All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Etanercept (Enbrel®▼)

Pfizer Limited

Advice No: 0210 – March 2010

Recommendation of AWMSG

Etanercept (Enbrel®▼) is not recommended for use within NHS Wales for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of eight years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. The cost effectiveness data presented was insufficient for AWMSG to recommend the use of etanercept (Enbrel®▼) in NHS Wales.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 3rd March 2010

The recommendation of AWMSG is:

Etanercept (Enbrel®▼) is not recommended for use within NHS Wales for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of eight years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. The cost effectiveness data presented was insufficient for AWMSG to recommend the use of etanercept (Enbrel®▼) in NHS Wales.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Etanercept (Enbrel®▼) is indicated for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of eight years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies[1].

The other licensed indications for etanercept can be viewed by consulting the summary of product characteristics (SPC). The company submission and this assessment report focuses on the use of etanercept in paediatric plaque psoriasis which is a licence extension[2].

2.2 Dosing

The recommended dosage regimen is 0.8mg/kg (up to a maximum of 50mg per dose) by subcutaneous injection once weekly for up to 24 weeks. Treatment should be discontinued if the patient shows no response after 12 weeks[1].

2.3 Market authorisation date

22 December 2008[2]

2.4 UK Launch date

22 December 2008[2]

3.0 DECISION CONTEXT

3.1 Background

Psoriasis is an inflammatory skin condition characterised by an accelerated rate of turnover of the top layer of the skin (epidermis). Although it is a chronic progressive condition, its course may be erratic, with flare-ups and remissions[3]. Psoriasis is thought to have a strong genetic component and is mediated by abnormal T lymphocytes. Environmental factors, stress, infection and medication may exacerbate the condition[3]. Psoriasis effects on quality of life (QoL) measures have been found to be comparable to other chronic illnesses such as cancer, arthritis, hypertension, heart disease, diabetes and depression. The impact on QoL can vary depending upon the sites involved, with often lower scores for the face, feet and hands[4].

Plaque psoriasis is the most common form of psoriasis, accounting for 80-90% of all cases and affecting approximately 2% of the population[4,5]. In about one-third of patients, psoriasis starts in the first or second decade of life[5]. Approximately 80% of those affected will have mild to moderate disease, with 20% having moderate to severe disease affecting over 5% of the body surface area (BSA) or affecting crucial body areas (hands, feet, face or genitals)[4]. The company estimates that of the 376,400 eight to seventeen year olds residing in Wales, 176 would be eligible for therapy with etanercept, with two new cases each year. This takes into account a lower estimate rate of 65% for plaque psoriasis amongst all paediatric patients diagnosed with a form of psoriasis (refer to section 8 of the report for further details)[2].

Treatment of mild to moderate disease, particularly affecting only a small area, include topical treatments such as emollients, salicylic acid, coal tar (smell unacceptable to some children), dithranol, corticosteroids, tazarotene (not recommended in under 18's) and vitamin D analogues (calcipotriol is licensed for six years and above, tacalcitol is not licensed in children)[6-10].

For more severe, resistant and/or extensive psoriasis the following options are available:

- Phototherapies: ultraviolet B radiation (UVB), long wave ultraviolet A radiation with a psoralen (PUVA) (use limited in children by concerns over carcinogenicity and premature aging[7]. PUVA is contraindicated in young children but may be used in adolescents if absolutely necessary[11])
- Oral treatment (licensed for severe disease resistant to other therapies): acitretin (contraindicated in children unless benefits outweigh risks), ciclosporin, methotrexate (not licensed in children) [6.7,12]
- Oral treatment (not licensed in psoriasis): hydroxycarbamide, mycophenolate
- Biological therapies (not licensed in children): adalimumab, infliximab, ustekinumab[6,7,13-15]
- Biological therapies (licensed in children): etanercept[1]

Though many of these medicines are not licensed in children they have been used to treat symptoms. Most of the systemic therapies available have the potential to cause severe long-term side effects and monitoring is required. The toxic effects are often cumulative and therefore many people with psoriasis require 'rotational therapy' in order to minimise the cumulative toxicity of any one treatment[3].

Etanercept is a human recombinant tumour necrosis factor (TNF) receptor p75 fusion protein which is thought to competitively inhibit TNF binding to the cell surface TNF-receptor preventing TNF mediated cellular responses[1]. Etanercept may also modulate biologic responses controlled by additional downstream molecules that are induced or regulated by TNF[1].

3.2 Comparators

Etanercept is the first biological therapy to be licensed for use in children and adolescents[1]. There are no licensed comparators for this patient group but refer to section 3.1 on treatment options for severe disease.

3.3 Guidance and related advice

The British Association of Dermatologists has produced guidelines for use of biological interventions in psoriasis in adults and children (2009). They recommend that etanercept is used for the treatment of severe plaque psoriasis in children from the age of eight years who fulfil the stated disease severity criteria (see Appendix 1). Disease response should be assessed at three to four months and in patients who respond, treatment may be continued according to clinical need, although long term data on efficacy are limited to one year[16]. Refer also to section 9.3.

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The company submission includes one pivotal phase III study undertaken in children and adolescents aged four to seventeen with moderate to severe plaque psoriasis. The study was divided into three stages, stage one compared etanercept 0.8mg/kg once weekly to placebo. Subjects receiving etanercept were significantly more likely to achieve symptom improvement than those receiving placebo in terms of clinical scores and QoL measurements. In the second stage all patients received open label etanercept and for the responders who were previously on placebo response was comparable to those originally randomised to etanercept. Not all subjects responded to treatment and just over half of all subjects were eligible to enter phase three of the study where subjects were re-randomised to either placebo or etanercept to assess withdrawal effects. Results from this phase indicate that around half of the patients on placebo did not require re-treatment with etanercept within 12 weeks of stopping therapy, though at least some of this effect may have been due to the relapsing/remitting nature of this condition. No new safety concerns with etanercept have been identified from this study.

4.2 Review of the evidence on cost-effectiveness

The company submission provides brief details of a cost utility analysis of etanercept against placebo/non-systemic treatment. This appears to be based on a model designed for the adult indication, which has been unaltered, other than the inclusion of 12- and 24-week response rates obtained from the phase III trial in children and adolescents.

The company submission reports that this model demonstrates etanercept to be both more effective and less expensive than the comparator, i.e. etanercept treatment dominates placebo/non-systemic treatment. However, there are many issues - presentational and methodological - which limit the interpretation of the economic evidence that has been provided. There is a lack of detail provided regarding the modelling methods and it is unclear whether the parameter values other than the psoriasis area and severity index (PASI) response rates have been amended from those that were used in the adult model. It appears that all patients receive weekly doses of 25mg, and the impact of increasing to the maximal permissible weekly dose of 50mg has not been explored. There is also little detail regarding the model outputs for the base case and sensitivity analyses, and the results presented in the company submission have not been verified.

4.3 Limitations of the evidence

- The subjects included within the clinical trial may not be representative of patients likely to be treated in clinical practice, in that subjects were not required to be inadequately controlled or intolerant to other systemic therapies or phototherapies.
- The many presentational and methodological issues limit the interpretation of the economic evidence that has been provided.

5.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

5.1 Clinical evidence

The evidence included within the company submission is taken from one phase III 48 week study in children and adolescents aged 4-17 years old who had stable moderate to severe plaque psoriasis (refer to Table 1A, Appendix 1 for definition and full results)[17]. Subjects must have received prior phototherapy or systemic therapy and/or must have been poorly controlled with topical therapy. There were three stages to this study; in stage one subjects were randomised to etanercept or placebo for 12 weeks, from week four if the PASI score worsened by more than 50% subjects were eligible to pass into an escape group to receive open label etanercept until week 12. In stage two all subjects remaining in the study (including those who entered the escape group) were transferred to open label etanercept for 24 weeks. If PASI 50 was not reached by week 24 or PASI 75 was not reached at week 36, patients could discontinue the study or were eligible to receive additional topical therapy and continue to receive open label etanercept until week 48. In stage three the remaining subjects who had achieved PASI 50 at week 24 or PASI 75 at week 36 were considered responders and were randomised again to placebo or etanercept to evaluate disease relapse and durability of response. If PASI 75 was lost subjects were eligible for re-treatment with etanercept. Baseline characteristics were similar between groups with the exception of more patients having a diagnosis of psoriatic arthritis in the placebo group (13% versus 5%). Refer to Table 1A, Appendix 1 for more details and results.

The primary endpoint is taken from the first stage of this trial and assessed the PASI 75 at week 12 using the intention-to treat (ITT) analysis set. A significantly higher percentage of subjects in the etanercept group achieved a PASI 75 response compared with placebo (57% versus 11%; $p<0.001$). In addition a significantly higher percentage of subjects in the etanercept group achieved a physicians global assessment (sPGA) status of clear/almost clear compared with placebo as early as week four (secondary endpoint)[5]. In terms of QoL, the mean percentage improvement in the children's dermatology life quality index (CDLQI) from baseline to week 12 measured as a secondary endpoint was significantly greater for the etanercept groups compared with the placebo group. By week 36 (following 24 weeks of open label etanercept in all subjects) QoL results were comparable between those originally assigned in stage one to etanercept and those to placebo[17]. Other QoL measures were not significantly different between groups[5].

Of the 208 who had entered stage two of the clinical trial only 130 subjects had achieved a PASI 75 (note: an additional eight were included in error) and were eligible for entry into stage three of the study[17]. By week 48, 29 of the 69 subjects assigned to placebo had relapsed (loss of PASI 75) and were re-treated with etanercept. After four and eight weeks of retreatment with etanercept 27% and 36%, respectively had achieved a PASI 75 response indicating that overall responses were slightly lower and took longer to become evident than for the original responders[5]. However nearly 50% of those assigned to placebo in stage three maintained a PASI 75 score at week 48

despite not receiving etanercept for 12 weeks[5]. For a full definition of terms refer to the glossary.

5.2 Safety

The most common adverse events reported with etanercept are injection site reactions (14%), allergic reactions, headache and upper respiratory tract infection[16]. TNF-α inhibitors have been associated with infections including tuberculosis, sepsis, opportunistic infections, reactivation of hepatitis B virus and worsening of hepatitis C. Before, during and on stopping therapy patients should be tested for active infections and, in the case of tuberculosis, latent infections. Solid and haematopoetic malignancies have been reported with etanercept during the postmarketing period. Non-melanoma skin cancer (NMSC) has been reported and periodic skin examination is recommended for all patients who are at an increased risk for NMSC including patients with psoriasis and patients who have previously received PUVA therapy[1]. Other effects reported include blood dyscrasias, and rarely worsening heart failure and demyelinating disorders[1].

During the initial 12-week double-blind period of the pivotal phase III trial, adverse events or infections were comparable between the etanercept (64.2%) and placebo (59.0%) groups[5]. Six subjects withdrew from the study because of an adverse event or infection. Three in the etanercept group: one in stage one of the trial due to bronchospasm and two in stage two of the trial due to skin infection and lobar pneumonia. No new safety signals have been observed in this new population[5] however the data are relatively short-term. Refer also to section 9.4.

6.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- Patients included in the pivotal phase III study had moderate to severe plaque psoriasis with 30% of subjects having received prior systemic therapy and 48% phototherapies[5]. Intolerance or inadequate response to these therapies was not part of the inclusion criteria. In addition, the age range included within the trial was 4-17 years. Therefore subjects in the trial do not fully represent the patients who are likely to be eligible for therapy with etanercept (refer to section 7.4).
- Due to the limited proportion of subjects included within the trial that were under eight years old the licence excludes the use of etanercept in children seven years and younger[1,5].
- The study was carried out in the US and Canada with 26% of patients analysed at week 48, weighing greater than the 97th percentile[2]. Therefore it may be assumed that the demographics of the study population are different to the target population in Wales.
- Analysis of the data by length of disease duration indicated that response rates were comparable up to ten years (ranges 0 to 2, 3 to 6, 7 to 10) but for those subjects with a disease course of ten years or more response was lower[5].
- Reassuringly no patient had a rebound of the disease (defined as a worsening of PASI by more than 125% from baseline) within the 12 weeks following cessation of open-label etanercept[5].
- Nearly half of the subjects completing stage three of the clinical trial required re-treatment with etanercept, indicating that a treatment period of up to 36 weeks may be insufficient[5].
- Psoriasis is a chronic-relapsing disease and the possibility of repeat courses in subjects who relapse quickly was raised as a concern by CHMP due to the limited safety data available[5].
- Due to the potential risks of repeated immunosuppression in children and lack of long terms safety data the CHMP indicated that the duration of treatment and

frequency of re-treatment needs to be further addressed[5]. An extension to the Phase III trial is ongoing.

- The British Association of Dermatologist Biologics guidelines state that at present the risks and benefits of biologic therapies relative to standard systemic therapies are largely unknown[16]. This is reflected in the licensed indications for these drugs.

7.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

7.1 Context

The company submitted evidence[2] which provides very brief details of a cost utility analysis of intermittent treatment with etanercept in its licensed indication for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies[1]. There are no other licensed medicines in this specific patient group, and the comparator in the analysis is placebo/non-systemic therapy. The perspective of the analysis is NHS Wales[2].

7.2 Methods

Modelling approach: Few details are provided in the submission. A Markov model has been developed with a 28-day cycle length to represent intermittent treatment with etanercept over a 10-year time horizon of analysis. See Table 2A, Appendix 2 for details. Patients are modelled to receive initial therapy for 12 weeks. Those who fail to achieve a PASI 50 response (at least a 50% improvement over baseline PASI score) are considered as treatment failures and stop active therapy. It appears from the model that those achieving a PASI of 50 or more continue treatment for a further 12 weeks, after which those who achieve/maintain a PASI 75 response are eligible to commence intermittent treatment (comprising a treatment-free period, with treatment re-initiated in those who experience relapse), or remain on continuous treatment. It is assumed that 75% of patients commence intermittent treatment. It appears from the model that those who achieve a PASI of 50 but less than 75 by this point (week 24 of treatment) remain on continuous treatment, i.e. intermittent treatment is not an option. Failure to achieve/maintain a PASI 50 response leads to treatment discontinuation.

It appears that the model was originally designed to evaluate TNF-α inhibitors for the treatment of adults, and efficacy data for etanercept have been overwritten with that from the phase III trial in children and adolescents.

Inputs: Patient-level data from the phase III, placebo-controlled trial of etanercept in patients with moderate to severe plaque psoriasis[17] have reportedly been used to model the efficacy of etanercept. The company submission may be taken to imply that health-related quality of life (HRQoL), as measured in the phase III trial as a secondary endpoint using the CDLQI instrument[17], has been used to generate utility values via a published study that mapped the dermatology life quality index (DLQI [i.e. the adult version of the instrument]) to the EQ-5D[18]. However, inspection of the model indicates that utility scores are derived from the adult studies of etanercept. Utility gains were assumed to be the same regardless of the treatment used to achieve DLQI scores, but to vary according to severity of disease[2].

In terms of resource use, the costs of etanercept are reported in the submission to be based on doses used in the phase III trial, at 0.8 mg/kg body weight up to a maximum intended dose of 50mg and delivered in pre-filled syringes[2,17]. However, inspection of the model suggests that the cost of etanercept is based on weekly doses of 25mg. The British Association of Dermatologist guidelines informed the model decisions on clinic

visit frequency[19], and the Health Technology Assessment (HTA) that informed the 2006 National Institute for Health and Clinical Excellence (NICE) Technology Appraisal of etanercept in adults with psoriasis informed the length of hospital stay for patients who failed treatment[3,20]. Unit costs for hospitalisation and outpatient attendances were taken from the 2006-2007 NHS reference costs for dermatology[21].

No other parameter inputs are discussed in the submission, and it appears that all the other inputs from the original model in adults have been retained in the paediatric model.

7.3 Results

The company reports that the model outputs suggest that etanercept is both less expensive and more effective than placebo/non-systemic treatment, i.e. etanercept is the dominant treatment strategy[2]. Few further details are provided in the submission, and it is not possible to verify this claim from the model that has been provided.

The company submission reports that one-way sensitivity analyses were performed but no results are provided. It is stated that all arms of the model are sensitive to the long-term prognosis of patients who receive placebo, but without further details it is not possible to interpret this statement. Multi-way and probabilistic sensitivity analyses to explore the combined impact of uncertainty in several parameter values are not considered within the company submission, although the model appears capable of this.

7.4 Critique of the company's economic evidence

It is not possible to judge whether or not the base case analysis represents the most plausible estimate of the cost-effectiveness of etanercept based on the information provided in the company submission. There are several limitations of the economic evidence provided in the company submission and in the model that has been supplied, including:

- A lack of detail regarding the modelling methods, including the extrapolation of the short term efficacy and utility data over a 10-year horizon
- Uncertainty around whether the parameter values in the model for the paediatric population other than the PASI response rates have been adequately amended from those that were used in the adult model. For example, it appears that the utility data in the model relate to trials of adult populations; and adverse events appear to be based on adult study populations. This is not discussed in the submission.
- Etanercept appears to be costed on the basis of 25mg per week. The impact of increasing the cost to that of the maximum permissible weekly dose of 50mg has not been explored. In the clinical trial, 44% of patients received the maximum dose of 50mg per week and 56% received a weekly dose of 0.8mg per kilogram. The median weight of all patients in the trial was around 60kg[17], which based on a dose of 0.8mg per kilogram per week would have equated to a median dose that approaches 50mg per week. The model that has been provided appears to be very sensitive to the assumed weekly cost of etanercept.
- Use of PASI 50 at 12 weeks as the threshold for further treatment. The 2006 HTA report, that supported the NICE technology appraisal of etanercept in adults, noted that some clinicians would not consider PASI 50 as an adequate threshold of response[20].
- Use of efficacy data from the entire phase III trial population in the base case analysis. The phase III trial recruited patients aged 4-17 years, with moderate to severe plaque psoriasis and with previous or current treatment with phototherapy or systemic psoriasis therapy or psoriasis considered by the

investigator as poorly controlled with topical therapy[17]. In contrast, the licensed indication is for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies[1]. At most, only 57% of the trial population met the subsequent licensed indication, based on their treatment history[17].

- Lack of detail regarding the model outputs for the base case and sensitivity analyses, and inability to verify the results presented in the company submission. The company submission states that etanercept dominates placebo/non-systemic treatment, but the model that has been provided appears to report positive incremental cost effectiveness ratios (ICER) of the order of £1-2,000/quality adjusted life year (QALY) gained.

7.5 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published evidence on the costs effectiveness of etanercept in the treatment of chronic, severe plaque psoriasis in children and adolescents.

The company submission makes reference to "A recent economic evaluation of TNF-α inhibitors for the treatment of adults with chronic plaque psoriasis found that estimates of incremental cost-effectiveness for etanercept 50mg once weekly were £4,171 per QALY gained. An indirect comparison suggests that etanercept is at least as effective in children and adolescents as in adults (PASI 75: 57% versus 34 to 49%, respectively) at a dose less than or equal to the adult dose. This leads to the conclusion that, due to the lower or equal dose, etanercept is at least as cost-effective in children and adolescents as in adults." However, the cited reference[22] does not appear to relate to etanercept dosed at 50mg once weekly, and an ICER of £4,171 per QALY gained is not reported.

8.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

8.1 Methods

The company submission reports that, based on 2007 Office for National Statistics data, there are 376,400 people aged eight to seventeen years in Wales, which is equivalent to 5.01% of the UK population in this age range[2]. Reportedly based on these data and a range of other sources, including the NICE Technology Appraisal of efalizumab and etanercept, and the baseline characteristics of patients enrolled in the pivotal phase III trial of etanercept, the company estimates that there are 176 patients in Wales who meet the licensed indication for etanercept, and two new cases each year[2].

Estimation of the uptake of etanercept in Wales in each of the next five years is based on 5.01% of the company estimates of uptake for the UK as a whole. The UK estimates of uptake are commercial forecasts. In the first year, the company estimates there will be two patients eligible for etanercept treatment in Wales, rising to nine in year 5[2].

The estimates of net budget impact provided by the company relate to the drug acquisition costs for etanercept, plus the costs of two outpatient visits (one for initial prescription and one for assessment of response at 12 weeks) per 24-week treatment period. No displaced alternative medicines are considered. The annual per patient costs of etanercept treatment are based on the assumption of two 24 weeks treatment periods and a one-month treatment holiday, amounting to £8,824 per patient.

8.2 Results

The annual budget impact estimate included in the company submission is summarised in Table 1. No further scenario or sensitivity analyses have been provided.

Table 1. Annual budget impact estimate for each of the next 5 years

Year	1	2	3	4	5
Predicted uptake	2	3	5	6	9
Annual cost per patient	£8,824	£8,824	£8,824	£8,824	£8,824
Estimated annual cost to NHS Wales	£17,648	£26,472	£44,120	£52,944	£79,416

The company submission also reports results from a US database study[23], which compared the resource use and costs for 186 patients treated with biologic agents for six months against their non-biologic treatment in the previous six months. The study suggests that the use of biologic treatment in severe psoriasis significantly increased drug costs but significantly reduced resource use associated with hospitalisations and outpatient visits, such that the overall costs of treatment with biologic agents is numerically but not significantly greater than with non-biologic treatment[23]. A further study is also cited to suggest that clinical measures of the severity of psoriasis may not adequately capture the impact of the condition, and that patients with low quality of life make greater use of healthcare resources than patients with higher quality of life[24]. Etanercept has been observed in the pivotal phase III trial to improve HRQoL compared with placebo treatment[17].

8.3 Critique

The budget impact estimates are based upon company commercial forecasts of uptake of etanercept in the UK. It is assumed implicitly that, as there are no other medicines licensed specifically in this patient group, there are no comparator medicines and so the company's estimates of budget impact do not consider displaced medicines. The extent to which other direct costs associated with hospitalisations and outpatient visits will be offset in clinical practice is uncertain.

8.4 Comparative unit costs

There are no other licensed medicines in this specific patient group. The company submission indicates that the acquisition cost of etanercept at the maximum dose of 50mg once weekly for 24 weeks is £4,290. Including an assumed two outpatient visits (one for initial prescription and one for assessment of response at 12 weeks), the cost is £4,412[2]. Per patient annual costs are estimated by the company as in Table 1.

9.0 ADDITIONAL INFORMATION

9.1 Shared care arrangements

Etanercept should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of paediatric plaque psoriasis. This product would not be deemed suitable for shared care.

9.2 Ongoing studies

Publication of efficacy and safety data from an extension to the paediatric psoriasis study is likely to be during the latter quarter of 2010. See also section 9.4.

9.3 Previous NICE advice

In 2006 NICE recommended the use of etanercept in adult patients with plaque psoriasis when it met the following criteria: (1) in those patients with severe disease defined as a total PASI score of 10 or more and a DLQI of more than 10 and (2) the psoriasis had failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA; or the person is intolerant to, or has a contraindication to, these treatments. Etanercept was to be discontinued in patients whose psoriasis had not responded adequately (defined as a 75% reduction in PASI score from when treatment was started [PASI 75] or a 50% reduction in PASI score [PASI 50] and a five point reduction in DLQI from when treatment started) at 12 weeks with further treatment cycles not recommended in these patients (NICE TA103)[3].

NICE is currently considering a proposal for a Single Technology Assessment of etanercept for the treatment of plaque psoriasis in children (20th wave)[25].

9.4 Other information

- The British Association of Dermatologists holds a Biological Interventions register (BADBIR) to evaluate the long-term safety of biological agents used to treat psoriasis. This register currently holds information on adults but the European Public Assessment Report (EPAR) reports that the market authorisation holders are in consultation with the BADBIR investigators regarding the possibility of including paediatric patients receiving etanercept onto the register[5]. However the company note that the data will be of limited value to this licensed population as patients are over 16 years of age.

- A patient organisation submission by the Psoriasis and Psoriatic Arthritis Alliance and Centre for Equality and Human Rights were provided.

- Medical expert views were provided.

GLOSSARY

Children's Dermatology Life Quality Index (CDLQI)
The CDLQI is a 10-item questionnaire completed by the patient that measures the effect of all skin diseases, including psoriasis, on quality of life. Each question is then scored according to response from zero (no effect) to three (affected very much). Hence the higher the overall score the greater the impact on quality of life[26].

EQ-5D:
This is a measure of health status for use in evaluating health and healthcare. It describes health status according to five dimensions and provides a simple descriptive profile generating a single index for health status on which full health is assigned to a value of one and death a value of zero. It has been specifically designed to complement other quality of life measures[27].

Incidence:
The rate at which new cases occur in a population during a specified period[28].

Psoriasis area and severity index (PASI) score:
PASI is a measure of overall psoriasis severity and coverage that assesses BSA and erythema, induration and scaling in four anatomical regions (head, trunk, arms and legs). Scores range from 0 to 72, a score of 10 or more has been shown to correlate with a number of indicators commonly associated with severe disease such as need for hospital admission or use of systemic therapy and reflects the minimal level of disease severity required for patient inclusion in most of the clinical trials of biologic therapies to date[16]. Though commonly used in clinical trials it is rarely used in clinical practice. PASI is typically measured at baseline, during and at the end of the clinical trial. It can be measured as a percentage improvement, a 75% improvement in the PASI score (PASI 75) is predominantly used to document effectiveness of individual therapies and is recognised by the European Medicines Agency (EMEA) as an indicator that severe psoriasis has responded to treatment. PASI is considered to be less sensitive when the BSA involvement is below 10%[4].

Physicians global assessment score (PGA):
PGA is a tool used to measure overall psoriasis severity[4] relative to baseline. In the paediatric study the score ranged from 0 (clear) to 5 (severe psoriasis). A score of ≥ 3 indicating moderate to severe psoriasis[17].

Prevalence:
The proportion of a population that are cases at a point in time[28].

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Appendix 1. Additional Clinical Information

British Association of Dermatologists
Recommendations: Eligibility criteria for biologic therapy (abbreviated)

Following careful assessment of associated risks and benefits:

Must have severe disease defined as a PASI score of 10 or more (or BSA of ≥10%) and a DLQI >10. In exceptional circumstances patients with severe disease may fall outside this definition but should be considered for treatment
AND
Fulfil at least one of the following clinical categories:

- Phototherapy and alternative standard systemic therapy are contraindicated or cannot be used due to development of or risk of developing, treatment related toxicity
- Are intolerant to standard systemic therapy
- Are unresponsive to standard systemic therapy
- Have significant co-existent unrelated co-morbidity which precludes use of systemic agents
- Have severe, unstable, life-threatening disease

Further details can be found in the full guidelines[16].

Table 1A. Prospective study of etanercept in paediatric plaque psoriasis

Ref	Study type	No. patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimens	Outcomes (etanercept versus placebo)
Paller A et al 17	**Three stages:** **Stage (1):** RCT, DB, placebo-controlled, multicentre (US & Canada) with option to enter escape arm (OL etanercept) from week 4 if disease progression (12 weeks duration) **Then, Stage (2):** OL treatment period with option to withdraw from study or enter an incomplete responder arm† (24 weeks duration) **Then, Stage (3):** Randomised, DB withdrawal-retreatment period (12 weeks duration)	**Stage 1:** n =211(ITT) (105 placebo, 106 etanercept) **Stage 2:** n =208 (34/103 placebo and 25/105 etanercept patients were incomplete responders) **Stage 3:** n =138 (40/69 placebo and 55/69 etanercept patients completed blinded treatment in withdrawal stage)	**Inclusion:** • Age: 4 to 17 years • History of stable moderate to severe plaque psoriasis (defined as sPGA ≥ 3, PASI score of ≥ 12 and BSA involvement ≥ 10% for ≥ 6 months at time of randomisation) • Current or past treatment with phototherapy or systemic psoriasis therapy and/or be considered poorly controlled with topical psoriasis therapy* **Exclusion:** • Presence of guttate, erythrodermic or pustular psoriasis/other skin conditions • Chronic or recurrent active infection within 6 months of screening • Recent (within 2 weeks) or current use of systemic or topical (excl. topical steroids) psoriasis therapy† • Current use of PUVA, UVA or UVB therapy • Recent receipt (within 12 weeks) of live vaccine • IDDM • Demyelinating disease • History of cancer	• Median age 13 years (4 to 17) • 36% aged 4 to 11 years • 64% aged 12 to 17 years • 49% Female • 75% Caucasian • Median duration of psoriasis of 5.9 years (0.3 to 17.9) • Median affected BSA of 20% (10 to 95) • Median PASI score of 16.4 (12 to 56.7) • 99% PGA ≥ 3 • 57% prior systemic or phototherapy • 9% psoriatic arthritis	Etanercept 0.8mg/kg (up to maximum of 50mg) QW (stages 1, 2 and 3) versus placebo for phases 1 and 3 only.	**Primary efficacy endpoint (ITT)§:** **PASI 75 response at week 12:** 57% versus 11%; p <0.001 **Secondary efficacy endpoints:** **PASI 50 response at week 12:** 75% versus 23%; p<0.001 **PASI 90 response at week 12:** 27% versus 7%; p<0.001 **Clear/almost clear status of sPGA at week 12:** 53% versus 13%; p<0.001 **% mean improvement from baseline in CDLQI at week 12:** 52% versus 18%; p<0.001

BSA: body surface area; CDLQI: children's dermatology life quality index; DB: double-blind; IDDM: insulin-dependent diabetes mellitus; ITT: intention-to-treat; OL: open label; PASI: psoriasis area and severity index; QW: once a week; RCT: randomised controlled trial; sPGA: static physician global assessment

* persistence of moderate to severe psoriasis (at least moderate erythema, induration and scaling over clinically significant part of body) despite current or previous course of ≥ 6 weeks duration of at least moderate potency corticosteroids or vitamin D analogue.

† subjects who entered the incomplete responder arm (phase 2) could be treated with topical standard of care such as vitamin A and vitamin D analogues, calcineurin inhibitors and mild to moderate potency corticosteroids

§ subjects who entered the escape arm (OL etanercept if disease progression) or who had missing data were considered treatment failures from the time this occurred.

Appendix 2. Additional Health Economic Model Information

Table 2A. Health economic model detail[2]

Base Case Model		Appropriate?
Comparator(s)	Etanercept compared against placebo	Yes – no other medicines licensed in this specific age group. Assume placebo and etanercept recipients both also receive non-systemic therapies
Population	Modelled population stated to reflect the licensed indication. It is reported that patient-level data from the pivotal phase III trial has been used.	Stated population meets licensed indication. But note the discrepancy between the trial population[17] and the licensed indication[1] (see Efficacy below) and the use of a lower dose of etanercept (25mg per week) in the model
Model type and description	Markov model with 4-week cycle length.	Model type appropriate but unclear whether the modelled pathway is fully appropriate. The model permits patients who achieve a PASI 50 response or more to continue on etanercept treatment, but it is unclear whether or not this would happen in practice, where a PASI 75 may be required for continued use of etanercept (see section 8.4). The model appears to have been developed originally for the adult indication, and efficacy values (PASI response rates) have been overwritten with data derived in children. However, it is not clear which, if any, other input parameters have been amended (see section 8.4)
Perspective	Considers direct medical costs only, from perspective of NHS Wales	Yes
Time Horizon	10 year	Yes – is in line with the NICE technology appraisal of efalizumab and etanercept in the treatment of adult psoriasis patients[3]
Discount rate	3.5% per annum	Yes
Efficacy	Pivotal phase III trial in children and adolescents with moderate to severe plaque psoriasis	Yes, as this provides the pivotal efficacy data. But note that this trial recruited patients aged 4-17 years, with moderate to severe plaque psoriasis and with previous or current treatment with phototherapy or systemic psoriasis therapy or psoriasis considered by the investigator as poorly controlled with topical therapy[17]. In contrast, the licensed indication is for the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies[1]. At most, only 57% of the trial population met the subsequent licensed indication, based on their treatment history[17]; however, the model uses efficacy data based on the entire trial population.
Adverse effects	Are included in the model but appear to relate to adverse events in several adult studies rather than the privotal study in children and adolescents	Unclear why adverse events from the pivotal study in the relevant population were not used
Utility values	Utility weights have been mapped from an adult version of a validated HRQoL instrument, and appear to be adult-based values.	No - relies upon a mapping exercise from the adult HRQoL instrument to utility weights being applicable to the children in the pivotal trial (see section 8.4)
Resource use	Drug use reportedly based on pivotal trial, but appears to be based on 25mg per week. Other resource use based on clinical guidelines and the literature	It is not clear that the drug doses and costs used in the model relate specifically to those used in the paediatric population
Unit costs	Based mainly on published unit costs and BNF	Yes
Model Provided?	Yes	Model was subsequently provided at request of WMP