AWMSG Secretariat Assessment Report – Advice no. 0812
Adalimumab (Humira®▼) 40 mg solution for injection

This assessment report is based on evidence from a limited submission by Abbott Laboratories Ltd on 23 November 2011[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Adalimumab (Humira®▼) in combination with methotrexate is indicated 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. Adalimumab has not been studied in children aged less than 4 years[2].
Dosing	The recommended dose of adalimumab for patients aged 4–12 years with polyarticular juvenile idiopathic arthritis is 24 mg/m² body surface area (up to a maximum single dose of 40 mg adalimumab) administered every other week via subcutaneous injection. For adolescents aged 13–17 years, a dose of 40 mg administered every other week is administered regardless of body surface area. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	Licence extended on 25 August 2008 to include treatment of active polyarticular juvenile idiopathic arthritis in adolescents from 13 to 17 years of age. This was further extended on 18 March 2011 to include treatment of active polyarticular juvenile idiopathic arthritis in the paediatric population aged from 4 to 12 years[3] (originally licensed on 8 September 2003[4] for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate[5]).

2.0 DECISION CONTEXT

2.1 Background

Juvenile idiopathic arthritis (JIA) is an autoimmune disease in children under the age of 16 years, characterised by persistent joint swelling, pain and limitation of movement that lasts for more than six weeks[6,7]. It is the most common rheumatic disease of childhood[6] with an estimated incidence in the UK of 1000 cases per year and prevalence in the order of 1 per 1000 children[7,8]. An annual report produced by the Welsh Paediatric Surveillance Unit suggested that the incidence of JIA in Wales is approximately 0.038 per 1000 children under the age of 16 years, based upon the notification of new incident cases between July 2003 and July 2006[9].

There are several JIA subgroups presenting with different clinical signs and symptoms, including polyarticular arthritis[10], which is defined as arthritis affecting five or more joints during the first six months of disease[11]. Of the 10,000 children with JIA in England and Wales, 40% are suggested to have polyarticular-course disease[7].

Tumour necrosis factor alpha (TNFα) is a pro-inflammatory mediator that has been identified as a key molecule in the development of JIA: overexpression of TNFα is responsible for the damaging inflammatory processes that occur in articular cartilage and bone[7]. Adalimumab is a recombinant human monoclonal antibody that binds to TNFα and blocks its interaction with cell surface receptors[2,6].

This submission specifically covers the licence extension on 25 August 2008 for the treatment of active polyarticular JIA in adolescents from 13 to 17 years of age[3] and the further extension on 18 March 2011 to include treatment of active polyarticular JIA in the paediatric population aged from 4 to 12 years[3]. It should be noted that in this indication adalimumab can be used in combination with methotrexate (MTX). Oral MTX is not currently licensed for use in this indication for the age group under consideration[12].

2.2 Comparators

The comparator requested by the Welsh Medicines Partnership (WMP) was etanercept (Enbrel®▼).

2.3 Guidance and related advice

- National Institute for Health and Clinical Excellence (NICE). Technology appraisal 35. Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis (2002)[7].
- Royal College of Nursing. Assessing, managing and monitoring biologic therapies for inflammatory arthritis (2003)[13].
- British Society of Paediatric and Adolescent Rheumatology (BSPAR). BSPAR guidelines on methotrexate use in paediatric rheumatology (2005)[14].
- BSPAR Standards of Care for children and young people with juvenile idiopathic arthritis (2010)[15].
- NICE. Biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology (2010)[16].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

3.1 Clinical effectiveness evidence

The company submission is based on a comparison of two phase III studies. Study DE038 and the etanercept JIA study (Study 16.0016) report on the effectiveness and tolerability of adalimumab and etanercept respectively.

The company submission notes that the European Medicines Agency (EMA) dictates that paediatric trials in inflammatory arthritis cannot include a true placebo arm for ethical reasons, and therefore an indirect comparison of adalimumab and etanercept, versus a common comparator (placebo) is not possible. A crude comparison of outcome measures is provided for the purpose of demonstrating clinical effectiveness in comparison to etanercept. The company concludes that the data indicate a comparable effectiveness between adalimumab and etanercept, but advises caution when interpreting data due to the limitations inherent in this approach, which are discussed further in Section 3.2.

3.1.1 Study DE038: the clinical effectiveness of adalimumab in JIA treatment

This multinational, phase III randomised, double-blind, stratified, parallel-group study evaluated the efficacy and safety of adalimumab in children (aged 4 to 17 years old) with polyarticular JIA[1,17]. Prior to study enrolment, patients underwent stratification into two groups: a MTX and a non-MTX treated stratum[6,17]. During a 16-week open-label lead-in phase, all patients (n = 171) received a subcutaneous injection of 24 mg/m^2 of adalimumab (maximum 40 mg) every other week. At week 16, patients (n = 133) with an American College of Rheumatology Pediatric 30% (ACR Pedi 30) response (see Glossary for more information) entered the double-blind phase of the study: patients were randomised within their treatment stratum in a 1:1 ratio to receive subcutaneous injections of either placebo or 24 mg/m^2 adalimumab every other week for 32 weeks. Patients who enrolled in the double-blind phase were then eligible to enter the open-label extension phase of the study (n = 128) and received 24 mg/m^2 body surface area (BSA) of adalimumab every other week[17]. The length of this phase was variable with a maximum duration of treatment of 104 weeks. After this phase patients were enrolled in a fixed dose phase (n = 106), where adalimumab was administered every other week as a fixed dose of either 20 mg or 40 mg based on body weight for a further 64 weeks[6].

The primary endpoint for this study was the percentage of patients in the non-MTX stratum who experienced a disease flare during the double-blind phase of the study. Disease flare was defined as a worsening of 30% or more in at least three of the six core criteria for JIA and an improvement of 30% or more in no more than one of the criteria between baseline and (see Glossary for further details regarding core criteria for determining disease flare in JIA patients). Secondary endpoints included an assessment of ACR Pedi 30, 50, 70 and 90 responses (see Glossary for more information)[6].

During the 32-week double-blind phase, disease flare occurred in a significantly lower proportion of the non-MTX stratum treated with adalimumab than in those receiving placebo (43% [13/30] versus 71% [20/28], p = 0.03). This was also observed for patients in the MTX stratum (37% [14/38] versus 65% [24/37], p = 0.015). ACR Pedi 30, 50 and 70 responses were more common in patients treated with adalimumab than those in the placebo arm but were only statistically significant for the MTX stratum. These ACR Pedi responses were sustained during the open-label extension phase in all patients regardless of whether adalimumab was dosed according to BSA or body weight[17].

In the European Public Assessment Reports for this licence extension, the Committee for Medicinal Products for Human Use (CHMP) concluded that there were no new safety signals in children and adolescents treated with adalimumab when compared with that previously observed in adults[6,18]. The most frequently reported adverse events (AEs) were infections and injection-site reactions; withdrawal due to AE occurred in 12 patients. Serious AEs considered possibly related to study treatment were balanced between the MTX and non-MTX strata and occurred in 14 patients, of which seven were serious infections. Of the other serious AEs, JIA flare was the most common[17].

3.1.2 Study 16.0016: the clinical effectiveness of etanercept in JIA treatment

Study 16.0016 was a randomised, multicenter, double-blind trial of etanercept for the treatment of polyarticular JIA in children (aged 4 to 17 years old) who did not tolerate or who had an inadequate response to MTX[19,20]. Patients in the open-label phase (n = 69) received 0.4 mg/kg (maximum 25 mg) etanercept as a subcutaneous injection twice weekly for up to three months. At the end of this period, patients whose condition had improved (n = 51) were randomised to receive either etanercept or placebo until

disease flare or four months elapsed in the double-blind study phase[19,20]. All patients from Study 16.0016 were then eligible to enrol in an open-label extension study[20–22].

During the double-blind phase, significantly fewer disease flares (primary endpoint) occurred in etanercept-treated patients when compared with the placebo arm (p = 0.003): disease flares occurred in 28% (7/25) and 81% (21/26) of patients in each group respectively[20,23].

At the time of licensing, CHMP concluded that etanercept has a reasonably tolerable safety profile[19]. The most common AEs in the open-label study phase were injection-site reactions, infections and headaches; there were no significant differences in the frequencies of AEs between the etanercept and placebo treatment arms[20].

Data obtained at two and four years from patients in the open-label extension study demonstrate that clinical improvement was sustained and there were no increases in the rates of serious AEs[21,22].

3.2 WMP critique

- The submission includes a crude comparison of the outcome measures for the purpose of demonstrating the clinical efficacy of adalimumab when compared with etanercept. The company acknowledges that it is not possible to carry out a methodologically sound indirect comparison and advises caution when interpreting the data[1]. Although the clinical studies of adalimumab and etanercept were similarly designed, the open-label lead-in, double-blind and open-label extension phases were conducted over different time periods[1,17,20–22]. Further, the crude comparison allows no methodologically sound comparison of the safety profile for the two treatments.
- Following a consultation exercise and scoping workshop, NICE decided not to conduct a full appraisal of adalimumab for this indication. Consultees at the scoping workshop indicated that the clinical effectiveness of adalimumab and etanercept was thought to be comparable in JIA[24].
- At the time of licensing, CHMP concluded that the results of the primary efficacy analysis were questionable due to the low threshold for flare and the use of imputation during primary and secondary endpoint analyses[6,17]. CHMP accepted that adalimumab prevents disease flares compared to placebo but stated that due to the trial design, its superiority over placebo may be overestimated. Additionally, CHMP noted that there were a high number of disease flares during the double-blind phase in adalimumab-treated patients, although not as high as in the placebo treatment arm, which makes long term efficacy uncertain[6]. The measurements of response to treatment and disease flare were recorded by changes to values from different starting points in the study[17]. Response to treatment was measured as the change from baseline values, whereas disease flare was measured as the change from the time of randomisation, which occurred after 16 weeks of treatment in the lead-in period[17]. The company have noted that this means a patient could be recorded as undergoing a disease flare and also show a response to treatment[1]. A registry of JIA patients has been set up which aims to assess long term safety and effectiveness of adalimumab[18]. Recently presented data established that efficacy of adalimumab is maintained at up to six years, with no new safety signals observed[25].
- Subjects that entered the open-label extension phase of the DE038 study received a dose based on BSA for a variable period, followed by a fixed dose of adalimumab in order to gather safety and efficacy data on a fixed dosing regimen. A number of patients, particularly in the lower age groups, received a

dose increase greater than 10 mg during the fixed dosing regimen phase compared to that received during the BSA-based dose. Duration of treatment with the BSA-based dose varied for each subject enrolled in the extension phase, resulting in uncertainty interpreting data of long term treatment with the BSA-based regimen. Additionally, due to the few subjects included and the design of the open-label phase, CHMP considered the fixed-dose data of limited value. The company justified the fixed dosage regimen by stating that BSA-based dosing could be disadvantageous since increased efforts are needed to calculate and administer the correct dose and patients/parents may attempt to reuse a dosage unit, increasing the potential for infection. This justification was endorsed by CHMP[6]. However, CHMP concluded that there was not sufficient evidence to support use of the fixed dose in younger children and, following the development of a presentation which allowed for accurate dosing according to BSA, approved only BSA-based dosing of adalimumab for the treatment of patients aged 4 to 12 years old[6,18].

- The licensed dosing schedule for adalimumab requires treatment administration every other week[2], while patients receiving etanercept are treated twice weekly[26]. Adalimumab is available in a pre-filled vial and does not need to be formulated using powder and solvent for injection[2].
- At the time of licensing, CHMP noted that there were more responders in the MTX stratum than in the non-MTX stratum, indicating an increased efficacy with combination therapy[6,18].
- Non-infectious uveitis is an inflammation of the middle layer of the eye that occurs in around 10%-20% of JIA patients[27,28]. Adalimumab is currently being investigated in clinical studies as a potential therapy for the treatment of non-infectious uveitis and the company suggests that for this reason clinicians may prefer to use this treatment for patients with JIA suffering from non-infectious uveitis[1]; however, the use of adalimumab in this indication is not licensed[2].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

Cost-effectiveness evidence is not required for a limited submission.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company assumes that adalimumab will displace etanercept, since both medicines are considered to be comparable in the treatment of JIA (according to expert opinion) and both have similar acquisition costs (approximately £360 per two weeks). Using NICE estimates of the proportion of children eligible for etanercept[7] and Welsh population statistics, the company estimates that 74 patients aged 4–17 years may potentially be eligible for adalimumab treatment in Wales. However, the company notes that many eligible patients will already be receiving treatment with etanercept[1]. The company has been unable to provide estimates of the number of newly diagnosed patients or the anticipated uptake of adalimumab in Wales.

According to the company estimates, adalimumab treatment would cost £9,156 per patient per year (£352.14 × 26 doses). Since adalimumab is anticipated to displace

etanercept, which has a similar cost (£89.375 × 104 doses = £9,295 per patient per year) the company assumes there would be no additional budgetary impact if adalimumab is recommended as a treatment option in Wales.

5.1.2 WMP critique

- Due to a reported lack of information about the number of eligible patients and anticipated market uptake data for adalimumab, the estimated number of children who may be prescribed adalimumab in Wales is subject to uncertainty.
- For a proportion of patients who may be referred to a nurse for injections, medicine administration costs could be lower for adalimumab compared to etanercept due to the different dose frequencies.
- No alternative scenario analyses have been presented to address the uncertainty of the budgetary impact associated with the number of eligible patients or associated resource use.

5.2 Table of comparative unit costs

Table 1 lists examples of annual treatment acquisition costs for the management of active polyarticular JIA in children and adolescents aged 4 to 17 years who have had an inadequate response to one or more DMARD. This table assumes ongoing treatment benefit over at least 12 months.

Table 1. Example acquisition costs for adalimumab and etanercept in the treatment of children with polyarticular JIA.

Treatment	Regimen	Annual cost per patient
Etanercept (Enbrel®▼) 25 mg/ml powder and solvent for solution for injection for paediatric use	0.4mg/kg body mass twice weekly	£9,295
Adalimumab (Humira®▼) 40 mg/0.8 ml solution for injection for paediatric use (single dose vial)	4–12 years: 24 mg/m^2 BSA every other week; 13–17 years: 40 mg every other week.	£9,156
Costs are based on MIMS[29] list prices. *See the relevant SPCs[2,26] for full dose and storage details.* *This table does not imply therapeutic equivalence of treatments or the stated doses.*		

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

WMP is of the opinion that adalimumab is not suitable for shared care within NHS Wales.

GLOSSARY

American College of Rheumatology Pediatric 30% (ACR Pedi 30) response: a standardised outcome measure to assess relative efficacy in clinical trials. It is defined as an improvement of 30% or more in a minimum of three variables in the core set of six with worsening of one variable by no more than 30%[6,17,18].

American College of Rheumatology Pediatric 50% (ACR Pedi 50) response: a standardised outcome measure to assess relative efficacy in clinical trials. It is defined as an improvement of 50% or more in a minimum of three variables in the core set of six with worsening of one variable by no more than 30%[6,17,18].

American College of Rheumatology Pediatric 70% (ACR Pedi 70) response: a standardised outcome measure to assess relative efficacy in clinical trials. It is defined as an improvement of 70% or more in a minimum of three variables in the core set of six with worsening of one variable by no more than 30%[6,17,18].

American College of Rheumatology Pediatric 90% (ACR Pedi 90) response: a standardised outcome measure to assess relative efficacy in clinical trials. It is defined as an improvement of 90% or more in a minimum of three variables in the core set of six with worsening of one variable by no more than 30%[6,17,18].

Core set of variables used to determine disease flare in JIA patients:

- Physician's Global Assessment of subject's disease severity by visual analog scales (VAS).
- Parent's Global Assessment of subject's overall well-being by VAS.
- Number of active joints defined as joints with swelling not due to deformity or joints with limitation of passive motion (LOM) and with pain, tenderness or both.
- Number of joints with LOM.
- Disability Index of the Childhood Health Assessment Questionnaire (DICHAQ).
- C-reactive protein (CRP). Change in CRP from baseline was evaluated for clinical improvement or worsening only if at least one of the CRP values, baseline value, or the visit value was outside the normal reference range[6,18].

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