

## 7.01 ADALIMUMAB

**40 mg/0.8 mL injection, 2 x 0.8 mL cartridges**

**40 mg/0.8 mL injection, 2 x 0.8 mL syringes**

**40 mg/0.8 mL injection, 6 x 0.8 mL cartridges**

**40 mg/0.8 mL injection, 6 x 0.8 mL syringes**

**Humira<sup>®</sup>**

**AbbVie Pty Ltd**

### 1 Purpose of Application

- 1.1 To request a Section 85, Authority Required, listing for adalimumab for the treatment of moderate to severe ulcerative colitis (UC). The first submission was November 2013; the second submission was July 2014.

### 2 Requested listing

- 2.1 The proposed restriction wording is aligned with the current restriction for infliximab which is PBS listed for moderate to severe UC; however, it does not include paediatric patients. Given the potential complexity of the restriction and the likely need for consultation with the Department of Human Services, the Restrictions Working Group and the sponsor in the event of a positive recommendation, the Secretariat has not suggested wording at this stage.
- 2.2 The basis for listing is cost-minimisation against infliximab.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

### 3 Background

- 3.1 TGA status at the time of PBAC consideration: adalimumab was TGA registered on 23 July 2013 for treatment of moderate to severe UC.
- 3.2 Two previous PBAC considerations (summarised in the following table).

**Table 1: Summary of the previous submission and current re-submission**

	<b>Adalimumab July 2014: Previous submission</b>	<b>Adalimumab July 2015 Current re-submission</b>
Requested PBS listing	Was similar to that recommended for infliximab in March 2014, but did not include required prior systemic therapy (5-aminosalicylate therapies). <b>PBAC Comment:</b> "... expect that the restriction for adalimumab be aligned with infliximab's restriction for moderate to severe ulcerative colitis as much as practical..."	The restriction was updated to be aligned with infliximab's restriction for moderate to severe UC.

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	Adalimumab July 2014: Previous submission	Adalimumab July 2015 Current re-submission
Requested price	The proposed effective price for: 6 x 40 mg ADA = \$ [REDACTED] * 2 x 40 mg ADA = \$ [REDACTED] * * Includes a [REDACTED] % price rebate. RSA proposed	The DPMQ for: 6 x 40 mg ADA = \$ [REDACTED] 2 x 40 mg ADA = \$ [REDACTED] Specific terms for an RSA were not proposed, however the sponsor is willing to enter into a RSA.
Main comparator	Best Supportive Care (Standard care) <b>PBAC Comment:</b> “further evidence of non-inferiority against infliximab needs to be presented in future major re-submission.”	Infliximab
Clinical evidence	Key trial: ULTRA 2, a 52-week maintenance study (n=518). Supportive trial: ULTRA 1, an 8-week induction study (n=576). Extension trial: M10-223 enrolled patients from the ULTRA, used for safety outcomes. An additional trial (Suzuki, 2014), conducted in Japan, was found, but ( <i>inappropriately</i> ) excluded from the re-submission. A Bayesian network meta-analysis was presented between adalimumab and infliximab (Freemantle Report (2014)) <b>PBAC Comment:</b> The PBAC noted the excluded Suzuki (2014) trial, but considered the exclusion did not significantly alter the interpretation of the clinical trial results.	An indirect comparison between adalimumab and infliximab was presented. It included the previously presented ULTRA 1 and ULTRA 2 trials plus Suzuki (2014) (n=274) and three Infliximab trials: included: ACT 1 (n=364), ACT 2 (n=364), Probert (2003) (n=n43) In addition an indirect comparison to vedolizumab using GEMINI I (n=747, 374 induction and 373 maintenance) was included in an Attachment.
Clinical claim	Adalimumab is superior in terms of comparative effectiveness and marginally worse in terms of comparative safety when compared to placebo. <b>PBAC Comment:</b> PBAC reaffirmed its views on the results of the ULTRA 1 and ULTRA 2 trials from November 2013 in that adalimumab treatment appears to be associated with a real but modest incremental clinical benefit over placebo.	The breadth of evidence suggests no statistically significant differences in efficacy and considered similar in safety for adalimumab vs infliximab.
Economic evaluation	Cost-utility model with cost/QALY of \$15,000 - \$45,000. <b>PBAC Comment:</b> PBAC accepted the ESC’s advice that the true ICER realised in practice is likely to be significantly greater than the \$15,000 - \$45,000/QALY. The PBAC noted the sponsor’s willingness to accept listing on a cost-minimisation basis to infliximab.	Cost-minimisation analysis versus infliximab.
Number of patients	Less than 10,000 patients in Year 1 increasing to less than 10,000 in Year 5.	Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5.

	<b>Adalimumab July 2014: Previous submission</b>	<b>Adalimumab July 2015 Current re-submission</b>
Estimated total cost to PBS	\$10 - \$20 million (revised during evaluation) in Year 1 increasing to \$10 - \$20 million (revised during evaluation) in Year 5 for a total of \$60 - \$100 million (revised during evaluation) over the first 5 years of listing. <b>PBAC Comment:</b> noted the potential for the estimated financial implications to the PBS to be greater or less than what was estimated in the submission due to variability in the estimated number of eligible patents, treated patients and number of patients achieving an adequate response to be eligible for continuing treatment. The PBAC considered that certainty in the financial implications to the PBS would be increased if adalimumab was recommended on a cost-minimisation basis against infliximab.	\$10 - \$20 million in Year 1 increasing to \$20 - \$30 million in Year 5 for a total of \$60 - \$100 million over the first 5 years of listing.
PBAC decision	The PBAC rejected the request to extend adalimumab's indications to include the treatment of moderate to severe ulcerative colitis on the basis that an economic comparison comparing adalimumab to infliximab is the most relevant comparison and on the basis that the evidence presented did not conclusively establish non-inferiority of adalimumab to infliximab.	-

Source: Compiled during the evaluation

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

#### **4 Clinical place for the proposed therapy**

- 4.1 Treatment of moderate to severe UC after failure of conventional agents (5-aminosalicylic acid compounds, corticosteroids, and immunomodulators), per that for infliximab (i.e. first-line biologic therapy). The ESC noted that the availability of a tumour necrosis factor (TNF) inhibitor with a different mode of administration to infliximab (i.e. subcutaneous injection compared with infusion) would be valuable.
- 4.2 Re-submission's proposed place in therapy: first-line and beyond. The pre-PBAC response stated that the clinical place of therapy and the restriction wording should reflect the evidence where adalimumab has demonstrated efficacy in both treatment naive patients (first line biologic) and patients with prior exposure to anti-TNF agents (second line biologic due to loss of response or intolerance).

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

#### **5 Comparator**

- 5.1 Infliximab. The ESC considered this was appropriate. The PBAC previously noted that infliximab was considered to be the most relevant comparator and the comparative data of most interest to the PBAC was adalimumab versus infliximab data from randomised controlled trials. The submission also presented an indirect comparison against vedolizumab.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

## 6 Consideration of the evidence

### **Sponsor hearing**

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the proposed clinical positioning of adalimumab and noted that the available evidence supported both first and second line therapy, which was the preferred listing by treating physicians. It was further noted that a better clinical response is observed in first line therapy. The clinician acknowledged that the clinical evidence for adalimumab is not as good in the induction phase, but stated that the maintenance phase is more important from a clinical perspective. The clinician also raised some concerns about the proposed restriction wording, noting that patients may be able to shortcut standard care, and requested clinician input to the final restriction. The clinician addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (74), health care professionals (9) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with adalimumab including: the option of another therapy for those patients who fail on or are intolerant to infliximab; and the availability of a subcutaneous injection which would remove the need for intravenous infusions, reduce the need to attend health services, and allow patients to avoid travel to hospital and take less time off work for infusions. A number of comments addressed the high cost of adalimumab, noting that without PBS-listing, the drug will remain unaffordable for many patients.
- 6.3 The PBAC noted the advice received from Crohn's & Colitis Australia and the Australian Inflammatory Bowel Disease Association, Gastroenterological Society of Australia clarifying the likely use of adalimumab in clinical practice. The PBAC specifically noted the advice that listing adalimumab would allow patients to switch to another biologic following loss of response to infliximab and may help to avoid surgery. In addition, the advice noted the issues of distance and travel for regional and remote patients and time off from school and work for hospital-based intravenous infusions with infliximab which would be avoided with a subcutaneous injection that can be self-administered. The PBAC noted that this advice was supportive of the evidence provided in the submission.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

### **Clinical trials**

- 6.4 This re-submission was based on:
- Three randomised controlled trials (RCTs) comparing adalimumab to placebo (ULTRA 1 (M06-826), ULTRA 2 (M06-827) and Suzuki (M10-447);
  - An indirect comparison of adalimumab versus infliximab, which was based on the above plus - three RCTs comparing infliximab to placebo (ACT 1, ACT 2 and Probert); and

- One RCT comparing vedolizumab to placebo (GEMINI I) and an indirect comparison of adalimumab (using the adalimumab versus placebo RCTs) and vedolizumab.
- Four published network meta-analyses comparing adalimumab to infliximab (Archer et al (2014), Danese et al (2014), Stidham et al (2014), Thorlund et al (2014), and an unpublished network meta-analysis of adalimumab versus infliximab (██████████ unpublished).

6.5 Details of the trials presented in the re-submission are provided in the following table.

**Table 2: Trials and associated reports presented in the re-submission**

Trial ID	Protocol title/publication title	Publication citation
<b>Adalimumab trials</b>		
ULTRA 1 (M06-826), NCT00385736	Clinical Study Report. Study of the human anti-TNF monoclonal antibody adalimumab for the induction of clinical remission in subjects with moderately to severely active UC.  Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active UC: results of a randomised controlled trial.  Reinisch W. Sandborn WJ. Panaccione R. Huang B. Pollack PF. Lazar A. Thakkar RB. (2013) 52-week efficacy of adalimumab in patients with moderately to severely active UC who failed corticosteroids and/or immunosuppressants.	Abbott Laboratories. Internal report. 16 Mar 2012  Gut. 2011;60(6):780-787  Inflammatory Bowel Diseases. 19(8):1700-9, 2013 Jul.
ULTRA 2 (M06-827), NCT00408629	Clinical Study Report. Study of the human anti-TNF monoclonal antibody adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active UC.  Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate to severe UC.  Sandborn WJ, Colombel JF, D'Haens G, Van Assche G, Wolf D, Kron M, Lazar A, Robinson AM, Yang M, Chao JD, Thakkar R. (2013) One-year maintenance outcomes among patients with moderately-to-severely active UC who responded to induction therapy with adalimumab: subgroup analyses from ULTRA 1.  Wolf D, D'Haens G, et al. (2014) Escalation to weekly dosing recaptures response in adalimumab-treated patients with moderately to severely active UC.	Internal report. 16 Mar 2012  Gastroenterology. 2012;142(2):257-65[e1-3]  Aliment Pharmacol Ther. 2013 Jan;37(2):204-13.  Alimentary Pharmacology & Therapeutics 40(5): 486-497.
Suzuki (M10-447), NCT00853099	A Multi-Centre, Randomized, Double-Blind, Placebo-controlled Study of Adalimumab in Japanese Subjects With Moderately to Severely Active UC. NCT00853099  <i>Suzuki Y, Motoya S, Hanai H, et al. Efficacy and safety of adalimumab in Japanese patients with moderately to severely active UC.</i>	Study results from US NIH ClinicalTrials.gov.  J Gastroenterol. 2014;49(2):283-94.
<b>Infliximab trials</b>		
ACT 1 (NCT00036439)  and	Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for UC.  Feagan BG, Reinisch W, Rutgeerts P, et al. The effects of	New England Journal of Medicine. 2005;353(23):2462-2476  American Journal of

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Trial ID	Protocol title/publication title	Publication citation
ACT 2 (NCT00096655)	<p>infliximab therapy on health-related quality of life in UC patients.</p> <p>Sandborn WJ, Rutgeerts P, Feagan BG, et al. Colectomy rate comparison after treatment of UC with placebo or infliximab.</p> <p>Colombel JF, Rutgeerts P, et al. (2011) Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in UC.</p> <p>Feagan BG, Reinisch W, et al. (2007) The effects of infliximab therapy on health-related quality of life in UC patients.</p> <p>Lichtenstein GR, et al. (2009)a Clinical trial: benefits and risks of immunomodulators and maintenance infliximab for IBD-subgroup analyses across four randomized trials.</p> <p>Lichtenstein GR, et al (2012)b A pooled analysis of infections, malignancy, and mortality in infliximab- and immunomodulator-treated adult patients with inflammatory bowel disease.</p> <p>Reinisch WW, Sandborn J, et al. (2007) Response and remission are associated with improved quality of life, employment and disability status, hours worked, and productivity of patients with UC.</p> <p>Reinisch WW, Sandborn J, et al. (2012) Long-term infliximab maintenance therapy for UC: the ACT-1 and -2 extension studies.</p> <p>Reinisch WF, et al. (2012) Infliximab concentration and clinical outcome in patients with UC.</p>	<p>Gastroenterology. 2007;102(4): 794-802.</p> <p>Gastroenterology. 2009;137(4):1250-1260</p> <p>Gastroenterology 141, 1194-1201.</p> <p>The American journal of gastroenterology 102(4): 794-802.</p> <p>Alimentary pharmacology &amp; therapeutics 30(3): 210-226.</p> <p>The American journal of gastroenterology 107(7): 1051-1063.</p> <p>Inflammatory bowel diseases 13(9): 1135-1140.</p> <p>Inflammatory bowel diseases 18(2): 201-211.</p> <p>Gastroenterology 142 (5 Suppl 1), S114.</p>
Probert	Probert CSJ, Hearing SD, Schreiber S, et al. Infliximab in moderately severe glucocorticoid resistant UC: A randomised controlled trial.	Gut 2003; 52 (7): 998-1002.
<b>Vedolizumab trial</b>		
GEMINI I, NCT00783718	<p>A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicentre Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe UC</p> <p>Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for UC.</p> <p>Feagan et al. (2014) "DOP076 Improvements in health-related quality of life in patients with UC treated with vedolizumab."</p> <p>Feagan et al. (2012) "Vedolizumab maintenance therapy for UC: Results of gemini I, a randomized, placebo-controlled, double-blind, multicentre phase 3 trial."</p> <p>Feagan et al. (2014) "P501 Effects of continued vedolizumab therapy for UC in week 6 induction therapy nonresponders."</p>	<p>2012</p> <p>NEJM 2013; 369 (8): 699-710.</p> <p>Journal of Crohn's and Colitis 8, Supplement 1(0): S51-S52.</p> <p>American journal of gastroenterology 107, S609-s610.</p> <p>Journal of Crohn's and Colitis 8, Supplement 1(0): S276-S277.</p> <p>Inflammatory Bowel Diseases 18: S1-S2.</p>

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Trial ID	Protocol title/publication title	Publication citation
	<p>Feagan et al. (2012) "Efficacy of Vedolizumab in UC by Prior Treatment Failure in GEMINI I, a Randomized, Placebo-Controlled, Double-Blind, Multicentre Trial."</p> <p>Feagan et al. (2012) "Efficacy of Vedolizumab in UC by Prior Treatment Failure in GEMINI I, a Randomized, Placebo-Controlled, Double-Blind, Multicentre Trial."</p> <p>Feagan et al. (2014) "Mo1223 Health-Related Quality of Life in Patients With UC After Treatment With Vedolizumab: Results From the Gemini 1 Study."</p> <p>Feagan et al. (2014) "Mo1222 Effects of Continued Vedolizumab Therapy for UC in Week 6 Induction Therapy Nonresponders."</p> <p>French et al. (2014) "Mo1229 Exposure-Response Relationship of Vedolizumab Treatment in Adults With UC."</p> <p>Parikh (2012) "Efficacy of Vedolizumab in UC by Prior Treatment Failure in GEMINI I, a Randomized, Placebo-Controlled, Double-Blind, Multicentre Trial."</p> <p>Rosario et al. (2014) "P489 Exposure-response relationship during vedolizumab induction therapy in adults with UC."</p> <p>Sandborn et al. (2012) "Sustained Therapeutic Benefit of Vedolizumab Throughout 1 Year in UC in GEMINI I, a Randomized, Placebo-Controlled, Double-Blind, Multicentre Trial."</p> <p>Sandborn et al. (2013) "P323 Sustained therapeutic benefit of vedolizumab throughout 1 year in UC in GEMINI I, a randomized, placebo-controlled, double-blind, multicentre trial."</p>	<p>Inflammatory Bowel Diseases 18: S25-S26.</p> <p>Gastroenterology 146(5, Supplement 1): S-590.</p> <p>Gastroenterology 146(5, Supplement 1): S-590.</p> <p>Gastroenterology 146(5, Supplement 1): S-592.</p> <p>Inflammatory Bowel Diseases 18: S26-S26.</p> <p>Journal of Crohn's and Colitis 8, Supplement 1(0): S270-S271.</p> <p>Inflammatory Bowel Diseases 18: S25-S25.</p> <p>Journal of Crohn's and Colitis 7, Supplement 1(0): S138-S139.</p>
<b>Meta-analyses and indirect comparisons</b>		
Archer et al (2014) (NICE Assessment report)	Archer R, Tappenden P, Ren S, Martyn-St James M, Harvey R, Basarir H, Stevens J, Carroll C, Cantrell A, Lobo A, NHS Foundation Trust and Hoque S. Infiximab, adalimumab and golimumab for treating moderately to severely active UC after the failure of conventional therapy (including a review of TA140 and TA262): Clinical effectiveness systematic review and economic model.	The University of Sheffield.
Danese, 2014	Danese S, Fiorino G, Peyrin-Biroulet L, Lucenteforte E, Virgili G, Moja L and Bonovas S. "Biological agents for moderately to severely active UC: a systematic review and network meta-analysis."	Annals of internal medicine 160(10): 704-711.
Stidham, 2014	Stidham RW, Lee TCH, Higgins PDR, et al. Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor-alpha agents for the treatment of UC.	Alimentary Pharmacology and Therapeutics. 2014;39:660-671.
Thorlund, 2014	Thorlund K, Druyts E, Mills EJ, et al. Adalimumab versus infliximab for the treatment of moderate to severe UC in adult patients native to anti-TNF therapy: an indirect treatment comparison meta-analysis.	Journal of Crohn's and Colitis. 2014. Available from: dx.doi.org/10.1016/j.crohns.2014.01.010

- 6.6 The key features of the direct randomised trials are summarised in the following table.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
<b>Adalimumab vs. placebo</b>					
ULTRA 1	260	R, DB, MC, PC 8 weeks	Low	Moderate to severe UC; Anti-TNF naïve	Remission, response, mucosal healing
ULTRA 2	494	R, DB, MC, PC 52 weeks	Low	Moderate to severe UC	Remission, response, mucosal healing, IBDQ response
Suzuki (2014)	186	R, DB, MC, PC 52 weeks	Low	Moderate to severe UC; Anti-TNF naïve	Remission, response, mucosal healing, IBDQ response
<b>Infliximab vs. placebo</b>					
ACT 1	242	R, DB, PC 54 weeks	Low	Moderate to severe UC. Prior treatment with a TNF $\alpha$ antagonist not allowed.	Remission, response, mucosal healing, IBDQ response, colectomy
ACT 2	244	R, DB, PC 30 weeks	Low		Remission, response, mucosal healing, IBDQ response, colectomy
Probert (2003)	43	R, DB, PC, 8 weeks	Unclear		Remission week 6 (UC symptom score)
<b>Vedolizumab vs. placebo</b>					
GEMINI I	374 (Cohort 1) 373 (Cohort 2)	R, DB, 6 weeks and 52 Weeks	Low	Moderate to severe UC Failed $\geq 1$ of TNF $\alpha$ antagonist, immunomodulator or corticosteroids. Response to VED at wk 6 from GEMINI I (OL or DB)	Full Mayo response, remission week 6 and week 52

IBDQ = Inflammatory Bowel Disease Questionnaire; DB=double blind; MC=multi-centre; OL=open label; PC = placebo controlled; R=randomised.

Source: compiled during the evaluation

- 6.7 The trials and outcomes assessed in each of the Bayesian network meta-analyses are summarised in the following table.

**Table 4: Summary of Bayesian network meta-analyses comparing adalimumab vs infliximab included in the re-submission\***

Study	Treatments included	Adalimumab studies included	Infliximab studies included	Other studies included	Outcomes assessed
Archer, et al. (2014) (NICE Assessment Report)	Adalimumab, infliximab, golimumab	ULTRA 1, ULTRA 2, M10-447 (i.e. Suzuki 2014)	ACT 1, ACT 2, Probert 2003, UC-SUCCESS#	PURSUIT-SC induction, PURSUIT-Maintenance	Probit model: clinical response remission in: 1) induction phase, 2) weeks 8-32 for patients starting in a) response or b) remission, 3) weeks 32-52 for patients starting in a) response or b) remission
Danese, et al. (2014)	Adalimumab, infliximab, golimumab, Vedolizumab	ULTRA 1, ULTRA 2, M10-447 (i.e. Suzuki 2014)	ACT 1, ACT 2	PURSUIT-SC induction, PURSUIT-Maintenance, GEMINI I	ORs: clinical response (primary outcome), clinical remission, mucosal healing at end of induction and maintenance phase
Stidham, et al. (2014)	Adalimumab, infliximab, golimumab	ULTRA 1, ULTRA 2	ACT 1, ACT 2, Probert 2003	PURSUIT-SC induction, PURSUIT-Maintenance	RRs: response or remission at end of induction, maintenance of response or remission at 52 weeks
Thorlund, et al. (2014)**	Adalimumab, infliximab	ULTRA 1, ULTRA 2	ACT 1, ACT 2	None	ORs: clinical remission, clinical response, mucosal healing at 8 weeks (induction), sustained remission and response (52 weeks)
Unpublished (2014)	Adalimumab, infliximab	ULTRA 1, ULTRA 2, M10-447 (i.e. Suzuki 2014)	ACT 1, ACT 2, Probert 2003	None	Clinical remission and clinical response at weeks 8 and 52, sustained remission and response at weeks 8 and 52, mucosal healing, adverse events and serious adverse events

\*Excluding studies that pooled adalimumab and infliximab trials for comparison versus placebo.

\*\* Used an informative prior

#Infliximab vs azathioprine vs infliximab + azathioprine

Abbreviations: NICE, National Institute of Clinical Excellence; OR, Odds ratio; RR, Relative risk.

Source: Archer et al (2014), Danese et al (2014) and Stidham et al (2014).

For more detail on PBAC's view, see section 7 "PBAC outcome".

## Comparative effectiveness

6.8 The results of the indirect comparisons are shown in Table 5.

**Table 5: Summary of results of the indirect comparisons (adalimumab vs infliximab) and (adalimumab vs vedolizumab)**

	Induction Phase, Indirect RR (95% CI)	Maintenance Phase Indirect RR (95% CI)	Conclusion for adalimumab
<b>ITT population, adalimumab vs infliximab</b>			
Clinical remission	■ (■, ■) <sup>a</sup>	■ (■, ■) <sup>a,c,d</sup>	Non-inferior
Clinical response	■ (■, ■) <sup>a</sup>	■ (■, ■) <sup>a,c,d</sup>	<b>Inferior in IP/Non-inferior in MP</b>
<b>TNFα antagonist naïve patients, adalimumab vs infliximab</b>			
Clinical remission	■ (■, ■) <sup>a</sup>	■ (■, ■) <sup>a,c,d</sup>	Non-inferior
Clinical response	■ (■, ■) <sup>a</sup>	■ (■, ■) <sup>a,c,d</sup>	<b>Inferior in IP/Non-inferior in MP</b>
<b>ITT population, adalimumab vs vedolizumab</b>			
Clinical remission	■ (■, ■) <sup>b</sup>	■ (■, ■) <sup>a,c</sup>	Non-inferior
Clinical response	■ (■, ■) <sup>b</sup>	NR	Non-inferior

IP = induction phase; ITT = intention to treat; MP = maintenance phase; RR= relative risk; NR = not reported.

a: excludes Probert (2003), b: excludes Suzuki (2013); c: excludes ULTRA 1; d: excludes ACT2

**Bold** indicates statistically significant.

Source: b: ULTRA 1, ULTRA 2, Suzuki (2013), GEMINI I trials.

- 6.9 Table 6 presents the efficacy results of the Bayesian network meta-analyses comparing adalimumab vs infliximab included in the re-submission.

**Table 6: Incremental efficacy (95% credible intervals) for adalimumab vs infliximab in network meta-analyses**

Efficacy/safety outcome	Archer 2014 Infliximab vs adalimumab Pr (95% CrI) <sup>a</sup>	Danese 2014 Infliximab vs adalimumab OR (95% CrI) <sup>b</sup>	Stidham 2014 Infliximab vs adalimumab RR (95% CrI) <sup>c</sup>	Thorlund 2014 <sup>d</sup> adalimumab vs Infliximab OR (95% CrI) <sup>e</sup>	Unpublished 2014 adalimumab vs Infliximab OR (95% CrI) <sup>e</sup>
Clinical remission, end of induction		2.79 (0.95–8.83)	2.08 (0.32–12.03)	<b>0.42</b> ( <b>0.17–0.97</b> )	( <b>█</b> to <b>█</b> )
Clinical response, end of induction		<b>2.36</b> ( <b>1.22–4.63</b> )	2.15 (0.73–5.80)	<b>0.45</b> ( <b>0.23–0.89</b> )	( <b>█</b> to <b>█</b> )
Clinical remission, end of maintenance				0.72 (0.31–1.76)	( <b>█</b> to <b>█</b> )
Clinical response, end of maintenance				0.54 (0.25–1.13)	( <b>█</b> to <b>█</b> )
Clinical response/remission, induction phase	-0.52 (-1.03, 0.00)				
Clinical response/remission, maintenance phase (8-32 weeks) for patients starting in response	-0.20 (-1.09, 0.69)				
Clinical response/remission, maintenance phase (8-32 weeks) for patients starting in remission	-0.29 (-1.41, 0.85)				
Clinical response/remission, maintenance phase (32-52 weeks) for patients starting in response	-0.67 (-2.04, 0.66)				
Clinical response/remission, maintenance phase (32-52 weeks) for patients starting in remission	0.78 (-0.53, 2.14)				

Abbreviations: CrI, credible interval; OR, odds ratio; Pr, Probit function; RR, relative risk.

<sup>a</sup> In Archer (2014) a Pr less than zero indicated a relatively lower number of events in the adalimumab group (i.e. favours infliximab). <sup>b</sup> In Danese (2014) an OR smaller than 1.00 indicates a relatively lower number of events in the infliximab group (i.e. favours adalimumab). <sup>c</sup> In Stidham (2014) an RR smaller than 1.00 indicates a relatively lower number of events in the infliximab group (i.e. favours adalimumab). <sup>d</sup> Thorlund (2014) includes anti-TNF naïve subjects only. <sup>e</sup> In Thorlund (2014) and █ (2014) an OR smaller than 1.00 indicate a relatively lower number of events in the adalimumab group (i.e. favours infliximab).  
**Bold** indicates statistically significant.

6.10 The █ (unpublished, 2014) results are very similar to the Thorlund (2014) results, however the credible intervals are wider in █ (2014) due to the use of uninformative priors (i.e. statistical distributions which were not pre-specified on the basis of previously collected data).

6.11 The re-submission claimed that the published network meta-analyses concluded there to be no significant difference in the efficacy of either adalimumab or infliximab in the requested PBS indication. However, Danese (2014) and Thorlund (2014) reported that clinical response with adalimumab is statistically significantly inferior to infliximab in the induction phase. Thorland (2014) also found that clinical remission with adalimumab was statistically significantly inferior to infliximab in the induction phase; however, this is likely due to the use of uninformative priors which reduced

the width of the credible intervals. For all of the other outcomes in all studies there was a non-significant trend towards adalimumab being inferior. These results are similar to the indirect comparison results.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

### Comparative harms

6.12 The results of the indirect comparisons of safety are shown in Table 7.

**Table 7: Results of indirect comparison of safety (adalimumab vs infliximab) and (adalimumab vs vedolizumab)**

	Maintenance Phase Indirect RR (95% CI)	Conclusion for adalimumab
<b>Adalimumab vs infliximab</b>		
SAEs		Non-inferior
AEs leading to discontinuation		Non-inferior
<b>Adalimumab vs vedolizumab</b>		
SAEs		Non-inferior

AEs = adverse events; RR= relative risk; SAEs = serious adverse events.

Note: indirect results for AEs leading to discontinuation between adalimumab and vedolizumab were not estimated, because there were zero events in the vedolizumab arm of the GEMINI I trial.

### Clinical claim

6.13 The re-submission described adalimumab as having no significant differences in terms of comparative effectiveness and no significant differences in terms of comparative safety over infliximab. The evaluation considered that this claim in relation to clinical efficacy and safety was not adequately supported. The following issues need to be considered:

- The indirect comparisons were not powered to demonstrate non-inferiority and there was no pre-specified margin for non-inferiority. In terms of clinical response, adalimumab is statistically significantly inferior to infliximab in the induction phase. For all of the other outcomes there was a non-significant trend towards adalimumab being inferior. The Pre-Sub-Committee Response (PSCR) argued that the non-inferiority margins were not pre-specified as the placebo controlled trials of adalimumab, infliximab and vedolizumab were powered to detect absolute differences in response and remission, whereas for the indirect comparison the odds ratio or relative risk is a more appropriate measurement of relative efficacy. It further argued that as indirect comparisons are conducted post-hoc, they are never powered a priori to test non-inferiority. The ESC noted the concerns raised during the evaluation, in particular that adalimumab was statistically inferior to infliximab in the induction phase; however, it considered that on balance, given the comparative efficacy of anti-TNF $\alpha$  drugs in other settings, the claim of non-inferiority was reasonable.
- There were issues with the exchangeability of the trials used in the indirect comparisons, these included:
  - the inclusion of patients with prior anti-TNF treatment in the key adalimumab (ULTRA 2) trial;
  - the availability of rescue treatment in some trials, at different doses and times of the treatment;

- the difference in the timing of measurement of primary and secondary outcomes;
- the difference in the event rates in the placebo arms; and
- the differences in the induction therapy number of doses across the trials.

The PSCR stated that some of the nominated exchangeability issues, such as, disease locality and duration, were not clinically meaningful. The ESC considered that while there were exchangeability issues, most of the differences between the trials were not meaningful.

- The ULTRA 2 trial was not powered to assess the efficacy of adalimumab in patient subgroups defined by prior anti-TNF therapy.
- The indirect comparisons of adalimumab and infliximab in terms of safety were based on two of the six available trials. The PSCR argued that the submission presented long-term relative safety data at 52 and 54 weeks from two studies (ULTRA 2 and ACT 1) as this was the most appropriate assessment for a chronic treatment; noting that the remaining pivotal studies reported safety data at earlier time points only: 8 weeks (ULTRA 1, Suzuki 2014), 30 weeks (ACT 2) or 6 weeks (Probert 2003).

- 6.14 The ESC agreed that the indirect comparison of adalimumab and infliximab suggested that adalimumab is inferior to infliximab for the clinical response outcome but probably non-inferior for the clinical remission outcome in the induction phase. However, it considered that on balance, given the comparative efficacy of anti-TNF $\alpha$  drugs in other settings, the claim of non-inferiority in terms of comparative effectiveness was reasonable. The pre-PBAC response noted the ESC's conclusion that a claim of non-inferiority is reasonable and stated that the maintenance phase is the most clinically relevant treatment period for a chronic disease like UC, where induction therapy is only used as an indicator of initial treatment response.
- 6.15 Attachment A of the re-submission described adalimumab as having similar efficacy in terms of comparative effectiveness and non-inferior in terms of comparative safety over vedolizumab.
- 6.16 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.
- 6.17 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

### ***Economic analysis***

- 6.18 The re-submission presented a cost-minimisation analysis to infliximab. The previous submission presented a cost-utility analysis to best supportive care (standard care).
- 6.19 The equi-effective doses were estimated as: adalimumab 160 mg administered at week 0, adalimumab 80 mg at week 2, and adalimumab 40 mg fortnightly thereafter is equivalent to infliximab 5 mg/kg administered at week 0, week 2, week 6 and every 8 weeks thereafter. The equi-effective doses are the same as previously accepted by the PBAC for adalimumab in paediatric Crohn's disease (for patients weighing more than 40 kg). The ESC agreed that the equi-effective doses were reasonable.

- 6.20 The re-submission also included a cost offset for the administration cost of infusion of infliximab, calculated by Jordan et al (2013), estimated to be \$ [REDACTED] per administration. The ESC considered that this was not reasonable and \$ [REDACTED] was likely to be an overestimate of the administration costs. The PSCR argued that the administration cost of \$ [REDACTED], comprised of pharmacy, Day Procedure Unit and hospital administration cost data is consistent with infliximab infusion occurring in hospital on a day case or outpatient basis and is more reflective of the true cost of infusion administration than the MBS fee of \$97.95 for item 14245. The ESC considered that the application of the \$ [REDACTED] administration cost was unreasonable and a likely overestimate, noting that the PBAC did not accept this cost offset in its consideration of adalimumab for paediatric Crohn's disease. The ESC considered that the MBS fee for MBS item 14245 for the administration by intravenous infusion was the more appropriate cost to use in the cost-minimisation analysis.
- 6.21 The pre-PBAC response reiterated the argument that MBS item 14245 underestimates the total cost of an infliximab infusion as it does not include supervision by nurses and physicians, bed costs, consumables and overheads. The response further argues that according to the Manual of resource items and their associated costs (Version 4.0, December 2009, 4.5 Drug administration costs) where there are additional medical service costs of administering the drug (the most common circumstance being where a drug is administered by infusion), these costs should be included. The sponsor contends that applying the MBS fee would bias against adalimumab in the cost-minimisation analysis.
- 6.22 Based on the arguments presented above, the sponsor proposed that a more appropriate cost for the administration of an intravenous infusion would lie between the MBS item fee and the infusion cost calculated by Jordan et al (2013). The pre-PBAC response suggested that this fee may be approximated by the day stay hospital administration DRG suggested in the PSCR (i.e. DRG R63Z with an average cost per separation of \$ [REDACTED] after pharmacy costs are removed).

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

**Drug cost/patient/month:** \$ [REDACTED].

- 6.23 The estimated DPMQ per package for the maintenance phase (adalimumab 40 mg/0.8 mL injection, 2 x 0.8 mL) was \$ [REDACTED]. Each package provides treatment for one month in the maintenance phase. The treatment is ongoing for respondents.

***Estimated PBS usage & financial implications***

- 6.24 This re-submission was not considered by DUSC. The re-submission used a mixed epidemiological and market share approach to estimate the use of adalimumab. The estimated net cost was based on the listing of infliximab. At year 5, the estimated number of patients would be less than 10,000 and the net cost to the PBS would be less than \$10 million.

**Table 8: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated	█	█	█	█	█
Number treated – July 2014	█	█	█	█	█
6 x 40 mg induction packs dispensed	█	█	█	█	█
6 x 40 mg packs dispensed – July 2014	█	█	█	█	█
2 x 40 mg continuation packs dispensed	█	█	█	█	█
2 x 40 mg packs dispensed – July 2014	█	█	█	█	█
<b>Estimated total cost to PBS/RPBS (excluding co-payments)</b>					
Total cost to PBS	\$ █	\$ █	\$ █	\$ █	\$ █
Total cost to PBS July 2014 (revised)	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Estimated total net cost to PBS/RPBS (excluding co-payments)</b>					
Net cost PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost PBS/RPBS July 2014	-	-	-	-	-

Source: Compiled during the evaluation. Each patient in a steady-state maintenance phase is estimated to receive 26 scripts.

- 6.25 The future market share of adalimumab is likely to be affected by the listing of vedolizumab, which was recommended for the treatment of moderate to severe UC in March 2015 (PBAC Outcomes, March 2015). The PSCR agreed that the recommendation of vedolizumab may result in adjustment to the financial estimates, and noted that that the sponsor would be willing to finalise appropriate estimates with the Department. The prevalence rates used from an Australian treatment practice survey were uncertain. The assumptions of market share rates and continuation rates for adalimumab were based on the DUSC Advice (February 2015) for Crohn’s Disease (for adalimumab and infliximab). The UC market may be different to Crohn’s disease market.

**Quality Use of Medicines**

- 6.26 The re-submission advised that a patient support program, AbbVie Care, aims to improve patient education, support and quality of life and enhance the quality use of adalimumab. This program partners with clinicians and pharmacists and is offered to all patients treated with adalimumab. This is different from the previous submission in which another program was mentioned that included in home nurse support and pharmacy liaison.

**Financial Management – Risk Sharing Arrangements**

- 6.27 The re-submission was open to a risk sharing arrangement with the Department of Health for the treatment of moderate to severe UC; based on the knowledge that infliximab is listed with an effective price and with a broader restriction (adult and paediatric). █

## **7 PBAC Outcome**

- 7.1 The PBAC rejected the request to extend the PBS listing for adalimumab to include the treatment of moderate to severe UC on the basis that the evidence presented did not establish non-inferiority of adalimumab to the nominated comparator (infliximab).
- 7.2 The PBAC noted that the requested listing for adalimumab had been updated and is aligned to that for infliximab, with the exception that the adalimumab restriction does not include paediatric patients. The PBAC considered that the exclusion of paediatric patients from the restriction was not adequately justified and should be addressed in any future major re-submission.
- 7.3 The PBAC noted the proposed clinical place for adalimumab in the re-submission was after failure of conventional agents (5-ASAs, corticosteroids, and immunomodulators), as for infliximab. The PBAC recalled that in March 2015 it recommended listing vedolizumab for moderate to severe UC in the same line as infliximab. The PBAC noted that the main point of difference for adalimumab (compared with infliximab and vedolizumab) was that adalimumab is a subcutaneous injection which can be self-administered. In this regard, the PBAC noted the consumer comments received which, in particular, note the convenience and equity of access benefits of a subcutaneous injection being listed on the PBS for this indication. Given that non-inferiority between adalimumab and infliximab was not demonstrated, however, the PBAC considered the clinical positioning to be unreasonable and that adalimumab may be more appropriately placed as a subsequent line biologic, following failure of, or intolerance to, infliximab or vedolizumab.
- 7.4 The PBAC considered that infliximab was the appropriate comparator. The PBAC noted that the submission appropriately presented an additional indirect comparison against vedolizumab.
- 7.5 No direct head-to-head randomised controlled trials comparing adalimumab to infliximab were available to present in the re-submission. To support the claim that adalimumab is non-inferior to infliximab, the re-submission presented an indirect comparison based on three RCTs comparing adalimumab to placebo (ULTRA 1, ULTRA 2 and Suzuki 2014) and three RCTs comparing infliximab to placebo (ACT 1, ACT 2 and Probert). In addition, the re-submission presented four published network meta-analyses comparing adalimumab to infliximab and an unpublished network meta-analysis of adalimumab versus infliximab. The PBAC noted that the ULTRA 1 and ULTRA 2 trials informing the comparison of adalimumab to placebo were the same as those previously presented in the November 2013 and July 2014 submissions.
- 7.6 The PBAC noted that the risk of bias within the trials was assessed as low during the evaluation. While the PBAC agreed that this was true for the remission phase, it considered that the risk of bias was high for the maintenance phase. The PBAC noted that the data for the maintenance phase were incomplete due to a large number of discontinuations and substantial loss to follow up. Accordingly, the PBAC considered that there was less evidence for relative effectiveness in the maintenance phase.

- 7.7 The PBAC considered that the trials comparing adalimumab versus placebo and infliximab versus placebo were similar in design and noted that both adalimumab and infliximab were associated with a benefit over placebo. However, for the indirect comparison of adalimumab to infliximab, the PBAC observed that there was a trend of inferior efficacy for adalimumab across all outcomes. The PBAC considered that the indirect comparisons presented in the submission provided low certainty evidence for the claim on non-inferiority between adalimumab and infliximab, both in the remission phase and in the maintenance phase.
- 7.8 The PBAC considered that the results of the network meta-analyses, which appeared to give results that were broadly consistent, reinforced its concerns that adalimumab may be inferior to infliximab, noting that at 8 weeks all point estimates favoured infliximab and that in all studies there was a non-significant trend towards adalimumab being inferior. The PBAC acknowledged that 8 weeks was a short time period, but considered that looking at a longer timeframe would not significantly change the response. Accordingly, the PBAC did not agree with the ESC that, given the comparative efficacy of anti-TNF $\alpha$  drugs in other settings, the claim of non-inferior comparative effectiveness was reasonable.
- 7.9 Given that the PBAC did not consider that the submission had conclusively demonstrated that adalimumab was non-inferior to infliximab, it also did not accept the cost-minimisation analysis.
- 7.10 The PBAC recalled that in its November 2014 consideration of adalimumab for paediatric Crohn's disease, it did not accept the inclusion of an in-patient resource cost of \$■■■■ per infliximab infusion. In line with this, the PBAC agreed with ESC that the application of a \$■■■■ administration cost for each infliximab infusion was unreasonable, noting that the MBS fee for item 14245 (\$97.95) was the more appropriate cost to use in the cost-minimisation analysis. The PBAC noted that the sponsor had proposed a lower administration cost (\$■■■■) in its pre-PBAC response. The PBAC considered that this remained an overestimate of the administration costs. The PBAC disagreed with the argument raised by the sponsor in its pre-PBAC response that additional costs (such as bed costs, consumables and overheads) should be included in the cost offset.
- 7.11 The PBAC recalled that it recommended vedolizumab for the treatment of moderate to severe UC at the March 2015 meeting on the basis of non-inferior comparative effectiveness compared with infliximab. The PBAC acknowledged that similar concerns regarding the indirect comparison of vedolizumab and infliximab were raised during the evaluation and PBAC consideration as have been raised for adalimumab, including difficulty obtaining a meaningful interpretation of non-inferiority due to the use of an indirect comparison and the point estimates consistently favouring the comparator. The PBAC noted that in the indirect comparison of vedolizumab and infliximab, the non-significant point estimate of clinical response in the induction phase favoured infliximab, with a relative risk of ■■■■ (95% CI: ■■■■, ■■■■). By comparison, in the indirect comparison of adalimumab and infliximab, adalimumab was found to be inferior in the induction phase for clinical response, with a relative risk of ■■■■ (95% CI: ■■■■, ■■■■). In addition, the PBAC noted that the relative risk point estimate and lower confidence limit for clinical response in the maintenance phase for the indirect comparison of adalimumab and infliximab was low (RR: ■■■■, 95% CI: ■■■■, ■■■■). The submission also presented an indirect

comparison of adalimumab and vedolizumab which resulted in a non-significant point estimate that favoured vedolizumab (RR [REDACTED], 95% CI: [REDACTED], [REDACTED]). The PBAC also considered that the network meta-analyses presented in the adalimumab submission provided additional evidence that adalimumab may be inferior to infliximab.

- 7.12 The PBAC considered that further evidence of non-inferiority against infliximab would need to be provided in any future major re-submission, preferably in the form of a head-to-head randomised trial. Alternatively, the PBAC considered that a way forward could be to position adalimumab as a later-line biologic treatment option following failure of, or intolerance to, infliximab or vedolizumab.
- 7.13 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**  
Rejected

## **8 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.

## **9 Sponsor's Comment**

AbbVie is disappointed with the PBAC recommendation.

AbbVie believes the data presented in its submission demonstrates non-inferiority of adalimumab (compared with both infliximab and vedolizumab) in maintenance treatment of moderate to severe ulcerative colitis (refer Table 5). This is the most clinically relevant outcome for long term treatment of patients with ulcerative colitis.

AbbVie understands that there is a significant unmet patient need for an alternative route of administration, so will continue to work with the PBAC to find a way forward.