AWMSG Secretariat Assessment Report
Abatacept (Orencia®)
250 mg powder for concentrate for solution for infusion

This assessment report is based on evidence submitted by Bristol-Myers Squibb Pharmaceuticals Ltd on 5 August 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Abatacept (Orencia®) in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in paediatric patients 6 years of age and older who have had an insufficient response to other disease-modifying anti-rheumatic drugs including at least one tumour necrosis factor inhibitor[2].
Dosing	The recommended dose of abatacept for polyarticular juvenile idiopathic arthritis patients aged 6 to 17 years who weigh less than 75 kg is 10 mg/kg, calculated based on the patient's body weight at each administration. Paediatric patients weighing 75 kg or more should follow the abatacept adult dosing regimen and should not exceed a maximum dose of 1,000 mg. Abatacept should be administered as a 30-minute intravenous infusion. Following the initial administration, abatacept should be given at two and four weeks after the first infusion, and every four weeks thereafter. The safety and efficacy of abatacept in children below six years of age have not been studied and therefore, abatacept is not recommended for use in children under six years old. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	20 January 2010[3] (originally licensed for treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease-modifying anti-rheumatic drugs including at least one tumour necrosis factor inhibitor on 21 May 2007; this indication has subsequently been updated[2,4]).

2.0 DECISION CONTEXT

2.1 Background

Juvenile idiopathic arthritis (JIA) encompasses all forms of arthritis of unknown aetiology that persist for at least six weeks and begin in patients aged less than 16 years[5]. JIA is characterised by persistent joint swelling, pain and limitation of movement, and has an estimated incidence in the UK of 1 per 10,000 children and prevalence in the order of 1 per 1000 children[6].

JIA comprises several heterogeneous subtypes, presenting with different clinical signs and symptoms (see Glossary for classification of subtypes)[7–9]. Polyarticular JIA (classifiable as polyarthritis [rheumatoid factor positive or negative]) is characterised by

arthritis affecting five or more joints during the first six months of disease[7,8,10,11], and affects 13%–37% of JIA patients[7].

Management of JIA typically involves use of non-steroidal anti-inflammatory drugs (NSAIDs) during diagnosis, while other arthritis causes are excluded[6,7]. Patients with a diagnosis of polyarticular JIA that is refractory to intra-articular steroids can be considered for treatment with disease-modifying anti-rheumatic drugs (DMARDs), the most widely used of which is methotrexate (MTX)[6,7]. It is recommended that patients with polyarticular JIA whose condition has not responded adequately to a DMARD, such as MTX, should receive a tumour necrosis factor α (TNFα) inhibitor – etanercept or adalimumab[6,12,13]; see also section 2.3. Where polyarticular JIA patients fail to achieve an adequate response after receiving treatment with a TNF inhibitor, subsequent treatment options can be limited. Biological therapies with an alternative mode of action, such as abatacept or tocilizumab[2,14], could increase the treatment options in the patient group.

Abatacept inhibits a key costimulation signal pathway that is required for full activation of T lymphocytes, and decreases T lymphocyte production of antigen-specific TNFα, interferon-γ and interleukin-2[2]. 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[6].

2.2 Comparators

The comparators included in the company submission were:

- Adalimumab
- Etanercept
- Tocilizumab

2.3 Guidance and related advice

- National Institute for Health and Care Excellence (NICE). Biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology. Juvenile idiopathic arthritis commissioning algorithm (2012)[15].
- NICE. Biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology (2010)[16].
- Arthritis and Musculoskeletal Alliance. Standards of Care for children and young people with juvenile idiopathic arthritis (2010)[17].
- RCN. Assessing, managing and monitoring biologic therapies for inflammatory arthritis (2009)[18].
- British Society for Paediatric and Adolescent Rheumatology (BSPAR). BSPAR Standards of Care for children and young people with juvenile idiopathic arthritis (2010)[19].
- NICE. Technology Appraisal 35. Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis (2002)[6].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of adalimumab:

- Adalimumab (Humira®) is recommended as an option for use within NHS Wales, 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 (2013)[13].

- Adalimumab (Humira®) in combination with methotrexate is recommended as an option for use within NHS Wales 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 (Humira®) can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (2012)[12].

AWMSG is also considering:

- Etanercept (Enbrel®) for the treatment of polyarthritis (rheumatoid factor positive or negative) from 2 to < 4 years of age and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate; the treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate; and the treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy (scheduled for appraisal November 2013)[20].
- Tocilizumab (RoActemra®) in combination with methotrexate (MTX) for the treatment of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate (scheduled for appraisal February 2014)[21].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

As evidence of comparative clinical effectiveness, the applicant company has provided a phase III study (AWAKEN)[1,22], which assessed the safety and efficacy of abatacept for the treatment of JIA, and a qualitative indirect comparison of abatacept against adalimumab, etanercept and tocilizumab[1].

3.1 AWAKEN

AWAKEN was a phase III double-blind, randomised, placebo-controlled withdrawal trial, which evaluated the efficacy and safety of abatacept in JIA patients (aged 6–17 years)[22]. All patients (n = 190) initially received abatacept (10 mg/kg; maximum dose: 1000 mg) by 30-minute intravenous infusion on days 1, 15, 29, 57 and 85 of a 4-month open-label period. Patients (n = 123) who had improved by 30% according to the American College of Rheumatology (ACR) Pediatric (ACR Pedi 30) response definition (see Glossary) were randomly assigned (1:1) to receive either abatacept (10 mg/kg) or placebo at randomisation and at 28-day intervals for six months thereafter, or until a flare of arthritis. Patients were given the option to receive open-label treatment with abatacept in a five-year follow-up period if they had flare of arthritis in the double-blind period, completed the double-blind period without flare, or completed the lead-in period without an adequate response[22].

Eligible patients had at least five active joints (defined as those with swelling or, in the absence of swelling, limited range of motion, accompanied by either pain or tenderness) and active disease (at least two active joints and two joints with a limited range of motion). Patients were enrolled with the following JIA subtypes: polyarticular disease (positive or negative for rheumatoid factor), oligoarticular disease (extended and persistent) and systemic JIA without systemic manifestations (see Glossary). Additionally, patients were eligible only if they had had an inadequate response to, or intolerance to, at least one DMARD, including biological agents such as etanercept, infliximab, and adalimumab. All DMARDs, except MTX, were withdrawn and prohibited during the trial[22].

The primary endpoint was time to JIA flare, defined as worsening of 30% or more in at least three of the six ACR core JIA outcome variables, and an improvement of 30% or more in no more than one of the variables from baseline during the double-blind period (see Glossary for further details regarding ACR core outcome variables for assessment of JIA patients). Median time to JIA flare was six months in patients receiving placebo; insufficient events had occurred in the abatacept group for median time to flare to be assessed ($p = 0{\cdot}0002$ using log-rank test). Secondary objectives assessed at the end of the double-blind treatment phase included the proportion of patients who had disease flare, which was 12/60 (20%) patients receiving abatacept, compared with 33/62 (53%) patients in the placebo group ($p = 0{\cdot}0003$). Additionally, as an exploratory analysis, the proportion of patients demonstrating improvements was evaluated, and tended to be higher in the abatacept group (ACR Pedi 30 response: 82% in the abatacept group versus 69% in the placebo group [$p = 0.1712$]; ACR Pedi 50 response: 77% versus 52%, respectively [$p = 0.0071$]; ACR Pedi 70 response: 53% versus 31% [$p = 0.0185$]; ACR Pedi 90 response: 40% versus 16% [$p = 0.0062$])[22].

Of the 190 patients enrolled in the AWAKEN study, 153 entered the long-term extension phase and received abatacept treatment; 58 had previously received abatacept during the double-blind phase, 59 had received placebo during the double-blind phase and 36 were non-responder patients from the initial open-label phase[23]. By day 589, of the 51 patients with available data who had received abatacept continuously through the double blind phase and into the open label study: 90%, 88%, 75%, 57%, and 39% of these patients achieved ACR Pedi 30, ACR Pedi 50, ACR Pedi 70, ACR Pedi 90, and ACR Pedi 100 responses, respectively. Similar data was obtained from patients treated with placebo during the double-blind phase and non-responders from the initial open-label phase; however, the proportion of patients achieving responses tended to be lower[23].

3.2 Indirect comparison

In the absence of direct evidence for abatacept versus etanercept, adalimumab and tocilizumab for the treatment of polyarticular JIA, the company submission includes a qualitative indirect comparison of data (see Table 1).

Table 1. Qualitative comparison of studies evaluating licensed biological DMARDs for the treatment of JIA[1].

	Abatacept[22]	Etanercept[24]	Adalimumab[25]	Tocilizumab[26]
Study characteristics				
Number enrolled	190	69	171	188
Population	Active JIA (oligoarticular, polyarticular or systemic without systemic manifestations)	Active JIA (pauciarticular arthritis [four or fewer joints], polyarticular arthritis or systemic arthritis)	Active polyarticular JIA	Active JIA (polyarticular or extended oligoarticular arthritis)
Age	6–17 years	4–17 years	4–17 years	2–17 years
Design	Double-blind, randomised controlled withdrawal trial	Double-blind, randomised controlled withdrawal trial	Double-blind, randomised controlled withdrawal trial	Double-blind, randomised controlled withdrawal trial
Duration of double-blind period	six months	four months	32 weeks	24 weeks
Primary outcome	Time to flare of JIA during double-blind period	Number of patients with disease flare during double-blind period	Percentage of patients not receiving MTX with disease flare during double-blind period	Proportion of patients with disease flare during double-blind period
Secondary and ancillary outcomes	Proportion of patients with disease flare during double-blind period. Change from baseline in each of the six ACR core variables during double-blind period. Safety and tolerability	ACR Pedi 30 responses in double-blind period. Time to flare in double-blind period.	Percentage of patients with disease flare during double-blind period. ACR Pedi 30 responses in double-blind period.	JIA ACR core set variables; long-term efficacy and maintenance of clinical response; safety and tolerability
Results				
Proportion of patients who experienced a flare during the double-blind period	Abatacept: 20% Placebo: 53% p = 0.0003	Etanercept: 28% Placebo: 81% p = 0.003	Adalimumab without MTX: 43% Placebo without MTX: 71% p = 0.03 Adalimumab plus MTX: 37% Placebo plus MTX: 65% p = 0.02	Tocilizumab: 26% Placebo: 48% p = 0.0024
Proportion of patients with an ACR Pedi 30 response at end of double-blind period	Abatacept: 82% Placebo: 69% p = 0.1712	Etanercept: 80% Placebo: 35% p < 0.01	Adalimumab without MTX: 57% Placebo without MTX: 32% p = 0.06 Adalimumab plus MTX: 63% Placebo plus MTX: 38% p = 0.03	Tocilizumab: 74% Placebo: 54% p = 0.0084
Median time to flare during double-blind period	Abatacept: insufficient events Placebo: six months p = 0.0002 (using log-rank test)	Etanercept: > 116 days Placebo: 28 days p < 0.001	Not reported	Not reported

3.3 Safety

Direct comparative evidence for abatacept versus other biological DMARDs in the treatment of polyarticular JIA was not available in the company submission[1]. Safety evidence for abatacept versus placebo was reported in the AWAKEN study[22,23]. During the double-blind phase, the overall incidence of patients reporting adverse events (AEs) was 37/60 (62%) in abatacept-treated patients and 34/62 (55%) in the placebo group[22]. No fatalities or AE-related discontinuations were reported and no significant differences in AE frequencies between the treatment groups were identified. The most common system organ class reported was infections and infestations; however, incidence was comparable between the groups[22].

Following a mean duration of exposure of 53.6 months, the overall incidence of patients reporting AEs was 140/153 (92%) and of these 30 (20%) patients reported AEs that were considered serious[27]. Six patients (4%) discontinued treatment due to an AE (urticaria and bronchospasm; worsening of vitiligo; temporal lobe epilepsy and multiple sclerosis; appendicitis; skin lesions; and bacterial arthritis), of which three were considered serious (temporal lobe epilepsy and multiple sclerosis; appendicitis; and bacterial arthritis).

3.2 AWTTC critique

- In the absence of direct comparative evidence of abatacept versus other biological DMARDs for the treatment of polyarticular JIA, the applicant company has provided a study evaluating abatacept versus placebo and a qualitative indirect comparison versus adalimumab, etanercept and tocilizumab[1]. The applicant company noted that the submitted studies were broadly similar in design, but the paediatric population enrolled into the abatacept study was a broader population that included more JIA subtypes than that studied in the etanercept, adalimumab and tocilizumab trials[1,22,24–26]. Additionally, the abatacept study included patients with an age range of 6–17 years, whereas the comparator trials also included patients who were younger. Further, endpoint definition, treatment duration and baseline patient characteristics differed between studies[1,22,24–26]. Any conclusions drawn from this data should be viewed in the light of these limitations.
- The licensed indication for abatacept specifies that use should be in patients who have had an insufficient response to other DMARDS, including at least one TNF inhibitor[2]. Of the patients enrolled in the AWAKEN study, including those with oligoarticular JIA, polyarticular JIA or systemic JIA without systemic manifestations, only 27% (51/190) had previously discontinued TNF inhibitor treatment due to ineffectiveness[22]. However, in this subgroup of patients who had previously discontinued TNF inhibitor treatment, 22/57 (39%) had an ACR Pedi 30 response during the four-month initial open-label period[22].
- The Committee for Medicinal Products for Human Use (CHMP) guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis recommends use of the ACR Pedi 30 response criteria as the primary endpoint[28]. During the AWAKEN study, more patients demonstrated an ACR Pedi 30 response in the abatacept group than the placebo group; however, this was not statistically significant and was conducted as an exploratory analysis[22].
- The rate of discontinuation during the open-label long-term extension phase (mean total abatacept exposure: 53.6 months) of the AWAKEN study was 29/58 (50%) in patients who received abatacept during the double-blind phase and 32/59 (54%) in patients who received placebo during the double-blind phase; however, few discontinued due to lack of efficacy (9% and 14%, respectively)[27]. In patients who failed to respond during the initial open-label lead-in phase, 11/36 (31%) discontinued due to lack of efficacy.
- Abatacept is administered at two and four weeks after the first infusion, and every four weeks thereafter[2]; a subcutaneously administered formulation is

available but was not licensed for use in children at the time this ASAR was prepared[29]. By contrast, adalimumab and tocilizumab are administered once every two weeks[14,30] and etanercept can be administered as either a once or twice weekly dose[31–35]. However, abatacept is administered by intravenous infusion over a period of 30 minutes[2], while adalimumab and etanercept are administered by subcutaneous injection, and are available in a pre-filled pen or vial, which does not require reconstitution and dilution prior to administration[30–35]. These factors may impact upon the preferences of children with polyarticular JIA and their carers.

- Abatacept is under consideration for the treatment of polyarticular JIA in paediatric patients; however, polyarticular JIA can persist in patients over the age of 17[16].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-minimisation analysis (CMA) of abatacept intravenous infusion compared against adalimumab, etanercept, and tocilizumab in patients with polyarticular JIA aged 6 to 17 years[1].

There are no direct comparative trial data for abatacept and these comparators. The company has briefly described the key trials of abatacept and each of the comparators (see Table 1), and has reported that, although there are similarities in the trial designs, the trial populations differ in terms of the age range of patients and JIA subtypes exhibited. Moreover, the primary endpoint of the abatacept trial (time to disease flare) differed from that of the comparators (proportion of patients experiencing a flare). No quantitative comparisons have been undertaken and it is assumed that the efficacy and safety profiles of these biologics are comparable.

Total drug acquisition and administration costs are estimated over one- and five-year (undiscounted) time horizons. To reflect their different dosing requirements, estimates are presented for patients with body weights of less than or greater than 75 kg for abatacept, less than or greater than 62.5 kg for etanercept (in first year; unclear dosing assumed over five years), and less than or greater than 30 kg for tocilizumab (in first year; unclear dosing assumed over five years). Adalimumab dosing is not differentiated by body weight. Drug cost estimates for the lower body weights are based on the assumption of an average patient age of 12 years (as observed in the abatacept trial) and average body weight or body surface area for a child of that age. Abatacept costs reflect a confidential discount as part of a Patient Access Scheme (PAS). It is assumed that abatacept and tocilizumab attract administration costs of £154 per infusion based on previous NICE costing estimates, while adalimumab and etanercept attract no administration costs due to their subcutaneous route of administration.

4.1.2 Results

The results of the base case analysis are presented in Table 2. Abatacept is reported to be the least costly of all the biologic agents considered in the analysis. No sensitivity or scenario analyses are presented.

Table 2. Company-estimated costs of abatacept and comparator regimens over one and five years.

Costs	Abatacept	Adalimumab	Etanercept	Tocilizumab
Year 1: drug acquisition*	§	£9,156	£9,296	£6,656
Year 1: drug administration†	£2,156	£0	£0	£2,002
Year 1: total cost*	§	**£9,156**	**£9,296**	**£8,658**
Year 5: cumulative cost*	§	**£45,778**	**£46,478**	**£43,290**

* Incorporates a confidential discount on list price of abatacept, agreed as part of PAS.
† Abatacept administered by intravenous infusion on week 0, 2 and 4 and then every four weeks; tocilizumab administered by intravenous infusion every four weeks; no administration costs assumed for adalimumab or etanercept.
§ Commercial in confidence data removed.

4.1.3 AWTTC critique

The reliability of the CMA presented by the company is dependent upon the extent to which intravenous abatacept is considered to be therapeutically equivalent to the relevant comparators. There is a lack of direct comparative data for abatacept and the comparators in this setting, and the company reports it has not been possible to conduct any quantitative, adjusted indirect comparisons. Abatacept and tocilizumab require intravenous administration in the hospital setting, in contrast to subcutaneous adalimumab and subcutaneous etanercept. Such differences in routes of administration may plausibly impact upon treatment preferences, convenience, safety and health-related quality of life. Collectively, there appears to be a high level of uncertainty in the assumption of therapeutic equivalence, and the CMA approach precludes exploration of uncertainty in all but costs.

Limitations of the economic evidence:

- There is a lack of direct comparative data for abatacept and the comparators. A qualitative discussion of key trial data is provided, and the company concludes that differences in the relevant trial populations preclude formal quantitative, indirect comparisons. There are no details of a systematic literature review to identify relevant trials and it is assumed that abatacept and the comparator biologics have comparable efficacy and safety profiles.
- The licensed indication for abatacept is for second-line use in patients who have had an insufficient response to previous TNF inhibitor therapy[2]. The majority of patients (70%) enrolled in the key abatacept trial had not previously received TNF inhibitor therapy and only 27% of patients enrolled had discontinued therapy due to an insufficient response[22].
- The CMA framework assumes equivalence in all domains of health outcomes, which precludes exploration of the differences that may exist in efficacy, safety and health-related quality of life. There are potentially important differences in routes of administration, which may plausibly impact upon patient and carer preferences, convenience, and safety.
- Tocilizumab has a Department of Health-approved Patient Access Scheme (PAS). The PAS-agreed price for tocilizumab has not been taken into account in the evidence of cost-effectiveness[1]. AWMSG will be appraising tocilizumab for the treatment of juvenile idiopathic polyarthritis in February 2014[21].

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC identified one published cost-effectiveness analysis of abatacept in the treatment of polyarticular JIA. Using probabilistic sensitivity analyses, this estimated the one-year incremental costs (Canadian dollars, 2008) per ACR Pedi 30 responder compared with MTX to be $16,204 (95% CI: $11,393–$22,608) for abatacept, $26,061 (95% CI: $17,070–$41,834) for etanercept, $46,711 (95% CI: $30,042–$75,787) for adalimumab and $31,209 (95% CI: $16,659–$66,220) for infliximab, respectively[36]. There are differences in healthcare settings and acquisition costs for biologics in Canada and the UK, and this analysis does not consider the cost-effectiveness of abatacept in its UK-licensed indication as a second-line agent following insufficient response to previous TNF inhibitor therapy. The analysis also does not address the potential for differences in health-related quality of life associated with administration routes for the different biologics. Collectively, the relevance of this analysis to the use of abatacept in NHS Wales is limited.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on a prevalence of around 1 case per 1,000 children[6], the company estimates there to be 420 children with JIA in Wales. Based on the NICE costing template for the use of biologics in rheumatoid arthritis, the company estimates 10% of these patients (42) have an inadequate response to conventional DMARD therapy[37], and so are eligible for treatment with an TNF inhibitor therapy. Of these, it is estimated 27% (12) discontinue their first-line TNF inhibitor treatment and are therefore potentially eligible for treatment with abatacept, based on registry data for patients using TNF inhibitor therapies for the treatment of rheumatoid arthritis[38]. The company assumes uptake in 20–25% of these patients, equivalent to 2–3 patients per year receiving abatacept. An alternative estimate is provided, in which 50% of patients eligible for TNF inhibitor therapy (21) are assumed to receive second-line TNF inhibitor therapy, and of these 1–2 patients are estimated to receive abatacept each year[1].

The company states that the majority of first-line TNF inhibitor therapy would be etanercept, as this agent has been licensed the longest. It has also assumed that tocilizumab has little or no market share given its recent licensing. For the second-line TNF inhibitor therapy the company submission assumed that 80% of eligible patients will receive adalimumab or etanercept, and 20% will receive abatacept, rising to 25% over a five-year period. This is estimated to equate to 1–2 patients/year in years 1 to 4 and 2–3 patients in year 5.

5.1.2 Results

Table 3 presents the net cost estimates provided by the company.

Table 3. Company-reported net cost implications.

	Year 1	Year 2	Year 3	Year 4	Year 5
No. patients receiving abatacept	1	1	1	1	2
Total cost abatacept (< 75 kg)	*	*	*	*	*
Total cost abatacept (75–100 kg)	*	*	*	*	*
No. patients receiving etanercept	2	2	2	2	4
Total cost etanercept	£18,591.04	£18,591.04	£18,591.04	£18,591.04	£37,182.08
No. patients receiving adalimumab	2	2	2	2	2
Total cost adalimumab	£18,311.28	£18,311.28	£18,311.28	£18,311.28	£18,311.28
* Commercial in confidence data removed.					

5.1.3 AWTTC critique

- The estimate of numbers of eligible patients is based on all JIA patients, rather than the licensed population of patients with polyarticular JIA. The company suggests this approach is more conservative, as polyarticular JIA is assumed to account for only 40% of JIA cases.
- The company acknowledges there are limited data with which to estimate market share and uptake and has provided different estimates of the number of patients potentially eligible for treatment with abatacept. However, the company has then simply assumed the lowest of its estimates of patient numbers to be treated with abatacept.
- In response to AWTTC queries, the company has provided the revised budget impact figures in Table 3. It is unclear how these figures relate to the estimate of 12 patients who discontinue their first-line TNF inhibitor treatment and are therefore potentially eligible for treatment with abatacept, or the 50% of these as was stated to be assumed. The company has provided cost estimates rather than net budget impact estimates.
- Collectively, the analysis provided by the company is subject to considerable uncertainty; however, given the small numbers of eligible patients, and under the assumption of therapeutic equivalence and the confidential discount on the acquisition costs used for the company's economic analysis, the use of abatacept is unlikely to increase costs significantly compared with the use of alternative biologics.

5.2 Table of comparative unit costs

Table 4 provides example comparative acquisition costs for abatacept and potential comparators. These biologic agents are individually dosed according to patient body weight or surface area. Therefore, Table 4 reflects only illustrative examples of the range of possible costs for patients aged 6 years (assumed body weight 20 kg) to 17 years (assumed body weight up to 75 kg), as covered by the abatacept licensed indication, and is based on current list prices in the first year of treatment.

Table 4. Examples of acquisition costs for abatacept and comparators in JIA.

Drug	Example prescribing requirements†	Approximate first year cost*
Abatacept (Orencia®) for intravenous infusion, 250 mg vial	1–3 vials by intravenous infusion on week 0, 2 and 4, and then every 4 weeks	£4,234 to £12,701
Adalimumab (Humira®) for subcutaneous injection, 40 mg prefilled pen/syringe and vial	1 x 40 mg single-use, prefilled pen/syringe for subcutaneous injection every other week	£9,156
Etanercept (Enbrel®) for subcutaneous injection, 25 mg or 50 mg prefilled pen/syringe	1 x 25 mg single use, prefilled syringe for subcutaneous injection twice weekly	£9,296
Tocilizumab (RoActemra®) for intravenous infusion, 200 mg or 400 mg vial	(1 x 200 mg vial) to (1 x 200 mg plus 1 x 400 mg vials) by intravenous infusion every 4 weeks	£3,328 to £9,984

† Note that doses need to be individually tailored for body weight or surface area. Prescribing requirements relate to number of prescribing units required to provide required dose for patients aged 6 years to 17 years (maximum assumed weight 75 kg). See all relevant SPCs for full dosing details[2,14,30–35].
* Costs based on Monthly Index of Medical Specialities (MIMS) list prices as of 22 October 2013[39], assuming vial wastage.
Note that abatacept and tocilizumab are available at a confidential discounted list price as part of agreed Patient Access Schemes.
Excludes administration costs which would differ markedly for subcutaneous and intravenous routes of administration.
This table does not imply therapeutic equivalence of the medicines and doses listed.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

The company do not anticipate that abatacept (Orencia®) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 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).

6.4 Evidence search

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

GLOSSARY

American College of Rheumatology (ACR) core outcome variables for assessment of children with juvenile idiopathic arthritis (JIA)[22,28,40]

- Physician global assessment of overall disease severity.
- Parent (or patient, if of an appropriate age) global assessment of overall well-being.
- Number of joints with active arthritis, defined as joints with swelling not due to deformity or joints with limitation of passive motion accompanied by pain, tenderness or both.
- Number of joints with limited range of motion.
- Functional ability assessed using the validated translated version of the Childhood Health Assessment questionnaire (CHAQ).
- Erythrocyte sedimentation rate.

American College of Rheumatology Pediatric 30% (ACR Pedi 30) response[40,41]

A standardised outcome measure used to assess relative efficacy in clinical trials. It is defined as an improvement of 30% or more in a minimum of three variables of the six core outcome variables with worsening of no more than one variable by more than 30%.

American College of Rheumatology Pediatric responses: ACR Pedi 50, ACR Pedi 70, ACR Pedi 90, ACR Pedi 100[41]

An improvement of 50%, 70%, 90% or 100% (respectively) or more in a minimum of three variables of the six core outcome variables with worsening of no more than one variable by more than 30%.

Juvenile idiopathic arthritis (JIA) subtypes[7,42]

- **Oligoarticular arthritis** (also known as oligoarthritis): arthritis affecting one to four joints involved in the first six months of disease:
  - Persistent: four or fewer total joints involved throughout the course of the disease;
  - Extended: more than four joints involved after the first six months of disease.
- **Polyarticular arthritis** (more recently known as polyarthritis): arthritis affecting five or more joints involved in the first six months of disease:
  - Rheumatoid factor positive: Two or more positive tests for rheumatoid factor at least 3 months apart during the first six months of disease;
  - Rheumatoid factor negative: Tests for rheumatoid factor negative.
- **Systemic onset**: arthritis in one or more joints with, or preceded by, fever of at least two weeks' duration. Signs or symptoms must have been documented daily for at least three days and accompanied by one or more of the following: evanescent rash, generalised lymphadenopathy, hepato/splenomegaly, and serositis.
- **Psoriatic arthritis**: arthritis and psoriasis, or arthritis and at least two of the following: dactylitis; nail pitting; onycholysis; or psoriasis in a first-degree relative.
- **Enthesitis-related arthritis**: arthritis and/or enthesitis with at least two of the following: sacroiliac joint tenderness with or without inflammatory lumbosacral pain; HLA-B27 antigen positive; onset in male patient over six years old; acute anterior uveitis; HLA-B27-associated disease in first-degree relative. Previously known as juvenile spondyloarthropathy.
- **Undifferentiated arthritis**: arthritis that fulfils criteria in no specific category or meets criteria for more than one category.

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