adalimumab, 40mg solution for injection (Humira®) No. (468/08)
Abbott Laboratories Ltd

09 May 2008

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission:

adalimumab 40mg solution for injection (Humira®) is accepted for restricted use within NHS Scotland for treatment of chronic plaque psoriasis in adult patients who failed to respond to or have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA.

Its use should be restricted to patients with severe disease as defined by a total Psoriasis Area Severity Index (PASI) score of ≥10 and a Dermatology Life Quality Index (DLQI) of >10. Adalimumab improves both signs and symptoms of psoriasis and quality of life compared to placebo and an active non-biological comparator. The manufacturer presented a sufficiently robust economic case to gain acceptance by the SMC for patients with severe disease who achieve a PASI 75 response from baseline at 16 weeks. Continuation of therapy beyond 16 weeks should be carefully reconsidered in patients not responding within this time period.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA.

Dosing information

80mg administered subcutaneously followed by 40mg every other week starting one week after the initial dose.

Product availability date

Not applicable

Summary of evidence on comparative efficacy

Adalimumab is a human monoclonal antibody that binds to tumour necrosis factor (TNF) and exerts an immunonomodulatory effect in a range of conditions.

The sponsor company has requested consideration for use within the licence for adalimumab but restricted to patients with severe disease.

In all the studies described below, the maintenance dose of adalimumab described was preceded by a single loading dose of 80mg, and the primary efficacy endpoint was based on the Psoriasis and Severity Index score (PASI). PASI is a composite index indicating the severity of erythema, scaling and thickness weighted by the amount of coverage in three main body areas.

There is one active-comparator study involving patients with plaque psoriasis who were candidates for systemic therapy or phototherapy. Adults with moderate to severe disease for at least one year were randomised 2:2:1 to adalimumab 40mg every other week (eow), methotrexate dose escalation from 7.5mg to 25mg (if required and tolerated) or placebo over 16 weeks in a double blind, double dummy fashion. The primary endpoint was the proportion of subjects achieving ≥75% improvement in PASI from baseline to 16 weeks (PASI 75) in the intention to treat (ITT: as randomised) population. If superiority of adalimumab over placebo was established superiority of adalimumab over methotrexate was tested.

Patients (n=271) had a baseline PASI score of around 20. The proportion of subjects achieving PASI 75 was 80% in the adalimumab group, 36% in the methotrexate group and 19% in the placebo group. The risk difference was significant for the comparisons of adalimumab versus placebo (60%; 95% confidence intervals [CI] 44% to 77%) and for adalimumab versus methotrexate (44%; 95% CI 31% to 57%). Differences were also significantly in favour of adalimumab over both groups for PASI 90 and PASI 100 at week 16, the percentages of patients reporting good or complete disease severity control.

In a second trial (n=1212) involving patients with moderate to severe plaque psoriasis for at least six months, adalimumab was significantly superior to placebo in achieving a PASI 75 response over a 16-week double-blind period (71% versus 6.5%) and showed sustained response over an open-label period of 17 weeks during which all patients who responded in the first phase received adalimumab. Patients with sustained response were re-randomised to adalimumab or placebo in a second 19-week double-blind period during which loss of

adequate response was defined as <PASI 50 compared with week 0 and at least a 6-point increase in PASI score relative to week 33. Adalimumab was associated with a significantly lower rate of loss of response than placebo (4.9% versus 28%).

Open label extension data have shown sustained efficacy for up to 120 weeks.

In both pivotal studies quality of life was assessed using the Dermatology Quality of Life Index (DLQI). Adalimumab was significantly superior to all comparators for change from baseline in DLQI score and to placebo for the proportion of patients with a score of 0 (no dermatology-specific impairment in quality of life).

Summary of evidence on comparative safety

In the active comparator trial adverse events (AE) occurred in 74% (79/107) patients in the adalimumab groups compared with 82% (90/110) for methotrexate and 79% (42/53) with placebo. Serious adverse events occurred in 1.9%, 0.9% and 1.9% of patients respectively and 0.93%, 5.5% and 1.9% of patients discontinued due to adverse events. There was no significant difference between groups in the percentage of patients with infectious AE and there were no serious infections in any group. There were two reports of elevated liver function tests with adalimumab, ten with methotrexate and four with placebo.

From a pooled safety analysis of patients receiving at least one dose of adalimumab for plaque psoriasis in seven studies, the sponsor company concludes that the safety data do not represent new safety findings and are consistent with the safety database for adalimumab in other indications.

Summary of clinical effectiveness issues

The only active-comparator data are against methotrexate whereas adalimumab is licensed for use in patients who have failed to response to systemic agents, including methotrexate, or where these are contraindicated or intolerant. Patients with previous exposure to systemic therapy were included in both pivotal trials, however this was not a requirement for inclusion and the active-comparator trial excluded patients previously exposed to methotrexate.

The sponsor company has requested consideration for use within the licence for adalimumab but restricted to patients with severe disease. The pivotal trials recruited patients with moderate to severe psoriasis with about half of patients overall classified as severe or very severe by Physician's Global Assessment at baseline. The submission provided *post-hoc* analysis which indicated that response rates were similar in patients with more severe disease compared to the overall study populations. However these did not correspond exactly to the definitions of severity used to define severe disease eligible for the use of biological therapy in UK guidelines (see below).

Although there are long-term data from extension studies these tended to include fewer patients as the trials proceeded.

Adalimumab offers the advantage of reduced frequency of dosing compared with other anti-TNF agents given by injection (every other week compared with twice weekly for etanercept and weekly for efalizumab). While infliximab is given less frequently, it requires to be given by infusion.

Summary of comparative health economic evidence

The manufacturer adapted the economic model developed by York University for the NICE assessment of treatment of severe psoriasis. This assessed the cost-effectiveness of individual treatments relative to supportive care, and in the light of this the optimum treatment sequence for a given willingness to pay.

The clinical data inputs were the various response rates of treatments. These were derived by the manufacturer in an update of the meta-analysis of the NICE assessment of psoriasis, this being extended to include the relevant adalimumab trials. A range of comparator treatments were considered including intermittent and continuous use etanercept. SMC experts indicated that among severe patients etanercept is most likely to be displaced among the comparator treatments. They also noted that whilst intermittent etanercept was used in NHSScotland, due to flares, many if not most patients would progress to continuous use of etanercept.

Most other inputs were as per the original York model, though the submission differed on a number of points, notably:

- The dosing for intermittent etanercept was drawn from US data;
- The quality of life associated with intermittent etanercept was adjusted to account for psoriasis flares;
- Quality of life increments for the various response states were derived from adalimumab trial data.

Applying the quality of life increments anticipated among the severe patient sub-group, the main result of the analysis was that all the biological treatments including adalimumab had marginal cost-effectiveness estimates relative to best supportive care. But among the biological treatments, the manufacturer estimated that adalimumab was by far the most likely to be cost-effective and should be used in sequence prior to other biologicals. Adalimumab has a cost per QALY of approximately £30k which was lower than the other biological agents.

The cost-effectiveness of the biological treatments relative to best supportive care was sensitive to assumptions around the incidence of hospitalisation among non-responders and their average length of stay. The position of adalimumab within the cost-effective sequence of treatments was sensitive to the dosing assumed for intermittent use etanercept.

Weaknesses of the analysis included: not all patients within the adalimumab trials having failed on systemic therapy; the dosing for intermittent etanercept use being derived from US sources with an assumption that all patients were using etanercept intermittently, resulting in low dose intermittent use being 88% of low dose continuous use; and 100% of non-responders being hospitalised for 21 days per year.

However, despite this the manufacturer presented a reasonable case that among patients with severe psoriasis adalimumab would be more cost-effective than continuous use etanercept. As a consequence, the manufacturer presented a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

In June 2005, the British Association of Dermatologists (BAD) issued guidelines on the use of biologics. These stipulate that eligible patients for treatment with etanercept, efalizumab and infliximab should have had severe disease defined by a PASI of at least 10 or more and a DLQI of more than 10 for at least six months, should be resistant to treatment and a candidate for systemic therapy, and should fulfil at least one of a range of other criteria.

The National Institute for Health and Clinical Excellence (NICE) published guidance on the use of etanercept and efalizumab for adults with psoriasis in the UK in July 2006. Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met:

- The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10.

- The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments.

Efalizumab, within its licensed indications, is recommended for the treatment of adults with plaque psoriasis only if their psoriasis has failed to respond to etanercept or they are shown to be intolerant of, or have contraindications to, treatment with etanercept.

Additional information: previous SMC advice

After review of a full submission the Scottish Medicines Consortium (SMC) issued guidance on 7 May 2007 that infliximab (Remicade®) is accepted for restricted use within NHS Scotland for the treatment of severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant of other systemic therapy including ciclosporin, methotrexate or psoralen ultraviolet A (PUVA). Infliximab, compared to placebo, improves both signs and symptoms of psoriasis and quality of life in adults with plaque psoriasis. The economic case was demonstrated when used for patients with severe psoriasis who achieve a PASI 75 response or a 50% reduction in PASI and a 5 point reduction in DLQI from baseline at 10 weeks. It is one of several biologic interventions for the treatment of plaque psoriasis, some of which have lower drug acquisition costs.

After review of a full submission the Scottish Medicines Consortium (SMC) issued guidance on 10 January 2005 that efalizumab (Raptiva®) is not recommended for use within NHS Scotland for the treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or have a contra-indication to, or are intolerant to other systemic therapies, including ciclosporin, methotrexate and PUVA (photochemotherapy). For patients with moderate to severe psoriasis, efalizumab was superior to placebo in producing a Psoriasis Area Severity Index (PASI) 75 improvement response. However

cost-effectiveness was not demonstrated. The licence holder has indicated their decision to resubmit.

Additional information: comparators

Three other biologicals are licensed in moderate to severe psoriasis in patients for whom standard systemic therapy is ineffective or inappropriate.

Cost of relevant comparators

Drug	Dose regimen	Cost per course (£)
Adalimumab	**80mg sc followed by 40mg every other week starting one week after initial dose**	**5005[A]**
Infliximab	5mg/kg iv at weeks 0,2 and 6 then every 8 weeks	6294-8392*[A]
Etanercept	25mg or 50mg sc twice a week	4290 - 6435 [B]
Efalizumab	700 micrograms/kg then 1mg/kg sc weekly	4061*[A]

* for 60kg to 80kg patient; A = based on 24-week course, although summary of product characteristics do not define a maximum duration; B =based on maximum recommended courses of 25mg twice weekly for 24 weeks or 50mg twice weekly for 12 weeks, then 25mg twice weekly for 12 weeks; iv = intravenous infusion; sc = subcutaneous injection. Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 7th March 2008.

Additional information: budget impact

The manufacturer estimated a gross drug cost of £5.8 million in year 1, falling to £4.5 million for years 2 to 5. A net drug cost of between £4 million and £5 million was estimated by the manufacturer, on the assumption that these patients would otherwise be on systemic therapy. The manufacturer estimated possible additional savings in terms of reduced hospitalisations of £2.5 million annually.

If used then adalimumab is most likely to displace other biologicals and therefore the net drug cost would be more modest.

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.

This assessment is based on data submitted by the applicant company up to and including 18 April 2008.

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.

The undernoted references were supplied with the submission.

Saurat J, Stingl G, Dubertret L, Papp K, Langley R, Ortonne J, Unnebrink K, Kaul M Camez A. Efficacy and seafety results from the randomised controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). British Journal of Dermatology 2007; DOI 10.1111/j.1365-2133.2007.08315.x Article in Press.

Menter A, Tyring S, Gordon K, Kimball A, Leonardi C, Langley R et al. Adalimumab therapy for moderate to severe psoriasis: A randomised, controlled phase III trial. Journal of the American Academy of Dermatology, 2007; 0.1016/j.jaad.2007.09.010. Article In press.