Scottish Medicines Consortium

Infliximab 100mg powder for intravenous infusion (Remicade®) No. (318/06)

Schering-Plough UK Ltd

9 March 2007

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

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.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of moderate to 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).

Dosing information

5mg/kg by intravenous infusion over two hours at weeks 0, 2 and 6, then every eight weeks

Product availability date

29th September 2005

Summary of evidence on comparative efficacy

Infliximab, a TNF-antagonist, is a human-murine monoclonal antibody against TNF. It binds to TNF and antagonises its biological activity.

Three double-blind trials recruited adults with plaque psoriasis for at least 6 months that was moderate to severe, as defined by at least 10% body surface area involvement and psoriasis area and severity index (PASI) score at least 12. All included patients who had received prior systemic or phototherapy for psoriasis, with the larger two trials also including patients who were candidates for these therapies. After discontinuing any topical and systemic therapies for psoriasis for at least 2 and 4 weeks respectively, patients were randomised in 1:2, 1:4 and 2:3 ratios in the respective trials to placebo or infliximab 5mg/kg by intravenous (iv) infusion over two hours at weeks 0, 2 and 6. In the two larger trials double-blind treatment continued up to one year. In one of these studies patients assigned to infliximab continued to receive this every 8 weeks and patients assigned to placebo received infliximab 5mg/kg by iv infusion at weeks 24, 26, 30, 38 and 46. In the other study patients in the placebo group received infliximab 5mg/kg by iv infusion at weeks 16, 18, 22, 30, 38 and 46 and patients assigned to infliximab were re-randomised at week 14, with stratification for week 10 PASI response status, to regular infliximab every 8 weeks or to “as required” infliximab given when PASI improvement from baseline was less than 75% at study visits that occurred every 4 weeks. Some trials included additional infliximab treatment arms using unlicensed doses and results for these are not presented here. In all studies the primary outcome, which was the proportion of all randomised and treated patients achieving at least 75% improvement on the PASI score (PASI 75) at week 10, was significantly greater with infliximab 5mg/kg compared to placebo, as were the proportions of patients achieving improvements of 50% and 90% on the PASI score (PASI 50 and PASI 90) and responses on the physician global assessment scale (PGA), as shown in the table.

Psoriasis area and severity index (PASI) and physician global assessment (PGA) results at week 10 in patients with moderate-to-severe plaque psoriasis.

	Study A		Study B		Study C	
	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo
	N=99	N=51	N=301	N=77	N=314	N=208
PASI 75 responders	88%	5.9%	80%	2.6%	75.5%	1.9%
PASI 50 responders	97%	22%	91%	7.8%		
PASI 90 responders	58%	2.0%	57%	1.3%	45%	0.5%
PGA responders	90%	9.8%	83%	3.8%	76%	1.0%

PASI 50, 75 and 90 response = improvement of ≥50%, ≥75% and ≥90%, respectively, of psoriasis area and severity index (PASI) score from baseline; PGA response = minimal or cleared symptoms on the static physician global assessment scale (PGA) for studies A and B and, for study C, = 100% clear (clear) or 75-99% clear (excellent clearing) relative to baseline score.

Maintenance treatment

In the large trial where patients received infliximab or placebo up to 24 weeks, analyses at this point, which censored data for 25 infliximab-treated patients who were lost to follow-up, indicated that significantly more patients achieved PASI and PGA responses with infliximab compared to placebo. Similar analyses were conducted at week 50, which also censored data for 9 patients in the placebo group who did not receive infliximab after week 24. In the other large trial 299 patients from the infliximab 5mg/kg group were re-randomised at week 14 to continue this as regular maintenance therapy every 8 weeks (n=150) or “as required” (n=149). In analyses of PASI and PGA responses at week 50 data were censored for 15 to 16 patients in each of the groups who were lost to follow-up. No statistical comparison between the groups was reported. The results are detailed in the table below. In both trials response rates with infliximab had declined at week 50 compared to week 10, and would be lower if the analyses had been performed on an intention-to-treat basis without censoring of data from patients lost to follow-up.

Psoriasis area and severity index (PASI) and physician global assessment (PGA) results at weeks 24 and 50 in patients with moderate-to-severe plaque psoriasis.

	Study B				Study C	
	Week 24		Week 50		Week 50	
	Infliximab	Placebo	Infliximab	Placebo / infliximab	Infliximab regular	Infliximab as required
	N=276	N=77	N=281	N=68	N=134	N=134
PASI 75 responders	82%	3.9%	61%	77%	55%	38%
PASI 50 responders	90%	7.8%	69%	90%	72%	74%
PASI 90 responders	58%	1.3%	45%	50%	34%	10%
PGA responders	74%	2.6%	53%	68%	58%	42%

PASI 50, 75 and 90 response = improvement of ≥50%, ≥75% and ≥90%, respectively, of psoriasis area and severity index (PASI) score from baseline; PGA response = minimal or cleared symptoms on the static physician global assessment scale (PGA) for studies A and B and for study C = 100% clear (clear) or 75-99% clear (excellent clearing) relative to baseline score.

Quality of life

In all trials described previously improvements from baseline to week 10 on the dermatology life quality index (DLQI) were significantly superior with infliximab compared to placebo, with significant differences between infliximab and placebo at week 24 in one of the larger trials. In this study there were significant improvements on the physical and mental composite score of the short-form (SF-36) questionnaire with infliximab compared to placebo at week 10 and 24. In the two larger studies within the groups treated with infliximab for 50 weeks, improvements in quality of life score were smaller at week 50 than at week 10. One of these trials was included in the review by the European regulatory authority and it considered that this was most likely driven by the proportion of patients who lost response by week 50.

Summary of evidence on comparative safety

Infliximab and etanercept are associated with increased incidences of infection, including opportunistic infections and tuberculosis, probably due to suppression of the immune system, which may also mask signs of fever. Efalizumab, (a recombinant human IgG antibody that antagonises the activity of leucocytes) also affects the immune system and its summary of product characteristics notes that its effect on active and / or chronic infections is not fully understood. There is concern that drugs that modify the immune system may increase the risk of malignancies. There is no clinical evidence of this, however, long-term data are required to exclude this.

Summary of clinical effectiveness issues

Infliximab is licensed for patients who are unresponsive to or intolerant of systemic therapies including ciclosporin, methotrexate or psoralen ultraviolet A (PUVA). In the smaller trial all patients had received at least one previous systemic or phototherapy and in the larger trials prior systemic therapies, including PUVA, methotrexate, ciclosporin, or acitretin had been received by many of the patients. However, the European regulatory authority noted that patients were not necessarily resistant to these. In practice, it is possible that patients treated with infliximab and the benefits obtained with it may differ from those in the trials. The European regulatory authority also noted that subgroup analysis within one of the larger studies indicated that PASI response rates were consistent across previous systemic agent subgroups supporting the possibility that infliximab may be efficacious in those who may have been intolerant or resistant to other medications. These findings were supported by subgroup analyses of the other large trial.

There are no trials directly comparing infliximab with etanercept or efalizumab in adults with psoriasis who have failed to respond to systemic therapies. An indirect comparison of these was performed using methodology from the health technology assessment of etanercept and efalizumab for treatment of psoriasis performed by the National Institute for Health and Clinical Excellence (NICE). It indicated that infliximab was associated with greater PASI 75 response rates than etanercept or efalizumab. However, as noted in the health technology assessment report, it was not possible to exclude the possibility of systematic differences between the sets of trials used to compare different treatments.

Summary of comparative health economic evidence

The manufacturer submitted a probabilistic cost-utility model to examine the cost effectiveness of infliximab compared to etanercept 25mg or 50mg (continuous use and intermittent use) and also compared to efalizumab in patients with severe psoriasis.. Intermittent etanercept is the regimen indicated in recent NICE guidance however Scottish experts indicate that there currently is some usage of continuous etanercept. An indirect comparison was necessary and this used the Bayesian hierarchical approach adopted in the NICE report. The model looked at the costs and benefits of treatment over a ten-year period, with treatment being continued only in patients who demonstrated a PASI 75 response after 10 to 12 weeks. Patients who failed to respond were assumed to revert to supportive care, which involved an average 21-day inpatient stay per patient per year. Utility values were taken from the NICE report.

On the basis of the indirect comparison, infliximab was more effective than etanercept or efalizumab, but also was more expensive. The results showed that the incremental cost effectiveness ratio (ICER) of infliximab compared to twice weekly 25mg etanercept used continuously was £27,354 per quality adjusted life year (QALY). Compared to 25mg of intermittent etanercept, the ICER was £34,196. Extensive sensitivity analysis was provided. This indicated that the ICER versus continuous etanercept exceeded £30,000 if the utility gains with treatment fell, the length of hospitalisation for non-responders reduced below 18.5 days per annum, or the 97.5 centile of etanercept effectiveness was used. However, the ICER improved to around £23,000 if the annual inpatient resource usage increased to 25 days per year. The ICER versus intermittent etanercept fell below £30, 000 if the annual inpatient resource usage was 25 days or greater or if higher utility values were used.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The 2005 British Association of Dermatologists guidelines for use of biological interventions in psoriasis recommend these for patients who have severe disease, defined as a PASI score of at least 10 (or an affected body surface area of at least 10% if PASI is not applicable) and a DLQI score of at least 10. Disease should have been severe for at least six months duration; resistant to treatment and the patient should be a candidate for systemic therapy. Also patients should fulfil one additional clinical criteria in line with the guidance.

The July 2006 NICE technology appraisal of etanercept and efalizumab for the treatment of adults with psoriasis recommends etanercept and efalizumab, within their licensed indications, for the treatment of adults with plaque psoriasis according to defined criteria. Efalizumab is however only recommended if their psoriasis has failed to respond to etanercept or they are shown to be intolerant of or have a contraindication to etanercept.

Additional information: previous SMC advice

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 10th December 2004 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.

Additional information: comparators

The TNF-antagonist, etanercept, and efalizumab, a recombinant human IgG antibody that antagonises the activity of leucocytes, are licensed for the treatment of moderate to severe plaque psoriasis in adults who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate or PUVA. NICE recommends both of these drugs for the treatment of adults with plaque psoriasis.

Additional information: costs

Drug	Dose	Cost per course (£)
Infliximab	**5mg/kg iv at weeks 0, 2 and 6 then every 8 weeks**	**8392*[B]**
Etanercept	25mg or 50mg sc twice a week	4290-6435[A]
Efalizumab	700mcg/kg initially then 1mg/kg sc weekly	4061[B]

* for 60kg to 80kg patient, for a patient weighing <60kg costs would be £6294; A = 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; B = based on 24-week course, although summary of product characteristics do not define a maximum duration; doses do not imply therapeutic equivalence; iv = intravenous infusion; sc = subcutaneous injection.

Annual costs of topical preparations depend upon the area of skin affected and severity of this relapsing and remitting condition. These are generally lower than the cost of infliximab, with 100g packs of the commonly prescribed moderate, potent and very potent corticosteroid creams, clobetasone butyrate 0.05% (Eumovate®), betamethasone valerate 0.1% (generic) and clobetasol propionate 0.05% (Dermovate®) costing £5.77, £2.96 and £8.39, respectively, and 120g and 100g packs of the commonly prescribed vitamin D analogues, calcipotriol (Dovonex®) and calcitriol (Silkis®) costing £24.04 and £16.34, respectively. Twelve packs of these respective types of topical treatment would cost approximately £35 to £100 and £200 to £300.

Additional information: budget impact

The manufacturer estimated a gross drug cost of infliximab of £545k in year one rising to £1.8m in year five. The net budget impact was £270k in year one and £1.07m by year five after taking account of the costs if these patients were to be treated with supportive care instead. The net costs take account of the levels of inpatient usage and other supportive care costs that were used in the economic model for non-responders. These figures assumed that 38 patients would be treated in year one rising to 150 by year five and that infliximab would be used in 40% of eligible patients. These figures assume that responding patients receive continuous treatment with infliximab every 8 weeks. Some Scottish clinical experts have suggested that these figures underestimate the likely patient numbers and the number of eligible patients could be up to ten times greater than the manufacturer's prediction.

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 16 February 2007

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.

Gottlieb AB, Evans R, Li S et al. Infliximab induction therapy for patients with severe plaque psoriasis: a randomised, double-blind, placebo-controlled trial. J Am Acad Dermatol 2004; 51: 534-42.

Reich K, Nestle FO, Papp K et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet 2005; 366:1367-74

Menter A, Feldman SR, Weinstein GD et al. A randomised comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol 2006; 1-13.