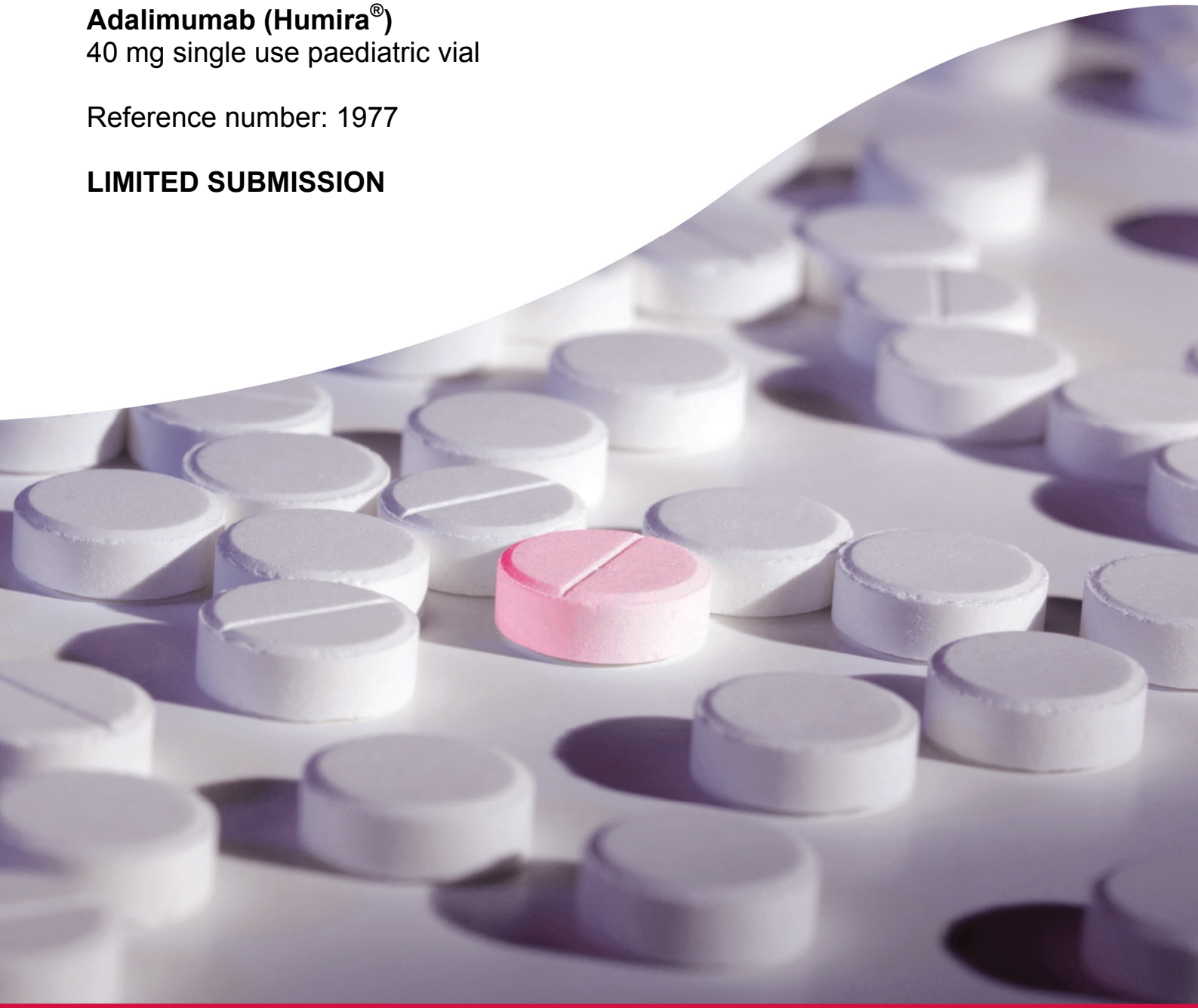
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Adalimumab (Humira®)
40 mg single use paediatric vial

Reference number: 1977

LIMITED SUBMISSION



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

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AWMSG Secretariat Assessment Report
Adalimumab (Humira®) 40 mg single use paediatric vial

This assessment report is based on evidence from a limited submission by AbbVie Ltd on 28 March 2013[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Adalimumab (Humira®) in combination with methotrexate for the treatment of active polyarticular juvenile idiopathic arthritis, in children aged 2 to 4 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has not been studied in children aged less than 2 years[2].
Marketing authorisation date	25 February 2013[1] (licensed on 18 March 2011 in combination with methotrexate for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents aged 4 to 17 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs. Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate[3]).
Comparators	The comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) was etanercept (Enbrel®).
Limited submission details	Adalimumab (Humira®) for the above indication met the following criteria for eligibility for a limited submission: • A minor licence extension.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Summary of evidence

The company submission provides interim details of an open-label, multicentre, phase IIIb trial, M10-444, which compared the efficacy and safety of adalimumab in patients aged 2 to < 4 years old or ≥ 4 years weighing < 15 kg with moderately to severely active polyarticular juvenile idiopathic arthritis (JIA)[1,4]. Patients (n = 32) received adalimumab subcutaneously at a dose of 24 mg/m^2 body surface area (BSA) every other week for a minimum of 24 weeks (maximum of 20 mg/dose). At the completion of 24 weeks, in the United States of America, subjects could continue in the study until reaching the age of 4 and ≥15 kg; whereas in the European Union, patients could continue treatment for a maximum of one year after reaching four years old and weighing ≥ 15 kg[1,4]. Concomitant methotrexate was allowed[4]. The primary objective of this study was assessment of safety. No primary efficacy endpoint was defined[5]. Efficacy was assessed using the pediatric American College of Rheumatology (PedACR) response, with PedACR30/50/70/90 defined as ≥ 30/50/70/90% improvement in at least three of the six JIA core set variables and ≥ 30/50/70/90% worsening in not more than one of the six JIA core set criteria[1,5]. When missing responses were imputed as nonresponders, 84% of patients achieved PedACR30 at week 24[1,4]. Results are outlined in Table 1.

Table 1. PedACR response at week 24[4]

	Response rate: observed (n = 30)	Response rate: NRI (n = 32)
PedACR30, n (%)	27 (90.0)	27 (84.4)
PedACR50, n (%)	25 (83.3)	25 (78.1)
PedACR70, n (%)	22 (73.3)	22 (68.8)
PedACR90, n (%)	11 (36.7)	11 (34.4)
NRI: Nonresponders imputed (includes missing responses imputed as nonresponders) PedACR: Pediatric American College of Rheumatology response		

A total of four patients discontinued from the study; one before week 24 and three after. No patient discontinued due to adverse events (AEs)[1]. Throughout the study, 84.4% of patients reported at least one treatment-emergent AE (TEAE)[5]. Most TEAEs were considered by the investigator to be not related or probably not related to adalimumab. TEAEs considered by the investigator as possibly or probably related to adalimumab occurred in eight patients (25.0%)[5]. The incidence of serious, infectious and serious infectious TEAEs was 16%, 69% and 9%, respectively. No deaths were reported[4].

2.2 Points to note

- In April 2012, the All Wales Medicines Strategy Group (AWMSG) recommended adalimumab (Humira®) in combination with methotrexate as an option for use in NHS Wales for the treatment of active polyarticular JIA, in children and adolescents aged 4 to 17 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs[6].
- The applicant company has not provided evidence to inform a comparison between adalimumab and etanercept. The company state there are no etanercept trial data specific to the population under consideration[1]. At the time of writing, there was no advice available for the use of etanercept in JIA patients aged 2 to 4 years.
- The company submission did not include efficacy or safety outcomes for adalimumab in patients aged 2 to 4 years with JIA beyond 24 weeks. The Committee for Medicinal Products for Human Use (CHMP) has requested that a long-term observation of adalimumab treatment in patients within this age range should be ensured through a registry recording data for at least ten years of observation[5].
- CHMP stated that there were no new safety signals identified in the paediatric JIA trial for patients aged 2 to 4 years. They concluded that the safety data obtained was consistent with prior paediatric JIA studies in patients aged 4 to 17 years[5].
- The licensed dosing schedule for adalimumab requires administration every other week, while patients receiving etanercept are treated once or twice weekly[2,7]. Adalimumab is available in a pre-filled vial and does not need to be reconstituted using powder and solvent for injection[2].
- Ongoing clinical trials are investigating adalimumab as a treatment for non-infectious uveitis, which occurs in around 10–20% of JIA patients. The applicant company suggests that clinicians may prefer to use this treatment for patients with JIA who also suffer from non-infectious uveitis; however, the use of adalimumab in infectious uveitis is not licensed[1].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence[1]

The company reports that there is an estimated 11 patients with active polyarticular JIA in Wales who are aged 2 to 4 years and who would meet the eligibility criteria to

receive adalimumab (i.e. have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs), are intolerant to methotrexate or in whom continued treatment with methotrexate is inappropriate). This is based on an estimated incidence of polyarticular JIA of 15 per 100,000 in England and Wales, taken from the updated National Institute for Health and Care Excellence (NICE) Commissioning guide for biologics[9], and a Welsh population of 71,400 aged 2 to 4 years.

According to the company's submission, adalimumab would cost £9,156 per patient per year, taking into account drug wastage[1]. The dosing of etanercept is based on body weight alone and cost is estimated to be £3,718 per patient per year (assuming average body weight of < 25 kg for patients aged 2 to 4 years). The maximum licensed dose of etanercept in this age group is 25 mg twice weekly[7]; using this dose, the annual cost per patient would be £9,295. Administration costs are not included in these estimates.

Given the reported lack of data regarding the current use of etanercept in this patient population, the company assumed a maximum possible uptake of adalimumab (100%) which is expected to result in a total budget impact of £100,712 in the first year. The company anticipates that this estimate is likely to be reduced in future years as patients lose response or stop therapy due to intolerance[1].

3.2 AWTTC critique of the budget impact analysis

The average body weight of children aged 2 to 4 years in the UK is estimated to be in the range of 12 to 16 kg[10]. The cost of using etanercept could theoretically range from £1,859 to £3,718 per patient per year, although only patients <12.5kg could receive a dose with the lower acquisition cost. Irrespective of this, the company assumes that etanercept is not currently used in this patient group and has estimated the total budget impact of adalimumab based on 100% uptake, giving the maximum possible budget impact for the estimated patient numbers (£100,712 in the first year). Uncertainty is introduced, but not assessed, from a lack of recent Welsh specific data on the prevalence and incidence of polyarticular JIA, and from the omission of incident cases. Budget impact estimates are not provided for subsequent years. The company assumed that adalimumab would be provided via home care service for all patients and, hence, would incur no administration costs. In case of alternative administration arrangements, medicine administration costs could be lower for adalimumab compared to etanercept due to the different administration frequencies[2,7,11].

3.3 Comparative unit costs

Table 2 lists examples of annual treatment acquisition costs for the management of active polyarticular JIA in children aged 2 to 4 years who have had an inadequate response to one or more DMARD.

Table 2. Examples of acquisition costs for adalimumab and etanercept for the treatment of active polyarticular Juvenile Idiopathic Arthritis (JIA).

Treatment	Example dose*	Example annual cost of treatment per patient†
Adalimumab (Humira®) Subcutaneous injection, 40 mg/0.8 ml vials	For patients with polyarticular JIA, aged 2 to 12 years, the recommended dose is 24 mg/m² body surface area up to a maximum single dose of 20 mg adalimumab (for patients aged 2 to <4) and up to a maximum single dose of 40 mg adalimumab (for patients aged 4 to 12) administered every other week via subcutaneous injection. The volume for injection is selected based on the patients' height and weight (See Summary of Product Characteristics [SPC][2]). Reassess if no response within 12 weeks.	**£9,155.64**
Etanercept (Enbrel®) Powder and solvent for solution for injection for paediatric use, 10 mg and 25 mg vials.	The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3 to 4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatment should be considered in patients who show no response after 4 months.	**£3,718§**

* Doses need to be individually tailored based on patient body weight
† Costs are based on MIMS list prices as of 8/04/2013[12]; costs will differ based on response;
§ Etanercept cost is calculated using average body weight range of 12-16kg for 2-4 year old[10]. A lower cost estimate could apply only to patients ≤12.5kg receiving etanercept once weekly. A higher maximum cost of £9,295 per year is theoretically possible for etanercept, based on the SPC[7,11]
This table does not imply therapeutic equivalence of treatments or the stated doses.
See the relevant SPCs for licensed indications and full dosing details[2,7,11]

4.0 ADDITIONAL INFORMATION

4.1 Appropriate place for prescribing

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

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: 5 April 2013 and 9 April 2013
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 AbbVie Ltd. Form C: Limited appraisal submission. Adalimumab (Humira®). 2013.
2 AbbVie Ltd. Humira®. Summary of Product Characteristics. Mar 2013. Available at: http://www.medicines.org.uk/emc/medicine/21201/SPC/Humira+Pre-filled+Pen%2c+Pre-filled+Syringe+and+Vial/. Accessed Apr 2013.
3 European Medicines Agency. Humira®. Procedural steps taken and scientific information after the authorisation. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000481/WC500050869.pdf. Accessed Apr 2013.
4 Kingsbury DJ, Quartier P, Patel G et al. Safety and efficacy of adalimumab in children with active polyarticular juvenile idiopathic arthritis aged 2 to < 4 years or > 4 years weighing < 15 kg. Presented at ACR annual conference.
5 European Medicines Agency. Assessment Report for Humira. Procedure No.: EMEA/H/C/000481/II/0102. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000481/WC500142038.pdf. Accessed Apr 2013.
6 All Wales Medicines Strategy Group. Final Appraisal Recommendation. Advice no. 0812. Adalimumab (Humira®). Mar 2012. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/8. Accessed Apr 2013.
7 Pfizer Ltd. Enbrel®. Summary of Product Characteristics. 2013. Available at: http://www.medicines.org.uk/emc/medicine/19160/SPC/Enbrel+25mg+ml+powder+and+solvent+for+solution+for+injection+for+paediatric+use/. Accessed Apr 2013.
8 European Medicines Agency. Assessment Report for Humira. Procedure No.: EMEA/H/C/000481/II/00081-G. 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000481/WC500106499.pdf. Accessed Apr 2013.
9 National Institute for Health and Care Excellence. Commissioning guides - supporting clinical service redesign. Biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology. 2012. Available at: http://www.nice.org.uk/usingguidance/commissioningguides/biologicaltherapies/home.jsp. Accessed Apr 2013.
10 Royal College of Paediatrics and Child Health. UK-WHO growth charts. 2012. Available at: http://www.rcpch.ac.uk/child-health/research-projects/uk-who-growth-charts/uk-who-growth-charts. Accessed Apr 2013.
11 Pfizer Ltd. Enbrel®. Summary of Product Characteristics. 2013. Available at: http://www.medicines.org.uk/emc/medicine/24761/SPC/Enbrel+10+mg+powder+and+solvent+for+solution+for+injection+for+paediatric+use./. Accessed Apr 2013.
12 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). 2013. Available at: http://www.mims.co.uk/. Accessed Feb 2013.