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

adalimumab, 40mg/0.8mL, solution for injection (Humira®)

SMC No. (858/13)

AbbVie Ltd (previously part of Abbott)

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 full submission

adalimumab (Humira®) is accepted for use within NHS Scotland.

Indication under review: treatment of adults with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Adalimumab, compared to placebo, improves symptoms of severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis in adults.

Adalimumab should be prescribed in accordance with Assessment in Spondyloarthritis International Society (ASAS) guidance.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of adults with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Dosing Information

40mg administered every other week as a single dose via subcutaneous injection.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which adalimumab is indicated.

Product availability date

23 July 2012

Summary of evidence on comparative efficacy

Adalimumab is a recombinant human monoclonal antibody that binds to tumour necrosis factor (TNF). It is licensed for a range of conditions; rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis (AS), psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis.

SMC has previously accepted adalimumab for use in patients with severe active AS. This submission relates to the recent licence extension, allowing its use in the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS (nr-axSpA) but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to NSAIDs. The Assessment in Spondyloarthritis International Society (ASAS) classification of nr-axSpA requires the presence of diagnostic criteria for axial spondyloarthritis (SpA) without meeting the modified New York criteria for AS. The criteria for axial SpA in patients with at least 3 months back pain and age at onset less than 45 years are sacroiliitis on imaging and ≥1 SpA feature or human leukocyte antigen-B27 (HLA-B27) and ≥2 other SpA features. SpA features are: inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's/colitis, good response to NSAIDs, family history for SpA, HLA-B27, elevated CRP.[1]

ABILITY-1 is a phase III, multi-centre, double-blind study that commenced in 2009; the double-blind phase is complete but the open label extension phase is ongoing. Patients were ≥18 years and fulfilled the ASAS classification criteria for axial SpA without meeting the modified New York criteria for AS. Patients had active disease, measured by a total back pain score of ≥4 on a 0 to 10cm visual analogue scale (VAS) (or ≥40 on a 0 to 100mm VAS) and a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4. Patients had responded

inadequately or been intolerant to one or more NSAIDs or had a contraindication to NSAIDs based on the clinical judgement of the investigator. Patients were randomised equally to receive adalimumab 40mg via subcutaneous injection every other week or matching placebo for 12 weeks for the double-blind period. Patients who completed the double-blind period were eligible to receive open-label adalimumab for a further 144 weeks. Patients were permitted to continue on concomitant NSAIDs, prednisolone ≤10mg/day, methotrexate ≤25mg/week, sulfasalazine ≤3g/day and/or hydroxychloroquine ≤400mg/day or azathioprine ≤150mg per day (not with any other disease modifying antirheumatic drug) if the dose met pre-specified stability requirements prior to randomisation and remained stable during the first 24 weeks except as medically required due to an adverse event.[2]

The primary outcome was the proportion of patients who achieved an ASAS40 response at week 12. ASAS40 response was defined as a ≥40% improvement and an absolute improvement from baseline of ≥2 units (range 0 to 10) in ≥3 of the following four domains: Patient Global Assessment of Disease Activity (0 to 10cm VAS), pain (total back pain, 0 to 10cm VAS), function (Bath Ankylosing Spondylitis Functional Index [BASFI], 0 to 10cm VAS) and inflammation/morning stiffness (mean score of items five and six of the BASDAI, 0 to 10cm VAS) without any worsening in the remaining domain. This was measured in the full analysis set which consisted of all randomised patients who received at least one dose of blinded study medication but excluded seven patients from one site due to investigator non-compliance.[2]

ASAS40 response at week 12 was achieved by 36% (33/91) of patients in the adalimumab group compared with 15% (14/94) of patients in the placebo group, $p<0.001$. In the licensed population subgroup of patients with objective signs of inflammation by elevated CRP and/or MRI, ASAS40 response at week 12 was achieved by 41% (28/69) of patients in the adalimumab group compared with 14% (10/73) of patients in the placebo group, $p<0.001$.[2]

There were nine ranked secondary endpoints supporting the primary outcome that were all significantly improved in the adalimumab group compared with the placebo group in the whole study population and in the licensed subgroup.[2]

There were significant improvements in quality of life in the adalimumab group compared with the placebo group. The mean change from baseline in short form 36 (SF-36) physical component summary score was 5.5 and 2.0 in the adalimumab and placebo groups respectively, $p=0.001$. The mean change from baseline measured by the Health Assessment Questionnaire modified for Spondyloarthropathies (HAQ-S) total score was -0.3 and -0.1 respectively, $p=0.025$.[2]

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

Summary of evidence on comparative safety

The incidence of adverse events during the double-blind period was similar between the treatment groups; 58% and 59% of patients in the adalimumab and placebo groups respectively experienced an adverse event. The most common adverse events experienced in the adalimumab group were nasopharyngitis (11.6% versus 3.1%), nausea (7.4% versus 8.2%) and headache (6.3% versus 3.1%). A serious adverse event was experienced by 3.2% and 1% of patients respectively. An adverse event led to study drug discontinuation in 2.1% and 1% of patients respectively.[2]

The safety profile of adalimumab for other indications is well established, no new safety concerns were identified in the ABILITY-1 study.

Summary of clinical effectiveness issues

Adalimumab is the first treatment to be licensed for patients with severe nr-axSpA. This is a chronic, debilitating, multifaceted disease of the joints and surrounding tissue, which mainly affects young and middle aged adults. Patients can have similar signs and symptoms as AS but do not have x-ray evidence of structural damage. There is an unmet need for effective therapies in patients who have achieved an inadequate response or are intolerant of NSAIDs. The ASAS recommended anti-TNF drugs for patients with axial SpA who have achieved an inadequate response or are intolerant of NSAIDs in 2010 despite none of them being licensed for this indication.[3] SMC clinical experts advise that patients may currently receive best supportive care including NSAIDs and physiotherapy, disease modifying antirheumatic drugs such as sulfasalazine or off-label use of anti-TNF agents.

In ABILITY-1 the response rate at week 12, measured by ASAS40, was significantly higher in patients with nr-axSpA treated with adalimumab compared with placebo. The primary outcome was supported by several secondary endpoints.

ASAS40 is an established outcome measure for AS however it is not validated for axial SpA. The European Medicines Agency (EMA) considered it justified to use ASAS response. The primary outcome was measured at week 12 which is short for a potentially life-long therapy; the open-label extension study is currently ongoing. Data are available to week 68, and the week 12 efficacy results have been sustained at week 68.[2] Intolerance to NSAIDs was only defined in the study protocol by the investigators discretion. There were a high number of protocol violations in the study however the EMA considered that this did not affect the outcome of the study.[1]

The EMA requested an ad-hoc expert group meeting which confirmed that axial SpA is a clinical entity that is considered established in the rheumatology community. Symptom control is an acceptable treatment goal for anti-TNF therapy. The EMA was concerned that the ASAS definition of nr-axSpA was not specific enough and that patients who did not have nr-axSpA could potentially be treated with adalimumab. A positive MRI or elevated CRP improves the specificity of the ASAS classification therefore this was added to the marketing authorisation. The marketing authorisation is therefore based on a subgroup (77%) of the clinical study by population.[1]

Patients in the study were required to have received at least one NSAID prior to study entry or have a contraindication to NSAID treatment. According to the ASAS 2010 recommendations, patients should have tried two NSAIDs for a minimum of four weeks in total as first line therapy (unless contraindicated) before considering an anti-TNF agent.[3] In the ABILITY-1 study, 70% of all patients had received two NSAIDs before study entry.[1]

Increased use of an anti-TNF agent will impact on the service; monitoring for adverse events, such as infections, will be required. Clinicians are accustomed to using these drugs in other rheumatology indications so will be familiar with the adverse effect profile.

Adalimumab is administered by subcutaneous injection every other week, patients can be taught to self administer or have the injection administered by district nurses.

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

Summary of comparative health economic evidence

The company submitted a cost-utility analysis evaluating adalimumab versus continuing conventional therapy only (combination of physiotherapy and NSAIDS, or palliative care for those unable to tolerate NSAIDs) for patients with nr-axSpA confirmed by elevated C-reactive protein (CRP) or positive MRI and who have had an inadequate response, or are intolerant to, NSAIDs. There may be some element of conventional therapy provided with adalimumab although what this consists of was not clear from the company submission. The comparator was justified on the grounds that conventional therapy represents standard of care in nr-axSpA and there are no other licensed anti-TNF agents for these patients. However, SMC clinical experts have indicated that current practice also involves off-label use of anti-TNFs. The economic model consisted of two health states: responder or non-responder until 12 weeks, with a responder defined as achieving an ASAS40 response. The BASDAI and BASFI scores of responders and non-responders drive the utility outcomes in the model. As nr-axSpA is a chronic disease the post 12 week outcomes are modelled over a 40 year time horizon in the base case.

The primary data source for the economic analysis was the pivotal ABILITY-1 study sub-population with elevated CRP or a positive MRI, with the placebo arm representing conventional therapy. Data for the 12 week double blind period were used to determine 12 week ASAS40 responder status in the model, representing 40.6% and 13.7% in the adalimumab and placebo/conventional therapy groups respectively. A key assumption is that 12 week responders to adalimumab are assumed to continue treatment, whereas responders to placebo/conventional therapy are assumed to instantly lose response and their BASDAI and BASFI scores are assumed to return to baseline scores. Regression analysis using open label ABILITY-1 follow-up data available in published form to week 68 was used to model an estimated improvement over time in BASDAI and BASFI scores for adalimumab responders. After week 12 the BASDAI scores were assumed to remain constant for patients receiving only conventional therapy (i.e. who had discontinued adalimumab or who were the placebo/conventional therapy only patients), whereas the BASFI scores were assumed to worsen over time for patients on conventional therapy based on linear regression analysis of symptom duration and BASFI using baseline data from the ABILITY-1 study. Discontinuations from adalimumab treatment over time were also modelled with regression analysis using the 68 week data. Utility estimates were based on a modelled association of BASDAI and BASFI scores with to EQ- 5D data collected within the ABILITY-1 study. Mortality was assumed to be the same as in the general population.

The cost of adalimumab included resources associated with patient monitoring with estimates used in previous anti-TNF health technology assessments, and expert opinion. All patients were assumed to be able to self-administer adalimumab hence no cost was included for administration. The costs of serious adverse events including TB were estimated based on published data. Resource use associated with the healthcare management of nr-axSpA, including the use of NSAIDs, physiotherapy, GP and specialist appointments, and hospitalisations, was derived from an observational study in ankylosing spondylitis patients and

was conducted in Netherlands, France and Belgium. Regression analysis was used to determine a relationship between BASDAI score and healthcare costs, with BASFI score used in sensitivity analysis.

The base case result was an incremental cost per quality adjusted life year (QALY) gained for adalimumab of £16,154 per QALY vs conventional therapy, based on an incremental cost of £8,349 and incremental QALYs gained of 0.52. The incremental drug cost was £12,228 but there were estimated healthcare cost offsets with adalimumab of -£4,913. In a sub-group analysis of patients receiving ≥2 prior NSAIDS, in line with ASAS guidelines, the incremental cost effectiveness ratio (ICER) was only slightly higher at £17k/QALY. The ICER varied within a reasonably narrow range (£14k - £21k/QALY) in a variety of scenario analyses covering alternative criteria for response, constant discontinuation rates, alternative utility and cost equations, shorter time horizons, varying discount rates, or assuming no BASFI worsening. However, a combined scenario in which the placebo responders BASDAI/BASFI was assumed not to return to baseline at week 12, assuming constant rather than time-dependent discontinuation rates and BASFI not assumed to worsen with conventional therapy increased the ICER vs conventional therapy to £39,838/QALY gained.

The main issue with the economic analysis is the immediate loss of benefit assumed for conventional therapy responders. The company argued that the response in the ABILITY-1 study for placebo/conventional therapy at 12 weeks was likely to be due to a placebo response that would not be seen in clinical practice. However, it seems implausible that conventional therapy alone in practice would not be associated with some benefit. Additional analysis provided by the company assuming conventional therapy responders retained a level of clinical benefit over the model time horizon has resulted in more plausible ICERs between £25-£28k/QALY gained.

The additional analyses have provided an indication of the effect of varying the level of benefits associated with conventional therapy therefore the economic case for adalimumab has been demonstrated.

SMC clinical experts advised that there is some off-label use of anti-TNFs in patients who satisfy criteria for nr-axSpA and noted that biologic agents would not be used unless patients had imaging evidence of AS.

Summary of patient and public involvement

A Patient Interest Group submission was received from the National Ankylosing Spondylitis Society (NASS)

Additional information: guidelines and protocols

The ASAS published a 2010 update to the recommendations for the use of anti-TNF agents in patients with axial SpA. All patients should have tried a minimum of two NSAIDs for a minimum of four weeks in total, unless contraindicated. Pre-treatment with a DMARD is not required in patients with predominately axial manifestations. All patients with axial SpA should be considered for the use of an anti-TNF agent as the burden of disease is similar in patients with

radiographic and non-radiographic SpA and the efficacy of anti-TNF drugs was considered similar. Anti-TNF therapy should be continued for at least 12 weeks to assess for response.[3]

Additional information: comparators

There are no other treatments licensed for nr-axSpA. Patients may currently receive best supportive care including NSAIDs and physiotherapy, disease modifying antirheumatic drugs such as sulfasalazine or off-label use of anti-TNF agents.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Adalimumab	**40mg by subcutaneous injection every other week**	**9,156**

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 18 December 2012.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 596 in year 1 rising to 813 in year five with an estimated uptake rate of 100% and a discontinuation rate of 59.4% in all years. The gross impact on the medicines budget was estimated to be £3.035m in year 1 and £3.104m in year 5. As no other drugs were assumed to be displaced the net medicines budget impact is expected to remain as £3.035m in year 1 and £3.104m in year 5. Please note these figures are for all patients (responders and non-responders). The net budget impact may be significantly less than the company estimates as SMC clinical experts state that some of the costs will be offset from displaced medicines.

References

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

1. The European Medicines Agency (EMA) European Public Assessment Report. Adalimumab (Humira®). 21/06/2012, EMEA H-C-000481/II/0085. www.ema.europa.eu

2. Sieper J, van der Heijde D, Dougados M et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Annals of the Rheumatic Diseases 2012;0:1-8

3. Van der Heijde D, Sieper J, Maksymowych WP et al. 2010 update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70:905–908

This assessment is based on data submitted by the applicant company up to and including 15 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.

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.