PUBLIC SUMMARY DOCUMENT

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

Sponsor: Schering-Plough Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission requested an extension to the previously recommended Section 100 (Highly Specialised Drug) Authority Required listing to include the treatment of refractory moderate to severe Crohn's disease in paediatric patients (aged 6-17 years inclusive).

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This drug has not previously been considered for this patient group by the PBAC.

At the March 2007 meeting, the PBAC recommended the listing of infliximab for the treatment of patients with severe Crohn's disease (Crohn's Disease Activity Index ≥ 300) or patients with an ileostomy or colectomy due to Crohn's disease on the basis of high and acceptable cost-effectiveness, compared to placebo. Acceptable cost-effectiveness was demonstrated at a dose of 5 mg/kg infliximab for three doses (weeks 0, 2 and 6) and when continuation of treatment beyond three doses was determined by remission (CDAI ≤ 150) at approximately 12 weeks from the commencement of treatment. The PBAC recommended that where a response to infliximab was not demonstrated patients would not be eligible to recommence treatment with infliximab within 12 months of the date on which the treatment ceased. *(See also Public Summary Document for March 2007).*

3. Registration Status

Infliximab is registered by the TGA for the following indications:
RHEUMATOID ARTHRITIS IN ADULTS: infliximab, in combination with methotrexate, is indicated for the reduction of signs and symptoms and prevention of structural joint damage (erosions and joint space narrowing) in: patients with active disease despite treatment with methotrexate; patients with active disease who have not previously received methotrexate. Infliximab should be given in combination with methotrexate. Efficacy and safety in Rheumatoid Arthritis have been demonstrated only in combination with methotrexate.

ANKYLOSING SPONDYLITIS: infliximab is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease.

CROHN'S DISEASE IN ADULTS AND IN CHILDREN AND ADOLESCENTS (6-17 YEARS): infliximab is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.

REFRACTORY FISTULISING CROHN'S DISEASE: infliximab is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.

PSORIATIC ARTHRITIS: infliximab is indicated for the treatment of the signs and symptoms of active psoriatic arthritis in adults where previous response to disease-modifying anti-rheumatic drugs (DMARDS) has been inadequate.

PSORIASIS: infliximab is indicated 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.

ULCERATIVE COLITIS: infliximab is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy

4. Listing Requested and PBAC's View

Section 100 Public and private hospital - Authority required

Initial treatment by a gastroenterologist or paediatrician of paediatric patients (aged 6 to 17 inclusive) with moderate to severe Crohn's disease who meet all of the following initiation criteria:

1. Confirmed Crohn's disease, defined as standard clinical, endoscopic and/or imaging features, including histological evidence, with diagnosis confirmed by a gastroenterologist, and

2. Severity of disease activity results in a Paediatric Crohn's Disease Activity Index Score (PCDAI) > 30 or by clinical discretion if the patient has an ileostomy or has had a colectomy[1], and

3. Have failed an adequate trial of conventional therapy; ie, unless contraindicated, patients must be unable to tolerate, or be unresponsive to two of the following three treatments:

   (a) A tapered course of steroids, starting at ≥ 40 mg prednisolone (or equivalent), over a six week period,

   (b) An eight week course of enteral nutrition

   (c) Immunosuppressive therapy, including azathioprine or 6-mercaptopurine or methotrexate at optimal dosage for at least 3 months.

Failure of conventional therapy is shown by a PCDAI > 30 despite an adequate trial of these treatments as defined above.

The authority application must be in writing and must include the information used to determine the patient's eligibility as defined by the above criteria. Dose and maximum

quantity for initial course of infliximab: 3 doses at 5 mg/kg body weight per dose at weeks 0, 2 and 6.

Public and private hospital – Authority required

Continuing treatment by a gastroenterologist, paediatrician or consultant physician in consultation with a gastroenterologist, of paediatric patients (aged 6 to 17 inclusive) with moderate to severe Crohn's disease who have received three doses of PBS-subsidised treatment with infliximab.

A maximum of 24 weeks of treatment (3 infusions) with infliximab will be authorised under this criterion. At the time of the authority application, medical practitioners should request the appropriate

[1] This would be expected to be negligible amongst paediatric patients

number of vials, based on the weight of the patient, to provide sufficient for a single infusion at a dose of 5 mg per kg. Up to a maximum of 2 repeats will be authorised. No applications for increased repeats will be authorised. Where fewer than 2 repeats are initially requested with the authority prescription, authority approvals for sufficient repeats to complete a maximum of 24 weeks of treatment may be requested by telephone.

Applications for PBS-subsidised treatment will not be authorised for paediatric patients who have failed two PBS-subsidised courses of treatment with infliximab.

The PBAC recommended therapy be limited to patients with a Paediatric Crohn's Disease Activity Index (PCDAI) of more than 30 points despite an adequate trial of two of three conventional treatments (corticosteroids, enteral nutrition, or immunosuppressants). A course of three doses at 5 mg/kg per dose at weeks 0, 2 and 6 was recommended for initial treatment, and for continuation therapy, three doses (24 weeks) treatment could be authorised subject to the patient demonstrating an improvement in the PCDAI of at least 15 points and a total PCDAI score of 30 points or less. Further continuation therapy providing 3 doses per authority application would be subject to the level of improvement being maintained at least 15 points below the baseline PCDAI level and below 30 points.

The PBAC considered a continuation rule was required not only to ensure that use remained cost-effective, but also to reduce the potential for harm due to the risk of infection and malignancy, following long-term usage.

The PBAC also considered prescribing of infliximab should be limited to gastroenterologists and paediatricians.

5. Clinical Place for the Proposed Therapy

Infliximab would provide clinicians with a biological Disease Modifying Anti-Rheumatic Drug (bDMARD) therapy for Crohn's patients who continue to have active disease despite optimal treatment with conventional therapies.

6. Comparator

The nominated comparator was placebo as add on to immunosuppressive agents.

7. Clinical Trials

The submission presented a single direct randomised open-label comparative trial (REACH) comparing infliximab 5 mg/kg induction (weeks 0, 2, 6) and maintenance regimen every 8 weeks with every 12 weeks over 54 weeks in paediatric patients with moderate to severe Crohn's disease. Only patients responding at week 10 were eligible to continue with the maintenance phase of treatment. This trial had not been published at the time of submission.

No comparison against placebo was available.

8. Results of Trials

Comparative effectiveness

1. The primary outcome in the REACH trial was the proportion of patients achieving a response at week 10, where response was defined as a decrease from baseline in the PCDAI score of at least 15 points with a total score of no more than 30 points. Secondary outcomes included response and remission at week 54. Remission was defined as a PCDAI score ≤12.5.

2. All patients were in clinical response at week 10. At week 30, 73.1% of patients in the 8-weekly treatment arm were responders compared with 47.1% in the 12 weekly treatment arm. At week 54, 63.5% of patients in the 8- weekly treatment arm were responders compared to 35.3% in the 12-weekly treatment arm. The patient remission rates were 59.6% and 35.3% at week 30 and 55.8% and 23.5% at week 54, for the 8-weekly and 12-weekly treatment arms, respectively.

Based on the presented remission and response rates in REACH for patients receiving infliximab maintenance treatment every 8 weeks or every 12 weeks, the PBAC considered there was uncertainty associated with the clinical evidence submitted as the single trial presented was an open label comparative trial in which all patients received an induction regimen of infliximab 5 mg/kg and then were randomly assigned to maintenance regimens every 8 or 12 weeks at the same dose, but with no comparison against placebo.

Comparative toxicity

The proportion of patients with one or more adverse event in the 8-weekly arm (96.2%) was similar to that for the 12-weekly arm (92.0%). The system-organ class with the highest incidence of adverse events was the gastrointestinal system (75.5% versus 72%, respectively), followed by the respiratory system (60.4% versus 66%, respectively). The most common infusion reactions observed in REACH were flushing, injection site infiltration and dyspnoea, and the rates comparable between trial arms (17% versus 18%), respectively.

The long-term safety of maintenance infliximab in Crohn's disease was uncertain, but the potential for the development of some rare but serious adverse events including hepatosplenic T-cell lymphoma is of concern.

9. Clinical Claim

The submission described infliximab as having significant advantages in effectiveness over placebo but having more toxicity.

See Recommendation and Reasons for PBAC's view.

10. Economic Analysis

The submission presented a trial-based economic evaluation. The choice of the cost-effectiveness approach was considered valid. The resources included were drug and drug administration costs.

The trial based incremental cost effectiveness ratio (ICER) was estimated to be in the range of $15,000 - $45,000 for both response and remission.

The submission presented a modelled economic evaluation. The choice of the cost-utility approach was considered valid. The resources included were drug costs, administration costs, health resource use (number of GP and specialist visits, hospital days, emergency and casual visits, and other Crohn's disease related medication costs).

The base case modelled incremental cost/QALY was estimated to be in the range $15,000 - $45,000.

The PBAC questioned the utility values derived from a small survey of Australian clinicians and agreed that the utility values obtained lacked face validity.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of vials dispensed/year to be less than 10,000 in Year 5 (2012).

The submission estimated the financial cost/year to the PBS to be less than $10 million in Year 5 (2012).

12. Recommendation and Reasons

The PBAC noted the advice provided during the hearing that Crohn's disease in children is a severe phenotype with adverse effects on growth and development and which may cause depression. The PBAC was advised that the PCDAI is a better validated instrument than the CDAI though not all components would have an impact on utility.

The PBAC recommended the listing of infliximab for the treatment of Crohn's disease in patients aged 6-17 years inclusive who are refractory to conventional therapies, on the basis of acceptable cost-effectiveness compared to placebo, and in line with the comments and recommendations reflected in this Public Summary Document.

Recommendation

INFLIXIMAB, powder for I.V. infusion, 100 mg
For full restriction, see
http://www.health.gov.au/internet/wcms/publishing.nsf/Content/public-summary-documents

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

The sponsor chose not to make a comment.