7.1 ADALIMUMAB, 40 mg/0.8 mL injection, 2 x 0.8 mL cartridges and 2 x 0.8 mL syringes, 40 mg/0.8 mL injection, 6 x 0.8 mL cartridges and 6 x 0.8 mL syringes, Humira®, AbbVie Pty Ltd

1 Purpose of Application

1.1 The major re-submission sought an Authority Required listing for the treatment of chronic refractory moderately to severely active ulcerative colitis.

2 Requested listing

2.1 The re-submission sought the following listing:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
ADALIMUMAB				
40 mg in 0.8 mL injection, 2 x 0.8 mL cartridges	1	1	Humira	AbbVie
40 mg in 0.8 mL injection, 2 x 0.8 mL syringes	1	1	Humira	AbbVie
40 mg in 0.8 mL injection, 6 x 0.8 mL cartridges	1	0	Humira	AbbVie
40 mg in 0.8 mL injection, 6 x 0.8 mL syringes	1	0	Humira	AbbVie

Authority required (abridged version)

Initial treatment (new patients)

Initial PBS-subsidised treatment with adalimumab by a gastroenterologist or a consultant physician, of a patient with moderately to severely active ulcerative colitis who satisfies the following criteria:

(a) has confirmed active ulcerative colitis as defined by standard clinical, endoscopic and/or imaging features;

(b) has signed a patient acknowledgement indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criterion for ongoing PBS-subsidised treatment; and

(c) has failed to achieve an adequate response to prior systemic therapy, dependent, intolerant or contraindicated to prior systemic therapy, including:

  i. a tapered course of corticosteroid starting at a dose of at least 40 mg prednisolone (or equivalent) and

  ii. immunosuppressive therapy including:
  - azathioprine at a dose of at least 2 mg per kg daily OR
  - 6-mercaptopurine at a dose of at least 1 mg per kg daily.

The following initiation criterion indicates failure to achieve an adequate response to prior systemic therapy and must be demonstrated in all patients at the time of application:

(a) have a severity of disease activity which results in a Full Mayo Score greater than or equal to 6 as assessed.

A maximum of 12 weeks treatment will be authorised under this criterion.

An assessment of the patient's response to this initial course of treatment must be made following a minimum of 8 weeks of therapy so that there is adequate time for a response to be demonstrated.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
ADALIMUMAB				
40 mg in 0.8 mL injection, 2 x 0.8 mL cartridges	1	5	Humira	AbbVie
40 mg in 0.8 mL injection, 2 x 0.8 mL syringes	1	5	Humira	AbbVie

Continuing treatment of moderate-to-severely active ulcerative colitis

Continuing PBS-subsidised treatment with adalimumab by a gastroenterologist, a consultant physician or other consultant physician in consultation with a gastroenterologist, of a patient aged 18 years or older who:

(a) has a documented history of moderately to severely active ulcerative colitis; or
(b) has demonstrated or sustained an adequate response to treatment with adalimumab.

An adequate response to adalimumab treatment is defined as:

(a) decrease in partial Mayo Score of ≥ 2 points; or
(b) decrease in full Mayo Score of ≥ 3 points.

The assessment of the patient's response to a continuing course of therapy must be made within the 4 weeks prior to completion of that course and posted Medicare Australia no less than 2 weeks prior to the date the next dose is scheduled, in order to ensure continuity of treatment for those patients who meet the continuation criterion.

2.2 Listing was requested on a cost-utility basis compared with best supportive care.

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

3 Background

3.1 Adalimumab was approved by the TGA for the treatment of moderately to severely active ulcerative colitis in adult patients in July 2013. The extended TGA-registration now includes the following:

> "Adalimumab is indicated for patients who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. Patients should show a clinical response within 8 weeks for treatment to continue treatment beyond that time (see CLINICAL TRIALS)."

3.2 Adalimumab is currently listed on the PBS for the treatment of severe active rheumatoid arthritis, severe active psoriatic arthritis, active ankylosing spondylitis, severe active juvenile idiopathic arthritis, severe refractory Crohn disease, fistulising Crohn disease and severe chronic plaque psoriasis.

3.3 The PBAC had previously considered adalimumab for the treatment of moderately to severely active ulcerative colitis once. In November 2013, the PBAC rejected a submission on the grounds that the cost-effectiveness of adalimumab was not able to be estimated by the economic analysis presented in the submission (paragraph 7.1, Nov 2013 PBAC minutes).

4 Clinical place for the proposed therapy

4.1 Adalimumab is intended for use in adult patients with moderately to severely active ulcerative colitis who have not responded to, are contraindicated or intolerant of conventional therapies.

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

5 Comparator

5.1 The main comparator in the re-submission remained best supportive care, which was accepted by PBAC in November 2013 as appropriate. The ESC noted that infliximab was recommended for PBS listing for moderate to severe ulcerative colitis in March 2014 but that the recommendation is yet to become effective. Should the infliximab recommendation become effective, the ESC considered that infliximab would be the most appropriate comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (12), health care professionals (4) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment and improvements in quality of life with adalimumab, including the following:

- Less time spent in hospitals;
- Avoidance of surgery (3 episodes per patient) and associated complications, including adhesions/pouchitis;
- Avoidance of side-effects associated with corticosteroid use;
- Increasing the available treatment options once corticosteroid therapy has failed or is inadequate;
- Attainment of disease control and remission;
- Improved ability to work, less sick leave;
- Increased energy to look after family;
- Facilitating a normal social life which was not possible before treatment;
- Less stress and less anxiety around potential of "losing bowel' and having to undergo major surgery with long term emotional and physical impact;
- Improved financial position by taking financial pressure off families;
- Reassurance about supply, though not having to rely on a sponsor compassionate access program; and
- Increased equity in access.

6.3 The PBAC also noted the support for listing from the Gut Foundation.

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

Clinical trials

6.4 The two trials (M06-826 and M06-827), hereafter referred to as ULTRA I and II respectively) relied upon in the re-submission are the same as in the previous submission. A literature search identified a new paper by Suzuki et al. (2014) which was excluded by the re-submission inappropriately.

6.5 The Suzuki (2014) study was excluded from the re-submission due to the patients being Japanese and the results generally confirming those of the key trials. The re-submission argued that the Japanese population provided limited applicability to the Australian treatment setting. The reasons for excluding the Suzuki (2014) trial in the re-submission were inappropriate. It would have been more appropriate to include this trial and perform meta-analyses including and excluding this trial. During the evaluation, an analysis of the efficacy including and excluding the Suzuki 2014 data was performed. The ESC agreed with this approach.

6.6 The re-submission also provided a sponsor commissioned, unpublished evaluation report, *(REDACTED)* contained in Attachment 8 of the July 2014 major submission), which critiqued network meta-analyses reports that include the pivotal adalimumab trials (ULTRA I and II) and infliximab trials (ACT I and II) for the treatment of ulcerative colitis.

6.7 The table below summarises the studies presented in the submission:

Trials, associated reports and meta-analyses presented in the evaluation of adalimumab and infliximab

Trial ID/First Author	Protocol title/publication title	Publication citation
Adalimumab trials		
ULTRA I	Study of the human anti-TNF monoclonal antibody adalimumab for the induction of clinical remission in subjects with moderately to severely active ulcerative colitis.	Internal report. 16 Mar 2012
Reinisch W,	Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial.	*Gut.* 2011;60(6):780-787
ULTRA II	Study of the human anti-TNF monoclonal antibody adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active ulcerative colitis.	Internal report. 16 Mar 2012
Sandborn WJ	Adalimumab induces and maintains clinical remission in patients with moderate to severe ulcerative colitis.	*Gastroenterology*. 2012;142(2):257-65[e1-3]
M10-447	A 52 week, phase 2/3, randomised, double blind study to evaluate the efficacy, safety and pharmacokinetics of adalimumab for induction and maintenance treatment in anti-TNF-naïve Japanese patients with ulcerative colitis who are refractory to corticosteroids, immunomodulators, or both.	NCT00853099
Suzuki Y	Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis.	*J Gastroenterol.* 2014; 49(2):283-94.
Infliximab trials		
ACT I, ACT II		
Rutgeerts P	Infliximab for induction and maintenance therapy for ulcerative colitis.	*New England Journal of Medicine*. 2005;353(23):2462-2476

Trial ID/First Author	Protocol title/publication title	Publication citation
Feagan BG	The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients.	*American Journal of Gastroenterology*. *2007;102(4): 794-802*
Sandborn WJ	Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab.	*Gastroenterology*. *2009;137(4):1250-1260*
Meta-analyses and indirect comparisons		
Chen	Efficacy of infliximab and adalimumab for the treatment of ulcerative colitis – an indirect comparison of RCT evidence.	*United European Gastroenterology Journal*. 2013;1(1S):A224 [Abstract]
Danese	Biological agents for moderately-to-severely active ulcerative colitis in adults: a network meta-analysis of randomized controlled trials.	*European Crohn's and Colitis Organisation*. 2014:P547 [Abstract]
Liu	Indirect comparison of adalimumab and infliximab in ulcerative colitis: cost per remitter analysis.	*American Journal of Gastroenterology*. 2013;108(1S): S520 [Abstract]
Stidham	Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor-alpha agents for the treatment of ulcerative colitis.	*Alimentary Pharmacology and Therapeutics*. 2014;39:660-671
Thorlund	Adalimumab versus infliximab for the treatment of moderate to severe ulcerative colitis 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

Source: Attachment 8 of the re-submission
AE = adverse events; C = comparable; QoL = quality of life; RCT = randomised controlled trial; TNF = tumour necrosis factor

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

Comparative effectiveness

Adalimumab versus placebo

6.8 The results for the comparative effectiveness of the ULTRA I and II trials, when compared to placebo, were unchanged from the previous submission. The PBAC had previously considered that adalimumab treatment is associated with a real but modest clinical benefit, noting that approximately 50% of patients treated with adalimumab respond (at week 8), while less than 20% achieve remission.

6.9 During the evaluation, meta-analyses of the effectiveness of adalimumab were performed using the ULTRA trials and the Suzuki (2014) trial. The results were compared to the results of the meta-analyses of the ULTRA trials alone (see Table below).

Results and meta-analyses of outcomes – ULTRA I and II and Suzuki 2014

Trial ID	Adalimumab	Placebo	ARD (95% CI)	RR (95% CI)	*NNT (95% CI)*
Clinical remission at 8 weeks					
ULTRA I	24/130 (18.5%)	12/130(9.2%)	9.2 (0.9, 17.6)	2.0 (1.1, 3.8)	*11 (6, 111)*
ULTRA II	41/248 (16.5%)	23/246 (9.3%)	7.2 (1.3, 13.1)	1.8 (1.1, 2.9)	*14 (8, 77)*

Trial ID	Adalimumab	Placebo	ARD (95% CI)	RR (95% CI)	*NNT (95% CI)*
Suzuki 2014	*9/90 (10.0%)*	*11/96 (11.5%)*	*-1.5 (-10.3, 7.4)*	*0.9 (0.4, 2.0)*	*-69 (NE)*
Meta-analysis of ULTRA I and II only (I^2 = 0%)			8.2 (3.0, 13.0)	1.9 (1.3, 2.7)	*12 (8, 33)*
Meta-analysis of ULTRA I and II and Suzuki (I^2 = 25%)				*1.6 (1.0, 2.4)*	
Clinical response at 8 weeks					
ULTRA I	71/130 (54.6%)	58/130 (44.6%)	10.0 (-2.1, 22.1)	1.2 (1.0, 1.6)	*10 (NE)*
ULTRA II	125/248 (50.4%)	85/246 (34.6%)	16.0 (7.0, 24.0)	1.5 (1.2, 1.8)	*6 (4, 14)*
Suzuki 2014	*45/90 (50.0%)*	*34/96 (35.4%)*	*14.6 (0.5, 28.7)*	*1.4 (1.0, 2.0)*	*7 (3, 200)*
Meta-analysis of ULTRA I and II only (I^2 = 11%)			13.9 (7.0, 21.0)	1.4 (1.2, 1.6)	*7 (5, 15)*
Meta-analysis of ULTRA I and II and Suzuki (I^2 = 0%)				*1.4 (1.2, 1.6)*	
Clinical remission at 52 weeks					
ULTRA II	43/248 (17.3%)	21/246 (8.5%)	8.8 (2.9, 14.7)	2.0 (1.2, 3.3)	*11 (7, 34)*
Suzuki 2014	*18/90 (20.0%)*	*7/96 (7.3%)*	*12.7 (2.9, 22.5)*	*2.7 (1.2, 6.3)*	*8 (4, 34)*
Meta-analysis of ULTRA II and Suzuki (I^2 = 0%)				*2.2 (1.4, 3.4)*	
Clinical response at 52 weeks					
ULTRA II	75/248 (30.2%)	45/246 (18.3%)	11.9 (4.5, 19.4)	1.7 (1.2, 2.3)	*8 (5, 22)*
Suzuki 2014	*28/90 (31.1%)*	*17/96 (17.7%)*	*13.4 (1.2, 25.6)*	*1.8 (1.0, 3.0)*	*7 (4, 83)*
Meta-analysis of ULTRA II and Suzuki (I^2 = 0%)				*1.7 (1.3, 2.2)*	

Source: Tables B-18 to B-19 and Figures B-5 to B-6, pp115-116 of the re-submission; Table 35, p225 of CSR ULTRA I. Table 14.2_11.1, p763 of CSR ULTRA I; Table 14.2_12.1; p766 of CSR ULTRA I; Suzuki 2014

ARD = absolute risk difference; CI = confidence interval; NE = not estimable; NNT = number needed to treat; RR = relative risk; **Bold** = statistically significant result; *Italics* = calculated during evaluation

6.10 Including data from the Suzuki (2014) trial in the meta-analyses of clinical outcomes supported the results of the ULTRA trials in suggesting that adalimumab is superior to placebo. The ESC noted that the inclusion of Suzuki (2014) results did not substantially alter the interpretation of the results.

<u>Adalimumab versus infliximab</u>

6.11 The table below summarises the results of the indirect comparison between adalimumab and infliximab using placebo as a common comparator, as presented by *(REDACTED)*

Summary of comparative benefits for adalimumab and infliximab – indirect comparison

Trial	ADA	PBO	IFX	OR (95% CrI)	Event rate/100 patients [c]			RD [d] (95% CI)
					ADA	PBO	*(REDACTED)*	
Clinical remission at 8 weeks								
ADA [a]	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*		*(REDACTED)*
IFX [b]		*(REDACTED)*	*(REDACTED)*	*(REDACTED)*		*(REDACTED)*	*(REDACTED)*	
Indirect comparison				*(REDACTED)*				
Clinical response at 8 weeks								
ADA [a]	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*		*(REDACTED)*
IFX [b]		*(REDACTED)*	*(REDACTED)*	*(REDACTED)*		*(REDACTED)*	*(REDACTED)*	
Indirect comparison				*(REDACTED)*				
Clinical remission at 52 weeks								
ULTRA II	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*		*(REDACTED)*
ACT I		*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	
Indirect comparison				*(REDACTED)*				
Clinical response at 52 weeks								
ULTRA	*(REDACT*	*(REDACT*		*(REDACTED)*	*(REDAC*	*(REDAC*		*(REDACT*

Trial	ADA	PBO	IFX	OR (95% CrI)	Event rate/100 patients [c]			RD [d] (95% CI)
					ADA	PBO	*(REDACTED)*	
II	*ED)*	*ED)*			*TED)*	*TED)*		*ED)*
ACT I		*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	
Indirect comparison				*(REDACTED)*				

a Meta-analysis of ULTRA I and II
b Meta-analysis of ACT I and II
c Maximum duration of follow-up: ULTRA I = 8 weeks; ULTRA II = 52 weeks; ACT I = 54 weeks; ACT II = 30 weeks
(REDACTED) ADA = adalimumab; CI = confidence interval; CrI = credible interval; IFX = infliximab; OR = odds ratio; PBO = placebo; RD = risk difference

6.12 The indirect comparison of adalimumab and infliximab performed *(REDACTED)* indicated a trend for inferior efficacy for adalimumab across all outcomes. Although the indirect comparisons of the relative risks and odds ratios resulted in no statistically significant differences between the agents, the credible intervals were large (e.g. for response at 8 weeks OR *(REDACTED)* 95% Credible Interval: *(REDACTED)*

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

Comparative harms

Adalimumab versus placebo

6.13 The results for the comparative effectiveness of the ULTRA I and II trials, when compared to placebo, were unchanged from the previous submission. The PBAC had previously considered that overall, the comparative harms of adalimumab are known and no new safety signals were observed in the trials and additional safety data presented in the November 2013 submission.

6.14 The table below provides a summary of the comparative harms for adalimumab and placebo as per the ULTRA trials.

Summary of comparative harms for adalimumab and placebo

Trial	ADA	PBO	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				ADA	PBO	
HARMS						
Iron deficiency anaemia						
ULTRA II	7/257	1/260	7.1 (0.9, 57.2)	2.7	0.4	0.02 (0.00, 0.5)
Gastroenteritis						
ULTRA II	9/257	2/260	4.6 (1.0, 20.9)	3.5	0.8	0.03 (0.00, 0.05)
Nasopharyngitis						
ULTRA II	48/257	27/260	1.8 (1.2, 2.8)	18.7	10.4	0.08 (0.02, 0.14)

* Maximum duration of follow-up: ULTRA I = 8 weeks; ULTRA II = 52 weeks
Source: Compiled during the evaluation
ADA = adalimumab; CI = confidence interval; PBO = placebo; RD = risk difference; RR = risk ratio; Italics = calculated during evaluation

Adalimumab versus infliximab:

6.15 *(REDACTED)* report did not provide a comparative assessment of safety for adalimumab and infliximab. Although no further extended safety data was provided in the re-submission, the updated M10-223 clinical study report (M10-223 was an extension trial that enrolled patients from the ULTRA trial and is used to provide safety outcomes) allowed the key adverse events identified in the November 2013 Commentary to be updated. The information is provided in the table below.

Summary of key adverse events in the long-term open-label trial M10-223 (safety set)

	Week 60 (PY = 346.6)	**Week 180 (PY = 1,312.4)**
Number of subjects	498	592
Adverse events	288 (57.8%)	482 (81.4%)
AE at least possibly drug related	111 (22.3%)	206 (34.8%)
Any severe AE	50 (10.0%)	117 (19.8%)
Any serious AE	48 (9.6%)	130 (22.0%)
Any AE leading to discontinuation of study drug	29 (5.8%)	83 (14.0%)
Death	1 (0.2%)	3 (0.5%)

Source: Table B-31, p110 of the submission; Table 33 p174 of M10-223 CSR
AE = adverse event; PY = patient years

6.16 The ESC noted that the results in the above table indicate that adalimumab toxicity increases with increasing treatment exposure. The ESC also recalled that anti-TNF alpha drugs may increase risk of infections, lymphomas and other malignancies.

Benefits/harms

6.17 The table below provides a summary of the comparative benefits and harms for adalimumab and placebo as per the ULTRA trials.

Summary of comparative benefits and harms for adalimumab and placebo

Trial	ADA	PBO	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				ADA	PBO	
BENEFITS						
Clinical remission at 8 weeks						
ULTRA I	24/130	12/130	2.0 (1.1, 3.8)	18.5	9.2	0.09 (0.01,0.18)
ULTRA II	41/248	23/246	1.8 (1.1, 2.9)	16.5	9.3	0.07 (0.01, 0.13)
Meta-analysis (I^2 = 0%)			1.9 (1.3, 2.7)			0.08 (0.03, 0.13)
Clinical response at 8 weeks						
ULTRA I	71/130	58/130	1.2 (1.0, 1.6)	54.6	44.6	0.10 (-0.02, 0.22)
ULTRA II	125/248	85/246	1.5 (1.2, 1.8)	50.4	34.6	0.16 (0.07, 0.25)
Meta-analysis (I^2 = 11%)			1.4 (1.2, 1.6)			0.14 (0.07, 0.21)
Clinical remission at 52 weeks						
ULTRA II	43/248	21/246	2.0 (1.2, 3.3)	17.3	8.5	0.09 (0.03, 0.15)
Clinical response at 52 weeks						
ULTRA II	75/248	45/246	1.7 (1.2, 2.3)	30.2	18.3	0.12 (0.05, 0.19)
HARMS						
Iron deficiency anaemia						
ULTRA II	7/257	1/260	7.1 (0.9, 57.2)	2.7	0.4	0.02 (0.00, 0.5)
Gastroenteritis						
ULTRA II	9/257	2/260	4.6 (1.0, 20.9)	3.5	0.8	0.03 (0.00, 0.05)
Nasopharyngitis						
ULTRA II	48/257	27/260	1.8 (1.2, 2.8)	18.7	10.4	0.08 (0.02, 0.14)

* Maximum duration of follow-up: ULTRA I = 8 weeks; ULTRA II = 52 weeks
Source: Compiled during the evaluation
ADA = adalimumab; CI = confidence interval; PBO = placebo; RD = risk difference; RR = risk ratio; Italics = calculated during evaluation

6.18 On the basis of the meta-analyses of the direct comparison of the ULTRA I and II evidence presented by the submission, for every 100 patients treated with adalimumab in comparison to placebo, at week 8:

- Approximately 8 additional patients would have clinical remission; and
- Approximately 14 additional patients would have clinical response.

6.19 On the basis of the ULTRA II evidence presented by the submission, for every 100 patients treated with adalimumab in comparison to placebo, at week 52:
- Approximately 9 additional patients would have clinical remission;
- Approximately 12 additional patients would have clinical response;
- Approximately 2 additional patients would have had iron deficiency anaemia;
- Approximately 3 additional patients would have had gastroenteritis; and
- Approximately 8 additional patients would have had nasopharyngitis.

6.20 The ESC considered that an estimate of the incremental clinical benefit and harms of adalimumab treatment needs to take account of changes in the natural disease progression of ulcerative colitis over time (i.e. an increased remission/response in placebo patients over time suggests that disease activity tends to decrease over time, reducing the size of treatment effect beyond that observed at week 52 in the trials) and the impact of chronic adalimumab treatment on safety in terms of increased risk of adverse events and risk of chronic adverse events (especially risks of malignancy) beyond week 52.

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

Clinical claim

Adalimumab versus placebo

6.21 In the re-submission, adalimumab was described as superior to placebo in patients with moderately to severely active ulcerative colitis in terms of comparative effectiveness and marginally worse in terms of comparative safety.

6.22 The ESC advised that this claim in the re-submission was adequately supported and appeared reasonable as::
- The issues surrounding the applicability of superior efficacy to the requested PBS population had been addressed by the proposed complex Authority Required restriction which does not allow:
  - continued therapy unless a patient is assessed to have achieved an adequate response; and
  - increased maximum quantities (any patient who requires dose escalation to weekly dosing must receive adalimumab through the *(REDACTED)*; and
- The claim in terms of safety had been modified.

Adalimumab versus infliximab

6.23 The re-submission described adalimumab as non-inferior in terms of comparative effectiveness over infliximab, stating that there is no evidence at a conventional level of statistical significance that either agent is superior.

6.24 The ESC advised that this claim may not have been reasonable as:
- There were no head-to-head randomised trials of adalimumab versus infliximab, an indirect comparison was the only means of comparison;
- The indirect comparison indicated a trend for inferior efficacy for adalimumab, although this was not statistically significant.

6.25 No claim with regards to comparative safety was provided in the re-submission.

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

Economic analysis

6.26 The re-submission presented both a preliminary trial-based economic evaluation, based on the efficacy results from the ULTRA trials, and a modelled economic evaluation.

6.27 The type of economic evaluation presented was a cost-utility analysis with a ten-state Markov modelled economic analysis.

6.28 The model compared the cost-effectiveness of adalimumab (as an adjunct to standard care) to standard care for patients with moderately to severely active ulcerative colitis. Patients were cycled through ten health states in four-weekly cycles for 10 years. Long-term costs and outcomes were calculated in each treatment group via a Markov state transition model.

6.29 The new model aimed to rectify the issues of the previous model in the following aspects:

- It was a 10 state Markov model explicitly linking costs of treatment with response and remission;
- Clinical response was used to determine costs and efficacy of treatment;
- Loss of response and/or remission over time was incorporated into the model based on efficacy data from the clinical trials; and
- Discontinuation, due to adverse events and other reasons, was taken into account.

6.30 Overall, the evaluation considered the structure of the model to be appropriate. All the necessary healthcare resource costs were included.

6.31 The discounted incremental cost per QALY for adalimumab treatment (plus best supportive care), compared to best supportive care alone was calculated by the re-submission to be in the range of $15,000/QALY - $45,000/QALY, compared to $*(REDACTED)* in the previous submission (20-year model duration). In line with the key economic drivers, the ESC advised that the incremental cost effectiveness ratio (ICER) of $15,000/QALY - $45,000/QALY gained to be potentially underestimated to a significant extent for the following reasons:

- Health state costs derived from a *(REDACTED)* clinician treatment survey were potentially underestimated. The ESC advised that there are significant differences in health state costs between the remission and non-response states as derived from the clinician survey compared to those from the published Australian study by Gibson (2013) which the ESC considered could be used in the economic evaluation.
- Utility values associated with various health states may not be accurate. The ESC advised that there are significant differences in utility values between remission and non-response health states as derived from Tsai (2008) than recently published Australian data from Gibson (2013). The ESC noted that utility values from Gibson (2013) have higher values for patients in the non-response health state (Tsai: EQ-5D - 0.42; Gibson: AQol - 0.66 and EQ-5D - 0.68) which if used in the economic evaluation, would decrease the gains in QALYs and therefore reduce the estimated incremental cost-effectiveness of adalimumab.

- The probability of maintaining response beyond 1 year is not consistent across treatments. For placebo, the corresponding four weekly probability of 0.917 of maintaining response was based on loss of response between weeks 8 and 52. The same probability was observed for adalimumab between weeks 8 and 52, but a post-52 week, four weekly probability of 0.997 for maintaining response was used in the economic model for adalimumab patients. The probability of 0.997 was informed by a single arm extension study of patients on adalimumab. An extension study of placebo patients was not available. The ESC advised that the use of a 0.917 transition probability for placebo patients yet a 0.997 transition probability for adalimumab unfairly favours adalimumab and that the transition probability for maintaining response should be consistent between adalimumab and placebo.

6.32 The table below provides the results of the key univariate sensitivity analyses presented in the re-submission and key univariate and multivariate analyses conducted during the evaluation.

Results of univariate and multivariate sensitivity analyses

	∆ cost	**∆ QALY**	ICER
Univariate analyses			
Base case	$*(REDACTED)*	*(REDACTED)*	$*(REDACTED)*
Upper 95% CL of treatment effect (8 + 52 weeks response/remission)	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Lower 95% CL of treatment effect (8 + 52 weeks response/remission)	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Costs			
Costs as per Gibson 2013	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Utility scores (base case = Tsai 2008)			
Australian AQoL scores as per Gibson 2013	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Australian EQ-5D scores as per Gibson 2013	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Multivariate analyses			
Costs *(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Costs *(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*

(REDACTED) CL = confidence limit; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; Italics = calculated during evaluation

6.33 The ESC advised that an expanded multivariate analysis which includes costs and utilities from Gibson (2013) might better represent a revised base case ICER from which an acceptable price could be identified that lowered the ICER to an acceptable level. In addition, the ESC noted that if an expanded multivariate analysis also included the use of the same post-52 week transition probability (e.g. 0.917) for maintaining response across both the adalimumab and placebo treatment arms, the ICER would vary as follows:

Expanded multivariate analysis

	ΔCost	**ΔQALY**	ICER
(REDACTED) transition probability for maintaining response post wk52+ for all treatment arms	$*(REDACTED)*	*(REDACTED)*	$*(REDACTED)*
Multivariate: *(REDACTED)* transition probability for maintaining response post wk52 for all treatment arms	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*

6.34 In summary, based on the sensitivity analyses above, the ESC considered that the ICER realised in practice could be substantially higher than the submission's estimated base case ICER of $15,000/QALY - $45,000/QALY.

Cost-minimisation analysis

6.35 The re-submission did not provide an economic evaluation comparing adalimumab with infliximab.

6.36 However, in the Pre-PBAC response (p.1), the sponsor indicated a willingness to accept listing on a cost-minimisation basis to infliximab with administration costs adjusted to reflect differences in the mode administration.

6.37 Using data from the ULTRA I and II and ACT I and II trials, the estimated equi-effective doses of adalimumab and infliximab for the treatment of moderately to severely active ulcerative colitis were:

- Adalimumab – 160 mg at week 0, 80 mg at week 2, and 40 mg fortnightly thereafter (with the option to increase to 40 mg weekly if there is a decrease in response);
- Infliximab – 5 mg per kg at weeks 0, 2 and 6 and then every 8 weeks thereafter.

6.38 As infliximab had not yet been listed on the PBS at the time of PBAC consideration in July 2014, a cost minimisation analysis between adalimumab and infliximab was not possible. The evaluation considered that the mode of administration (injection for adalimumab and infusion for infliximab) should be taken into consideration for a cost minimisation analysis.

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

Estimated PBS usage & financial implications

6.39 The submission was not considered by DUSC.

6.40 The re-submission proposed the following key aspects to contain the overall cost to the Government:

- A proposed price reduction on the DPMQ of *(REDACTED)* %
- Patients who need dose escalation after the induction period (i.e. from fortnightly injection to weekly injection) *(REDACTED)*

6.41 The likely number of patients treated 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 of $10 - $20 million in Year 5. The table below summarises the estimated use and financial implications of listing adalimumab on the PBS, as presented in the re-submission.

Estimated use and financial implications of adalimumab listing: current vs. previous submission

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Number treated - Nov 2013	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
(REDACTED)	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
(REDACTED)	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
(REDACTED)	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
(REDACTED)	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Estimated net cost to PBS/RPBS					
Net cost to PBS	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*

	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost saving to PBS	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Estimated total net cost [d]	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Estimated net cost to PBS/RPBS - Nov 2013					
Net cost to PBS/RPBS	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Net cost saving to PBS	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Estimated total net cost - Nov 2013	*$(REDACTED)*	*$(REDACTED)*	*$(REDACTED)*	*$(REDACTED)*	*$(REDACTED)*

(REDACTED)[b] Assuming number of scripts per year equals that estimated by the submission.
[c] Calculations in the re-submission included dose escalating patients, which results in double counting. *(REDACTED)*
[d] updated by correcting calculations errors described in table notes a and c
PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

6.42 There was the potential for the estimated total net cost to be greater or less than what was calculated due to assumptions made surrounding the estimated number of eligible patients, treated patients and prescriptions per patient, costs-offsets and the cost of adverse events and calculation errors.

6.43 The Sponsor proposed a risk sharing arrangement similar to the original Deed of Agreement in place for Crohn disease, which would see two market subsidisation caps set at varying levels above the estimated usage of adalimumab as calculated in Section E of the re-submission. As per the Agreement for Crohn disease, these caps are set at *(REDACTED)* % and *(REDACTED)* % and are presented below:

Proposed market subsidisation caps for adalimumab

	2015	2016	2017	2018	2019
Estimated net cost to the PBS/RPBS	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Subsidisation cap 1 *(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*
Subsidisation cap 2 *(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*	*(REDACTED)*

Source: Table F-2, p248 of the re-submission
PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

6.44 The re-submission proposed that if Commonwealth expenditure exceeds the thresholds, the following price rebates (which were similar to those that apply in the Deed of Agreement for Crohn disease) would apply:

- A rebate of *(REDACTED)*% if in any calendar year the Commonwealth payment exceeds subsidisation cap 1 and is less than subsidisation cap 2 for that year; and
- A rebate of *(REDACTED)*% if in any year the Commonwealth payment exceeds subsidisation cap 2 for that year.

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

7 PBAC Outcome

7.1 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.

7.2 The PBAC noted that the requested listing for adalimumab differed slightly from that recommended for infliximab in March 2014 in terms of required prior systemic therapy (5-aminosalicylate therapies), defining moderate to severe disease through use of Mayo clinic or partial Mayo clinic or Paediatric Ulcerative Colitis Index (PUCAI) scores, and, the definition of an adequate or sustained response. The PBAC considered that if adalimumab was to be PBS-listed for moderate to severe ulcerative colitis, it would be reasonable to expect that the restriction for adalimumab be aligned with infliximab's restriction for moderate to severe ulcerative colitis as much as practical, noting that both drugs are anti-TNF alpha inhibitors and therefore expected to share the same clinical place in therapy.

7.3 The submission's proposed clinical place in therapy for adalimumab was as treatment following inadequate response to systemic immunosuppressive therapy (i.e. corticosteroids, azathioprine, 6-mercaptopurine). Noting the consumer comments about the application, the PBAC considered that it would be potentially worthwhile for patients and clinicians to have an additional treatment option for moderate to severe ulcerative colitis following an inadequate response to standard systemic immunosuppressive therapy, given the debilitating nature of the condition. The PBAC considered the clinical positioning of adalimumab to be reasonable but noted that this did not necessarily imply that best supportive care would be the therapy likely to be replaced the most in practice. The PBAC recalled that it had recommended infliximab for listing earlier in March 2014 for the same the indication and same clinical place in therapy as that proposed for adalimumab. With infliximab being in the same pharmacological class as adalimumab (i.e. anti-TNF inhibitor), the PBAC considered that infliximab would be the therapy most likely replaced in practice by adalimumab and that this would therefore influence the choice of comparator.

7.4 The re-submission's nominated comparator of best supportive care remained unchanged from the comparator nominated in the November 2013 adalimumab submission. The PBAC recalled that it had previously considered this to be appropriate in November 2013. However, the PBAC recalled that at the time of the November 2013 consideration of adalimumab, no other anti-TNF inhibitor was PBS-listed for moderate to severe ulcerative colitis or had received a positive recommendation to list. In view of the positive recommendation made for infliximab in March 2014 and for the reasons outlined above, the PBAC considered that infliximab would likely be the therapy replaced the most in practice. Therefore, 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.

7.5 No direct head-to-head randomised controlled trials comparing adalimumab to infliximab were presented in the re-submission. Instead, to support the clinical claim that adalimumab is non-inferior to infliximab, the PBAC noted that the re-submission relied upon the findings of the sponsor commissioned study by *(REDACTED)*. The two trials (ULTRA I and ULTRA II) informing the comparison of adalimumab to placebo were further noted to be the same as those previously presented in the November 2013 submission. The evaluation's literature search identified a new paper by Suzuki et al. (2014) which was excluded by the re-submission but which did not significantly alter the interpretation of the clinical trial results.

7.6 The PBAC reaffirmed its views on the results of the ULTRA I and ULTRA II trials from November 2013 in that adalimumab treatment appears to be associated with a real but modest incremental clinical benefit over placebo, noting that approximately 50% of patients treated with adalimumab respond (at week 8), compared to 35% treated with placebo, while 20% of patients achieve remission with adalimumab. However, for the comparison of adalimumab to infliximab, the PBAC observed that the indirect comparison of adalimumab to infliximab performed by *(REDACTED)* indicated a trend of inferior efficacy for adalimumab across all outcomes. Although the indirect comparisons of the relative risks and odds ratios resulted in no statistically significant differences between the drugs, the credible intervals were large (e.g. for response at *(REDACTED)* OR *(REDACTED)*; 95% Credible Interval: *(REDACTED)* to *(REDACTED*). Therefore, the PBAC was concerned that adalimumab may be inferior to infliximab in the treatment of moderate to severe ulcerative colitis despite considering adalimumab to have equivalent efficacy to infliximab in disease indications other than ulcerative colitis.

7.7 The PBAC noted the re-submission's suggestion that patients treated with infliximab in the supporting clinical trials may have had less severe disease compared to the adalimumab treated patients as justification for adalimumab's comparatively lower efficacy. However, this explanation alone was not adequate in providing the PBAC with conclusive evidence that adalimumab is non-inferior to infliximab in the treatment of ulcerative colitis. The PBAC considered that further evidence demonstrating that infliximab is at least non-inferior to infliximab is required. in the form of either new clinical trial data and/or substantive analysis of the baseline characteristics of the adalimumab and infliximab patients referred to in *(REDACTED)* report.

7.8 The PBAC reaffirmed its views with regards to comparative safety of adalimumab, in that adalimumab is marginally worse compared to placebo. The PBAC noted that no new safety information was provided in the re-submission and the *(REDACTED)* report did not provide a comparative assessment of safety for adalimumab and infliximab.

7.9 The PBAC noted the cost-utility analysis presented as a result of the re-submission nominating best supportive care as the comparator. The PBAC noted that the estimated ICER in the re-submission ($15,000/QALY - $45,000/QALY gained) was at face value low and acceptable but considered that it was highly sensitive to the health state values applied in the model, the source of the health state costs used and the estimate of the efficacy of adalimumab beyond trial duration. The PBAC accepted the ESC's advice that the true ICER realised in practice is likely to be significantly greater than the ICER claimed in the re-submission, noting that the biological disease modifying anti-rheumatic drugs (bDMARDs) generally have ICERs in the $45,000/QALY plus range for indications other than ulcerative colitis. Given adalimumab's modest incremental clinical benefit in ulcerative colitis compared to placebo, the PBAC doubted whether the true ICER would be significantly lower than the commonly high ICER ranges seen for bDMARDs in indications other than ulcerative colitis.

7.10 Although no formal cost-minimisation analysis was presented by the re-submission, the PBAC noted the sponsor's willingness to accept listing on a cost-minimisation basis to infliximab *(REDACTED).* However, as the PBAC was yet to accept the clinical claim of non-inferiority to infliximab, the PBAC was not prepared to recommend listing on a cost-minimisation basis at this stage.

7.11 The PBAC 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.

7.12 The PBAC considered that further evidence of non-inferiority against infliximab needs to be presented in future major re-submission. This may take the form of new data and/or further justification for why adalimumab's efficacy and safety compared to infliximab should be no different in ulcerative colitis than in other non-ulcerative colitis indications.

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 rejection made by the PBAC and will engage with PBAC to clarify the decision and consider its position regarding any future course of action. AbbVie is committed to ensuring patients with moderate to severe ulcerative colitis are able to access self-administered Humira.