PUBLIC SUMMARY DOCUMENT

Product: Infliximab, powder for I.V. infusion, 100 mg, Remicade®

Sponsor: Schering-Plough Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

The submission seeks to extend the Section 100 (Highly Specialised Drug) listing for infliximab to include the treatment of severe plaque psoriasis.

2. Background

The PBAC has not previously considered a submission from the sponsor requesting the PBS listing of infliximab, a biological disease modifying anti-rheumatic drug (bDMARD), for the treatment of severe plaque psoriasis.

Infliximab was listed for the treatment of rheumatoid arthritis on 1 November 2003 and for ankylosing spondylitis on 1 August 2004. Infliximab was recommended for listing for psoriatic arthritis at the March 2006 PBAC meeting; however, the listing had not been implemented at the time of writing. Several applications for use in Crohn's disease have been considered and rejected by the PBAC between 2000 and 2003.

3. Registration Status

Infliximab is TGA registered for the treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate. Safety and efficacy beyond 12 months have not been established.

4. Listing Requested and PBAC's view

Section 100 (HIGHLY SPECIALISED DRUGS PROGRAM)
Public and private hospital authority required
The requested Section 100 restriction for infliximab was expansive and based on the Section 85 restriction for efalizumab

The PBAC recommended that the restriction be closely aligned to the current restriction for efalizumab, noting that there it may be appropriate to allow co-administration of infliximab with methotrexate, as this has been shown to reduce the rate of formation of antichimeric antibodies and therefore possible tachyphylaxis with infliximab.

5. Clinical place for the proposed therapy

The PBS listing of infliximab for severe plaque psoriasis will provide clinicians with an alternative bDMARD therapy for patients whose condition is refractory to other systemic treatments or phototherapy.

6. Comparator

The submission nominated efalizumab as the appropriate comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented an indirect comparison via a Bayesian meta-analysis of 4 randomised trials of infliximab against placebo, and 4 randomised trials of efalizumab against placebo. Infliximab was dosed at 5 mg/kg intravenously at day 0, and at 2 and 6 weeks, and then every 8 weeks, however the PASI 75 response used in the comparison was measured at 10 weeks. Efalizumab was dosed at 0.7 mg/kg subcutaneously as an initial dose and then weekly doses at 1.0 mg/kg. Here, the PASI 75 response used in the comparison was measured at week 12.

The trials published at the time of the submission were as follows:

Trial/First author	Publication title	Publication citation
Gordon et al. 2003a/ Gordon KB.	Efalizumab for patients with moderate to severe plaque psoriasis: a randomised controlled trial.	JAMA 2004 Mar 3;291:1070.
Lebwohl et al. 2003b/ Lebwohl M.	A novel targeted T-cell modulator, efalizumab, for plaque psoriasis.	NJM 349:2004-2013.
Leonardi et al. 2005/ Leonardi CL.	Extended efalizumab therapy improves chronic plaque psoriasis: Results from a randomised trials phase III trial.	Journal of the American Academy of Dermatology 52:425-433.
Ortonne et al. 2005/ Ortonne JP.	Impact of efalizumab on patient-reported outcomes in high-need psoriasis patients: results of the international, randomised, placebo-controlled Phase III Clinical Experience Acquired with Raptiva (CLEAR) trial [NCT00256139].	BMC Dermatology 5:13.
Papp et al. 2001/Papp K.	The treatment of moderate to severe psoriasis with a new anti-CD11a monoclonal antibody.	Journal of the American Academy of Dermatology 45:665-674.
Krueger et al. 2005b/ Krueger GG.	Impact of efalizumab T cell modulation on immune response in psoriasis patients.	Journal of Investigative Dermatology 124:A44.
EXPRESS/ Reich K.	Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial.	Lancet 366(9494):1367-1374.
Chaudhari et al. 2001b/ Chaudhari U.	Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial.	Lancet 357:1842-1847.
SPIRIT/ Feldman SR.	Infliximab treatment results in significant improvement in the quality of life of patients with severe psoriasis: A double-blind placebo-controlled trial.	British Journal of Dermatology 152:954-960.

8. Results of Trials

The event rates for placebo were similar across the infliximab versus placebo and efalizumab versus placebo trials. Treatment with either infliximab or efalizumab resulted in statistically significant increases in PASI 75 response compared to placebo.

From the indirect analysis there was a statistically significant difference in number of PASI 75 responders at week 10 favouring infliximab (5 mg/kg) compared with efalizumab (1 mg/kg) at week 12. However, the PES Commentary noted that longer term data showed that at 24 weeks the number of patients with a PASI 75 response had dropped to 75% (from 79% at week 10). At 50 weeks, PASI 75% response in infliximab patients had further dropped to 54% of patients treated raising the concern of a possible decrease in effectiveness over time with infliximab.

The PBAC noted the Pre-Sub-Committee Response stated that although the proportion of PASI responders at week 50 had decreased to 56% from 75.4% at week 24, the ITT analysis was affected by patient drop-outs because after 24 weeks patients in the placebo group were permitted to cross-over to active treatment.

Infliximab was found to be more toxic than placebo with infections, infusion reactions, antinuclear antibodies (ANA) production of specific concern. However, infections and infusion reactions occurring in the 5 mg/kg infliximab group reached statistical significance at week 50 of the EXPRESS trial and week 10 of the SPIRIT trial. Efalizumab was also found to be more toxic than placebo with significantly higher incidences of infections, headaches, chills myalgia and pain at 12 weeks that becomes insignificant by 24 weeks of treatment (i.e. no worse than placebo). In terms of total adverse events, infliximab and efalizumab were similar at weeks 24 and 12 weeks respectively with around 80% of patients experiencing an adverse event. By 24 weeks the incidence of adverse events with infliximab was 81.9% rising to 93.3% by week 50.

The PBAC was advised of several safety related concerns with infliximab including:

- The safety of infliximab over the long term (appearance of hepatic enzymes, ANA). In the EXPRESS trial approximately 20% of patients developed antibodies to infliximab. The TGA evaluation noted that the number of patients developing antibodies increased with duration of use and questioned whether antibodies development had influenced the reduction in response rates over time. An additional concern was the development of allergic reactions, noting that in the UK, NICE requires that infliximab be administered with methotrexate, which is thought to reduce the incidence of allergic reactions at the time of infusion.

- The rate of discontinuation of infliximab over 50 weeks was 20.6% and 27.4% in the EXPRESS and EXPRESS II trials, respectively, despite the very good response rate with infliximab.

9. Clinical Claim

On the basis of an indirect comparison, the submission claimed that infliximab is more effective than efalizumab at 10 and 12 weeks respectively and had similar toxicity.

The PBAC accepted that the clinical data demonstrate that infliximab is more effective than efalizumab at 10 and 12 weeks respectively, but considered that there is good evidence to suggest that infliximab's efficacy declines over time and it is associated with more toxicity.

The PBAC recommended listing for the treatment of severe chronic plaque psoriasis in patients who meet certain criteria on a cost-minimisation basis with efalizumab. The equi-effective doses are infliximab 5mg/kg for 7.25 infusions for 1 year and efalizumab 1 mg/kg/week for 1 year.

10. Economic Analysis

A preliminary economic evaluation was presented. The resources included were study drug and cost of administration. The trial-based incremental cost per extra PASI 75 responder was estimated to be in the range of $15,000 - $45,000.

A modelled economic evaluation was presented. Costs of drug and administration were modelled over a period of 254 weeks. Utility values for three health states (responder, non-responder and discontinuation) were derived from correlating patient DLQI scores from each health state to a formula describing a relationship between DLQI and EQ-5D scores (determined from an independent data set). Discontinuation rates and PASI 75 response rates for which there was no clinical trial data were extrapolated from available trial data. The base case modelled incremental discounted cost per extra discounted QALY was in the range of $45,000 - $75,000.

The PBAC rejected the submission's claim of cost-effectiveness over efalizumab on the grounds of a high incremental cost-effectiveness ratio which would increase if the utility values derived by Zug et al (1995) are used.

11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS is estimated to be in the range of $10 million - $30 million in Year 3. Based on the assumption that there is continuous erosion of eligible patients the cost to the PBS is higher in the first year, in the range of $30 million - $60 million, than in the third. Therefore these calculations are likely underestimates.

12. Recommendation and Reasons

The PBAC recommended listing for the treatment of severe chronic plaque psoriasis in patients who meet certain criteria on a cost-minimisation basis with efalizumab. The equi-effective doses are infliximab 5mg/kg for 7.25 infusions for 1 year and efalizumab 1 mg/kg/week for 1 year. The PBAC considered that the administration costs agreed between the Department and the sponsor for the listing of infliximab in psoriatic arthritis were appropriate to this listing.

The PBAC recommended that the restriction be closely aligned to the current restriction for efalizumab, noting that there it may be appropriate to allow co-administration of infliximab with methotrexate, as this has been shown to reduce the rate of tachyphylaxis with infliximab, as this has been shown to reduce the rate of formation of antichimeric antibodies and therefore possible tachyphylaxis with infliximab.

The PBAC considered that interchangeability arrangements with efalizumab, similar to those applying to the biological agents for the treatment of rheumatoid arthritis and ankylosing spondylitis be developed, and that a 5 year exclusion period should apply following failure to demonstrate a response. Consultation with the sponsors and other relevant stakeholders will be required in developing interchangeability rules.

The PBAC accepted that the clinical data demonstrate that infliximab is more effective than efalizumab at 10 and 12 weeks respectively, but considered that there is good evidence to suggest that infliximab's efficacy declines over time and it is associated with more toxicity. Another issue of particular concern is tachyphylaxis. The PBAC rejected the submission's claim of cost-effectiveness over efalizumab on the grounds of a high incremental cost-effectiveness ratio in the range of $45,000 - $75,000 which would increase if the utility values derived by Zug et al (1995) are used.

Recommendation

Restriction to be finalised.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment