

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Infliximab for the treatment of psoriasis

Response to consultee, commentator and public comments on the ACD

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
British Association of Dermatologists		<p><i>Do you consider that all of the relevant evidence has been taken into account?</i></p> <p>Yes</p>	Comment noted
		<p><i>Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?</i></p> <p>The summaries are appropriate and the Appraisal Committee has recognised that infliximab is more effective with more rapid response and longer remissions than comparators. The resource impact could be influenced by the fact that most Dermatologists would recommend to use infliximab in two situations one in which the disease is very severe or potentially life threatening and requiring rapid response where this would be a first line intervention and the other where etanercept 25mg b/w and or efalizumab are ineffective or contra-indicated e.g. allergic reaction to etanercept.</p>	The preliminary recommendations have been revised in the FAD; infliximab is recommended as a treatment option for adults with very severe plaque psoriasis. See FAD sections 1 and 4.
		<p><i>Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?</i></p> <p>The opinion of the BAD is that the recommendations are not sound and that there is an over-riding case for infliximab being approved for treatment of the most severe and recalcitrant forms of psoriasis. The Technology Review Committee has agreed with our stated case that this is the most effective of the biologicals and that it is the most rapidly effective. While recognising that the arguments against approval are based on cost, on clinical grounds it would be perverse not to have it available for that small group of patients with the most severe disease for whom other options have failed or are inappropriate.</p> <p>Appendix C of the evaluation report implies greater cost effectiveness in patients with more severe QOL impairment measured by DLQI in the upper quartile. Intuitively, additional joint disease would improve utility scores and some of the trials (EXPRESS) have used measures such as SF-36 which might capture additional measures of improvement in general health in very severe disease.</p> <p>There is debate around the definition of “severe disease”. As a compromise based on cost effectiveness infliximab could have a higher requirement of “Very severe disease”. The available data might need to be interrogated to identify evidence for a suitable</p>	The preliminary recommendations have been revised in the FAD; infliximab is recommended as a treatment option for adults with very severe plaque psoriasis. See FAD section 1, 4.4, 4.5 and 4.13.

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		<p>definition, which might be a PASI score of over 20 and quality of life measures eg DLQI over a higher threshold than for "severe disease" as currently defined for etanercept and efalizumab.</p> <p>Not to approve infliximab would severely constrain treatment options for those patients with the most debilitating disease and deprive them of a dramatically effective therapy already in widespread use.</p>	
Hywel Williams Cochrane Skin Group		<p>In my view, the committee's requests for further clarification from the manufacturer of Infliximab are entirely reasonable. My main concerns with many of these single technology appraisals is interpretation at the other end by clinicians. We seem to be treading a familiar path - that of launching a new and very expensive, potentially very effective and also potentially very toxic product in the NHS. Such products are typically tested in 4 or 5 placebo controlled randomised controlled trials, and not surprisingly, the relative risks compared with placebo for efficacy measures are huge, ie. the drug works! Often these trials are short-term (10 weeks) which would not be the typical way they might be used in clinical practice in combination with other medicines. The absence of active comparator studies then leaves us struggling with less satisfactory methods such as indirect comparisons. We are told in section 3.4 that the pooled relative risk using a random effects model was 20.49 - how as a clinician do I use this information in practice?</p>	<p>Comment noted. The Committee considered the limitations of the indirect comparisons in this appraisal. See FAD section 4.8.</p>
		<p>Do I tell my patients that Infliximib used for 10 weeks is 20 times better than giving them sugar sweets? What I really need to know is the comparative efficacy over a long time window with alternative medication such as Etanercept or Methotrexate or photochemotherapy, as well as more emphasis on serious adverse events. If possible, these estimates should be given as absolute event rates according to a range of plausible baseline event rates of the sort of patients that we see in secondary care in the UK. Number needed to treat and number needed to harm are also very helpful summary measures for interpretation in clinical practice. I do appreciate that you have to work with relative risks for the mathematical modellings, but the clinical interpretability of the evidence suffers as a result unless they are supplemented by NNT and absolute rates.</p>	<p>Comment noted</p>
		<p>I have no objection to placebo controlled trials in principle (as long as only a few are done rather than scores), but I would like to see more realistic scenarios tested, ie. longer term administration with maintenance treatment or other combinations of treatment modelled over a one year period. Psoriasis is not a condition that goes after a few weeks when stopping a powerful treatment - it tends to come back and plague the patient on a continuous basis for many years. Time windows for comparisons are therefore crucial and I would suggest that one year is a reasonable time period to aim for.</p>	<p>This appraisal has been based on evidence available within the timelines of the process. There will be consideration for a review of this guidance and TA103 in 2008, which would allow the evidence base to be updated.</p>
		<p>Your choice of Etanercept as a principle comparator seems entirely reasonable, but I would love to see data on Methotrexate and photochemotherapy as well to put things in clinical context, if at all possible.</p>	<p>Infliximab has a marketing authorisation for only those who failed to respond to or have a contraindication to or are intolerant</p>

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			to other systemic therapies including ciclosporin, methotrexate or PUVA See FAD section 2.1 and SPC.
Psoriasis Association		<p>The Psoriasis Association is disappointed to learn that the Committee is minded not to recommend infliximab for the treatment of adults with moderate to severe plaque psoriasis because this limits the availability of effective treatments for this difficult group of patients.</p> <p>We feel that, when it is appropriate, patients should have access to the widest possible range of biologic therapies. Infliximab is recognised as 'an effective and rapidly acting treatment' and it is recognised that it 'could be more clinically effective than intermittent etanercept or efalizumab' both of which are already approved. Infliximab offers an alternative method of administration which some patients may prefer.</p> <p>We hope that the issues raised about cost effectiveness are resolved positively and quickly.</p>	The preliminary recommendations have been revised in the FAD; infliximab is recommended as a treatment option for adults with very severe plaque psoriasis. See FAD sections 1 and 4.
Royal College of physicians		<p><i>Do you consider that all of the relevant evidence has been taken into account?</i></p> <p>Yes.</p>	Comment noted
		<p><i>Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?</i></p> <p>The Institute has taken into account the relative costs and the possible duration of treatment of infliximab, etanercept and efalizumab and well as the response rate and efficacy of each therapy. The summary that infliximab can be a more effective therapy than either of the two other approved agents has been appropriately recognised.</p> <p>The cost comparison between infliximab and continuous etanercept has been preliminarily evaluated, but more detailed and perhaps more accurate costings would enable a better assessment.</p>	<p>Comment noted</p> <p>The manufacturer provided further analysis of infusion costs. See FAD 3.14 and 4.11.</p>
		<p><i>Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?</i></p> <p>No. The failure to recommend infliximab as a potential treatment for patients with moderate to severe plaque psoriasis will deny patients with a poor quality of life due to the skin disease an opportunity to experience disease remission. There is good evidence to support the use of infliximab in the management of patients with severe psoriatic skin disease.</p> <p>The definition of 'moderate to severe psoriasis' as a threshold for treatment with a</p>	The preliminary recommendations have been revised in the FAD; infliximab is recommended as a treatment option for adults with very severe plaque psoriasis. See FAD sections 1 and 4.

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		<p>biologic agent may need to be reviewed if a more expensive treatment is considered. Many patients with a PASI score of 10 plus a DLQI score of 10 may be eligible for treatment with the other biologic agents, etanercept and efalizumab, although may not receive the treatment due to other considerations which include finances. Patients at the more severe end of the spectrum, e.g. PASI 20 or greater, who may have failed with etanercept and/or efalizumab would be deprived of a potentially life-changing therapy if infliximab was given no place in the recommendations for use of biologic agents in the treatment of severe psoriasis.</p>	
Merck Serono	4.3	<p><b><u>1. Information presented in relation to TA 103</u></b></p> <p>Merck Serono agrees with the Appraisal Committee's description of the use of etanercept in paragraph 4.3 that etanercept is given continuously in routine clinical practice, despite this being contrary to that specified in marketing authorisation<sup>1</sup>. This conclusion is of crucial importance in conclusions derived with regards the Technology Assessment (TA) 103 of etanercept and efalizumab. The continuous use of etanercept is counter to that stated in TA 103 and was of crucial importance for decisions made in leading to the final recommendation.</p> <p>In TA 103 etanercept was assumed to be used intermittently. This resulted in a lower treatment acquisition cost for etanercept versus efalizumab, and etanercept was stated to be more cost effective principally because of the treatment-free periods that characterize intermittent therapy. As a result it was recommended for treatment ahead of efalizumab.</p> <p>With this new understanding of the continuous use of etanercept; the treatment costs are as follows:</p> <ul style="list-style-type: none"> <li>○ Etanercept used continuously: £9295.52 annual drug acquisition cost (104, 25mg vials)</li> <li>○ Efalizumab: £8798.40 annual drug acquisition cost (52, 125mg vials)</li> </ul> <p>Given this information, the proposed re-review of TA 103 should be brought forward, to allow a recalculation of relative cost effectiveness between the two treatments.</p>	<p>Comment noted. There will be consideration for a review of this guidance and TA103 in 2008. The inclusion of any other relevant technologies will be considered during the review process.</p>
		<p><b><u>2. Re-review dates for Infliximab vs re-review of TA 103 and STA for Adalimumab</u></b></p> <p>In the coming year NICE will be issuing guidance both with regard to Single Technology</p>	

		<p>Assessments of Infliximab and potentially adalimumab, as well as re-reviewing TA 103 Multiple Technology Assessment. Given the contrasting assumptions utilised in this appraisal versus that in TA 103, we believe it would be optimal to organise one multiple technology appraisal (MTA) of all recently introduced biological products in the treatment of psoriasis to produce a better integrated piece of guidance that reviewed all four technologies in the same context, and thus ensured a level playing field between them.</p>	
	3.4	<p><b><u>3. Efaluzimab as a comparator to Infliximab</u></b></p> <p>Whilst both infliximab and efalizumab are indicated for the treatment of patients with moderate to severe chronic plaque psoriasis, the Appraisal Committee does not utilize relevant advice from a previous decision, concerning use of biologics in Rheumatoid Arthritis. In that assessment, the appraisal committee have previously considered that using a second drug from the same class (in this case TNF-<math>\alpha</math> blockers) would not be cost effective. Efalizumab, being a T Cell modulator, has a different mode of action to the TNF-<math>\alpha</math> blockers and it should be considered first line in patients who are not suitable for anti TNF therapy to be consistent with conclusions made in other guidance regarding these technologies.</p> <p>In addition, infliximab has good short term efficacy but, like the other anti-TNF drugs, suffers from a plateau of efficacy. Section 3.4 of the ACD assesses relative efficacy over a 12 week period using a meta analyses. The appraisal committee should give more weight to data supporting continuous long term efficacy given the chronic nature of psoriasis, and high rates of relapse, a 24 week or longer treatment assessment may be more appropriate.</p> <p>As well as a discussion of efficacy, if a comparison of infliximab with etanercept and efalizumab is carried out, VAT costings should be an additional consideration for treatments administered in the hospital setting in comparison to those at home. Infliximab would be most suited to a particular population of patients with psoriasis as follows:</p> <ul style="list-style-type: none"> <li>○ Disease rating (PGA) of severe or very severe</li> <li>○ Patients who require rapid response to treatment</li> <li>○ And are willing to tolerate the potential side effects and required hospital visits for treatment.</li> </ul> <p>This is a group of patients for whom there are few other treatment options and infliximab is an ideal option given its rapid response. In addition, given such rapid response, infliximab may also be considered as an ideal treatment for controlling a patient's symptoms over a short period of time before transfer to a biologic intervention with a</p>	<p>The Committee has revised its recommendations. Infliximab is recommended as a treatment option for adults with very severe plaque psoriasis. See FAD section 1, 4.4, 4.5 and 4.13.</p>

		known longer duration of efficacy. Such a treatment practice would be optimal with regards patient outcomes and NHS resources and also address issues of diminishing efficacy over time which has been observed in the use of TNF inhibitor treatments.	
		<p><b>Conclusion</b></p> <p>Merck Serono would encourage NICE to recommend infliximab for patients with severe psoriasis who require a rapidly effective treatment. We believe infliximab is an efficacious treatment for that specific group of patients and we would urge NICE to make it available for patients who otherwise would have no other alternative treatment available to them</p> <p>I do hope that you find our comments to be of value and do please contact me if you require clarification on any point.</p>	The Committee has revised its recommendations. Infliximab is recommended as a treatment option for adults with very severe plaque psoriasis. See FAD section 1, 4.4, 4.5 and 4.13.
Wyeth	1.2	The assessment report for etanercept and infliximab for rheumatoid arthritis (Table 23, March 2002) states for infliximab a cost per administration of £124.	The Committee considered this cost within a plausible range of assumptions for infusion costs See FAD 3.14, 4.11.
	3.1	<p>Wyeth concurs with the appraisal committee's view that etanercept used intermittently, in accordance with its licensed posology and NICE guidance, should be the principal comparator (Section 4.3). However we do not accept that etanercept is used continuously in routine UK clinical practice.</p> <p>The manufacturers assertion of continuous use is based on an audit of just two 'leading' dermatology clinics. It is likely these clinics are tertiary referral centres of the sort run by the clinical experts who attended the first appraisal committee meeting. Caution must be exercised when extrapolating the practice within specialist centres to the rest of the dermatology community.</p> <p>Indeed in a survey of UK Consultant Dermatologists a minority (approx. 25%) of the 55 respondents who reported using etanercept did so on a continuous basis<sup>ii</sup>.</p> <p>It would therefore seem inappropriate to consider etanercept used continuously as a valid comparator.</p>	The Committee thought that the principal comparator should be etanercept, given intermittently in line with NICE guidance. The Committee accepted that in the subgroup of patients with very severe disease, continuous etanercept was more likely to be an appropriate comparator. See FAD sections 4.6 and 4.13.
	3.9	This section should refer to the assumptions described in section 3.8 rather than 3.7	Comment noted, see FAD section 3.9 and 3.10.
	4.6	We are not aware of any clinical data to support the anecdotal claim of a longer-lasting response with infliximab compared with alternative therapies e.g. etanercept. Section 4.8 of the infliximab SPC identifies that 'In psoriasis patients treated with infliximab as a maintenance regimen in the absence of concomitant immunomodulators, approximately 28% developed antibodies to infliximab. Section 4.4 warns that 'An association between development of antibodies to infliximab and reduced duration of response has also been observed.	Comment noted.

Karina Jackson		I have reviewed the evaluation report on the above consultation and have had sight of the British Association of Dermatologists (BAD) responses to the questions raised. I would like to state that I fully concur with the points the BAD have made and have no further comments to make.	Comment noted
Schering Plough		<p><b>The Committee's interpretation of the evidence is inconsistent with TA103 and fails to recognize that infliximab is a cost-effective treatment option for patients with severe psoriasis.</b></p> <p>The Committee did not take proper account of the evidence set out in Schering-Plough's submission with regards to the cost-effectiveness of infliximab in psoriasis. Schering-Plough's base case cost-effectiveness analysis was in accordance with the analysis that the York Assessment group used to identify a cost-effective subgroup of patients with psoriasis to be treated with biologics in their report for TA103.</p> <p>This group of patients was identified by having the worst quality of life at baseline (4th quartile DLQI) and the highest probability of hospitalization for non-responders (21 days). No further description of the 4th quartile DLQI is available either in the Assessment report or TA103 (information on HODaR analysis was marked as commercial in confidence). On the basis of this analysis and having received testimony from clinical experts and consultees, the Committee decided to recommend etanercept for the treatment of patients with severe psoriasis, described as having a PASI<math>\geq</math>10 and DLQI<math>&gt;</math>10.</p> <p>There was no further clarification given as to how this recommendation was derived. However, it is evident that the Committee considered that the subgroup of severe patients for which treatment with etanercept was cost-effective represented patients with a PASI<math>\geq</math>10 and DLQI<math>&gt;</math>10 and that this was a view that was informed by the 4th quartile DLQI population and expert opinion.</p> <p>Following this interpretation of the previous Guidance (TA103), Schering-Plough provided an analysis to NICE that was in agreement with the work that had been performed previously. The scenario presented was for patients in the 4th quartile DLQI that also had the highest probability of being hospitalized if they did not respond to treatment. As in the previous appraisal, this severe population of patients with a high probability of hospitalization is assumed to represent patients with a PASI<math>\geq</math>10 and DLQI<math>&gt;</math>10. The Committee failed to interpret the data presented in the S-P submission in the same manner as it had done in TA103 and therefore the interpretation is misleading and unfair.</p>	<p>The preliminary recommendations have been revised in the FAD; see FAD sections 1 and 4.</p> <p>The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of infliximab for the treatment of adults with psoriasis, having considered evidence on the nature of the condition and the value placed on the benefits of infliximab by people with psoriasis, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources (see FAD 4.1).</p> <p>In doing so for this appraisal, as in TA103, the Committee considered a number of scenarios in the economic analysis, including those in which all patient and 4<sup>th</sup> quartile utilities were used. In TA103, intermittent etanercept was considered cost effective in patients with DLQI greater than 10 (i.e. not just those with DLQI scores in the 4<sup>th</sup> quartile), who had severity of disease such that a lengthy hospital stay (21 days) would be required without response to treatment. See FAD sections 4.4, 4.5 and 4.13 for considerations of the evidence.</p>
		<p><b>The Committee has failed to adequately consider the implications for NHS resources in developing its preliminary recommendations for infliximab.</b></p> <p>The Committee's preliminary recommendation, that it is minded not to recommend infliximab, suggests that it has not adequately considered the implications for NHS</p>	<p>The preliminary recommendations have been revised in the FAD; see FAD sections 1 and 4. The remit of the appraisal is to appraise clinical and cost effectiveness. The economic evaluation</p>

		<p>resources of denying patients with severe psoriasis treatment with infliximab</p> <p>Severe psoriasis has a profound effect on both the quality of life and functionality of patients. These patients tend to suffer from highly visible and rapidly progressing psoriasis and are in need of rapid and effective control of the disease. In the absence of treatment with infliximab these patients are likely to require hospital admissions for treatment and this will have a high impact on NHS resources.</p> <p>The draft recommendations set out in the ACD are inconsistent with TA103, relying on a misinterpretation of the data, and would create significant unmet need for those patients with severe psoriasis in need of a rapid and longer-lasting response.</p>	<p>includes estimation of resource use and costs associated with infliximab treatment compared with that associated with comparator technologies.</p>
	<p>3.5</p>	<p><b>The ACD states in section 3.5 that the manufacturer did not provide specific reasoning for focusing on the 4th quartile group; however, the evidence suggested that this was in order to concentrate on patients with severe psoriasis.</b></p> <p>Schering-Plough's submission for infliximab in psoriasis was informed to a large extent by the prior appraisal of etanercept and efalizumab for psoriasis (TA103). This approach was intentionally pragmatic in as much as it attempted to follow an established framework for both modeling of cost-effectiveness and decision making.</p> <p>Whilst Schering-Plough was not party to the precise deliberations of the Committee during TA103, the available draft and final guidance as well as consultation documents provided clear evidence to support Schering-Plough's rationale in developing its submission for infliximab. As explained in detail earlier in this response, the 4th quartile group described as 'patients with low baseline quality of life' was clearly the group used to support the Committee's decision to recommend etanercept for the treatment of severe psoriasis, as defined by PASI<math>\geq</math>10, DLQI<math>&gt;</math>10.</p> <p>Schering-Plough accepts that its explanation for the focus on 4th quartile DLQI was concise in its submission. However, the unarguably clear relationship between recommendations set out in TA103 and the 4th quartile population offer a more than adequate rationale. We are concerned that the Committee appears to have overlooked this rationale.</p>	<p>The preliminary recommendations have been revised in the FAD; see FAD sections 1 and 4.</p> <p>The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of infliximab for the treatment of adults with psoriasis, having considered evidence on the nature of the condition and the value placed on the benefits of infliximab by people with psoriasis, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources (see FAD 4.1).</p> <p>In doing so for this appraisal, as in TA103, the Committee considered a number of scenarios in the economic analysis, including those in which all patient and 4<sup>th</sup> quartile utilities were used. In TA103, intermittent etanercept was considered cost effective in patients with DLQI greater than 10 (i.e. not just those with DLQI scores in the 4<sup>th</sup> quartile), who had severity of disease such that a lengthy hospital stay (21 days) would be required without response to treatment. See FAD sections 4.4, 4.5 and 4.13 for considerations of the evidence.</p>

3.7	<p><b>The ACD states in section 3.7 that the manufacturer did not present an ICER for infliximab compared with etanercept using the ‘all patients’ utilities.</b></p> <p>Schering-Plough accepts that this was an omission. The ICER for infliximab compared with continuous etanercept is £41,351 when applying the ‘all patients’ utilities.</p>	Comment noted
4.4	<p><b>The Committee considered in section 4.4 of the ACD that the principal comparator should be etanercept given intermittently in line with NICE guidance. The Committee noted however, that according to clinical specialists, the patient experts, the manufacturer and the ERG, etanercept is given continuously in routine UK clinical practice. The Committee was therefore persuaded that continuous etanercept was an appropriate comparator.</b></p> <p>Schering-Plough acknowledges the fact that the Committee has recognized the use of continuous etanercept in routine clinical practice. On this basis it seems difficult to support the Committee’s position that the principal comparator should be etanercept given intermittently, notwithstanding the fact that this reflects NICE guidance. It is Schering-Plough’s view that given the predominant use of continuous etanercept, as reflected in routine UK clinical practice, is the most appropriate principal comparator.</p>	The Committee thought that the principal comparator should be etanercept, given intermittently in line with NICE guidance. The Committee accepted that in the subgroup of patients with very severe disease, continuous etanercept was more likely to be an appropriate comparator. See FAD sections 4.6 and 4.13.
4.6	<p><b>The Committee accepted, as reported in section 4.6 of the ACD that due to the absence of RCT evidence to demonstrate any clinical difference between intermittent and continuous etanercept that it was reasonable to assume, as had been done in TA103, that there was no difference in clinical outcomes between continuous and intermittent. The Committee was therefore persuaded that infliximab could be more clinically effective than intermittent etanercept or efalizumab.</b></p> <p>Schering-Plough acknowledges that the Committee follows the logic established in TA103 in this particular instance in assuming that there is no difference in outcome between continuous and intermittent etanercept. Whilst currently unclear in the ACD, it is reasonable to assume that infliximab could also be more clinically effective than continuous etanercept.</p>	Comment noted. Due to uncertainty in inference from the indirect comparisons, the Committee could not conclude definitely whether infliximab had a statistically significantly greater clinical effectiveness than intermittent etanercept and efalizumab (see FAD section 4.8).
4.9	<p><b>The Committee considered the cost of administering infliximab in section 4.9. The Committee considered that the estimates for the cost of administration in Schering-Plough’s submission were inappropriate.</b></p> <p>Schering-Plough presented alternative estimates of cost-effectiveness based on additional scenarios for the cost of administering an infusion to reflect the uncertainty around this parameter in the economic model. Schering-Plough does not agree with the view as presented in the ACD that patients often need to spend at least half a day in hospital. It is Schering-Plough’s understanding that allocating the cost of half a day in hospital would not reflect the cost to the NHS of delivering infusions with infliximab and would lead to unreliable estimates of cost-effectiveness. Alternative scenarios presented by Schering-Plough earlier in this response were derived from other independent</p>	Comments noted See FAD 4.11 for considerations of the evidence relating to administration costs.

		published health technology appraisals involving infliximab.	
	4.10	<p><b>The ACD states in section 4.10 that the manufacturer did not provide ICERs of infliximab versus efalizumab for those patients in whom etanercept would be contraindicated or who would be intolerant to etanercept.</b></p> <p>Schering-Plough notes that these ICERs were not included in its submission. ICERs for infliximab versus efalizumab in this setting are presented in section I of this response.</p>	Comment noted
		<b>For full details of Schering Plough's response to the ACD, see separate document.</b>	

Reply received but no comments:

CASPE

No comments received from website consultation