PUBLIC SUMMARY DOCUMENT
Product: Infliximab, powder for IV infusion, 100mg, Remicade®
Sponsor: Janssen Pty Ltd
Date of PBAC Consideration: March 2013

1. Purpose of Application

The submission sought to extend the current Section 100 Highly Specialised Drugs Program Public and Private Hospital Authority required listings for infliximab to include the treatment of acute severe ulcerative colitis not responding to IV corticosteroids in a patient aged 6 years or greater and who meets certain criteria.

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

The PBAC had not previously considered infliximab for patients with acute severe ulcerative colitis.

3. Registration Status

Infliximab is TGA approved for the treatment of moderately severe to severe active ulcerative colitis in adults (February 2007) and in children and adolescents (6 to 17 years) who have had an inadequate response to conventional therapy (May 2012).

4. Listing Requested and PBAC's View

Section 100 Highly Specialised Drugs Program
Private Hospital Authority required
Public Hospital Authority required

Initial PBS-subsidised treatment by a gastroenterologist or consultant physician as specified in the NOTE below, of a patient aged 6 years or greater with acute severe ulcerative colitis who satisfies the following criteria:

(a) an adult who has severe ulcerative colitis as defined by the presence of more than 6 bloody stools per day, plus at least one of the following signs:
- temperature more than 37.5°C
- pulse rate more than 90 / minute
- haemoglobin less than 105 g / L
- Erythrocyte sedimentation rate greater than 30 mm/h.

OR

(b) a child aged six years or more who has severe ulcerative colitis as defined by a Paediatric Ulcerative Colitis Activity Index (PUCAI) ≥ 65 with the diagnosis confirmed by a gastroenterologist or a consultant physician as specified in the NOTE below.

AND

(c) who has failed to achieve an adequate response to at least 72 hours intravenous corticosteroids.

For adults, failure to achieve an adequate response is defined by the Oxford criteria where:
- If assessed on day 3, patients pass 8 or more stools per day or 3 or more stools per day with a CRP > 45 mg / L
- If assessed on Day 7 patients pass 3 or more stools per day with visible blood.

For children aged 6 to 15 years failure to achieve an adequate response means PUCAI score >45 at 72 hours. Before administering infliximab the treating clinician must have consulted with a paediatric gastroenterologist or with an institution experienced in performance of paediatric colectomy.

NOTE: Prescribers must be gastroenterologists (code 87), consultant physicians [internal medicine specialising in gastroenterology (code 81)] or consultant physicians [general medicine specialising in gastroenterology (code 82)].

5. Clinical Place for the Proposed Therapy

Patients with acute severe episodes of ulcerative colitis are usually admitted to hospital for monitoring and intravenous (IV) corticosteroids. Patients who respond to corticosteroids will have their steroids tapered and be offered maintenance therapy with 5-aminosalicylates or immunomodulators. Patients who fail to respond to IV corticosteroids in 3-7 days can be offered emergency surgery (colectomy), best supportive care (BSC) including continuing IV corticosteroids, infliximab or cyclosporin. Responding patients will have their steroids tapered orally and maintained on 5-aminosalicylates or immune-modulators whereas those who fail to respond will be considered for surgery (colectomy).

The submission stated that currently there are no other medical treatments approved by the TGA or reimbursed by the PBS for patients with acute severe ulcerative colitis who have not responded to IV corticosteroids. The submission proposed infliximab would fill this treatment gap.

6. Comparator

The submission nominated best supportive care (BSC) as the main comparator. BSC may include IV corticosteroids with monitoring and emergency colectomy if clinically necessary. Infliximab is also given in conjunction with monitoring and emergency colectomy if clinically necessary.

For PBAC's view, see Recommendation & Reasons.

7. Clinical Trials

The submission presented three randomised trials (Jarnerot et al. (2005), Sands et al. (2001) and Florholmen et al. (2011)) comparing infliximab to placebo (BSC). A total of 82 patients were followed up for 7-90 days, with extension data up to three years.

The submission also presented a supplementary randomised trial of infliximab in moderate to severe ulcerative colitis in paediatric patients (Hyams et al. (2012)).

In addition, the submission presented a comparison of infliximab with cyclosporin. This comparison was based on the abstract of one randomised controlled trial (CYSIF, published as Laharie et al. 2012) and six cohort studies.

The PBAC noted that the submission acknowledged that the goals for managing ulcerative colitis were to eliminate the symptoms of disease, improve quality of life, and avoid hospitalisation and colectomy. Accordingly, the submission relied on colectomy avoidance and remission of symptoms with improvement in disease severity as meaningful outcomes for the treatment of acute severe ulcerative colitis.

The PBAC noted that there were imbalances between the treatment arms, including gender and disease severity in the trial reported in Jarnerot et al. (2005). The method used in randomisation of patients to treatment may be the cause. The impact of these imbalances was uncertain. The PBAC also noted that the trial reported in Sands et al. (2010) was a pilot study

and included only six patients in the relevant arm of BSC or infliximab 5 mg/kg. The PBAC further noted that the trial reported by Florholmen et al. (2011) was a small (n=26), open label trial. The protocol deviated from its original design and was adjusted because of ethical concerns after detecting differences in the efficacy of infliximab and placebo. This change in the design of the study led to confounding in the results.

The PBAC considered the number of clinical trials presented in the submission to be small and restricted to the severe colitis patient population. The PBAC questioned the reasons for exclusion of various other infliximab trials in the moderate to severe ulcerative colitis population (i.e. ACT 1, ACT 2) and considered that these excluded trials could have been informative when looking at the efficacy of three infusions of infliximab.

Publication details of the trials presented in the submission are in the table below.

Trials and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Placebo controlled		
Jarnerot 2005 Jarnerot G et al.	Infliximab as Rescue Therapy in Severe to Moderately Severe Ulcerative Colitis: A Randomized, Placebo-Controlled Study.	Gastroenterology 2005 (128) 1805-1811.
Gustavsson A et al.	Clinical trial: colectomy after rescue therapy in ulcerative colitis – 3-year follow-up of the Swedish-Danish controlled infliximab study.	Aliment Pharm Ther 2010, 32(8)984-9.
Sands 2001 Sands B et al.	Infliximab in the Treatment of Severe, Steroid-Refractory Ulcerative Colitis: A Pilot Study.	Inflamm Bow Dis 2001, 7(2)83-88.
Active controlled		
Florholmen 2011 Florholmen J et al.	Short and Long Term Clinical Outcomes of Infliximab in Fulminant Ulcerative Colitis.	Ulcers 2011, Article 156407
CYSIF 2011 Laharie et al.	Cyclosporin Versus Infliximab in Severe Acute Ulcerative Colitis Refractory to Intravenous Steroids: A Randomized Trial	Gastroenterology 2011 (140) Abstract 619
Laharie et al*.	Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial.	Lancet 2012, 1;380(9857):1909-15
No Control		
Hyam 2012 Hyams J et al.	Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis.	Clin Gastro Hep 2012, 4(10) 391-9

*: published during the evaluation period

8. Results of Trials

The results from the Jarnerot 2005 trial are summarised in the table below.

Clinical outcomes from the Jarnerot trial (90 days) and 3 year (Gustavsson)

End points	IFX n/N (%)	PBO n/N (%)	p value [a]	RR (95% CI)	ARD (95% CI)	NNT [b] (95% CI)
90 days outcome						
Colectomy	7/24 (29%)	14/21 (67%)	**0.017**	**0.44 (0.22, 0.88)**	**38% (10%, 65%)**	**3 (2, 10)**
Complete clinical and endoscopic remission	6/24 (25%)	2/21 (9.5%)	0.176	0.58 (0.59, 11.6)	16% (-6%, 37%)	6 NE
3-year outcome [c, d]						
Colectomy	12/24 (50%)	16/21 (76%)	**0.012**	0.66 [b] (0.41, 1.05)	26% [b] (-1.0%, 53%)	4 NE

IFX = infliximab; PBO = placebo; RR = relative risk; ARD = absolute risk difference; NNT = number needed to treat; CI = confidence interval; **bold** = statistically significant; NE = not estimable

[a] Log-rank test of Kaplan-Meier plot

[b] Calculated during evaluation

[c] From Gustavsson *et al*.,2010

[d] Two patients initially randomised to placebo received rescue therapy with infliximab instead of colectomy

The trial reported by Jarnerot et al. (2005) showed that infliximab was more effective than best supportive care in preventing colectomy and inducing clinical response or remission in patients with acute severe ulcerative colitis.

The results from the CYSIF (Laharie 2012) trial (extracted during the evaluation) are summarised in the table below.

Clinical outcomes from the CYSIF trial

End points	IFX n/N (%)	CSP n/N (%)	p value	OR [a] (95% CI)	ARD (95% CI)	NNT [b] (95% CI)
Treatment failure at day 98	31/57 (54%)	35/58 (60%)	0.52	1.3 (0.6, 2.7)	6% (-7%, 19%)	17 NE
Clinical response at day 7	48/57 (84%)	50/58 (86%)	0.76	1.2 (0.4, 3.3)	2% (-11%, 15%)	50 NE
Colectomy (98 days) [c]	12/57 (21%)	10/58 (17%)	0.60	0.8 (0.1, 4.4)	-4% (-18%, 11%)	26 NE

IFX = infliximab; CSP = cyclosporin; OR = odds ratio; ARD = absolute risk difference; NNT = number needed to treat; NE = not estimable.

[a] Value above 1.0 indicates that infliximab is more effective than cyclosporin

[b] NNT was calculated during evaluation

[c] Laharie did not present the OR or ARD for colectomy and therefore these values were calculated during evaluation.

The results of the CYSIF trial (Laharie et al. 2012) suggested that there were no statistically significant or clinically meaningful differences observed between infliximab and cyclosporin for treatment failure, clinical response or colectomy rate.

Regarding adverse events, infliximab was associated with an increased risk of opportunistic infection and infusion reactions, fever or rash. The three infliximab versus placebo trials presented were small, and minimal safety data were reported. In general, however the adverse events were in line with the known safety profile of infliximab.

For PBAC's view, see Recommendation & Reasons.

9. Clinical Claim

The submission described infliximab as having superior efficacy and a different safety profile compared to placebo (BSC) for adult and paediatric patients with acute severe ulcerative colitis not responding to IV corticosteroids.

For PBAC's view, see Recommendation & Reasons.

10. Economic Analysis

The submission presented a cost utility analysis that assessed the incremental cost per quality adjusted life year (QALY) and life year gained (LYG) of infliximab compared to BSC (placebo) in patients with acute severe ulcerative colitis not responding to IV corticosteroids.

The submission used a 3-year Markov economic model, with four health states, and three-monthly cycles. The model relied on the efficacy data in terms of the colectomy rate from the Jarnerot et al. (2005) trial and its 3-year follow-up data from Gustavsson et al. (2010). The utilities applied in the model were sourced from published literature.

The submission estimated that infliximab compared to BSC would result in a cost saving, over the three-year time period, due to reduced colectomy costs and an increase in QALYs of 0.163 mainly due to reduced mortality due to colectomy and future QALY loss.

Excluding the QALYs lost due to deaths from colectomy, the incremental QALY gain was estimated to be 0.055. In this case, infliximab remained the dominant treatment option. The submission noted that the favourable results of the model were driven by the cost-offsets attributable to avoiding colectomy. Other drivers for the model were the cost per colectomy (both number of surgeries required and the cost per surgery), and the cost of the post treatment health state. The results of the economic evaluation showed the incremental cost per QALY to be dominant.

The submission did not present a modelled economic evaluation using cyclosporin as a comparator.

For PBAC's view, see Recommendation & Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated a total cost to the PBS of less than $10 million in Year 5 of listing.

The PBAC noted the advice of the Drug Utilisation Sub-Committee (DUSC) that the estimates presented in the submission were likely to be underestimated based on the following:

- The submission estimates were derived from an incident population and did not include the total pool of patients at risk of hospitalisation with acute severe ulcerative colitis.
- The base case estimates in the submission assumed that a patient will only have one severe acute ulcerative colitis attack requiring hospitalisation, while evidence suggests that a proportion of the population will have multiple attacks.
- Revised DUSC estimates of the number of patients and hospitalisations suggested that utilisation of infliximab for the requested listing was likely to be approximately twice that estimated in the submission, doubling the cost over 5 years.

- There is potential for infliximab to be commenced prior to patients receiving 3 days of steroid treatment.
- There is the potential for infliximab to be used in a maintenance setting to reduce the risk of flares.
- The number of vials per infusion is uncertain however probably reasonable.

For PBAC's view, see Recommendation & Reasons.

12. Recommendation and Reasons

The PBAC rejected the submission on the basis that the comparator should have also included cyclosporin, the evidence base for efficacy of infliximab was limited to a small number of trials in the acute severe colitis setting and could have included a broader range of trials, and uncertainty in the economic modelling that results in a high and unacceptable ICER.

Regarding the nominated comparator of BSC, the PBAC noted that current Australian and international ulcerative colitis guidelines for adult and paediatric patients, recommend calcineurin inhibitors (e.g. cyclosporin) following failure to respond to IV corticosteroids.

The PBAC considered that cyclosporin, despite not being currently PBS listed or TGA registered for use in ulcerative colitis, is an appropriate comparator, as it is currently included in a number of Australian hospital formularies and recommended as an appropriate treatment option according to current clinical practice guidelines.

The PBAC considered that infliximab has clinical benefit compared to BSC and that this is consistent with the fact infliximab is already included in various hospital formularies, despite limitations in the trial designs and uncertain applicability (Jarnerot et al. (2005) was a small European trial) of the results to the Australian population. The PBAC was uncertain about the absolute benefit of infliximab. The PBAC noted that rate of colectomy avoidance was potentially uncertain due to the risk of bias in the pivotal trial reported in Jarnerot et al. (2005) and because colectomy is a clinical decision and rates may vary with clinical practice.

The PBAC noted that the short-term and common infliximab adverse events reported in literature are similar to those observed in the clinical trials and are mild to moderate in severity.

The PBAC considered that the clinical claim was reasonable for adult patients. The PBAC considered that there was insufficient information regarding a claim of comparative effectiveness against use of cyclosporin, as cyclosporin is a drug that is likely to be replaced in some patients.

The PBAC noted that the ICER was highly sensitive to the estimate of treatment effect increasing to between $105,000 and $200,000 using the lower absolute risk difference. The four multivariate sensitivity analyses conducted during the evaluation adjusted the model inputs for three parameters which favoured infliximab: number of surgeries, cost per surgery, and post-treatment costs. These changes were combined with and without the following changes to the key model parameters: using the mean and lower absolute risk difference for treatment effect, and, including and excluding the submission's estimated QALY gain for

survivors. The ICER ranged from between $75,000 and $700,000 as a result of multivariate sensitivity analyses.

The PBAC noted that the dosing regimen for infliximab varied across the clinical trials. The submission requested PBS funding for three infusions (week 0, 2 and 6). However the clinical efficacy results used to inform the economic model were from the Jarnerot et al. (2005) trial, where a single infliximab infusion was given (week 0). The PBAC noted that limited evidence was presented to support the use of three rather than one infusions.

The PBAC considered that the duration of three years for the economic model was inappropriate, and that the estimation of various costs in the economic model was possibly inaccurate. The cost of colectomy was potentially overestimated because not all patients would undergo three surgeries - some patients may need only two procedures. The cost of the post treatment remission state was underestimated as some health care resources (i.e. hospitalisation and investigational procedures like colonoscopy) were not captured. The PBAC noted that the submission's Pre-Sub-Committee Response presented an article from the US showing post-surgery costs are higher than post-treatment costs but considered that without additional information and evaluation of this study its relevance to the Australian context was unclear.

The PBAC further considered that more conservative utility values from the SOLUTION UC, a Phase IV observational Australian study in patients with ulcerative colitis, may be more appropriate. This study reported utility values of 0.75 (AQoL-8D) and 0.77 (EQ-5L-5D) for patients with chronic ulcerative colitis post treatment (the submission used values of 0.92 for the post-surgery state and 0.96 for the post treatment state). However, the SOLUTION study did not include ulcerative colitis patients post surgery. The post treatment utility value was potentially overestimated as treatment is not curative and patients may experience further episodes in the future.

The PBAC noted DUSC advice that the estimates provided in the submission are an underestimation and that utilisation of infliximab for the requested listing is likely to be higher than that estimated in the submission.

The PBAC considered that any future re-submission could consider listing for 'acute colitis' and should present the results of a more comprehensive list of clinical trials to support the requested three infusions of infliximab. The PBAC considered that an examination of the absolute effect of infliximab would be informative. Inclusion of cyclosporin as a comparator would also be appropriate in any re-submission.

The PBAC further indicated that a revised economic analyses taking into consideration concerns regarding the duration of the economic model, cost of colectomy, cost of post treatment remission state, and, utility values would also be informative. The PBAC remained uncertain as to the number of infliximab doses/courses that would be required in practice following the initial induction treatment and advised that any resubmission should address this.

The PBAC noted the consumer comments received in relation to the submission.

The PBAC noted that the submission is eligible for an Independent Review.

Recommendation:
Rejected

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

Janssen submitted Remicade for reimbursement for patients with acute severe ulcerative colitis to address the current inequity that is occurring as some, but not all, hospitals are already funding use in this setting. Remicade was shown to be both more efficacious than best supportive care and the less expensive option in most variables of the economic model. Janssen are disappointed with the PBAC outcome and are working with the PBAC to understand the issues raised.