PUBLIC SUMMARY DOCUMENT
Product: INFLIXIMAB, powder for IV infusion, 100 mg, Remicade®
Sponsor: Schering-Plough Pty Ltd
Date of PBAC Consideration: March 2010

1. Purpose of Application:

The re-submission sought a Section 100 (Highly Specialised Drugs Program) Public and Private Hospital Authority Required listing for complex fistulising Crohn disease with a draining enterocutaneous or rectovaginal fistula.

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:

Infliximab is currently listed for the treatment of active ankylosing spondylitis, severe active rheumatoid arthritis, severe active psoriatic arthritis, severe chronic plaque psoriasis and severe refractory Crohn disease.

Infliximab has been considered on a number of occasions by the PBAC for fistulising Crohn disease. At the December 2000 meeting an application for an Authority required listing for treatment of draining enterocutaneous fistulae in patients with fistulising Crohn disease was rejected. The PBAC rejected the application because of the unknown clinical meaning of the trial endpoint, which did not necessarily indicate healing of fistulae, and unacceptable cost-effectiveness.

In September 2001, the PBAC rejected a resubmission because of unacceptably high cost-effectiveness ratios.

In a minor submission to the December 2001 meeting, the PBAC was asked to re-consider its decision to reject the listing of infliximab for fistulising Crohn disease. In the absence of any further information in support of the proposal that listing should be recommended on the basis of 'rule of rescue', the PBAC rejected the application.

3. Registration Status:

On 23 July 2004 the Therapeutic Goods Administration (TGA)-approved indication was amended to: refractory fistulising Crohn disease - for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure. The dosage was: induction - 5 mg/kg at weeks 0, 2 and 6; and maintenance – 5 mg/kg every 8 weeks after induction.

Infliximab was initially TGA registered on 23 June 2000 for the treatment of draining enterocutaneous fistulae in Crohn disease patients. The dose was to infuse 5 mg/kg IV, followed with additional 5 mg/kg doses administered at 2 and 6 weeks after the first infusion.

Infliximab is also TGA registered for rheumatoid arthritis in adults, ankylosing spondylitis, Crohn disease, psoriatic arthritis, plaque psoriasis and ulcerative colitis.

4. Listing Requested and PBAC's View:

The following is an abbreviation of the requested restriction.

Section 100 listing (Highly Specialised Drugs Program)

Public and private hospital authority required
Initial treatment of fistulising Crohn disease.
Complex fistulising Crohn disease with a draining enterocutaneous or rectovaginal fistula.
A maximum quantity and number of repeats to provide for an initial course of infliximab consisting of 5 doses at 5 mg per kg body weight per dose to be administered at weeks 0, 2, 6, 14 and 22 will be authorised.

Continuing treatment of fistulising Crohn disease.
An adequate response to infliximab treatment is defined as:
(a) closure of at least 50% in number of externally draining fistulae or
(b) a marked reduction in drainage of all fistulae together with less pain and induration as reported by the patient.

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.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy:

The submission claimed there are currently no other effective therapies available for patients with this condition.

6. Comparator:

The submission nominated placebo as the main comparator on the basis of no treatments being available for patients with complex fistulising Crohn disease which have proven efficacy for induction and maintenance of fistula closure. The PBAC considered this appropriate.

7. Clinical trials

The clinical evidence for this re-submission was provided by an indirect comparison of infliximab maintenance therapy from the ACCENT II trial with the placebo group of the T20 trial, by means of the common comparator arm of infliximab induction treatment. New trial toxicity data from the ACCENT II trial were also presented in the re-submission.

The ACCENT II trial evaluated 5 mg per kg infliximab induction plus maintenance therapy, but all patients received infliximab induction (the first 3 infusions) and were then randomised to maintenance treatment every 8 weeks with infliximab or placebo.
Trial T20 compared 5 mg per kg infliximab induction with placebo but there was no maintenance therapy.

The designs of the T20 and ACCENT II trials were different and consequently, the indirect comparison proposed by the submission was of uncertain validity, as the

infliximab induction arms were not the randomised 'common comparator' and did not represent the same patient spectrum. The T20 trial randomised patients to infliximab or placebo for induction. All patients in the ACCENT II trial underwent infliximab induction and then subsequently responders and non-responders were separately randomised to infliximab or placebo maintenance. Consequently, there was no valid common comparator for undertaking the indirect analysis. The eligible patients in T20 were in relapse. The eligible patients for ACCENT II which formed the basis of this submission were in remission.

Three reports of the studies included in the indirect comparison published at the time of submission are as follows:

Trial ID / First author	Protocol title / Publication title	Publication citation
Common reference infliximab induction treatment		
Infliximab		
Sands BE et al (2004)	Infliximab maintenance therapy for fistulising Crohn's disease.	Sands BE, Anderson FH, Bernstein CN, et al, NEJM 350(9):876–885. NEJM 2004; 350(9): 876-885
Sands BE et al (2004)	Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study.	Sands BE, Blank MA, Patel K, Van Deventer SJ, Clinical Gastroenterology & Hepatology 2004, 2(10): 912-920
Placebo		
Present DH et al. (1999)	Infliximab for the treatment of fistulas in patients with Crohn's disease.	Present DH, Rutgeerts P, Targan S, et al, NEJM 1999; 340(18): 1398-1405

8. Results of Trials

The primary outcomes used in the submission were not the primary outcomes from the randomised trials. The submission claimed that re-analysis of efficacy data was necessary to enable the use of a more practical and objective primary efficacy outcome of response ('proportion in response'). The primary outcome in the re-submission was the proportion of patients with response or complete response (remission) at Weeks 10 and 54, derived from re-analysis of data.

The primary outcome in the ACCENT II trial was the median time to loss of response. The median time to loss of response was greater than 40 weeks for the infliximab 5 mg per kg group and statistically significantly higher compared to 14 weeks in the placebo maintenance group (p=0.001).

The ACCENT II trial used a composite outcome to define loss of response. A loss of fistula response occurred when a patient had a reduction from baseline of less than 50 % in the number of draining fistulas; or a protocol-prohibited change in Crohn disease medication; or a surgical procedure for Crohn disease; or crossover to increased dose; or discontinuation of study follow-up because of lack of efficacy or loss of response.

Overall, 61 patients (62 %) in the placebo maintenance group had a loss of response, as compared with 40 patients (42 %) in the infliximab maintenance group. In both groups,

the most common criterion met for the loss of response was a need for a change in the treatment of Crohn disease (38 % of the placebo maintenance group and 25 % of the infliximab maintenance group) followed by the recrudescence of fistulas (22 % and 16 % respectively). This 6 % difference in the recrudescence of fistulas is the clinical outcome of most interest. However, the treatment effect modelled in the submission was different - using the post-hoc outcome of clinical response at 54 weeks, the incremental difference in treatment benefit in the economic model was 21.6 %.

The results of the primary outcome for Trial T20 showed a significantly greater proportion of infliximab 5 mg per kg (67.7 %) patients achieved a greater than or equal to 50 % reduction in draining fistulae for at least 2 consecutive evaluation visits, compared to placebo (25.8 %) patients (RR: 2.63: 95 % CI: 1.38, 5.00).

There was a significant difference in response rates of the common comparator arms of induction treatment in ACCENT II and trial T20 given the difference in the design of the two trials. Because of the difference, a calibration of the data was undertaken by dividing the time-weighted average of the common arm in ACCENT II by the time-weighted average of the common arm in T20, and applying the calibration factor to T20 placebo data. This was used to evaluate the clinical response and complete response (remission) rates over time, without stopping rules, for the treatment and comparator arms in the two key randomised trials (calibrated submission analysis), and extrapolate the calibrated T20 placebo and induction results using the rate of decay in response in the ACCENT II infliximab induction and maintenance arm over the same time period.

The PBAC was reassured however by the results of the alternative approach undertaken during the evaluation, which better maintained the with-in trial randomisation, to assess the treatment effect using the trial designs without any reanalysis, and followed by modelling the treatment effect of infliximab in series i.e. induction (from the T20) followed by maintenance (from the ACCENT II).

No statistically significant difference was observed between treatment arms of the ACCENT II trial. This was expected as both treatment arms had 3 induction doses of infliximab by week 10 and maintenance therapy had not begun. There were a statistically significantly greater proportion of responders in the infliximab compared with placebo arms in Trial T20. The response rates in the common reference arm of the two trials varied markedly (83.2 % compared with 54.8 % in ACCENT II and T20, respectively). The differences in the response rates for the common reference may have indicated that important differences between the trials exist, which are not obvious from the baseline characteristics of the trials nor from the design of the trials and the re-submission had not attempted to explain the differences.

The results of the indirect comparison indicated a statistically significant difference between infliximab and placebo treated patients (RR: 2.02; 95 % CI: 1.02, 4.02).

The effect of the calibration was to increase the response rate in the T20 common reference arm from 54.8 % to 73.8 % (the clinical response rate in the placebo arm was changed to 34.7 % from 25.8 %). Although closer, this remained different to the 83.2 % response rate in the common reference arm of the ACCENT II trial. The observed difference in the response rates to the common reference arm in the trials may have indicated that the use of these trial data in an indirect comparison may not be valid. The

method of calibration used to adjust these differences is also uncertain. The calibration effectively increased the placebo response and remission rates in Trial T20, however differences in the response rates remained. It was unclear whether the application of a calibration factor derived from time-weighted averages in the common reference arms of the trials was appropriate.

The results of the indirect comparison indicated a statistically significant difference between infliximab and placebo treated patients (RR: 1.98; 95 % CI: 1.16, 3.38), however, a claim of superiority based on the results of this indirect comparison is uncertain.

The re-submission presented new toxicity data for the ACCENT II trial. The key results are summarised below.

Summary of adverse events in the key randomised trials

Trial ID	Inflix 5mg/kg induction + continuous maintenance n/N (%)	Inflix 5mg/kg induction + placebo maintenance n/N (%)	RR (95% CI)
ACCENT II			
Any adverse event	123/138 (89.1%)	133/144 (92.4%)	*0.97 (0.90, 1.04)*
Serious adverse event	19/138 (13.8%)	33/144 (22.9%)	*0.60 (0.36, 1.00)*
Reasonably-related serious adverse event	3/138 (2.2%)	9/144 (6.3%)	*0.35 (0.10, 1.26)*
Adverse event leading to discontinuation	5/138 (3.6%)	12/144 (8.3%)	*0.43 (0.16, 1.20)*
Deaths	0	0	-
Infection	73/138 (52.9%)	66/144 (45.8%)	*1.15 (0.91, 1.46)*
Treated infection	47/138 (34.1%)	39/144 (27.1%)	*1.26 (0.88, 1.79)*
Serious infection	4/138 (2.9%)	9/144 (6.3%)	*0.46 (0.45, 1.47)*
Infusion reactions	13/138 (9.4%)	4/144 (2.8%)	***3.39 (1.13, 10.15)***
	Inflix 5mg/kg n/N (%)	**Placebo n/N (%)**	**RR (95% CI)**
Trial T20			
Any adverse event	20/31 (64.5%)	20/31 (64.5%)	*NC*
Serious adverse event	1/31 (3.2%)	0/31 (0%)	*3.00 (0.13, 70.92)*
Severe adverse event	6/31 (19.4%)	5/31 (16.1%)	*1.20 (0.41, 3.52)*
Adverse event leading to discontinuation	0	0	-
Treated infection	3/31 (9.7%)	3/31 (9.7%)	*NC*
Infusion reactions	2/31 (6.5%)	2/31 (6.5%)	*NC*

NC=not calculable

In the ACCENT II trial, the number of patients with infusion reactions was higher in the infliximab maintenance group compared with the placebo maintenance group (p=0.02). In trial T20, there were no differences in adverse events between infliximab 5 mg per kg and placebo.

The submission provided additional data on potential safety concerns beyond those identified in the clinical trials by providing the most recent Periodic Safety Update Report (PSUR). No other safety evidence beyond the randomised trials was provided.

9. Clinical Claim

The submission claimed infliximab as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over placebo.

The PBAC agreed that complex fistulising Crohn disease with a draining enterocutaneous or rectovaginal fistula is a difficult condition to treat –it is chronic, and spontaneously relapsing and remitting. Clinical evidence from both of the submitted trials demonstrated a substantial placebo response for both induction and maintenance treatment.
The induction trial T20 shows a 26 % response rate in the placebo arm; and the placebo response rate in the maintenance trial (ACCENT II) for patients without a prior response at induction was 16 % and for those patients with a prior response at induction a response was sustained for 38 % of patients. However patients were able to continue baseline standard therapies.

10. Economic Analysis

An updated modelled economic evaluation was presented. The utilities used in the re-submission were derived from an Australian study. Cost off-sets were calculated using resource utilisation in Jewell et al 2005[1] and relevant diagnosis-related group (DRG) costs from the National Hospital Cost Data Collection. The re-submission provided analyses assuming 3, 4 or 5 induction doses of infliximab.

The PBAC noted that the clinical evidence was presented as an indirect comparison of infliximab maintenance therapy in the ACCENT II trial with the placebo group of the T20 trial, via the common comparator arm of infliximab induction treatment. The design of the T20 and ACCENT II trials are different and consequently, the indirect comparison proposed by the submission is of uncertain validity, as the infliximab induction arms were not the randomised 'common comparator' and do not represent the same patient spectrum. The T20 trial randomised patients to infliximab or placebo for induction; all patients in the ACCENT II trial underwent infliximab induction and then subsequently responders and non-responders were separately randomised to infliximab or placebo maintenance. Thus, the validity of the common comparator for undertaking the indirect analysis is questionable. The eligible patients in T20 are in relapse. The eligible patients for ACCENT II which form the basis of this submission are both responders and non-responders. However, the PBAC was reassured by the results of the alternative approach, which maintained randomisation, to assess the treatment effect using the trial designs without any reanalysis, and then to model the treatment effect of infliximab in series i.e. induction (from the T20) followed by maintenance (from the ACCENT II).
The results of this approach, yielded an incremental cost per Quality Adjusted Life Year (QALY) gained in the range of $45,000 - $75,000, which was comparable with that claimed in the submission.

The results of the sensitivity analyses indicated that the model is most sensitive to changes in utility values. The model was also sensitive to hospitalisation cost offsets. The inclusion of hospitalisation costs lowered the incremental cost-effectiveness ratios substantially. The PBAC also noted that there was uncertainty about the hospital and procedure costs, based on a UK study included in the submission, which may have overestimated costs, favouring infliximab. There was also some uncertainty about the reliability of the Australian study used to derive utility values as a source for utilities with

[1] Jewell DP, Satsangi J, Lobo A et al, 2005, *Infliximab use in Crohn's disease: impact on health care resources in the UK*, Eur J Gastroenterol Hepatol., 17:1047−1052

and without fistula closure. However, these uncertainties were not considered sufficient to warrant rejection of the submission.

Details of the trial referred to above are noted in the table below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Jewell DP	Infliximab use in Crohn's disease: impact on health care resources in the UK.	Eur J Gastroenterol Hepatol; 2005: 17:1047−1052.

11. Estimated PBS Usage and Financial Implications:

The likely number of patients per year was estimated to less than 10,000 per year in the first year of listing. The submission estimated that the financial cost per year to the PBS minus any savings in use of other drugs would be less than $10 million per year for the Year 1 to Year 5 period. The PBAC noted that the submission's predictions of utilisation were a likely underestimate.

12. Recommendation and Reasons:

The PBAC recommended listing as a pharmaceutical benefit of infliximab under section 100 (Highly Specialised Drugs Program) Public and Private Hospital Authority Required for complex refractory fistulising Crohn disease with a draining enterocutaneous or rectovaginal fistula, on the basis of a high, but acceptable, cost effectiveness ratio, in the context of a serious medical condition that has a large impact on the quality of life of often otherwise healthy younger patients.

In terms of assessment for continuing therapy, the PBAC accepted that response could be assessed as either closure of at least 50 % in the number of externally draining fistulae (i.e. no drainage despite finger pressure in at least 50 % of fistulae) or a marked reduction in drainage of all fistulae together with less pain and induration as reported by the patient. The PBAC did not agree to the request for two extra doses in the initiation phase as this would not be consistent with the doses used in the trials or the TGA-approved dosing schedule.

The PBAC agreed that this is a difficult condition to treat - it is chronic, and spontaneously relapsing and remitting. Clinical evidence from both trials demonstrated a substantial placebo response for both induction and maintenance treatment. The induction trial T20 shows a 26 % response rate in the placebo arm; and the placebo response rate in the maintenance trial (ACCENT II) for patients without a prior response at induction was 16 % and for those patients with a prior response at induction a response was sustained for 38 % of patients.

The PBAC noted that the clinical evidence was presented as an indirect comparison of infliximab maintenance therapy in the ACCENT II trial with the placebo group of the T20 trial, via the common comparator arm of infliximab induction treatment. The design of the T20 and ACCENT II trials are different and consequently, the indirect comparison proposed by the submission is of uncertain validity, as the infliximab induction arms were not the randomised 'common comparator' and do not represent the same patient spectrum. The T20 trial randomised patients to infliximab or placebo for induction; all patients in the ACCENT II trial underwent infliximab induction and then subsequently responders and non-responders were separately randomised to infliximab or placebo

maintenance. Thus, the validity of the common comparator for undertaking the indirect analysis is questionable. The eligible patients in T20 are in relapse. The eligible patients for ACCENT II which form the basis of this submission are both responders and non-responders. However, the PBAC was reassured by the results of the alternative approach proposed by the ESC, which maintained randomisation, to assess the treatment effect using the trial designs without any reanalysis, and then to model the treatment effect of infliximab in series i.e. induction (from the T20) followed by maintenance (from the ACCENT II). The results of this approach yielded an incremental cost per Quality Adjusted Life Year (QALY) gained in the range of $45,000 to $75,000, which was comparable with that claimed in the submission.

The PBAC also noted that there was uncertainty about the hospital and procedure costs, based on a UK study included in the submission, which may have overestimated costs, favouring infliximab. There was also some uncertainty about the reliability of the Australian study used to derive utility values as a source for utilities with and without fistula closure. However, these uncertainties were not considered sufficient to warrant rejection of the submission.

The PBAC noted that the submission's predictions of utilisation were a likely underestimate.

Recommendation:
INFLIXIMAB, powder for IV infusion, 100 mg

Extend the current restriction to include:

Section 100 listing (Highly Specialised Drug)
Public and Private hospital authority required
To be finalised

Pack size: 1

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 welcomes the PBAC's decision to fund infliximab for complex fistulising Crohn's disease given the unmet clinical need for this debilitating condition. The sponsor also wishes to thank the clinical specialists for their contributions to the submission.