Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

Resubmission

abatacept 250mg powder for concentrate for solution for infusion (Orencia®) SMC No. (719/11)

Bristol Myers Squibb Pharmaceuticals Ltd

08 March 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

abatacept (Orencia®) is accepted for restricted use within NHS Scotland.

Indication under review: In combination with methotrexate, for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs including methotrexate or a TNF-alpha inhibitor.

SMC restriction: abatacept is restricted for use in patients with active rheumatoid arthritis as measured by disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart.

In combination with methotrexate, abatacept reduced the progression of joint damage and improved physical function more than placebo in patients with moderate to severe rheumatoid arthritis who responded inadequately to previous therapy with methotrexate alone.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of abatacept. This SMC advice is contingent upon the continuing availability of the patient access scheme or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In combination with methotrexate, for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs including methotrexate or a TNF-alpha inhibitor.

Dosing Information

The dose of abatacept is approximately 10mg/kg, (<60kg=500mg; ≥60kg to ≤ 100kg=750mg; >100kg =1,000mg)

It should be administered as a 30-minute intravenous infusion at weeks 0, 2 and 4 and then every four weeks thereafter.

If there is no response after six months, discontinuation of treatment should be considered.

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

Product availability date

July 2010

Summary of evidence on comparative efficacy

Abatacept is a fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte antigen 4 (CTLA4) linked to the modified Fc portion of human immunoglobulin G1. It is the only licensed anti-rheumatic drug that prevents T-lymphocyte activation.

Abatacept has been licensed for moderate to severe rheumatoid arthritis (RA) since 2007. Advice has already been issued for the population of patients who responded inadequately to previous therapy with a TNF inhibitor in guidance from NICE which was adopted by Healthcare Improvement Scotland. NICE Multiple Technology Appraisal 195 states that abatacept in combination with methotrexate is recommended as a treatment option in adult patients with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event. [1]

In this resubmission the submitting company has requested that SMC consider abatacept when used within the terms of its marketing authorisation in patients with moderate to severe rheumatoid arthritis (i.e. who have responded inadequately to previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) including methotrexate or a TNF-alpha inhibitor (i.e. allows use in patients who have not previously received a biologic therapy).

The evidence for abatacept in this indication comes from two randomised, placebo-controlled, double-blind studies in patients with active RA despite treatment with methotrexate.

The 12-month, ATTEST study recruited 431 adult patients (≥18 years) with RA for at least one year, who met American College of Rheumatology (ACR) criteria for RA and were receiving a

stable dose of methotrexate ≥15mg/week. Infliximab was included as an active control but the study was not powered for a comparison between the active drugs.[2]

The study consisted of two six month phases: in the first phase patients were randomised to intravenous (iv) abatacept 10mg/kg on days 1, 15 and 29, and then every four weeks (n=156); or iv infliximab (3mg/kg) on days 1, 15, 43 and 85 and then every eight weeks (n=165); or placebo (n=110). All patients received methotrexate ≥15mg weekly. No other disease modifying anti-rheumatic drugs (DMARDs) were allowed but stable doses of glucocorticoids (low-dose) and/or non-steroidal anti-inflammatory drugs were permitted. In the second phase, patients in the placebo group were reallocated to receive abatacept with the other two groups continuing treatment as before. If clinically required, one of the following specified DMARDs, (hydroxychloroquine, sulfasalazine, gold, or azathioprine) could be prescribed.[2]

The primary outcome was reduction in disease activity, measured by Disease Activity Score 28 (DAS28) joint count, based on erythrocyte sedimentation rate levels (ESR), [range 0 to 10; high disease activity >5.1; low disease activity ≤3.2; remission <2.6] at six months in the intention to treat (ITT) population. The minimum clinically important improvement in DAS28 (ESR) is 1.2 units. At randomisation, the mean DAS28 (ESR) was 6.8 to 6.9 and at six months abatacept had significantly decreased DAS28 (ESR) compared with placebo by 2.53 versus 1.48, respectively, with a reduction of 2.25 in the infliximab group. All results of secondary outcomes of disease activity were supportive of the primary outcome for both abatacept and infliximab. At six months, ACR 20, 50 and 70 responses were significantly greater with abatacept compared with placebo, and with infliximab compared with placebo. At baseline, the mean health assessment questionnaire disease index (HAQ-DI) was 1.7 to 1.8 (0 to 3 scale). At six months, significantly more abatacept and infliximab patients than placebo patients had a clinically significant improvement in physical function (HAQ-DI responses; 61% versus 41%).[2]

The one year AIM study used similar inclusion criteria and randomised 652 patients with severe RA (mean DAS28 of 6.4) and duration of RA eight to nine years, although only 11% of patients had received DMARDs other than methotrexate. Patients were randomised in a 2:1 ratio to iv abatacept, approximately 10mg/kg body weight, on days 1, 15 and 29 and then every four weeks (n=433), or placebo (n=219). All patients received methotrexate 10mg to 30mg/week. Permitted concomitant medication comprised stable doses of NSAIDs and corticosteroids.[3]

The three co-primary endpoints were analysed in the modified intention to treat (ITT) population defined as all randomised patients who received at least one dose of study medication. The outcomes in the abatacept group were significantly better than placebo for all three endpoints: ACR 20 response at six months, 68% versus 40%; clinically meaningful improvements in physical function (≥0.3 unit) in HAQ-DI at one year, 64% versus 39%; and an approximately 50% reduction in radiographic progression of structural damage assessed by mean Genant-modified Sharp (GMS) score at one year. The median change from baseline in GMS joint erosion score, based on radiographic data for 90% (586/652) of patients was 0.0 (25^{th} and 75^{th} percentiles 0.0 and 1.0) for abatacept patients versus 0.27 (25^{th} and 75^{th} percentiles 0.0 and 1.3).[3]

Results of secondary outcomes were supportive of the primary outcome. At six and 12 months significantly more patients achieved ACR 50 and 70 with abatacept compared with placebo, the reduction in DAS28 was significantly greater and significantly more patients achieved remission.[3]

More patients in the abatacept group (89%) completed the first year of treatment than in the placebo group (74%) and were eligible to enter the open-label follow up study. Lack of efficacy was the most common reason for discontinuation in the placebo group (18% versus 3% in the abatacept group).[3] After five years of follow-up, 70% (266/378) of patients originally randomised to abatacept remained on treatment. DAS28 remission was achieved by 34% of patients.[4]

Summary of evidence on comparative safety

In the ATTEST study the most common adverse events (AE) were infections and infestations, mostly of mild to moderate intensity, reported in 48%, 52% and 52% of the abatacept, infliximab and placebo patients and acute infusional AE reported in 5.1%, 18% and 10% of the abatacept, infliximab and placebo patients, respectively. Serious AEs (SAE) were less frequent with abatacept (5.1%) than infliximab (11%) or placebo (12%). Serious infections were less frequent in the abatacept group (1.3%) than in the infliximab (4.2%) and placebo (2.7%) groups. Discontinuation due to AE occurred in 1.9%, 4.8% and 0.9% patients in the abatacept, infliximab and placebo groups, respectively.[2]

One death (from pneumonia and sepsis) was reported as possibly related to study treatment; this was in a patient initially assigned to placebo who received abatacept after six months.[2]

In the AIM study, the most common AEs were headache, nasopharyngitis and nausea in both groups. More SAEs occurred in the abatacept than placebo group (15% versus 12%), leading to more discontinuation in abatacept patients (2.3% versus 1.4%). There were more protocol-prespecified serious infections in the abatacept group than in the placebo group (2.5% versus 0.9%). In each treatment group there was one death due to infection.[3]

Summary of clinical effectiveness issues

Abatacept has a different mechanism of action from other already available biologic DMARDs. In the two pivotal studies, ATTEST and AIM, abatacept has been shown to be significantly superior to placebo in improving the outcomes in severe RA.

Healthcare Improvement Scotland has endorsed NICE Multiple Technology Appraisal 195 which recommends abatacept as a treatment option for severe RA in patients who have had an inadequate response or intolerance to other DMARDs, including at least one TNF inhibitor. In this resubmission the submitting company has requested that SMC consider the use of abatacept in combination with methotrexate in the treatment of moderate to severe RA in adult patients who responded inadequately to previous therapy with one or more DMARDs including methotrexate or a TNF-inhibitor.

No head to head data has been presented comparing abatacept with other biologic DMARDs or with conventional DMARDs. The study that included an infliximab control was not powered for a comparison with abatacept and the dose of infliximab used was lower than the maximum dose now permitted for patients with an inadequate response.

Patients recruited to the pivotal studies had severe RA according to DAS28 at baseline. However, they may have received fewer previous DMARDs compared with patients in Scottish practice considered eligible for a first biologic treatment.

The infusion time for abatacept (30 minutes) is shorter than for tocilizumab (one hour) or infliximab (two hours, reducing in some circumstances to one hour); however abatacept and tocilizumab are administered every four weeks compared with every eight weeks for infliximab. A subcutaneous formulation of abatacept, administered weekly, has recently been marketed but has yet to be assessed by SMC.

To support the economic case, the company presented a published Bayesian mixed treatment comparison (MTC) in which abatacept plus methotrexate was indirectly compared with the following in combination with methotrexate: adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. The literature search to identify studies suitable for inclusion in the network of evidence was last updated in 2010. The network comprised 11 studies in adults with rheumatoid arthritis. The primary outcome compared and used in the economic case was the change from baseline at six months in the HAQ-DI score. Additional outcomes of the indirect comparison were the ACR20, ACR50, ACR70 response rates. The results of the MTC, when analysed in the favoured random-effects model, suggest that abatacept has similar efficacy to adalimumab, certolizumab pegol, etanercept, golimumab and infliximab when combined with methotrexate. An exception was the comparison with certolizumab pegol. The relative risk of achieving ACR20 was in favour of certolizumab pegol (0.67, 95% credible interval: 0.42 to 0.96).[5]

Discontinuation due to adverse events at six months was used as an outcome measure to compare safety. Six of the 11 studies reported this outcome, and the results suggest that there was no statistically significant difference between the biologic agents.

The studies included in the mixed treatment comparison, and therefore the MTC results can be generalised to the population of relevance to this SMC review.

Tocilizumab plus methotrexate was not included in the MTC. Comparative efficacy has been derived from the results of a previous indirect comparison submitted to SMC. The company acknowledged that this was a limitation of the analysis.

SMC clinical experts advised that most patients respond to one of the other biological therapies but acknowledged that the availability of a biological therapy with a different mode of action other than TNF inhibition was important for people in whom a TNF inhibitor is contra-indicated.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing abatacept with a variety of treatment options including etanercept, adalimumab, tocilizumab, certolizumab, golimumab and infliximab. The clinical evidence in the submission only related to patients who have had an inadequate response to methotrexate and hence this was the focus for the economic evaluation.

The general approach to economic modelling in the submission was similar to the first submission made by the company to SMC for this product. Briefly this involved using the Birmingham Rheumatoid Arthritis Model, which describes the natural history of the disease principally in terms of changes in HAQ scores, which are linked to changes in costs of care, quality of life (utility) values, and mortality risk.

Data on comparative clinical efficacy were taken from two MTCs, as discussed above. The MTC results used in the economics model were mean changes from baseline in HAQ scores for each treatment. As with the previous SMC submission, costs of care and utility values were taken from a published study and a study mapping HAQ to EQ-5D (which in turn can be converted to utility values) respectively.

Medicines costs were based on an assumed weight of 71kg or the licensed dose and included costs of administration.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price of the medicine.

There were several issues with the submission and a number of errors had to be corrected. The base case presented relied on differences from the mixed treatment comparison in HAQ scores where it was not evident any real difference existed. Once the differences between treatments in HAQ scores were excluded, the results, incorporating the PAS discount, are shown in the table below:

Base case results v conventional DMARD (cDMARD)

	Total QALY	**Total LY**	**Total cost**	**Incremental costs (£)**	**Incremental QALYs**	**ICER v cDMARD**
cDMARD	4.76	27.59	£37,743			
Abatacept	6.09	27.81	£68,799	£31,057	1.33	£23,357
Infliximab	5.87	27.77	£65,151	£27,408	1.11	£24,784
Certolizumab pegol	6.05	27.81	£68,208	£30,466	1.29	£23,577
Adalimumab	6.16	27.83	£73,456	£35,713	1.40	£25,526
Etanercept	5.99	27.81	£70,749	£33,007	1.23	£26,862
Golimumab	6.12	27.82	£78,732	£40,989	1.36	£30,112
Tocilizumab*	5.87	27.78	£77,670	£39,927	1.11	£35,949

*Note that the clinical inputs for the tocilizumab ICER are derived from a different MTC to the other biologics.

The company presented stepwise incremental analysis comparing the treatments but claimed it was not helpful because the difference in costs and QALYs of the different treatment options was so small.

Sensitivity analysis showed the biggest effect on the ICER (versus cDMARD) was from using a shorter time horizon.

A probabilistic analysis was also presented; the chance the cost per QALY for abatacept versus cDMARD was less than £30k was estimated to be 100%. Given the ICER for this comparison was £21,450 in the base case the figure of 100% (complete certainty) is surprising in view of the uncertainties involved and may be an overestimate.

Generally the submission tried to show there were differences between the treatments where it was not clear that meaningful clinical differences existed. For example, the results presented

above still include differences in discontinuation rates from the mixed treatment comparison but these were based on relatively small patient numbers.

Despite these limitations, it was concluded that abatacept is comparable to other treatments in terms of efficacy and rates of discontinuation and is available at a comparable price.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Interest Group submission was received from the National Rheumatoid Arthritis Society

Additional information: guidelines and protocols

In August 2010, the National Institute for Health and Clinical Excellence (NICE) published multiple technology appraisal guidance 195, "Adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor". It recommends adalimumab, etanercept, infliximab and abatacept, in combination with methotrexate, as treatment options for adults with severe active RA who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because of intolerance or contraindication. A decision whether to continue treatment or not should be made after six months using the DAS28 as a measure of treatment response.[1]

In October 2007, NICE published multiple technology appraisal guidance 130, Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. It recommends these drugs as options for the treatment of adults who have both of the following characteristics:

• Active rheumatoid arthritis as measured by disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart.
• Have undergone trials of two disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.[6]

In 2005, the BSR updated its guideline for prescribing TNFα blockers in adults with rheumatoid arthritis. Eligibility criteria for treatment with biologics therapies include:

Patients must:

- fulfil the ACR 1987 criteria for diagnosis of RA;
- have active RA defined as DAS28 score >5.1 measured on two occasions, one-month apart;
- have failed standard therapy, eg failure to respond or tolerate adequate therapeutic trials of at least two conventional DMARDs, one of which must be methotrexate. Adequate therapeutic trial is defined as:
    - treatment for at least six months, with two of those months being in a target dose unless significant toxicity limits the dose

- treatment for less than six months where treatment was discontinued due to intolerance or toxicity, but normally after at least two months at therapeutic doses.[7]

Additional information: comparators

With respect to the licensed indication, relevant comparators are:

- anti-tumour necrosis factor (anti-TNF) drugs (subcutaneous): adalimumab, certolizumab pegol, etanercept, golimumab
- TNF inhibitors (intravenous): infliximab
- interleukin inhibitor (subcutaneous): anakinra (not recommended by SMC)
- interleukin inhibitor (intravenous): tocilizumab
- conventional DMARDs

Cost of relevant comparators

Drug	**Dose Regimen**	**Cost per year (£)**
Abatacept	**By intravenous infusion 10mg/kg at weeks 0, 2 and 4 and then every four weeks**	**12,701 in the first year, then 11,794 in subsequent years**
Infliximab	By intravenous infusion, 3mg/kg at weeks 0, 2 and 6 and then every eight weeks. If response is inadequate after week 12, the dose can be increased stepwise to a maximum of 7.5mg/kg every eight weeks or 3mg/kg every four weeks	6,714 to 10,910 in first year, then 5,875 to 10,910 in subsequent years (calculated 3mg/kg [200mg] 4 or 8 weekly)
Certolizumab pegol	By subcutaneous injection, 400mg at weeks 0, 2 and 4, then 200mg every two weeks	10,368 in first year, then 9,295 in subsequent years
Tocilizumab	By intravenous infusion, 8mg/kg every 4 weeks	9,318
Etanercept	By subcutaneous injection, 25 mg twice weekly	9,295
Golimumab	By subcutaneous injection, 50mg once every calendar month	9,156
Adalimumab	By subcutaneous injection, 40mg every second week	9,156

Doses are for general comparison and do not imply therapeutic equivalence. Costs are based on 70kg body weight. Infliximab dose rounded to 200mg. Costs from MIMS online on 07 January 2013, except etanercept and adalimumab, from eVadis on 07 January 2013.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 16,916 in year 1 rising to 18,687 in year five with an estimated uptake rate of 1.95% in year 1 and 7.63% in year 5. The company has also estimated that there will be a discontinuation rate of 5.20% in all years.

Without PAS: The gross impact on the medicines budget was estimated to be £3.980m in year 1 and £15.948m in year 5. As other drugs were assumed to be displaced the net medicines budget impact is expected to be £3.655m in year 1 and £10.232m in year 5.

SMC clinical experts have advised that the cost savings from displaced medicines are understated and the net budget impact is expected to be significantly less in practice.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1) National Institute for Health and Clinical Excellence (NICE) multiple technology appraisal guidance 195**,** Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. August 2010. [online] Available from www.nice.org.uk [Accessed 11 Dec 2012].

2) Schiff M, Keiserman M, Codding C et al. Efficacy and safety of abatacept or infliximab versus placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate Ann Rheum Dis 2008;67:1096-103.

3) Kremer JM, Genant HK, Moreland LW et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis Ann Int Med 2006;144:865-76

4) Kremer JM, Russell AS, Emery P et al. Abatacept demonstrates consistent safety and sustained improvements in efficacy through 5 years of treatment in biologic-naïve patients with RA. EULAR 2009. Poster presentation FRI0263. www.abstracts2view.com

5) Guyot P, Taylor PC, Christensen R et al. Indirect comparison of abatacept with methotrexate versus other biologic agents for active rheumatoid arthritis despite methotrexate therapy in the United Kingdom. J Rheumatol 2012;39:1198-1206.

6) National Institute for Health and Clinical Excellence (NICE) multiple technology appraisal guidance 130**,** Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. October 2007. [online] Available from www.nice.org.uk [Accessed 11 Dec 2012].

7) Ledingham J, & Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNFα blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). Rheumatology 2005; 44: 157-63.

This assessment is based on data submitted by the applicant company up to and including 13 February 2013.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.