PUBLIC SUMMARY DOCUMENT

Product: INFLIXIMAB, 100 mg injection, 1 x 100 mg vial, Remicade®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: March 2014

1. Purpose of Application

The major submission sought to extend the current Section 100 (Highly Specialised Drugs Program), Authority Required listing for infliximab to include the treatment of moderate to severe ulcerative colitis in patients aged 6 and above.

The PBAC noted that the submission's requested moderate to severe ulcerative colitis patient population differed to the patient population with acute severe ulcerative colitis for which the PBAC made a positive recommendation in November 2013.

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 was the PBAC's first consideration of a submission to list infliximab for moderate to severe ulcerative colitis.

The PBAC recalled that it had recommended infliximab for the treatment of acute severe ulcerative colitis in November 2013.

Infliximab is currently listed on the PBS (Section 100 – Highly Specialised Drugs Program) for the treatment of severe active rheumatoid arthritis, active ankylosing spondylitis, severe active psoriatic arthritis, severe refractory Crohn disease; severe chronic plaque psoriasis and refractory fistulising Crohn disease.

3. Registration Status

At the time of the PBAC's consideration in March 2014, infliximab was TGA registered for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy, in adults and in children/adolescents (6 to 17 years), in addition to various other indications.

4. Listing Requested and PBAC's View

The requested abridged PBS listing of infliximab for moderate to severe UC is shown below:

<u>Section 100 (abridged version)</u>
<u>Authority Required (written approval)</u>
Initial treatment of moderate to severe ulcerative colitis in patients assessed by Mayo or PUCAI score.

Patient must be treated by a gastroenterologist or a consultant physician, OR
Patients aged 6 to 15 years must have been assessed or have an appointment to be assessed by a paediatrician or specialist paediatric gastroenterologist,

Patient must have failed to achieve an adequate response or have intolerance necessitating permanent treatment withdrawal to prior systemic therapy including:
i. a 5-aminosalicylate oral preparation in standard dose for induction of remission for 3 or more months; AND
ii. azathioprine at a dose of at least 2 mg per kg daily for 3 or more months; OR
iii. 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more months; OR
iv. a tapered course of oral steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period,

Adult patient must have a Mayo score greater than or equal to 6. (Endoscopy subscore is not required if the rectal bleeding and stool frequency subscores are both ≥ 2 and the partial Mayo score is ≥ 6), OR
The paediatric patient aged ≥ 6 must have a PUCAI Score greater than or equal to 30

Patients who fail to achieve a partial Mayo score ≤ 2, with no subscore > 1, or a PUCAI score < 10 within the first 12 weeks of receiving infliximab for ulcerative colitis, or have failed to maintain a partial Mayo score ≤ 2, with no subscore >1, or a PUCAI score <10 with continuing infliximab treatment will not be eligible to receive PBS-subsidised treatment with this drug within 12 months of the date on which treatment was ceased.

<u>Section 100</u>
<u>Authority Required (written approval)</u>
The first continuing treatment of ulcerative colitis in patients assessed by Mayo or PUCAI score.

The adult patient must have partial Mayo score ≤ 2, with no subscore > 1 while receiving infliximab, OR:
Paediatric patient must have a PUCAI score <10 while receiving infliximab,

A Mayo or PUCAI assessment of the patient's response must be made up to 12 weeks after the first dose so that there is adequate time for a response to be demonstrated.

<u>Section 100</u>
<u>Authority Required (telephone approval)</u>
Subsequent continuing treatment of ulcerative colitis in patients assessed by Mayo or PUCAI score.

Patients have been treated with infliximab for ≥ 30 weeks.

Patient must have partial Mayo score ≤ 2, with no subscore >1 while receiving infliximab, OR
Patient must have a PUCAI score < 10 while receiving infliximab.

Maximum Quantity: 1 vial (all restrictions)
Number of Repeats: 2 (all restrictions)

Listing was sought on a cost-utility basis compared with placebo plus best supportive care.

The PBAC considered that there is potential for use outside the PBS restriction requested, in patients who have a partial response but who do not quite meet the continuing criteria. However, the PBAC considered that this risk could be mitigated through the revised financial estimates accounting for a greater percentage of patients continuing with treatment (i.e. 51% compared with the base case of 38.8%) and an appropriate risk sharing agreement.

The PBAC noted that the submission's requested maximum number of repeats was consistent with the approved dosage regimen (i.e. doses for weeks 0, 2, and 6 for initial induction of therapy and every 8 weeks thereafter) but was not consistent with the number of repeats for the Crohn indication (0 repeats). Since the ulcerative colitis indication has the same dosing frequency as for Crohn disease, the PBAC agreed with the Secretariat's suggestion of nil

repeats for consistency between these 2 indications, whilst noting that prescribers are still able to request the desired number of repeats up to a maximum of 2.

The PBAC considered that the requirement to trial either of azathioprine, 6-mercaptopurine or an oral steroid at the proposed doses was reasonable as these doses are consistent with those for the PBS-listing for Crohn disease. However, as the proposed restriction attempted to cater for adult and paediatric patients in the one restriction (the Crohn PBS-indications are separated for adult and paediatric patients), the requested prednisolone dose of at least 40 mg is not applicable for every paediatric patient. The PBAC noted that the Therapeutic Guidelines' recommended prednisolone child dose is 1 to 2 mg/kg up to 40 to 60 mg and accepted the Secretariat's suggested amendment to account for paediatric prednisolone dosing.

The requirement to trial an oral 5-aminosalicylate drug is different to the Crohn indication but was considered reasonable by the PBAC because this is a standard therapy used in mild to moderate ulcerative colitis (according to the Therapeutic Guidelines - Gastrointestinal) and was an inclusion criterion in one of the main supportive trials (ACT II). A 'Standard dose' was not defined in the requested restriction but the PBAC agreed that physicians would interpret this within the context of clinical practice standards and approved Product Information so a definition was not considered necessary. The PBAC noted that the dose of a 5-aminosalicylate oral preparation in the ACT II trial was defined as a dose equivalent to or greater than 2.4 g of mesalazine per day for at least 6 weeks prior to screening, with a stable dose for at least 3 weeks.

The PBAC noted that the submission had proposed a provision for re-treatment in 12 months' time after failure or loss of response. However, the PBAC did not consider this provision to be appropriate at this time, as it was unclear how cost-effective infliximab is in this particular setting.

With respect to the use of a partial Mayo score to identify eligible patients and/or to assess responders, the PBAC agreed that patients and clinicians are unlikely to use endoscopy on a regular basis in order to assess mucosal healing as required for the full Mayo score. The PBAC therefore accepted the use of a partial Mayo score in the PBS restriction.

The PBAC noted that the submission's request to separate the continuing restriction into a first (written Authority only) and subsequent continuing (telephone Authority) restriction would not be consistent with the continuing restriction as for the Crohn disease PBS indication which is 'written only' for both initial and continuing restrictions. The submission had argued that this is in the interest of reducing prescriber administrative burden. The PBAC agreed to the request to allow telephone authority approval of continuing treatment, noting that a risk sharing agreement would be in place if listing proceeded.

The PBAC agreed with the Secretariat's suggestion of one continuing restriction (as opposed to an initial continuing and a second and subsequent continuing restriction) for consistency with the Crohn disease listing and on the basis that there did not appear to be any significant difference between the criteria of the proposed 'initial continuing' and 'subsequent continuing' restrictions.

The PBAC noted that the sponsor, in its pre-Sub-Committee response, stated that there are patients who have received infliximab for moderate to severe ulcerative colitis through other alternative funding sources such as hospital funded therapy, State funded therapy, private prescription and compassionate use, and that a Grandfathering clause would be beneficial. However, as no actual patient numbers were provided, the PBAC did not consider a Grandfathering clause to be adequately justified.

5. Clinical Place for the Proposed Therapy

Ulcerative colitis is a chronic disease characterised by the inflammation of the mucosa of the large intestine or colon. The inflammation is usually located in the rectum and lower colon but may involve other parts of the colon. Ulcerative colitis symptoms vary between individuals, but usually include severe diarrhoea, blood loss and progressive loss of peristaltic function leading to a rigid colonic tube. Some patients experience symptoms continuously, some a flare of symptoms every few months and others rarely have symptoms. Ulcerative colitis is usually classified by activity (active or in remission), severity (mild, moderate and severe, or acute severe) and anatomic extent (distal or extensive).

Infliximab was proposed to be used in patients aged 6 or above with moderate to severe ulcerative colitis, who have failed to achieve an adequate response or have intolerance necessitating permanent treatment withdrawal to conventional therapy such as 5 aminosalicylate and azathioprine/6-mercaptopurine ± corticosteroids.

The PBAC acknowledged the limited treatment options on the PBS for patients with moderate to severe ulcerative colitis and considered that a clinical need exists for further effective treatment options to be available to such patients. The PBAC noted that this sentiment was reflected in the consumer comments, as well as consumer views that listing for moderate to severe ulcerative colitis would also improve equity in access across infliximab's various treatment indications, in particular noting that infliximab is currently subsidised for Crohn disease but not for ulcerative colitis.

6. Comparator

The submission nominated placebo + best supportive care (BSC), which consists of conventional therapies, as the main comparator. The PBAC considered this to be the appropriate comparator.

The submission also included adalimumab as a minor comparator. The PBAC did not consider this comparison to be informative in determining the cost-effectiveness of infliximab in moderate to severe ulcerative colitis given the PBAC's negative November 2013 recommendation with regards to adalimumab. The PBAC acknowledged that the sponsor would not have known the outcome of the November 2013 adalimumab submission at the time of lodging this submission for infliximab.

7. Clinical Trials

The submission was based on two key clinical trials, ACT 1 and ACT 2. Both are randomised, double-blind, placebo-controlled trials, comparing infliximab 5 mg/kg + BSC with infliximab 10 mg/kg + BSC, and, with placebo + BSC, in an adult population. Results from these trials were extracted for the placebo arm and the infliximab 5 mg/kg arm, as this is the recommended dose in the Australian Remicade Product Information. The economic

model presented in the submission relied on the efficacy results of the ACT 1 and ACT 2 trials.

As there was no randomised-controlled trial identified for the paediatric population (6-17 years), the submission relied on Hyams et al. (2012). Patients in this trial were randomised into two open-label infliximab 5 mg/kg treatment arms after receiving three-dose induction of infliximab 5 mg/kg.

A summary description of the published trials presented in the submission is shown in the table below.

Trial ID/First Author	Protocol title/ Publication title	Publication citation
ACT 1 and ACT 2		
Rutgeerts	Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis.	*NEJM* 2005, 353(23) 2462-76.
Colombel	Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis.	*Gastroenterology.* 2011, 141(4):1194-1201.
Reinisch	Long-term infliximab maintenance therapy for ulcerative colitis: the ACT-1 and -2 extension studies.	*Inflamm Bowel Dis.* 2012, 18(2):201-11.
Reinisch	Response and remission are associated with improved quality of life, employment and disability status, hours worked, and productivity of patients with ulcerative colitis.	*Inflamm Bowel Dis.* 2007, 13(9):1135-40.
ACT 2		
Feagan	The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients.	*Am J Gastro* 2007, 102 (4) 794-802
Sandborn	Colectomy Rate Comparison After Treatment of Ulcerative Colitis With Placebo or Infliximab.	*Gastroenterology* 2009 (137) 1250-1260.
Hyams	Induction and Maintenance Therapy With Infliximab for Children With Moderate to Severe Ulcerative Colitis.	*Clinical Gastroenterology and hepatology* 10: 391-399

The PBAC noted and welcomed the input from individuals (25), health care professionals (8) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with infliximab, including an immediate relief of pain symptoms, significantly improved quality of life, increased equity in access, maintenance of response to treatment, and, avoidance of surgery (colectomy) and hospitalisation. The PBAC noted the support for listing received from The Children's Hospital at Westmead (NSW) clarifying the clinical need and place of infliximab relative to colectomy in paediatric patients, and separate comments regarding the clinical place of infliximab in ulcerative colitis from the Gastroenterological Society of Australia (GESA).

8. Results of Trials

Overall, the proportion of patients in clinical remission at week 8 was significantly greater in the infliximab 5 mg/kg treatment arm (36.4%) than in the placebo + BSC arm (10.2% - number needed to treat NNT= 4; 95% CI: 3 to 5). Patients treated with infliximab were more likely to have sustained remission at week 8 and 30 (NNT 8; 95% CI: 5 to 13) and week 8, 30 and 54 (NNT 8; 95% CI: 5 to 20) compared to placebo. These results are summarised in the table below.

Efficacy summary – ACT 1 and ACT 2

Outcome	N trials (N)	RR (95%CI)	Event rate (%) [a]		RD (95%CI)
			IFX 5 mg/kg	PBO	
Benefits					
Remission (Mayo score ≤2 and no individual subscore >1)					
Week 8	2 (486)	**3.78 [1.66, 8.45]**	36.4	10.2	**0.26 [0.19, 0.33]**
Sustained week 8 & 30	2 (486)	**3.52 [1.74, 7.13]**	19.0	5.3	**0.13 [0.08, 0.19]**
Sustained week 8, 30 & 54	1 (242)	**3.00 [1.40, 6.41]**	19.8	6.6	**0.13 [0.05, 0.22]**

RR = relative risk; RD = risk difference; IFX = infliximab; PBO = placebo; CI = confidence interval.
[a] percentage of patients with in remission during the time period

Hyams et al (2012) did not provide comparative effectiveness data for infliximab versus placebo. However, the remission rate for the “infliximab every eight weeks” arm appeared to be similar to that observed in the ACT 1 and 2 trials. The table below summarises the efficacy of infliximab in the paediatric population.

Efficacy summary – Hyams et al 2012

	IFX mono	IFX combined [b]	Total
Patient treated	28	32	60
Clinical remission at week 8 (Mayo score) [a]	11 (39.3%)	13 (40.6%)	24 (40%)
Patients evaluable for PUCAI at week 8	27	24	51
Remission (PUCAI score) at week 8 [a]	9 (33.3%)	8 (33.3%)	17 (33.3%)
Remission (PUCAI score) at week 54			
Eight-week arm [a]	3/10 (30.0%)	5/11 (45.5%)	8/21 (38.1%)
Twelve-week arm [a]	1/10 (10.0%)	3/12 (25.0%)	4/22 (18.2%)

[a] Patients with insufficient data were considered to not be in clinical response, clinical remission, remission, or in mucosal healing.
[b] Patients in infliximab combination therapy group were receiving concomitant treatment with AZA, 6-MP, or MTX at baseline.
IFX = infliximab; AZA = azathioprine; 6-MP = 6-mercaptopurine; MTX = methotrexate

In relation to infliximab’s comparative effectiveness in the paediatric population, due to the remission rate for the ‘infliximab every eight weeks’ arm appearing to be similar to that observed in the ACT 1 and 2 trials, the PBAC considered that the effectiveness of infliximab in the paediatric population to be reasonably demonstrated.

Overall, based on the comparative effectiveness results of the trials presented in the submission, the PBAC considered that infliximab is a modestly effective treatment for patients with moderate to severe ulcerative colitis who have failed to respond to previous conventional therapy.

With regard to comparative harms, there were no statistically significant differences between the placebo and infliximab arms for all incidences of adverse events, except for respiratory system disorders. While similar proportions of patients in both arms discontinued permanently because of an adverse event in ACT 1, a much higher proportion of placebo

patients discontinued in ACT 2. Approximately 10% of patients in each of the treatment arms had reported at least one infusion reaction and a small proportion of patients reported at least one serious infection in both trials. The majority of discontinuations were due to worsening of ulcerative colitis. A summary of the harms in the ACT 2 trial is shown in the table below.

Harm summary –ACT 2 trial

Outcome	N trials (N)	RR (95%CI)	Event rate (%) [a]	
			IFX 5 mg/kg	PBO
Week 30 (ACT 2)				
SAEs	244	0.55 [0.29; 1.03]	10.7	19.5
Infusion reaction	244	1.42 [0.66; 3.08]	11.6	8.1
Serious infection	244	2.03 [0.19; 22.1]	1.7	0.8

RR = relative risk; RD = risk difference; IFX = infliximab; PBO = placebo; SAE = serious adverse event;
[a] percentage of patients with in remission during the time period

The event rates for serious adverse events, infusion reaction and serious infection in the ACT 1 trial for the infliximab 5 mg/kg and placebo arms were similar, but numerically higher in the placebo group.

Hyams et al (2012) did not provide comparative safety data between infliximab and placebo. The number of infections and infusion reactions may be higher in the paediatric population compared to the adult population. Safety results in the paediatric population are summarised in the table below.

Summary of infliximab safety through week 54 in Hyams et al (2012)

	No maintenance	IFX q8w	IFX q12w
Patient treated	15	22	23
≥1 SAE	5 (33%)	4 (18%)	5 (22%)
≥1 infection	4 (27%)	13 (59%)	14 (61%)
≥1 infusion reaction	1 (7%)	4 (18%)	3 (13%)

IFX = infliximab; q8w = every 8 weeks; q12w = every 12 weeks; AE = adverse events; SAE = serious adverse events.

The PBAC noted that based on the ACT 1 and ACT 2 trial results, for every 100 patients treated with infliximab compared to placebo:

- Approximately 26 more patients would achieve remission at 8 weeks;
- Approximately 14 more patients would have a sustained remission at weeks 8 and 30;
- Approximately 13 more patients would have a sustained remission at weeks 8, 30 and 54;
- Approximately 7 less patients would experience a serious adverse event based on combining the results from the ACT 1 and ACT 2 trials;
- Approximately 1 more patient would experience an infusion reaction based on combining the results from the ACT 1 and ACT 2 trials; and
- There would be approximately no difference in the number of patients experiencing a serious infection based on combining the results from the ACT 1 and ACT 2 trials.

The PBAC considered that the comparative harms data supported the view that overall, infliximab is a comparatively safe medication.

9. Clinical Claim

The submission described infliximab 5 mg/kg as superior in terms of comparative effectiveness and equivalent in terms of comparative safety and tolerability over BSC in the treatment of patients with moderate to severe ulcerative colitis.

The PBAC considered the clinical claim to be adequately supported in both adult and paediatric populations.

10. Economic Analysis

The submission presented a cost utility analysis consisting of a stepped economic evaluation based on a 10-year Markov cohort model with three alternative treatment pathways (infliximab, placebo and adalimumab) and five disease states (induction, remission, non-remission, post-surgery and death). The economic model used data from ACT trials and the literature. Utility gains in the model were derived from the trial data, using the full Mayo score. The PBAC noted that as the proposed PBS restriction would allow prescribers to use the partial Mayo score for PBS eligibility, it was appropriate for the utility gains used in the model to be derived from the partial Mayo score.

The ESC noted that the economic model assumed that placebo patients could not achieve remission and therefore removed the number of remissions achieved by the placebo group from the number of remissions achieved by the infliximab group, in order to estimate a net probability of remission. This assumption favoured infliximab.

A revised economic model was provided in the sponsor's pre-sub-committee response (PSCR) in which:
(i) utility values were corrected by using the EQ-5D descriptive system instead of those obtained from the EQ-visual analogue scale (VAS);
(ii) a 24-week cycle for efficacy and costs for continuing therapy (compared to an 8-week cycle for efficacy and costs) was used;
(iii) use of infliximab for paediatric was included (reducing the average infliximab vial use compared to the submission); and
(iv) the incremental hospital days for cyclosporin treatment was reduced compared to the submission.

The revised model in the PSCR produced a base case ICER in the range of $45,000 – $75,000 per QALY. This was higher (although within the same range) than the submission's ICER.

The ESC noted several issues with the base case ICER produced from the revised economic model provided in the PSCR. The revised base case removed the assumption of a zero probability of remission for placebo patients, which was shown to bias the results in favour of infliximab. However, the transition probabilities for the loss of remission in severe placebo patients beyond week 8 were based on very small numbers – 2/6 patients remained in remission from week 8 to 30, and 0/2 patients remained in remission from week 30 to 54. For the ESC revised base case (ICER in the range of $45,000 - $75,000/QALY), the probability of losing remission for severe placebo patients in both time periods was set to 0.667. The sponsor, in its pre-PBAC response disagreed with the use of this transition probability of 0.667 and noted that if set to zero, the resulting ICER is only slightly lower and therefore that the economic model is not sensitive to this transition.

The PBAC noted that the model was sensitive to a range of input parameters, in particular, the assumed utility weights and the rate of elective colectomy. The sponsor argued in its pre-PBAC response that the sensitivity analyses performed by setting the elective surgery rate to 14.3% per 8 week cycle (from 0% in the base case) was an extreme assumption and not consistent with clinical practice.

The PBAC considered the 'ESC revised economic model structure and variables' to be the most reliable basis for estimating the true ICER. However, the PBAC considered an ICER in the range of $45,000-$75,000/QALY as estimated by the submission's revised economic model and the ESC's revised economic model, to be unacceptably high.

The PBAC further considered that an ICER in the range of $40,000 - $45,000/QALY as determined by the ESC's revised economic model, would be acceptable to enable infliximab to be considered cost-effective for use in ulcerative colitis

11. Estimated PBS Usage and Financial Implications

The submission was not considered by DUSC.

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS in the range of $10 - $30 million in Year 5.

The PBAC noted that the financial estimates used the full Mayo score to determine the number of patients who proceed to maintenance therapy. This would under-estimate the utilisation of infliximab and so revised financial estimates were conducted during the evaluation to account for the use of a partial Mayo score (i.e. the percentage of patients continuing on with maintenance therapy was increased from 38.8% in the base case to 51% in the revised estimates. The revised financial estimates resulted in a higher net cost per year to the PBS.

The PBAC considered the revised estimates that accounted for a higher than expected number of patients accessing maintenance therapy due to the use of a partial Mayo score as opposed to the full Mayo score, and, the lower number of vials used in paediatric patients than estimated in the submission to be reasonable.

The PBAC noted the sponsor's willingness to enter into a risk sharing agreement and in the absence of any detail proposed by the sponsor, recommended that the Government and sponsor enter into a risk sharing agreement to contain risks associated with a higher than expected number of patients accessing maintenance therapy due to the use of a partial Mayo score as opposed to the full Mayo score, and, risks associated with the potential for partial responders to continue treatment despite not quite meeting the continuing treatment eligibility criteria. The PBAC recommended that Government expenditure above the revised financial estimates for the new moderate to severe ulcerative colitis indication, be fully rebated.

12. PBAC Outcome

The PBAC recommended the listing of infliximab available as a Section 100 (Highly Specialised Drugs Program) Authority required benefit for the treatment of moderate to severe ulcerative colitis in adults and children.

The PBAC did not recommend infliximab be included in the list of PBS medicines for prescribing by nurse practitioners, noting that nurse practitioners are not able to prescribe infliximab for its current PBS-listed indications

Recommendation:
Add new indication (restriction to be finalised):

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
INFLIXIMAB				
infliximab 100 mg injection, 1 x 100 mg vial	1	0	Remicade	JC

Severity:	Moderate to severe
Condition:	Ulcerative colitis
Treatment phase:	Initial treatment
Restriction:	Section 100 – Highly Specialised Drugs Program Authority required (Public/Private Hospital) – WRITTEN ONLY
Treatment criteria:	Patient must be treated by a gastroenterologist (code 87) or a consultant physician [internal medicine specialising in gastroenterology (code 81)] or a consultant physician [general medicine specialising in gastroenterology (code 82)]; OR Patient must be treated by, or have an appointment to be assessed by, a paediatrician or specialist paediatric gastroenterologist if aged between 6 to 17 years;

Clinical criteria:	Patient must have failed to achieve an adequate response to a 5-aminosalicylate oral preparation in a standard dose for induction of remission for 3 or more months or have intolerance necessitating permanent treatment withdrawal; AND Patient must have failed to achieve an adequate response to azathioprine at a dose of at least 2 mg per kg daily for 3 or more months or have intolerance necessitating permanent treatment withdrawal; OR Patient must have failed to achieve an adequate response to 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more months or have intolerance necessitating permanent treatment withdrawal; OR Patient must have failed to achieve an adequate response to a tapered course of oral steroids, starting at a dose of at least 40 mg (for a child, 1 to 2 mg/kg up to 40 mg) prednisolone (or equivalent), over a 6 week period or have intolerance necessitating permanent treatment withdrawal; AND Patient must have a Mayo score greater than or equal to 6 if an adult patient; OR Patient must have a partial Mayo score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo score); OR Patient must have a Paediatric Ulcerative Colitis Activity Index (PUCAI) Score greater than or equal to 30 if aged 6 to 17 years;
Population criteria:	Patient must be 6 years of age or older;
Population criteria:	Patient must be 6 years of age or older;
Prescriber Instructions	*TO BE FINALISED*
Administrative Advice	NOTE: Special pricing arrangements apply

Severity:	Moderate to severe
Condition:	Ulcerative colitis
Treatment phase:	Continuing treatment
Restriction:	Section 100 – Highly Specialised Drugs Program Authority required (Public/Private Hospital)

Treatment criteria:	Patient must be treated by a gastroenterologist (code 87) or a consultant physician [internal medicine specialising in gastroenterology (code 81)] or a consultant physician [general medicine specialising in gastroenterology (code 82)]; OR Patients must be treated by a paediatrician or specialist paediatric gastroenterologist if aged between 6 to 17 years;
Clinical criteria:	Patient must have a partial Mayo score less than or equal to 2, with no subscore greater than 1 while receiving infliximab; OR Patient must have a Paediatric Ulcerative Colitis Activity Index (PUCAI) score less than 10 while receiving this drug if aged 6 to 17 years;
Prescriber Instructions	*TO BE FINALISED* Patients who have failed to maintain a partial Mayo score less than or equal to 2, with no subscore greater than 1, or, patients who have failed to maintain a PUCAI score less than 10 (if aged 6 to 17 years) with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug. Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain the response. 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. Where fewer than 2 repeats are requested at the time of application, authority approvals for sufficient repeats to complete a maximum of 24 weeks of treatment may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Administrative Advice	NOTE: Special pricing arrangements apply

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 acknowledges that in granting infliximab in moderate to severe ulcerative colitis a positive recommendation the PBAC see the benefit of treating patients with infliximab in this setting. We believe that the value of infliximab in ulcerative colitis offered in this submission was within the range previously accepted by the PBAC for use in Crohn's Disease. Janssen are working with the PBAC to permit patients with ulcerative colitis access to infliximab on the PBS. A resubmission will be considered at the PBAC's July 2014 meeting.