



All Wales Therapeutics
and Toxicology Centre

Canolfan Therapiwteg a
Thocsicoleg Cymru Gyfan

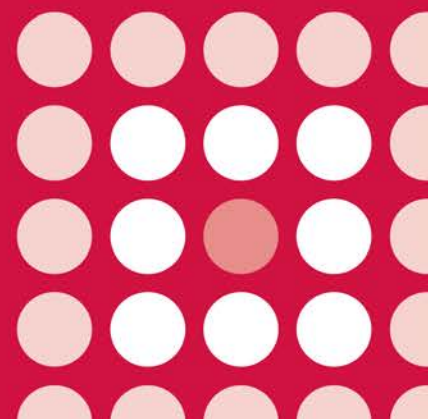
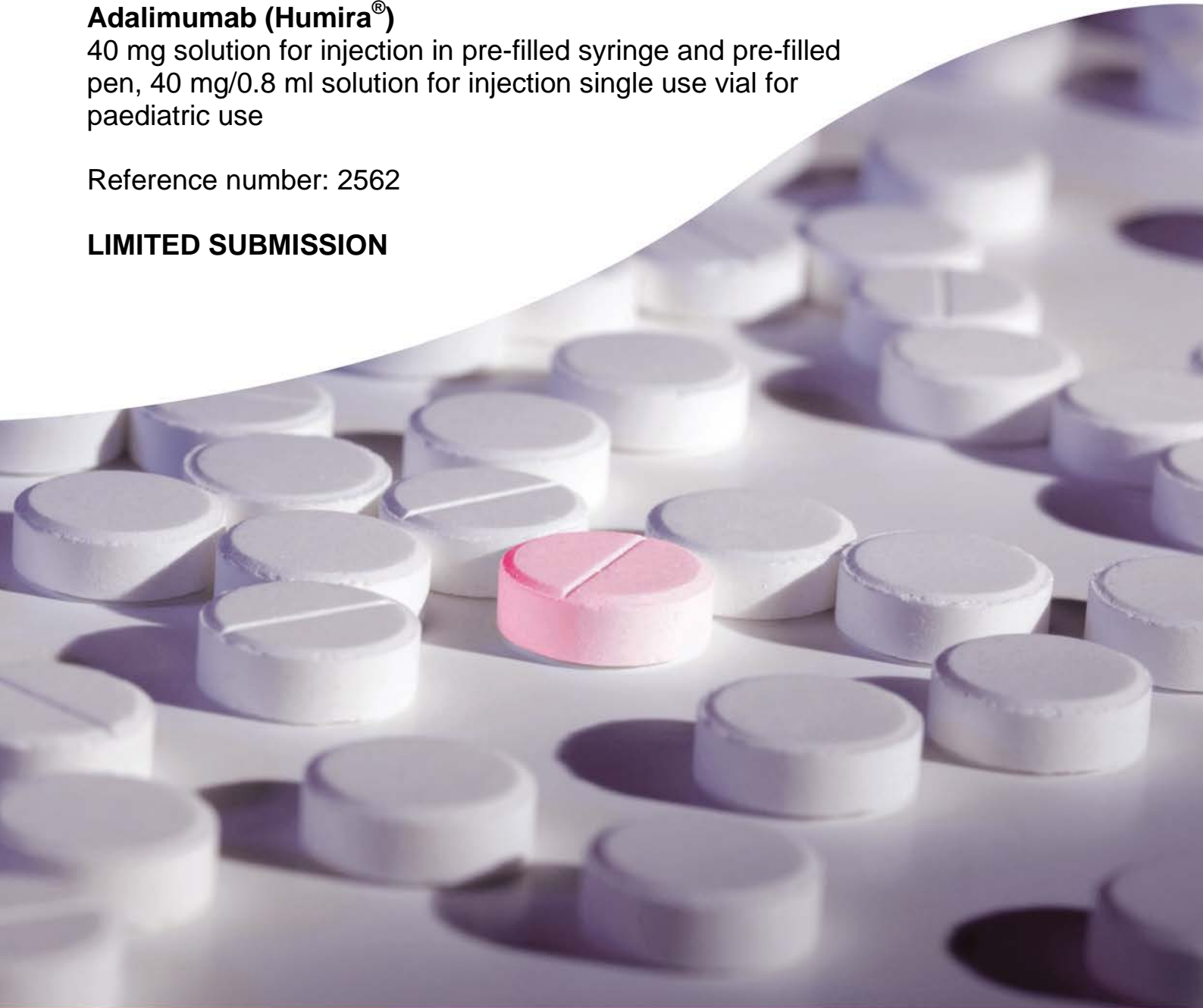
AWMSG SECRETARIAT ASSESSMENT REPORT

Adalimumab (Humira®)

40 mg solution for injection in pre-filled syringe and pre-filled pen, 40 mg/0.8 ml solution for injection single use vial for paediatric use

Reference number: 2562

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.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk

029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Adalimumab (Humira®). 40 mg solution for injection in pre-filled syringe and pre-filled pen, 40 mg/0.8 ml solution for injection single use vial for paediatric use. Reference number: 2562. March 2015.

AWMSG Secretariat Assessment Report
Adalimumab (Humira®)
40 mg solution for injection in pre-filled syringe and pre-filled pen,
40 mg/0.8 ml solution for injection single use vial for paediatric use

This assessment report is based on evidence from a limited submission by AbbVie Ltd on 10 December 2014¹.

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Adalimumab (Humira®) for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy ² .
Dosing	The recommended dose of adalimumab is 24 mg/m ² body surface area up to a maximum single dose of 40 mg administered every other week via subcutaneous injection. Refer to the Summary of Product Characteristics (SPC) for further information ² .
Marketing authorisation date	01 September 2014 ³ (licensed for rheumatoid arthritis in adults on 08 September 2003 ⁴).
Comparators	The comparator included in the company submission was etanercept ¹ .
Limited submission details	Adalimumab (Humira®) for the above indication met the following criteria for eligibility for a limited submission: <ul style="list-style-type: none"> • A minor licence extension • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact • Estimated small difference in cost compared to comparator.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes details of study M11-328 which investigated the efficacy, safety, pharmacokinetics and immunogenicity of adalimumab in paediatric patients with enthesitis-related arthritis (ERA)¹.

This was a 12-week, phase III, randomised, double-blind, placebo-controlled, multicentre, multi-dose study with an ongoing open-label rescue and extension study period of up to a maximum of 144 weeks; interim results are available up to week 52⁵. Patients (n = 46) aged ≥ 6 to < 18 years at baseline with a diagnosis of ERA as defined by the International League of Associations for Rheumatology (ILAR) were randomised 2:1 to receive subcutaneous adalimumab 24 mg/m² body surface area (BSA) up to a maximum of 40 mg administered every other week (n = 31) or matching placebo (n = 15). After 12 weeks, the open-label study commenced and all patients were treated with adalimumab. During the double-blind period, patients who met the criteria for early escape (worsening disease or failure to improve) commenced the open-label period at week 4 or week 8 depending upon when escape criteria were met^{5,6}.

The primary efficacy endpoint was the percent change in the number of active joints with arthritis from baseline to week 12. Pharmacokinetic data were collected during the first 12 weeks and during the open-label phase up to 52 weeks. Adverse events were recorded during the double-blind study and the open-label extension study^{5,6}.

In the intent-to-treat (ITT) analysis set (last observation carried forward [LOCF]) there was a mean percent decrease of -62.6 in the number of active joints with arthritis at week 12 in the adalimumab group compared to -11.6 in the placebo group (difference: -51.17, 95% confidence interval [CI] -99.69 to -2.66, $p = 0.039$)⁶. Sensitivity analysis excluding early escapers (three in the placebo group and four in the adalimumab group) produced a larger decrease of -83.3 in the adalimumab group versus -32.1 in the placebo group (difference: -51.58, 95% CI -93.60 to -9.55, $p = 0.018$)⁵. The improvement was maintained through to week 52 of the open-label study. Secondary endpoints and per protocol analysis were all numerically supportive of the primary ITT endpoint although did not reach statistical significance^{5,6}.

A comparison of the pharmacokinetic results was made with previous polyarticular juvenile idiopathic arthritis (pJIA) data. The Committee for Medicinal Products for Human Use (CHMP) concluded that the pharmacokinetics of adalimumab in paediatric patients with ERA is comparable to that of paediatric patients with pJIA and the chosen dose is considered appropriate⁵.

2.1 Safety

CHMP concluded that adalimumab was generally well tolerated in study M11-328 and the safety profile observed was consistent with previous clinical trials for adalimumab. Long-term data will become available through the open-label extension study and are part of the risk management plan⁵.

2.2 Points to note

- Adalimumab is the only licensed treatment option for ERA in patients in the 6–12 year age group¹. Etanercept is licensed for treatment of patients 12 years and above⁷. A clinical expert consulted by the All Wales Therapeutics and Toxicology Centre (AWTTC) stated that adalimumab may additionally be the most appropriate treatment for children with ERA at risk of uveitis.
- There are no direct comparative data available for adalimumab versus etanercept for the indication under consideration. A robust indirect comparison would not be feasible due to differences between the study designs and endpoints of the adalimumab and etanercept trials¹.
- In the pivotal study M11-328, CHMP noted that only a small number of patients were recruited and the 6–9 year age group was particularly under-represented ($n = 2$). The applicant company justified the limited patient numbers by the lower distribution of incidence of ERA in this age group supported by retrospective analysis of a literature review⁵.
- The choice of primary endpoint in study M11-328 was not consistent with current guidelines for clinical investigation of medicines for the treatment of JIA. However, CHMP agreed that this was understandable due to the low patient numbers recruited⁵.
- Adalimumab is provided as solution for subcutaneous injection for paediatric use administered once every other week². The comparator etanercept is provided as powder and solution for reconstitution prior to subcutaneous injection and is administered either once or twice weekly⁷. Differences in the preparation and frequency of administration of adalimumab and etanercept may influence patient/carer and prescribing preference.

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The applicant company estimate that, in Wales, eight patients aged 6–18 years would be eligible for treatment with adalimumab for the indication under consideration¹. This has been based on five patients aged 12 years and above, derived from an estimate from a previous AWMSG submission for etanercept⁸, and three patients aged less than

12 years, based on the assumption that the same proportion of patients in study M11-328 aged 6–12 years of age would apply to the ERA population in Wales.

The annual total cost of adalimumab for the estimated eight patients eligible for treatment in Wales is £73,248. The company anticipate that the cost for the five patients in the 12–18 year age group would be offset by using adalimumab in place of etanercept, resulting in a cost saving of £139 per patient.

Based on the company estimate of usage, the net budget impact of adalimumab would therefore be £26,773 (£27,468 for three patients aged 6–12 years minus £695 saving from the 12–18 year age group).

3.1.1 AW TTC critique

- The number of patients estimated by the applicant company to be treated with adalimumab is based on a number of assumptions and may not accurately reflect the number of patients in Wales who may be eligible for therapy. In addition, the company assumes 100% market share with no discontinuations, which may not reflect what would happen in clinical practice.
- No five-year forecast has been provided to take into account the number of newly diagnosed patients eligible for treatment each year after introduction.
- Collectively, the budget impact of adalimumab for this indication is subject to uncertainty.

3.2 Comparative unit costs

The annual acquisition costs for the various strengths and presentations of adalimumab and etanercept are shown in Table 1. It should be noted that vials for both medicines are single use and any remaining contents should be discarded^{2,7}.

Table 1. Examples of annual acquisition costs for adalimumab (Humira®) and etanercept (Enbrel®) in paediatric patients

Medicine	Example dose*	Annual cost†
Adalimumab (Humira®) 40 mg/0.8 ml solution for injection for paediatric use	24 mg/m ² every other week up to a maximum single dose of 40 mg for children over 6 years	£9,156
Adalimumab (Humira®) 40 mg pre- filled pen; 40 mg pre-filled syringe; 40 mg/0.8 ml vial	40 mg every other week for children with a BSA of ≥ 1.67 m ²	£9,156
Etanercept (Enbrel®) 25 mg powder and solvent for solution for injection	0.4 mg/kg twice weekly for children aged ≥ 12 years	£9,296
Etanercept (Enbrel®) 25 mg (pre- filled syringe)	25 mg twice weekly for children aged ≥ 12 years weighing ≥ 62.5 kg	£9,296
Etanercept (Enbrel®) 50 mg (pre- filled syringe and pre-filled pen)	50 mg once weekly for children ≥ 12 years weighing ≥ 62.5 kg	£9,295
BSA: body surface area * Calculations are based on single use † Costs are based on British National Formulary prices as of December 2014 ⁹ This table does not imply therapeutic equivalence of medicines or the stated doses. See relevant Summaries of Product Characteristics for full dosing details ^{2,7}		

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

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

The company anticipate that adalimumab (Humira®) may be supplied by a home healthcare provider¹.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

4.3 Evidence search

Date of evidence search: 29 December 2014

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

REFERENCES

- 1 AbbVie Ltd. Form C: Limited appraisal submission. Adalimumab (Humira®). Dec 2014.
- 2 AbbVie Ltd. Humira®. Summary of Product Characteristics. Nov 2014. Available at: <http://www.medicines.org.uk/emc/medicine/21201>. Accessed Dec 2014.
- 3 European Medicines Agency. Humira®. Procedural steps taken and scientific information after the authorisation. Dec 2014. 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 Dec 2014.
- 4 European Medicines Agency. Humira®. Procedural steps taken before authorisation. Mar 2006. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_before_authorisation/human/000481/WC500050868.pdf. Accessed Dec 2014.
- 5 European Medicines Agency. CHMP extension of indication variation assessment report for Humira®. Procedure No.: EMEA/H/C/0481/II/127. Jul 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000481/WC500175230.pdf. Accessed Dec 2014.
- 6 Burgos-Vargas R, Tse SM, Horneff G et al. A3: Efficacy and safety of adalimumab in pediatric patients with enthesitis related arthritis. *Arthritis & Rheumatology* 2014; 66 (S4).
- 7 Pfizer Ltd. Enbrel®. Summary of Product Characteristics. Oct 2014. Available at: <http://www.medicines.org.uk/emc/medicine/24761>. Accessed Dec 2014.
- 8 All Wales Medicines Strategy Group. 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) Formulation. Reference number: 1437. Oct 2013. Available at: <http://www.awmsg.org/awmsgonline/app/appraisalinfo/1437>. Accessed Jan 2015.
- 9 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. Dec 2014. Available at: <http://www.bnf.org/bnf/index.htm>. Accessed Jan 2015.