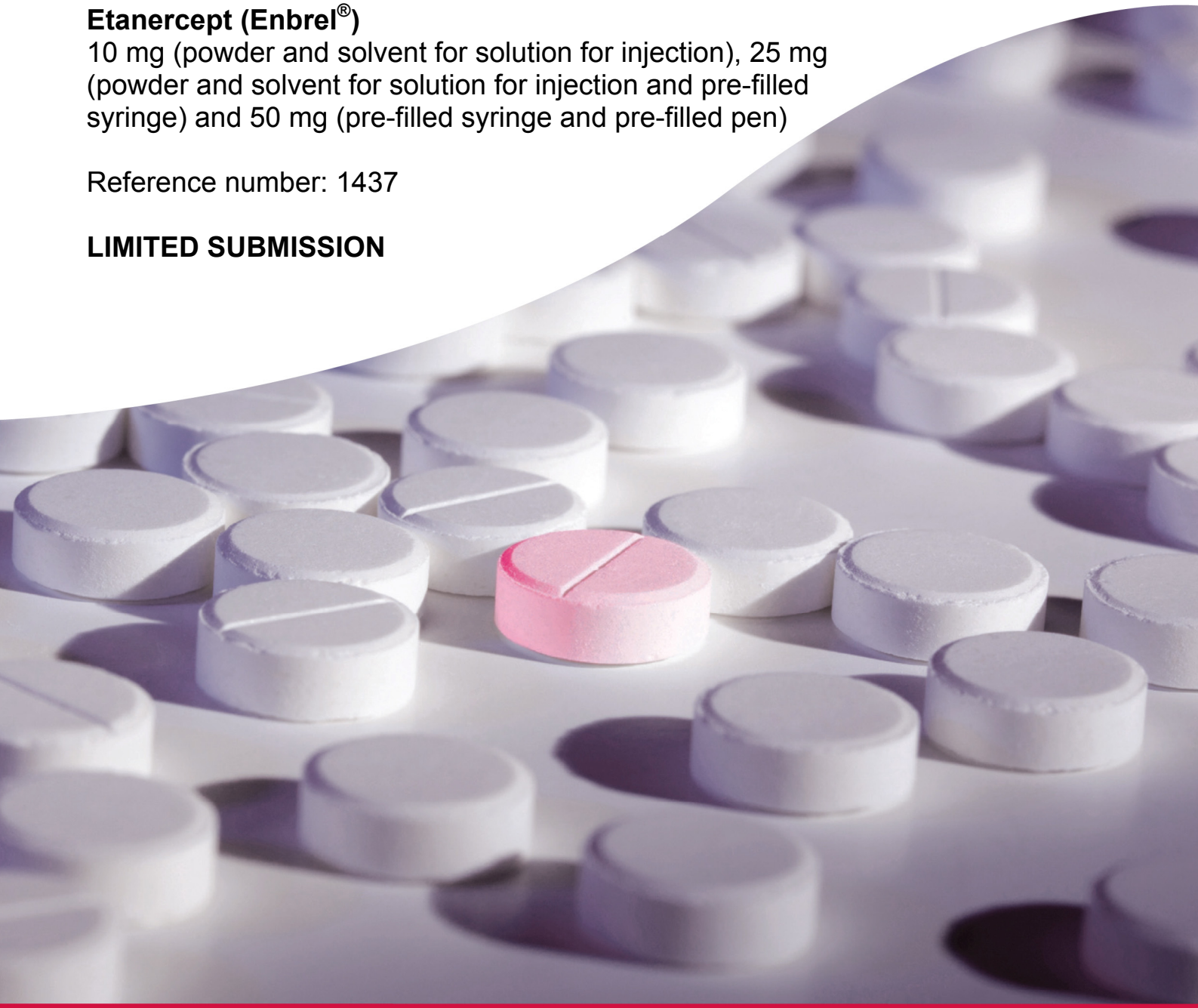
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Etanercept (Enbrel®)
10 mg (powder and solvent for solution for injection), 25 mg (powder and solvent for solution for injection and pre-filled syringe) and 50 mg (pre-filled syringe and pre-filled pen)

Reference number: 1437

LIMITED SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Etanercept (Enbrel®) 10 mg (powder and solvent for solution for injection), 25 mg (powder and solvent for solution for injection and pre-filled syringe) and 50 mg (pre-filled syringe and pre-filled pen)

This assessment report is based on evidence from a limited submission by Pfizer Ltd on 7 June 2013[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Etanercept (Enbrel®) for the treatment of: • polyarthritis (rheumatoid factor positive or negative) in children aged 2 to < 4 years* and extended oligoarthritis (eoJIA) in children and adolescents ≥ 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate; • psoriatic arthritis (PsA) in adolescents ≥ 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate; • enthesitis-related arthritis (ERA) in adolescents ≥ 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.
Marketing authorisation date	31 July 2012 (etanercept was licensed for the treatment of polyarticular juvenile idiopathic arthritis [JIA] in patients aged ≥ 4 years on 3 February 2000 and for patients aged ≥ 2 years on 24 August 2011)[2,3].
Comparators	The comparators included in the company submission were adalimumab (Humira®) and tocilizumab (RoActemra®).
Limited submission details	Etanercept (Enbrel®) for the above indication met the following criterion for eligibility for a limited submission: • A minor licence extension.
**National Institute for Health and Care Excellence Technology Appraisal 35 (TA35) covers etanercept for the treatment of children with polyarthritis aged ≥ 4 years*[4]	

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

Following the recategorising of polyarticular JIA by the International League of Associations for Rheumatology (ILAR), subjects previously classified as having polyarticular JIA are now classified as having polyarthritis (rheumatoid factor positive [RF+] or negative [RF−])[5]. Furthermore, etanercept has had an extension to its JIA licence to include individual JIA subtypes: extended oligoarthritis (eoJIA), psoriatic arthritis (PsA) and enthesitis-related arthritis (ERA)[5]. This report will focus on etanercept treatment of children aged 2 to < 4 years of age with polyarthritis (RF+ or RF−) who fall outside National Institute of Health and Clinical Excellence (NICE) Technology Appraisal 35 (TA35) (see Section 2.4)[4], and also the individual JIA subtypes mentioned above.

The company submission included a subgroup analysis of a registry of patients with polyarticular JIA (study 20021626[6]) and a study of etanercept in patients with the subtypes of JIA mentioned previously (study 3338[5])[1]. The company also highlighted an open-label study of etanercept (study 20021618[5]). The primary objective of this cumulative dataset (study 20021618[5]) was to evaluate the long-term safety of

etanercept in adults as well as paediatrics. Patients in this study however were aged > 4 years and were not identified by JIA subtype; this study is therefore not discussed further.

An interim analysis of a study of adalimumab in children with JIA[7] was provided as supporting evidence. Evidence for the use of tocilizumab in this indication was provided by the company from a non-systematic review of the published literature.

2.1 Use of etanercept in patients aged 2 to < 4 years with polyarticular JIA

Study 20021626 was a phase IV, open-label, multicentre registry, which included children and adolescents aged 2–18 years with a diagnosis of systemic, polyarticular or pauciarticular juvenile idiopathic arthritis (JIA)[6]. The objective of the registry was to compare the long-term safety of etanercept alone, methotrexate alone and etanercept plus methotrexate (n = 594); efficacy data was however also reported. A subgroup analysis studied 39 children aged 2 to < 4 years with polyarticular JIA at the time of enrolment, assigned at baseline to either methotrexate (n = 22), etanercept (n = 4) or etanercept plus methotrexate (n = 13). Patients with systemic JIA were not included. At the three-year endpoint, 25 discontinuations had occurred; eight out of 16 patients that discontinued from the methotrexate arm were reassigned to receive either etanercept (n = 2) or etanercept plus methotrexate (n = 6). The number of discontinuations from the etanercept only arm and the etanercept plus methotrexate arm were two and seven respectively. The most common reasons for discontinuation were "insufficient therapeutic effect" and "other". The mean improvement (± standard deviation) in the Physician Global Assessment (PGA) of overall disease activity (see Glossary), determined at three years, was 66.7% (42.5) for methotrexate (n = 5), 91.7% (16.7) for etanercept alone (n = 4) and 89.6% (23.4) for etanercept plus methotrexate (n = 12). At year 1, when there were more subjects with available PGA data, the mean percentage improvement in the PGA was 26.0% (85.1) for methotrexate (n = 11), 62.5% (28.5) for etanercept alone (n = 4) and 68.5% (34.8) for etanercept plus methotrexate (n = 16). The safety profiles from the different treatment arms were similar, with no significant difference in exposure-adjusted rates of adverse events (AEs). No deaths occurred during the study[6] .

2.2 Use of etanercept in patients with subtypes of JIA

Study 3338 is a phase IIIb, single-treatment, open-label, two-part, multicentre study of etanercept for the treatment of eoJIA in children and adolescents ≥ 2 years (n = 60), ERA in adolescents ≥ 12 years (n = 38) and PsA in adolescents ≥ 12 years (n = 29)[5]. Only results from the first part of the study, a 12-week assessment of the clinical benefit of etanercept[8], are made available and are discussed below. The second part of this study is ongoing and is designed to assess mainly the long-term safety of etanercept up to 96 weeks.

Results for the primary endpoint (American College of Rheumatology pediatric 30 response [ACR Pedi 30] at week 12) were compared with rates from historical placebo controls, derived from a meta-analysis of six JIA studies (see Table 1)[9]. In the overall population, 109/123 subjects (88.6%; 95% confidence interval [CI]: 81.6%, 93.6%) achieved an ACR Pedi 30 response at week 12[5].

Table 1. Response rates for etanercept at week 12 from study 338 compared to historical placebo controls[5]

Treatment arm	ACR Pedi 30 response rate for etanercept-treated subjects (% [95% CI])	ACR Pedi 30 response rate for historical placebo-treated subjects (95% CI)	Pooled odds ratio for etanercept-treated subjects versus historical placebo-treated subjects (95% CI)†
eoJIA	52/58 (89.7% [78.8, 96.1%])	28.9% (24.0, 34.2%)	24.27 (10.1, 58.5)
ERA	30/36 (83.3% [67.2, 93.6%])	28.9% (24.0, 34.2%)	14.00 (5.6, 34.8)
PsA	27/29 (93.1% [77.2, 99.2%])	28.9% (24.0, 34.2%)	37.80 (8.8, 162.4)

ACR Pedi 30: American College of Rheumatology pediatric 30 response; eoJIA: extended oligoarticular juvenile idiopathic arthritis, ERA: enthesitis-related arthritis; PsA: psoriatic arthritis; CI: confidence interval
†pooling of six historical studies as one in the unadjusted logistic regression model.

Since the lower bound of the CI for the odds ratios was > 1, the response rates for etanercept were significantly higher than the placebo controls[5].

The ACR Pedi 30 response rate from a historical etanercept study (study 16.0016) in subjects (n = 58) aged 4–17 years with polyarticular-course JIA was 73.9% (95% CI: 63.6%–84.3%). The company states in their submission that odds ratio analysis showed that this rate was comparable with the response rates for the different JIA subtypes in study 3338[5].

There were five discontinuations during the first part of study 3338 (eoJIA = 2; ERA = 2; PsA = 1); four were due to AEs (two were due to treatment-emergent infections; two were due to non-infectious treatment-emergent AEs). There were five discontinuations during the first part of study 3338 (eoJIA = 2; ERA = 2; PsA = 1); four were due to AEs (two were due to treatment-emergent infections; two were due to non-infectious treatment-emergent AEs). Serious AEs (SAEs), including three serious infections, occurred in four subjects (3.1%). No deaths occurred during study 3338[5].

2.3 Supporting studies

The company stated that direct comparison of etanercept-treated and adalimumab-treated patients aged 2 to < 4 years with polyarticular JIA was not possible due to differences in the study groups treated[1]. The company however highlighted an interim analysis of a phase IIIb, open-label, multicentre study analysing the efficacy of adalimumab in patients aged 2 to < 4 years and in patients ≥ 4 years weighing < 15 kg with moderate to severe JIA (n = 32)[7]. Concomitant methotrexate was permitted. The number of patients that achieved an ACR Pedi 30 response at week 24 was 27/32 (84.4%; with non-responder imputation). SAEs occurred in 5/32 (16%) of patients[7].

The company identified a phase III study evaluating the efficacy and safety of tocilizumab in patients aged 2–17 years with JIA (RF+ or RF-) or eoJIA. (n = 163). Patients continued concomitant treatment with NSAIDs, corticosteroids and methotrexate. The proportion of patients achieving ACR Pedi 30 at week 16 was 168/188 (89.4%). SAEs occurred in 17/188 (9%) of patients[10].

2.4 Points to note

- Etanercept for the treatment of polyarthritis (RF+ and RF−) in children aged ≥ 4 years meets the All Wales Medicines Strategy Group (AWMSG) exclusion criteria due to the availability of NICE TA35 for children previously categorised as having polyarticular JIA in this age group[4].
- Adalimumab is not licensed for the subtypes under consideration in this appraisal, but is indicated (in combination with methotrexate) in the treatment of active polyarticular JIA in children and adolescents aged 2–17 years, and can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. There is however no direct head-to-head data for comparison of etanercept and adalimumab.
- Tocilizumab is not licensed for all JIA subtypes but is indicated for the treatment of polyarthritis RF+ or RF− and eoJIA in patients aged ≥ 2 years who have responded inadequately to methotrexate[11]. Due to significant differences between the study designs and study groups of the etanercept and tocilizumab trials an indirect comparison of the efficacy of the two treatments was not possible.
- Committee for Medicinal Products for Human Use (CHMP) reported that the registry data for children with polyarticular JIA provides an acceptable level of support for efficacy of etanercept in children aged 2 to < 4 years and is similar to that seen in the whole population aged 2–18 years[6]. In addition, CHMP also reported that, whilst there is no etanercept pharmacokinetic data for JIA subjects aged 2 to < 4 years, etanercept exposure for this age group is expected to be in the same range as JIA subjects aged 4–17 years; a group for which etanercept pharmacokinetics data is available[6].
- The safety data from study 3338 did not demonstrate any new or unexpected signals in children with the JIA subtypes licensed. CHMP concluded that, in view of the unmet need for subjects with the JIA subtypes of eoJIA in patients aged ≥ 2 years, ERA in adolescents aged ≥ 12 years and PsA in adolescents aged ≥ 12 years, who are unresponsive to methotrexate or are intolerant to methotrexate, the advantages of etanercept treatment outweigh the safety concerns[5].
- CHMP stated that it is uncertain whether anti-tumour necrosis factor treatments can prevent patients with ERA progressing to axial disease. Post-marketing experience identified 23 deaths and 11 malignancies in patients aged < 18 years that had received etanercept, and analysis of background rates of malignancy suggested a potential increased risk of malignancy in paediatric patients with JIA. CHMP state that data expected from the ongoing 3338 trial should provide further information concerning unfavourable effects of etanercept, including infection, opportunistic infection, injection site reactions and bone marrow suppression. Further information is being collected from long-term studies to inform the decision on when to cease treatment in responding subjects[5]. Discontinuation of treatment with etanercept should be considered for JIA patients showing no response after four months[2].
- The 10 mg etanercept vial is a new strength specifically licensed for paediatric use where doses are ≤ 10 mg; however, it is the same formulation type as the 25 mg vial, which was used in trial 3338[2,12].
- In July 2012, the European Medicines Agency (EMA) approved a new dosing option which allows once-weekly treatment with etanercept; this option is licensed for paediatrics receiving treatment with etanercept up to a maximum of 50 mg per dose[3]. The company however state in their submission that if a dose of 0.4 mg/kg is used, it is assumed that etanercept will be given twice-weekly.

- Adalimumab is administered as a single dose every other week via subcutaneous injection[13]. Tocilizumab is given as an intravenous infusion over 1 hour, once every four weeks[14]. Differences in the preparation and frequency of administration of adalimumab, tocilizumab and etanercept treatments may influence prescribing preference[2,13].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The budget impact evidence presented by the company includes a simple comparison of the annual costs associated with the use of: etanercept, tocilizumab and adalimumab for the treatment of polyarticular JIA, and etanercept and tocilizumab for eoJIA. The costs of using etanercept only for PsA and ERA subtypes are also given. The company has estimated the number of patients with each JIA subtype. These figures are based on an estimate of the prevalence of JIA in Caucasian populations across Europe and North America[15], Welsh population estimates of patients aged 2–18 years[16], the proportions of patients with the different subtypes of JIA from diagnoses in Wales[17] and figures from a study regarding the response of JIA patients with different subtypes to methotrexate[18]. The company estimates that approximately 24 patients will receive etanercept, leading to a total annual cost of £161,733.

3.2 AWTTC critique of the budget analysis

- The low prevalence of JIA and wide range of estimates of the proportion of children and adolescents with the disease (0.003%–0.1%)[15,17] leads to uncertainty in the estimated patient numbers[17,18]. The use of Welsh data however is considered to be valuable.
- It is anticipated by the applicant company that both etanercept (Enbrel®) and adalimumab (Humira®) will be supplied by a home healthcare provider. Associated costs per patient per year for tocilizumab (RoActemra®) for outpatient administration or for day case administration have been provided by the applicant company using information from the public domain[19].
- No head-to-head comparative data or indirect comparative analysis of the treatments was available thus therapeutic equivalence of these treatments has not been proven.

3.3 Comparative unit costs

Table 2 provides comparative annual acquisition costs for etanercept 10 mg powder and solvent solution for injection for paediatric use, etanercept 25 mg powder and solvent for solution for injection for paediatric use, etanercept 25 mg pre-filled syringe, etanercept 50 mg solution for injection (pre-filled syringe and pre-filled pen) and adalimumab 40 mg/0.8 ml solution for injection for paediatric use. Additionally costs are provided for tocilizumab based on the number and type of vials (80 mg, 200 mg and 400 mg) needed to deliver the recommended dose.

The company state in their submission that the 10 mg vial is likely to be a cheaper option for those children whose weight is 25 kg or below; since availability of the 10 mg paediatric etanercept vial offers cost savings versus the 25 mg vial for patients aged 2–8 years, due to reduced wastage[1]. Patients who weigh more than 62.5 kg are eligible for either a twice-weekly 25 mg pre-filled syringe or once-weekly 50 mg pre-filled syringe or pen[1].

Table 2. Example of annual acquisition costs for etanercept and relative comparators

Medicine*	Example regimen	Cost of medicine per patient per year†
Etanercept (Enbrel®) 10 mg (powder and solvent for solution for injection)	≤ 10 mg (dosed by weight) twice-weekly for children aged ≥ 2 years and weighing ≤ 25kg	£3,718
Etanercept (Enbrel®) 25 mg (powder and solvent for solution for injection)	20-25 mg (dosed by weight) once weekly for children weighing 25 kg to 31.25 kg	£4,648
Etanercept (Enbrel®) 25 mg (powder and solvent for solution for injection)	> 10–25 mg (dosed by weight) twice-weekly for children weighing > 31.25 kg to < 62.5 kg	£9,295
Etanercept (Enbrel®) 25 mg (pre-filled syringe)	25 mg twice-weekly for children weighing ≥ 62.5 kg	£9,295
Etanercept (Enbrel®) 50 mg (pre-filled syringe and pre-filled pen)	50 mg once-weekly for children weighing ≥ 62.5 kg	£9,295
Adalimumab (Humira®) 40 mg/0.8 ml (solution for injection),	10–20 mg (dosed by body surface area) every other week for children aged 2 to < 4 years. Up to 40 mg (dosed by body surface area) every other week for children aged 4–12 years	£9,156
Adalimumab (Humira®) 40 mg/0.8 ml (pre-filled syringe and pre-filled pen)	40 mg every other week for children aged 13–17 years	£9,156
Tocilizumab (RoActemra®) 80 mg vials or 200 mg vial	100 mg–200 mg (dosed by weight) every 4 weeks for children aged ≥ 2 years weighing 10 kg to 20 kg	£4,053–£4,719 (£8,655–£9,321)§
Tocilizumab (RoActemra®) 80 mg vial(s) and/or 200 mg vial	200 mg–280mg (dosed by weight) every 4 weeks for children weighing 20 kg to 28 kg	£4,719–£6,050 (£9,321–£10,652)§
Tocilizumab (RoActemra®) 80 mg vial(s) and/or 200 mg vial	280 mg–320 mg (dosed by weight) every 4 weeks for children weighing 28 kg to 40 kg	£6,050–£6,716 (£9,321–£11,318)§
Tocilizumab (RoActemra®) 80 mg vial(s) and/or 200 mg vial and/or 400 mg vial	320 mg–400 mg (dosed by weight) every 4 weeks for children weighing 40 kg to ≤ 50 kg	£6,716–£8,047 (£11,318–£12,649)§
Tocilizumab (RoActemra®) 80 mg vial and 400 mg vial	> 400 mg–480 mg (dosed by weight) every 4 weeks for children weighing > 50 kg to 60 kg	£9,738 (£13,980)§

* All calculations are based on single use only.
† Costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of June 2013[20]
§ Tocilizumab costs include outpatient administration at £1,391 per year or (day care administration at £5,993 per year)[19]
This table does not imply therapeutic equivalence of medicines or the stated doses.
Refer to the Summaries of Product Characteristics for full dosing details[2,12–14,21–23].

Comparative annual costs (medicine costs only) for treating eight patients aged 2 to < 4 years with polyarticular JIA and seven patients with eoJIA are given in Table 3 for etanercept, adalimumab and tocilizumab. Etanercept costs, for four patients with PsA and five patients with ERA would be £37,180 and £46,475 respectively[24].

Table 3. Comparative annual costs of medicines categorised by JIA subtype[24]

	Etanercept	Adalimumab	Tocilizumab†
Eight patients with polyarticular JIA (aged 2 to < 4 years)	£29,744	£73,245	£32,427 (£69,243)
Eight patients with polyarticular JIA (aged 2 to < 4 years). Cost difference versus etanercept	-	£43,501	£2,683 (£39,499)
Seven patients with eoJIA*	£29,745–£48,334	-	£36,361–£55,663 (£68,575–£87,877)
Seven patients with eoJIA. Cost difference versus etanercept	-	-	£6,616–£7,329 (£39,010–£39,543)
*Based on three children aged ≤ 8 years and four children 9–17 years old when presenting for treatment. †Includes outpatient or (day care administration costs)[19]			

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, etanercept (Enbrel®) may be appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that etanercept (Enbrel®) may be supplied by a home healthcare provider.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 2 August 2013.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Physician's Global Assessment (PGA) of disease activity
PGA of overall disease activity may be recorded using a 0–10 scale, a 0–100 mm visual analogue scale or using descriptors such as remission or low, moderate or high disease activity. PGA can take account of the presence of joint pain, duration of morning stiffness, degree of fatigue, functional status, objective evidence of disease activity, mechanical joint problems, presence of extra-articular disease and the presence of radiographic damage[25].

American College of Rheumatology Pediatric 30 (ACR Pedi 30)
A validated measure of disease activity in JIA. The ACR Pedi 30 criteria for improvement are a ≥ 30% improvement from baseline in 3 of any 6 variables in the core set, with no more than one of the remaining variables worsening by > 30%. Variables in the core set consist of 1) PGA of disease activity; 2) parent/patient assessment of overall well-being; 3) functional ability; 4) number of joints with active arthritis; 5) number of joints with limited range of motion; and 6) erythrocyte sedimentation rate[26].

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