NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Adalimumab for the treatment of adults with psoriasis

Response to consultee, commentator and public comments on the ACD

Consultee	Section	Comment	Response
Abbott		Abbott welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) prepared for the appraisal of adalimumab for the treatment of chronic plaque psoriasis. Abbott welcomes the provisional recommendations for the use of adalimumab for the treatment of patients with severe chronic plaque psoriasis. However, Abbott considers that given the clinical and cost-effectiveness profile of adalimumab compared to etanercept, adalimumab should be recommended as the first choice biologic treatment for patients with severe psoriasis meeting the PASI and DLQI criteria as outlined in the ACD.	Owing to the limitations of the clinical effectiveness data and the uncertainty around the cost-effectiveness results, the Committee concluded that it could not recommend adalimumab in preference to etanercept and that clinicians would need to exercise their clinical judgement in choosing between the two treatments. See FAD section 4.11.
		Abbott is not aware of any relevant evidence that has not been taken into account by the appraisal committee.	Comment noted.
		Summary of clinical effectiveness Abbott considers that patients receiving adalimumab will have a higher probability of treatment response compared to etanercept. This view is supported by the clinical experts and the results of the mixed treatment comparison: "The Committee heard from the clinical experts that, based on clinical experience, adalimumab could provide greater clinical benefit than etanercept when an anti-TNF is considered appropriate for treatment in a person with severe psoriasis. The Committee also noted the results of the mixed-treatment comparison conducted by the manufacturer, which suggested a higher probability of response following treatment with adalimumab compared with etanercept." NICE Appraisal Consultation Document. Adalimumab for the treatment of Psoriasis. Abbott considers that patient heterogeneity in the clinical trials is unlikely to be a	The Committee was aware that the ERG had expressed concerns over the mixed treatment comparison conducted by the manufacturer and that the robustness of the results was uncertain (see FAD section 4.3). The Committee concluded that, although there is some evidence to suggest that adalimumab may be more effective in some circumstances than etanercept, clinical superiority of adalimumab over etanercept in the treatment of severe psoriasis has not been firmly established.

		major confounding factor that could account for the consistently higher PASI response rates observed in trials for adalimumab, when indirectly compared with trials for etanercept. It should also be noted that the difference in effectiveness of adalimumab and etanercept is consistent with indirect comparisons of the effectiveness of these two agents in treating psoriasis in trials conducted in patients with psoriatic arthritis. Given the strength of data on this point, Abbott considers that the summary of evidence on clinical effectiveness should emphasise the likely greater clinical benefits of adalimumab compared to etanercept.	
		Adalimumab versus high initial dose etanercept Consideration should be given to the dose of etanercept used in UK clinical practice. The model analyses presented by Abbott indicate that etanercept given at the higher initial dose of 100mg weekly is unlikely to be cost effective, in line with previous analyses conducted for the appraisal of etanercept in TA103. Therefore, use of adalimumab is likely to be more cost effective than etanercept, particularly if etanercept is initiated at the licensed but non-NICE recommended higher dose of 100mg weekly for the first 12 weeks of therapy. Abbott considers that the greater cost-effectiveness of adalimumab compared to etanercept when used at the higher dose should be more clearly stated in the content of the guidance.	High initial dose etanercept is not recommended by NICE, no UK data has been provided on its use, and clinical experts who attended the ACD meeting did not highlight this as being a relevant comparator for adalimumab.
		Adalimumab versus continuous-use etanercept It was acknowledged by the clinical experts consulted that some patients with severe psoriasis may require continuous dosing of etanercept. Based on the results of the available economic modelling Abbott considers that the summary of cost-effectiveness should emphasise more clearly the greater cost effectiveness of adalimumab versus continuous-use etanercept.	This is stated in sections 3.21, 4.6 and 4.8 of the FAD.
		Adalimumab versus intermittent-use etanercept Abbott acknowledges that the likely dosing regimen and time off treatment for intermittent use of etanercept in the UK is unclear. However, a greater source of uncertainty for the cost effectiveness of intermittent use etanercept is the effectiveness of long-term intermittent treatment, as data are currently only available for one period of retreatment with etanercept. The model presented by Abbott was highly favourable to etanercept by assuming that all patients retreated will be able to regain response after multiple periods off treatment. Furthermore, given the uncertainty over the length of time patients receiving etanercept would be off treatment, Abbott used a conservative assumption of 88% of	There is limited data available on the long-term efficacy of any of the biologics (see manufacturer's submission, page 94). In reaching its decision, the Committee took into account the incremental costs per QALY gained for adalimumab compared with both intermittent etanercept and continuous etanercept (see FAD section 4.8) as well as considering varying gaps in treatment courses during intermittent use.

		the dose of continuous etanercept in the economic modelling presented in the manufacturers submission. If in UK clinical practice patients with severe psoriasis are off treatment for shorter periods, as was agreed by the clinical experts consulted, the available data indicate that adalimumab will be a more cost effective treatment option than etanercept.	
		Furthermore, it should be borne in mind that the cost effectiveness results presented by Abbott and the ERG utilised a 16-week stopping rule for non-responders. Use of a 12-week stopping rule for adalimumab non-responders in line with that used for etanercept is likely to further reinforce the greater cost effectiveness of adalimumab compared to etanercept.	Guidance has been amended. It is recommended that adalimumab is discontinued in people whose psoriasis has not responded adequately at 16 weeks in line with the evidence base. See FAD sections 1.2 and 4.12.
		Abbott welcomes the provisional recommendations for the use of adalimumab for the treatment of patients with severe chronic plaque psoriasis. However, as outlined in section 2, Abbott considers that given the clinical and cost-effectiveness profile of adalimumab compared to etanercept, adalimumab should be recommended as the first choice biologic treatment for patients with severe psoriasis meeting the PASI and DLQI criteria as outlined in the ACD.	Owing to the limitations of the clinical effectiveness data and the uncertainty around the cost-effectiveness results, the Committee concluded that it could not recommend adalimumab in preference to etanercept and that clinicians would need to exercise their clinical judgement in choosing between the two treatments. See FAD section 4.11.
		Factual inaccuracies in the ACD PASI response in REVEAL study "During the open-label period of the trial, 89% of people originally randomised to adalimumab had at least a PASI 75 response at week 33". Page 6 The above statement in regard to the REVEAL study is not factually correct and could be amended to read as follows: “Adalimumab-treated patients who achieved a PASI 75 response at week 16 had a mean 92% PASI score improvement relative to baseline and had a mean 89% PASI score improvement relative to baseline at week 33.”	This sentence in the ACD was taken from the manufacturer’s submission (page 68 – 1st bullet of results for period B). Following clarification on this point with the manufacturer, the sentence has been amended to ‘During the open-label period of the trial, 89% of people originally randomised to adalimumab who achieved at least a PASI 75 response at Week 16, had at least a PASI 75 response at week 33’ (see FAD section 3.5).
Merck Serono		Merck Serono appreciates the opportunity to comment on the evidence base used to inform NICE’s preliminary decision regarding adalimumab for the treatment of adults with psoriasis in England and Wales. Merck Serono would like to comment on the following areas of the ACD: 1. Information presented in relation to TA 103 2. Clarification of cost-effectiveness and assumptions used in the decision-	Comment noted.

		making 3. Re-review dates for adalimumab vs re-review of TA 103	
		Information presented in relation to TA 103 Merck Serono agrees with the Appraisal Committee's description of the use of etanercept in paragraph 4.7 that etanercept is given continuously in routine clinical practice, despite this being contrary to that specified in the marketing authorisation. This follows a similar statement made by the Appraisal Committee during the recent assessment of infliximab. In Technology Appraisal (TA) 134 of infliximab for the treatment of adults with psoriasis, continuous etanercept was regarded as a suitable comparator only as infliximab was recommended for very severe psoriasis patients with a total Psoriasis Area Severity Index (PASI) of 20 or more and a Dermatology Life Quality Index (DLQI) of more than 18. In this Appraisal Consultation Document for adalimumab, however, the focus is on severe patients with a PASI of 10 or more and a DLQI of more than 10. When etanercept and efalizumab were assessed in TA 103 for this treatment group, intermittent etanercept therapy (74% of the continuous dose) was accepted as the appropriate comparator. To add transparency to decision-making, can the Institute please clarify the appropriate comparator considered? Is it intermittent or continuous etanercept? If it is intermittent therapy, is it 74% or 88% of the continuous dose, or an alternative?	The Committee was persuaded that, for some people with severe psoriasis, the periods of time between courses of intermittent treatment with etanercept could often be very short. In making its recommendations, the Committee therefore took into account the incremental costs per QALY gained for adalimumab compared with both intermittent etanercept and continuous etanercept (see FAD section 4.8). The Committee agreed that assumptions regarding the yearly dose for etanercept based on an intermittent dosing schedule should be consistent with those applied in TA103. (intermittent etanercept assumed to be 74% of the continuous etanercept dose). See FAD section 4.7.
		Clarification of cost-effectiveness and assumptions used in the decision-making The Appraisal Committee was concerned that in the manufacturer's analysis the dose of intermittent therapy of etanercept used to calculate the costs was inconsistent with that used to calculate utility gain. The incremental cost per QALY for adalimumab compared to etanercept using the assumptions in TA103 was therefore £36,700. Despite this, the committee felt that the true cost per QALY should take into account comparisons both with intermittent and continuous therapy. Based upon the lack of uncertainty around cost-effectiveness results the appraisal committee stated that 'clinicians would need to exercise clinical judgement in choosing between the two treatments'. This decision does not seem to follow the criteria on which recommendations were made for etanercept and efalizumab in TA 103. We therefore believe there needs to be consistency in the assumptions used for calculation of cost-effectiveness, particularly given the uncertainty over the comparator and the high cost per QALY ratio of adalimumab when using the	Comparators used in the economic evaluation have to reflect current clinical practice. The Committee heard from the clinical experts that people with severe disease are either not treated with intermittent therapy or have a very small gap (often no more than 1 week) between courses of treatment if the disease flares up very quickly. The Committee was therefore persuaded that, for some people with severe psoriasis, the periods of time between courses of intermittent treatment with etanercept could often be very short. In making its recommendations, the Committee therefore took into account the incremental costs per QALY gained for adalimumab

		appropriate TA 103 intermittent etanercept comparator (i.e. 74% of continuous dose).	compared with both intermittent etanercept and continuous etanercept. See FAD section 4.8.
		Re-review dates for Adalimumab vs re-review of TA 103 In the past year NICE will have issued guidance with regard to Single Technology Appraisals of both infliximab and adalimumab. We do not believe that a review date for adalimumab of June 2011 is appropriate 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 a;; four technologies in the same context, and thus ensured a level playing field between them. Further criteria that needs consideration in this review, particularly given the chronic nature of the plaque psoriasis, is both the long-term efficacy and the effect a specific mode of action has upon this. This should encapsulate assumptions around tumour necrosis factor inhibitors alluded to in technology appraisals for other indications (for example Rheumatoid Arthritis). Given NICE's decision that infliximab be used in very severe patients, we could envisage a treatment cascade as in figure 1 below. If a re-review of TA 103 were to proceed, such guidance will provide greater clarity on the place of all four biological therapies, evaluated on an equivalent basis, in this treatment pathway. Please note – Figure 1 not replicated here.	The review date has been re-considered based on internal discussions at NICE following comments on the ACD. The FAD states that the guidance will be considered for review in July 2008 at the same time that 'Etanercept and efalizumab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 103) and 'Infliximab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 134) are considered for review.
		Conclusion Merck Serono believe that NICE should recommend adalimumab as an option for patients with severe psoriasis on the condition that it meets cost-effectiveness criteria based upon the assumptions used in TA 103. If this is not the case, then we feel that adalimumab should not be recommended for the treatment of psoriasis patients with PASI of 10 or more and DLQI of more than 10 until the review of TA 103 (which needs to be initiated as a matter of urgency), where the original assumptions can be assessed and all four biologics therapies can be evaluated on the same basis.	Where possible, efforts have been made to ensure that the same assumptions have been used as in TA 103. The review date for adalimumab has been re-considered based on internal discussions at NICE following comments on the ACD. The FAD states that the guidance will be considered for review in July 2008 at the same time that 'Etanercept and efalizumab for the treatment of adults with psoriasis' (NICE technology appraisal guidance 103) and 'Infliximab for the treatment of adults with

		If adalimumab is recommended based upon etanercept usage being between intermittent (74% of continuous dosage) and continuous, then efalizumab would be deemed cost-effective on this basis to give patients an added choice of treatment, particularly if the Appraisal Committee now feels that intermittent therapy as defined in the etanercept SPC (i.e. up to 24 weeks for each treatment cycle is more appropriate than that defined in TA 103.	psoriasis' (NICE technology appraisal guidance 134) are considered for review. Within the current appraisal the Institute is not able to alter recommendations for any other technology other than that which is being appraised i.e. adalimumab.
Wyeth	3.11	'Etanercept given continuously was dominated by adalimumab' Wyeth does not recommend nor promote continuous use of Etanercept. There is no robust evidence that Etanercept is used off license in the majority of patients as stated in the manufacturer's submission. The SPC for Etanercept reports the licensed dosing for Etanercept to be the following: Plaque psoriasis The recommended dose of Enbrel is 25 mg administered twice weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed. The dose should be 25 mg twice weekly. 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. It would therefore seem inappropriate to consider etanercept used continuously as a valid comparator.	Comparators used in the economic evaluation have to reflect current clinical practice. The Committee heard from the clinical experts that people with severe disease are either not treated with intermittent therapy or have a very small gap (often no more than 1 week) between courses of treatment if the disease flares up very quickly. The Committee was therefore persuaded that, for some people with severe psoriasis, the periods of time between courses of intermittent treatment with etanercept could often be very short. See FAD section 4.8.
Wyeth	3.11	'Etanercept given intermittently (assumed to be 88% of the dose of continuous etanercept) … were ruled out on the grounds of extended domination (that is, the incremental costs per QALY gained were higher than for adalimumab even though either the cost or effectiveness was more favourable).' The cost for intermittent etanercept was calculated as 88% of the cost of continuous	The Committee agreed that assumptions regarding the yearly dose for etanercept based on an intermittent dosing schedule should be consistent with those applied in TA103 (intermittent etanercept assumed to be 74% of the continuous etanercept dose). See

		therapy, as guided by evidence from the IHCIS data. This data set is a US one, and not representative for UK practice. The York model assumptions should be used, as they have been used in an earlier appraisal.	FAD section 4.7.
Wyeth	3.14	'Changing the assumption regarding the dose for intermittent etanercept from 88% of the dose of continuous etanercept to 74% (the figure used in the York model) reduced the incremental cost per QALY gained for intermittent etanercept compared with supportive care from £37,300 to £27,600.' The cost for intermittent etanercept was calculated as 88% of the cost of continuous therapy, as guided by evidence from the IHCIS data. This data set is a US one, and not representative for UK practice. The York model assumptions should be used, as they have been used in an earlier appraisal.	The Committee agreed that assumptions regarding the yearly dose for etanercept based on an intermittent dosing schedule should be consistent with those applied in TA103 (intermittent etanercept assumed to be 74% of the continuous etanercept dose). See FAD section 4.7.
Wyeth	3.20	'The ERG was concerned that the manufacturer's base-case assumptions for intermittent etanercept did not seem appropriate, in particular that the dose of intermittent therapy used in the model (88% of continuous therapy) to calculate costs was inconsistent with the dose used to calculate utility gains (68%).' The assumptions for calculating costs and utility gains should be consistent, and need to reflect UK practice. The cost calculation provided by the manufacturer is based on US data, which therefore is not generalisable to a UK setting.	The Committee agreed that assumptions regarding the yearly dose for etanercept based on an intermittent dosing schedule should be consistent with those applied in TA103 (intermittent etanercept assumed to be 74% of the continuous etanercept dose). See FAD section 4.7
Wyeth	3.21	'The ERG re-ran the manufacturer's analysis changing the assumption for the dose of intermittent etanercept to the value used in the York model (74% of the continuous etanercept dose). In this analysis the incremental cost per QALY gained of adalimumab compared with intermittent etanercept was £36,700.' Wyeth concurs with the ERGs' analysis to change the assumption for the dose of intermittent etanercept to this of the York model.	The Committee agreed that assumptions regarding the yearly dose for etanercept based on an intermittent dosing schedule should be consistent with those applied in TA103 (intermittent etanercept assumed to be 74% of the continuous etanercept dose). See FAD section 4.7
Wyeth	4.3	'The Committee heard from the clinical experts that, based on clinical experience, adalimumab could provide greater clinical benefit than etanercept when an anti-TNF is considered appropriate for treatment in a person with severe psoriasis.'	No action.
Wyeth	4.4	'The Committee heard from the clinical experts and patient representatives that adalimumab is generally easier to use than etanercept because of the self-injection dosing regimen every other week.'	No action.
Wyeth	4.6	'The Committee noted that assumptions regarding the dose for intermittent etanercept had a large impact on the results. … The Committee was also concerned that, in the manufacturer's analysis, the dose of intermittent therapy used to calculate costs (88% of continuous therapy) was inconsistent with the dose used to estimate utility gains (68% of continuous therapy). Therefore, the Committee agreed that the	Comment noted.

		ERG's analysis represented the most appropriate analysis on which to base its decision regarding the use of adalimumab.' Wyeth concurs with the ERGs' analysis to change the assumption for the dose of intermittent etanercept to this of the York model.	
Wyeth	4.7	'The Committee considered whether the appropriate comparator for adalimumab should be etanercept given continuously or given intermittently in line with NICE technology appraisal guidance 103. It heard from the clinical experts that people with severe disease are either not treated with intermittent therapy or have a very small gap (not usually more than 1 week) between courses of treatment because the disease flares up very quickly. The Committee was therefore persuaded that, for some people with severe psoriasis, the periods of time between courses of intermittent treatment with etanercept could often be very short. The Committee agreed that, for people with severe psoriasis, the true incremental cost per QALY gained for adalimumab compared with etanercept would take into account the results calculated by the ERG for both intermittent etanercept and continuous etanercept and would be likely to fall within a range consistent with that which had previously been considered a cost-effective use of NHS resources.' Wyeth does not recommend nor promote continuous use of Etanercept. There is no robust evidence that Etanercept is used off license in the majority of patients as stated in the manufacturer's submission. The SPC for Etanercept reports the licensed dosing for Etanercept to be the following: Plaque psoriasis The recommended dose of Enbrel is 25 mg administered twice weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly. Treatment with Enbrel should continue until remission is achieved, for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed. The dose should be 25 mg twice weekly. 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 basisi. It	Comparators used in the economic evaluation have to reflect current clinical practice. The Committee heard from the clinical experts that people with severe disease are either not treated with intermittent therapy or have a very small gap (often no more than 1 week) between courses of treatment if the disease flares up very quickly. The Committee was therefore persuaded that, for some people with severe psoriasis, the periods of time between courses of intermittent treatment with etanercept could often be very short. See FAD section 4.8.

		would therefore seem inappropriate to consider etanercept used continuously as a valid comparator.	
British Association of Dermatologists		Do you consider that all of the relevant evidence has been taken into account? Yes	Comment noted.
		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? Yes, agree	Comment noted.
		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? Yes, excellent	Comment noted.
		Are there any equality related issues that need special consideration that are not covered in the ACD? No	Comment noted.
Royal College of Nursing		The Royal College of Nursing welcomes the opportunity to review the Appraisal Consultation Document (ACD) on the use of Adalimumab for the treatment of psoriasis. Nurses working in this area of health have reviewed the ACD for the health technology appraisal of Adalimumab for the treatment of psoriasis. The document is comprehensive. Psoriasis is a chronic debilitating condition, often resulting in hospitalisation for many patients. The RCN will welcome guidance to the NHS which will improve the quality of life these patients.	Comment noted.
Department of Health		Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted.
Welsh Assembly Government		Thank you for giving the Welsh Assembly Government the opportunity to comment on the above appraisal. We are content with the technical detail of the evidence supporting the appraisal and have no further comments to make at this stage.	Comment noted.