – PASI-75	I think a PASI 75 at 12 weeks is setting the bar too high for some patients. In particular Efalizumab is slower to work than Etanercept. In the recent paper "Efficacy and safety observed during 24 weeks of Efalizumab therapy in patients with moderate to severe plaque psoriasis". Menter et al 2005 Arch Dermatol 141: 31-38 it was hown that at 12 weeks only 27% achieved PASI 75, while at 24 weeks the number had risen to 44%. For people with this severity of psoriasis, a PASI 50 is already a huge clinical improvement. They are by definition at the bottom of the barrel and to forcibly withdraw either of the last available treatments because it has not virtually cleared it in a very short time is highly unreasonable. Much better to set the bar at PASI 50 at	The 12-week response criteria have been amended to: 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 5-point reduction in DLQI from when treatment started.

		12 weeks. As Menter et al showed, PASI 50 at 12 weeks 59% and at 24 weeks 67%.	
Individual respondent 5	2.12 – costs of treatment	The costs of treatment are seriously under-estimated. In my hospital one day of in patient treatment costs 536. The average stay for treatment of psoriasis is 3 weeks = 11,256. A 6 week course in our day treatment unit costs 4800; 1 year of treatment with Ciclosporin 125mg bd, with monitoring and clinic costs = 3694.	Costs noted.
Individual respondent 9	3 – dose of etanercept 25mg v 50mg	The evidence would suggest that the best pasi 75 rates are achieved with etanercept 50mgx2 per week. Perhaps induction with this dose and maintenance at 25 mg x2 per week would help more patients.	In all scenarios of the economic analysis etanercept 50 mg was less cost effective than intermittent etanercept 25 mg.
Individual respondent 5	5 – research recommendations	While research on rates of hospitalisation in these patients might be useful, there are at least 2 potentially confounding factors. Many hospitals have lost their dermatology beds so the option of admission is often not exercised - instead patients are treated with systemic drugs at a much earlier stage in the overall management programme. They will thus get to the bottom of the barrel more quickly and will become the patients requiring the biological agents. Second, patients with the most severe grades of psoriasis usually decline to come into hospital as they know at best it will require long admissions - 8 to 10 weeks to have any benefit and will almost always be followed by rapid relapse.	Comment noted.
Individual respondent 5	6 – Resource impact	At [XX] Hospital a 3 week in patient episode costs 11,256. It used to be commonplace to admit patients for a clearing course on an annual basis. One year of Efalizumab + monthly hospital visits and lab tests comes to 10170. WHen the severe patients have required liver biopsies, day beds, and have damaged kidneys from ciclosporin or multiple skin cancers from PUVA, the fully priced costs of their care will not be so different from the costs of giving these biological agents but the impact on quality of life will be immense.	Costs noted.
Individual respondent 5	7 – Implementation and audit	7.3.1 bullet 2 needs to be worded differently. The word "all" could indicate a number of other treatments not specified - hydroxycarbamide, acitretin, azathioprine, Fumaderm for example. Different centres may or may not include those in their normal repertoire. Therefore perhaps it should recommend "at least" or "the main drugs commonly used such as."	Comment noted and amendment made.
Individual respondent 5	9.2 – proposed date for review	This is a very sensible interval during which a lot of further data about efficacy etc will emerge.	Comment noted

[i] Finlay A.Y. Current severe psoriasis and the Rule of Tens. Br. J. Dermatol. 2005; 152: 861 – 867.

[ii] Smith C.H, Anstey A.V, Barker J.N.W.N et al. British Association of Dermatologists Guidelines on the use of Biological Interventions in Psoriasis. http://www.bad.org.uk/members/Biologics_Guideline.pdf

[iii] Fredricksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. Dermatologica 1978; 157: 238 – 244.

[iv] Ganguly R, Sato R Singh A et al. Assessment of etanercept therapy in patients with severe plaque psoriasis. Poster presentation at the 3rd EADV Spring Symposium, Sofia. May 2005. [P21.17]

[v] Leonardi C.L, Powers J.L, Matheson R.T et al. Etanercept as monotherapy in patients with psoriasis. N. Engl. J. Med. 2003; 349: 2014 – 2022.

[vi] Papp K.A, Tyring S, Lahfa M et al. A global phase III randomised controlled trial of etanercept in psoriasis: safety, efficacy and effect of dose reduction. Br. J. Dermatol. 2005; 152: 1304 – 1312.

[vii] Tyring S, Leonardi C, Papp K et al. Integrated analysis of 50 mg twice-weekly etanercept in patients with psoriasis from three phase 3 studies. J. Am. Acad. Dermatol. 2005; 52(3): P189 [P2771]

[viii] Zachariae R, Zachariae H, Blomqvist K et al. Quality of life in 6497 Nordic patients with psoriasis. Br. J. Dermatol. 2002; 146: 1006 – 1016.

[ix] Sampogna F, Sera F, Abeni D. Measures of clinical severity, quality of life and psychological distress in patients with psoriasis: A cluster analysis. J. Invest. Dermatol. 2004; 122: 602 – 607.

[x] Stern R.S, Nijsten T, Feldman S.R et al. Psoriasis is common, carries a substantial burden even when not extensive and is associated with widespread treatment dissatisfaction. J. Investig. Dermatol. Symp. Proc. 2004; 9: 136 – 139.

[xi] Touw C.R, Hakkaart-Van Roijen L, Verboom P et al. Quality of life and clinical outcome in psoriasis patients using intermittent cyclosporine. Br. J. Dermatol. 2001; 144: 967 – 972.

[xii] Fortune D.G, Main C.J, O'Sullivan T.M et al. Quality of life in patients with psoriasis: the contribution of clinical variables and psoriasis-specific stress. Br. J. Dermatol. 1997; 137: 755 – 760.

[xiii] Gaylor M.N. Generalized pustular psoriasis following withdrawal of efalizumab – case reports. J. Drugs in Dermatol. 2004; 3: 77 – 79

[xiv] Leonardi C.L, Menter A, Sterry W et al. Guidelines for the long-term management of plaque psoriasis with continuous efalizumab therapy. Poster presentation at the 3rd EADV Spring Symposium, Sofia. May 2005. [P21.30]

[xv] Papp K.A, Toth D, Rosoph L. Approaches to discontinuing efalizumab: Results of an open-label study comparing different transitioning therapies. Poster presentation at the 3rd EADV Spring Symposium, Sofia. May 2005. [P20.9]

[xvi] Dubertret L, Berth-Jones J, Yamauchi P et al. Etanercept is an effective treatment for patients with psoriasis regardless of previous psoriasis systemic treatment. Poster presentation at the 3rd EADV Spring Symposium, Sofia. May 2005. [P21.6]