PUBLIC SUMMARY DOCUMENT

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

Sponsor: Schering-Plough Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

The re-submission requested an extension to the Section 100 Authority Required listing to include the treatment of severe refractory Crohn's disease.

2. Background

Submissions requesting subsidy of infliximab for refractory moderate to severe Crohn's disease have been considered at three PBAC meetings: June 2000, December 2000, and September 2001. On each occasion the PBAC rejected the request for subsidy.

3. Registration Status

Infliximab is registered by the Therapeutic Goods Administration (TGA) for the following indications:
RHEUMATOID ARTHRITIS IN ADULTS: Remicade, 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: 1.patients with active disease despite treatment with methotrexate, 2.patients with active disease who have not previously received methotrexate. Remicade should be given in combination with methotrexate. Efficacy and safety in Rheumatoid Arthritis have been demonstrated only in combination with methotrexate.
ANKYLOSING SPONDYLITIS: Remicade is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease.
CROHN'S DISEASE: Remicade 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: Remicade is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure.
PSORIATIC ARTHRITIS: Remicade 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: Remicade 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.

Infliximab was approved by the TGA for maintenance treatment of moderate to severe Crohn's disease in July 2003.

4. Listing Requested and PBAC's View

Section 100 Authority Required Listing (Highly Specialised Drug)

Public and private hospital authority required
Initial treatment by a gastroenterologist of adult patients with severe Crohn's disease who satisfy the following criteria; and, who have signed a consent form, authorised by Medicare Australia, to indicate acceptance that PBS subsidy of infliximab will cease if the required response criteria are not met. Patients must meet 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 that results in a Crohn's Disease Activity Index Score (CDAI) $\geq$ 220 or by clinical discretion if the patient has an ileostomy or has had a colectomy, and

3. Failed an adequate trial of conventional therapy; unless contraindicated, patients must be unable to tolerate, or be unresponsive to:

- A tapered course of steroids, starting at $\geq$ 40 mg prednisolone (or equivalent), over a six week period, and
- Immunosuppressive therapy, including azathioprine or 6-mercaptopurine or methotrexate at optimal dosage for $\geq$ 3 months.

With failure of conventional therapy defined as having a CDAI $\geq$ 220 despite an adequate trial of conventional therapy defined above.

The authority application must be in writing and must include the information used to determine the patient's eligibility under the criteria above. 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, or consultant physician in consultation with a gastroenterologist, of adults with severe Crohn's disease who have received three doses of PBS-subsidised treatment with infliximab and who, at the time of application have achieved or sustained a response to treatment with infliximab. Response is defined as a reduction in Crohn's Disease Activity Index Score (CDAI) of $\geq$ 70 points from baseline CDAI.

The first application for continuing treatment should be made following administration of the first three infusions; (i.e. approximately 12 weeks from the commencement of treatment). Second and subsequent applications for continuing treatment must be made in writing and posted to Medicare Australia no less than 2 weeks prior to the date the next dose is scheduled, to ensure continuity of treatment.

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 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.

Patients who fail to demonstrate or sustain a response to treatment with infliximab for Crohn's disease as specified in the criteria for continuing treatment with infliximab will not be eligible to recommence treatment with this drug within 12 months of the date on which treatment was ceased.

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

Where re-treatment with infliximab after a break in PBS-subsidised treatment with infliximab is being sought, the reason for and date of cessation of the previous treatment course with infliximab must be included in the application.

Public and private hospital authority required
Initial treatment – Grandfather listing (to be developed by the Pharmaceutical Benefits Branch and Schering Plough)

Public and private hospital authority required
Continuing treatment – Grandfather listing (to be developed by the Pharmaceutical Benefits Branch and Schering Plough)

See Recommendation and Reasons for PBAC's view.

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 including surgery.

6. Comparator

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

7. Clinical Trials

The submission presented an unadjusted indirect comparison of infliximab 5 mg/kg induction and maintenance treatment (from the newly presented trial ACCENT 1) compared to placebo (from the previously presented trial T16, excluding patients with fistulae).

The trials published at the time of the submission are tabulated below:

Trial/First author	Protocol title/Publication title	Publication citation
Targan et al. (1997) (T16)	A short-term study of chimeric monoclonal antibody cA2 to tumour necrosis factor (alpha) for Crohn's disease.	NEJM 337 (15): 1029-1035.
Hanauer et al. (2002)	Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial.	Lancet 359 (9317): 1541-1549.

The original primary trial endpoints (ACCENT 1: loss of response to week 54; T16: clinical response at week 4) were not the primary endpoints used in the submission. Clinical response (CDAI score ≤70 from baseline) at week 14 was the new primary endpoint for the submission re-analysis, conducted using individual patient data. The Pre-Sub-Committee response advised the CDAI outcome of a reduction of 70 points or more was defined a-priori in T16 and ACCENT 1 and was agreed previously at a stakeholder meeting in 2002.

8. Results of Trials

Week 14 and 54 results of the unadjusted indirect re-analysis are summarised in the table below.

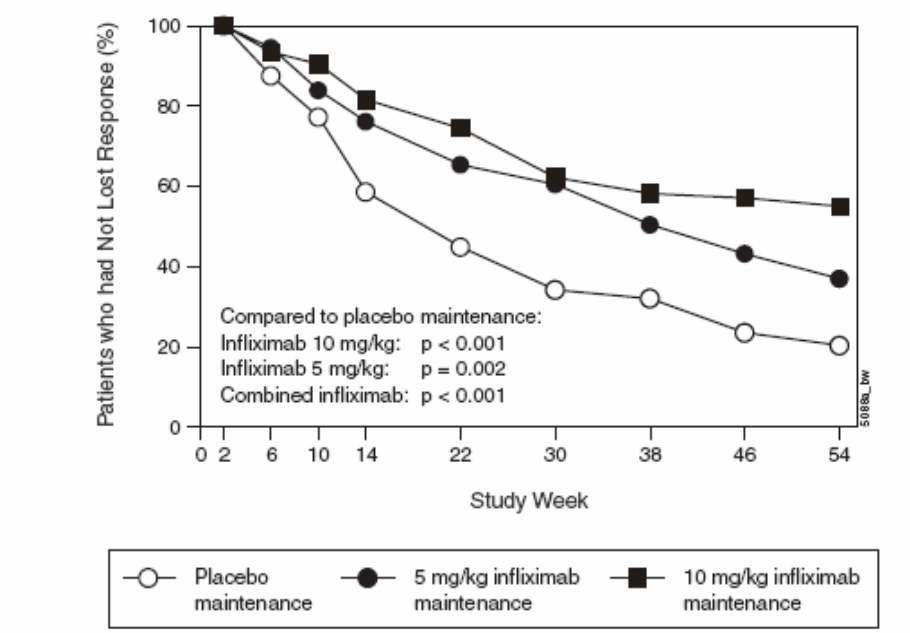
Clinical response and remission at week 14 – IPD re-analysis in the re-submission based on CDAI score

	ACCENT I 5mg/kg N=192	T16 Placebo N=19	Estimated effect (induction + active maintenance 5 mg/kg vs. placebo		
			OR (95%CI)	ARD (95%CI)	p value
Week 14					
Response (%ITT [a])	99 (51.6)	0 (0.0)	41.5 (2.47, 697.17)	51.6 (44%, 59%)	<0.0001
Remission (%ITT [a])	67 (34.9)	0 (0.0)	20.98 (1.25, 352.85)	34.9 (28%, 42%)	0.0006
Week 54					
Response (%ITT[a])	63 (32.8)	0 (0)	19.12 (1.14, 321.48)	32.8 (26%, 39%)	0.0011
Remission (%ITT [a])	44 (22.9)	0 (0)	11.69 (0.69, 197.45)	22.9 (17%, 29%)	0.0155

At week 14, 51.6% of the patients in the infliximab 5 mg/kg treatment arm, compared with 0.0% of patients in the placebo arm ($p<0.0001$), were considered to have a clinical response. Clinical remission was observed in 34.9% and 0.0% ($p=0.0006$) of the infliximab 5 mg/kg and placebo arms, respectively.

The PBAC also considered evidence in the ACCENT I publication (Hanauer et al 2002) which presented the results for patients randomised at week 2 as responders. See figures below.

Kaplan Meier estimate of the proportion of patients who had not lost response by time interval through week 54: ACCENT I (only patients randomised as responders at week 2)[a]



a: P-values for comparing Remicade active maintenance groups (each and combined) versus placebo maintenance group were log-rank tests. Patients included only those randomised as responders (as per study report Fig 14). NB. even placebo maintenance patients had received infliximab induction dose.

Incremental effect of multiple doses as compared to single dose:

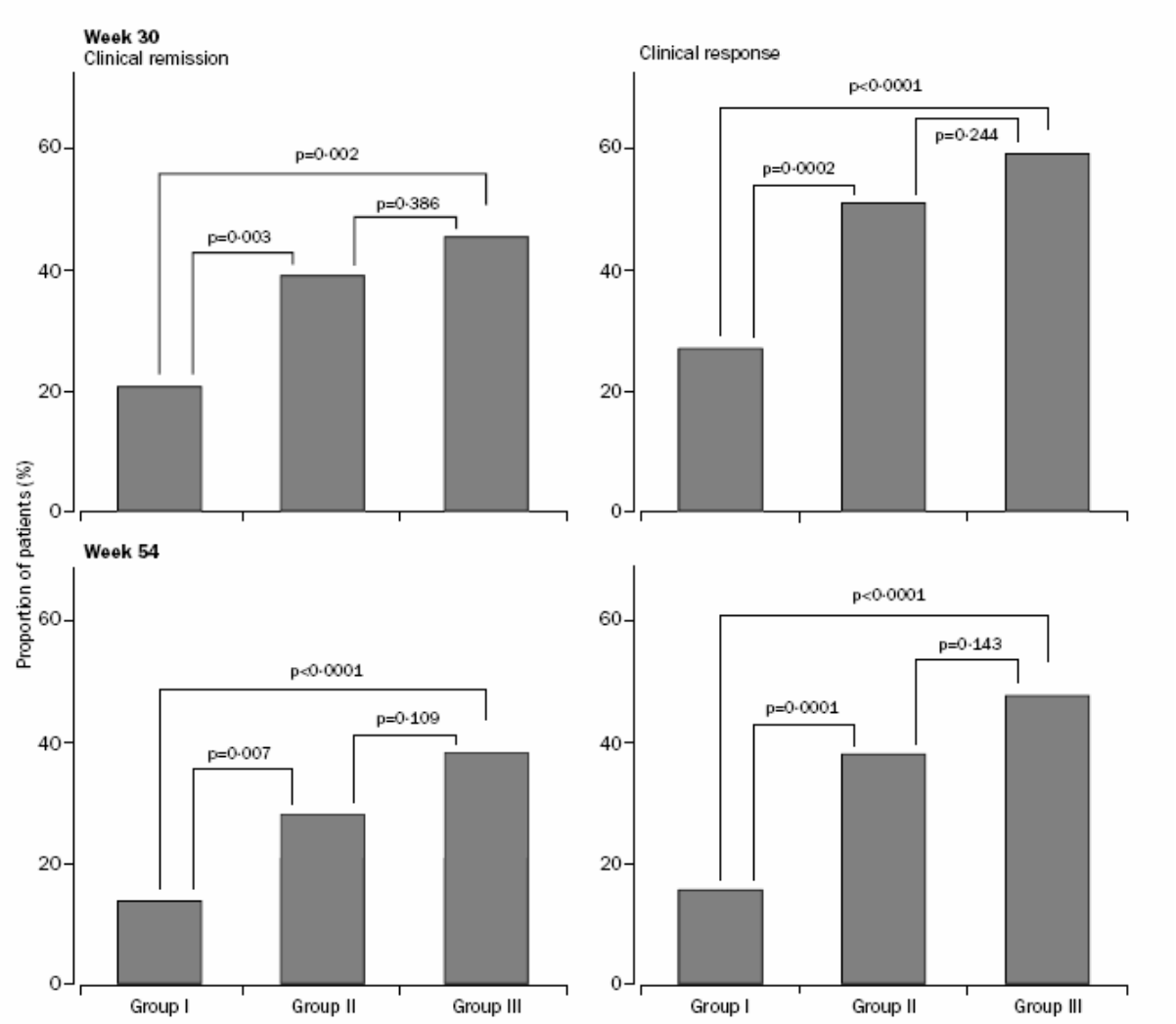


Figure 2: **Clinical response and clinical remission for week-2 responders**
Clinical response=reduction in CDAI to ≥70 points and ≥25% from baseline. Clinical remission=CDAI <150 points.

Median CDAI and IBDQ scores to week 54.

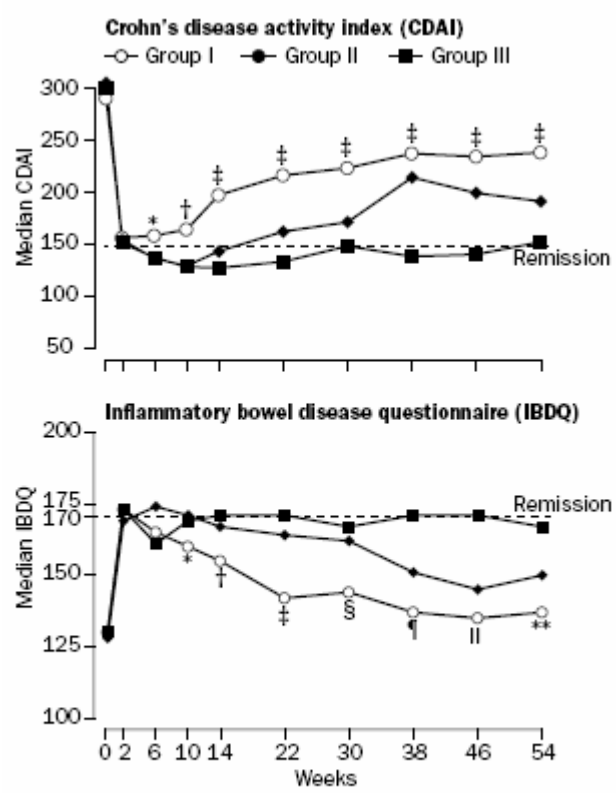


Figure 4: **Median CDAI and IBDQ scores to week 54 among week-2 responders**

The PBAC noted that the evidentiary basis for the re-submission's request for listing was weak, because the re-submission did not provide direct data comparing a maintenance regimen of multiple doses of infliximab with placebo, which was what the submission requested. The indirect comparison was hindered by differences in the populations enrolled in the placebo arm of T16 trial and the 5 mg/kg arm of ACCENT 1 trial. On the other hand, the data provided helped in identifying the relevant benefits and harms of short-term versus long term use of infliximab.

Adverse events data was derived directly from the included trials. No individual patient data was available for re-analysis of adverse events. Infliximab was associated with a greater frequency of adverse events than placebo (65% versus 24%). Mild infusion reactions were relatively common (6.1%), however, one serious allergic reaction occurred. The incidence of delayed hypersensitivity reactions was low (2.6%). Post-marketing surveillance continued to observe low rates of malignancy, delayed hypersensitivity reactions and auto-immune conditions.

9. Clinical Claim

The submission claimed that infliximab, through multiple injections, has significant advantages over placebo but has more toxicity.

See Recommendation and Reasons for PBAC's views.

10. Economic Analysis

An updated preliminary economic evaluation using a cost-effectiveness approach was presented.

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

An updated modelled economic evaluation adopting a cost utility approach was presented.

The base case modelled incremental cost/QALY was estimated to be in the range of $45,000 - $75,000.

The PBAC noted uncertainties associated with the model.

11. Estimated PBS Usage and Financial Implications

The likely number of vials sold/year was estimated to be < 10,000 in Year 2008-2009.

The financial cost/year to the PBS was estimated to be in the range of $10 - $30 million in Year 2007-2008.

12. Recommendation and Reasons

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.

The PBAC noted that listing had been sought for patients with moderate to severe disease (CDAI ≥ 220) based on an unadjusted indirect comparison of infliximab 5 mg/kg induction and maintenance treatment (ACCENT 1) compared to a subset of the small placebo arm of the T16 trial (n=19). The indirect comparison was hindered by differences in the populations enrolled in two arms of the different the trials, however, the data provided did help in identifying the relevant benefits and harms of short-term use versus long-term use of infliximab.

While there are biologically plausible concerns of infection, malignancy and auto-immune diseases associated with the use of infliximab in Crohn's disease, the PBAC noted post-marketing surveillance to date has shown low levels of malignancy and auto-immune conditions.

The PBAC noted there were concerns with the modelled economic evaluation. The PBAC also noted the evidence provided in the agenda papers and at the hearing in relation to the clinical need for the drug in this patient group, and the potential for patients to benefit in terms of quality of life (QoL).

Overall, the PBAC considered the cost/QALY of between $45,000 - $75,000 was high and uncertain. However, by limiting infliximab to a more severe population and requiring a demonstration of remission for continuing therapy, the PBAC considered that the incremental cost-effectiveness ratio would improve sufficiently (albeit by an unknown amount) to allow a positive recommendation. The PBAC recommended that those Crohn's disease patients with an ileostomy or colostomy also be eligible because the severity of their disease is underestimated by the CDAI and there is no suitable alternative instrument to gauge the severity of their disease in a way that can be correlated with the CDAI. However, the PBAC would be pleased to receive further information from the sponsor about the effect on the incremental cost-effectiveness ratio of relaxing these restrictions to allow either PBS subsidy for infliximab in less severe patients and/or continuation of PBS-subsidised infliximab for those achieving a response rather than a remission.

Recommendation
INFLIXIMAB, powder for I.V. infusion, 100 mg

Restriction: Restriction to be finalised

Maximum quantity: 1
Repeats: nil

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 commends the PBAC for its decision to recommend Remicade for a select group of Crohn's disease patients, however believes that the criteria proposed by the PBAC are too restrictive.

In the interest of patients with severe Crohn's disease the sponsor accepts the PBAC recommendation.

Schering-Plough views this listing as a positive first step to assisting all patients with Crohn's disease and will continue to work with the Gastroenterological Society of Australia and the Australian Crohn's and Colitis Association towards making Remicade available to a broader patient population.