5.19 VEDOLIZUMAB, injection, 1 x 300 mg vial, Entyvio®, Takeda Pharmaceuticals Australia Pty Ltd.

1 Purpose of Application

1.1 The major submission sought a Section 100 (Highly Specialised Drugs Program) Authority Required listing for the treatment of moderate to severe ulcerative colitis.

2 Requested listing

2.1 The submission sought the following listing:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
VEDOLIZUMAB vedolizumab 300 mg injection, powder for infusion, 1 x 300 mg vial	1	0	Entyvio	TK

Section 100 Highly Specialised Drug Public and Private (abridged version)
Authority Required

Initial
Initial treatment of moderate to severe ulcerative colitis in a patient assessed by complete Mayo score who satisfies the following criteria:

(a) has confirmed ulcerative colitis, defined by standard clinical, endoscopic and/or imaging features, including histological evidence; and
(b) has signed a patient acknowledgement; and
(c) Has failed to achieve an adequate response to prior systemic therapy to at least one of the following agents:
(i) Corticosteroids:
(ii) Immunomodulators:

The following initiation criterion indicates failure to achieve an adequate response and must be demonstrated in all patients at the time of the application:
(a) have a severity of disease activity which results in a complete Mayo score of 6 to 12 with an endoscopic subscore ≥ 2.

Continuation criteria
Option 1:
Continuing treatment of ulcerative colitis in a patient assessed by complete Mayo score:
(a) has a documented history of moderate to severe ulcerative colitis; and
(b) has demonstrated or sustained an adequate response to treatment with vedolizumab.

An adequate response to vedolizumab treatment is defined as a reduction in complete Mayo score of ≥ 3 points and ≥ 30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point.

For the first application, a complete Mayo score assessment of the patient's response must be made up to 6 weeks after the first dose (following a maximum of 2 induction doses of vedolizumab).

Patients are eligible to receive continuing vedolizumab treatment in courses of up to 24 weeks providing they continue to sustain the response.

Option 2:
Continuing treatment of ulcerative colitis in a patient assessed by partial Mayo score:
(a) has a documented history of moderate to severe ulcerative colitis; and

(b) has demonstrated or sustained an adequate response to treatment with vedolizumab. An adequate response to vedolizumab treatment is defined as a partial Mayo score of ≥ 2 points and ≥ 25% from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point. For the first application, a partial Mayo score assessment of the patient's response must be made up to 10 weeks after the first dose (following a maximum of 3 induction doses of vedolizumab). Patients are eligible to receive continuing vedolizumab treatment in courses of up to 24 weeks providing they continue to sustain the response.

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

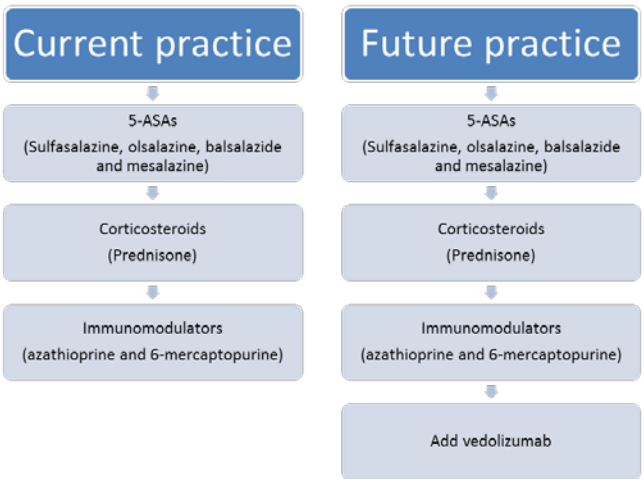
3 Background

3.1 The submission was made under TGA/PBAC parallel process provisions. At the time of PBAC consideration, vedolizumab had been approved by the Advisory Committee on Prescription Medicines (ACPM) in June 2014. The ratified ACPM outcome was received on 16 June 2014.

3.2 The PBAC had not previously considered vedolizumab.

4 Clinical place for the proposed therapy

4.1 The clinical management algorithm for the intended use of vedolizumab and for current practice is presented below. The clinical management algorithm was based on guidelines from the Gastroenterological Society of Australia for general practitioners and physicians (2013) and the Therapeutic Guidelines (2011) and concurred with the management algorithm of the main comparator.



Source: Figure A.5-1, p24 of the submission
5-ASAs = 5-aminosalicylic acid

4.2 The ESC noted that there is limited clinical experience with vedolizumab in Australia as vedolizumab was yet to gain TGA registration at the time of submission lodgement. Since vedolizumab is in the same pharmacological class as natalizumab, the PBAC was concerned that vedolizumab may have a theoretical potential to be

associated with an increased risk of progressive multifocal leukoencephalopathy (PML). The PBAC considered that due to the limited clinical experience with vedolizumab, its clinical position relative to existing anti-TNF alpha drugs is unclear at this stage but may be possibly behind (i.e. vedolizumab's use may be reserved for patients who do not initially respond to an anti-TNF alpha drug) these drugs if they were also PBS-listed for ulcerative colitis and therefore could influence the choice of comparator.

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

5 Comparator

5.1 The submission nominated standard of care, comprising 5-aminosalicylates, corticosteroids and immunomodulators as the main comparator. The main argument provided in support of this nomination was that this reflects baseline therapy in the clinical trial and is supported by current Australian clinical practice guidelines.

5.2 The submission presented two supplementary comparisons against adalimumab and infliximab for clinical efficacy, but not for cost-effectiveness.

5.3 Notwithstanding the ESC's comments on vedolizumab's place in clinical practice, the ESC advised that this was the appropriate comparator on the assumption that adalimumab and infliximab are not PBS listed for ulcerative colitis.

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 (2) and health care professionals (2) via the Consumer Comments facility on the PBS website. The comments described a range of improvements in quality of life with vedolizumab including the following:

- Achieving and maintaining remission from disease without the use of corticosteroids:
- Facilitate an improved social life and increased capacity to perform productive work
- Prevent or delay the need for surgery:
- Have a positive impact on not only physical wellbeing, but also psychosocial wellbeing;
- Reducing fatigue;
- Reduction in healthcare costs;
- Increase the availability of treatments; and
- Improve equity in access when compared to treatment availability in other countries.

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

Clinical trials

6.3 The submission was based on one head-to-head randomised trial comparing vedolizumab to placebo: GEMINI I. The full list of all the direct randomised trials identified in the literature search is presented below.

Trials and associated reports presented in the submission

Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trial - Vedolizumab		
GEMINI I Feagan, B. G.	A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients with Moderate to Severe Ulcerative Colitis Vedolizumab as induction and maintenance therapy for ulcerative colitis.	2012 NEJM 2013; 369 (8): 699-710
Randomised trials - adalimumab		
ULTRA 1	Reinisch, W., Sandborn, W. J., Hommes, D. W., *et al*. 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 2	Sandborn, W. J., Van Assche, G., Reinisch, W., *et al.* Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis	Gastroenterology 2012; 142 (2): 257-265
Suzuki	A Multi-Centre, Randomized, Double-Blind, Placebo-controlled Study of Adalimumab in Japanese Subjects With Moderately to Severely Active Ulcerative Colitis. NCT00853099 *Suzuki Y, Motoya S, Hanai H, et al. Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis.*	Study results from US NIH ClinicalTrials.gov. *J Gastroenterol. 2014;49(2):283-94.*
Randomised trials – infliximab		
Probert	Probert, C. S. J., Hearing, S. D., Schreiber, S., *et al*. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: A randomised controlled trial.	Gut 2003; 52 (7): 998-1002
ACT 1/ACT 2	Rutgeerts, P., Sandborn, W. J., Feagan, B. G., *et al*. Infliximab for induction and maintenance therapy for ulcerative colitis	NEJM 2005; 353 (23): 2462-2476
Jarnerot	Jarnerot, G., Hertervig, E., Friis-Liby, I., *et al*. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: A randomized, placebo-controlled study. Gustavsson, A., Jarnerot, G., Hertervig, E., *et al*. Clinical trial: Colectomy after rescue therapy in ulcerative colitis - 3-year follow-up of the Swedish-Danish controlled infliximab study	Gastroenterology 2005; 128 (7): 1805-1811 Aliment Pharmacol Ther. 2010; 32 (8): 984-989
Sands	Sands, B.E., Tremaine, W., Sandborn, W.J., *et al*. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: A pilot study.	Inflamm Bowel Dis 2001; 7 (2): 83-88

Trial ID/First author	Protocol title/ Publication title	Publication citation
UC SUCCESS	*Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis.*	*Gastroenterology. 2014 146(2):392-400.e3.*
	Panaccione, R., Ghosh, S., Middleton, S., *et al*. Infliximab, azathioprine, or infliximab + azathioprine for treatment of moderate to severe ulcerative colitis: The UC SUCCESS trial.	J Crohns Colitis 2011; 5 (1): S8
	Panccione, R., Ghosh, S., Middleton, S., *et al*. Infliximab, azathioprine, or infliximab + azathioprine for treatment of moderate to severe ulcerative colitis: The UC success trial	Gastroenterology 2011; 140 (5): S134
	Panaccione, R., Ghosh, S., Middleton, S., *et al*. Improvement in patient quality of life during treatment with infliximab, azathioprine, or combination infliximab+azathioprine for moderate-to-severe ulcerative colitis	Am J Gastroenterol 2013; 108): S544-S545

6.1 In GEMINI I, for the induction phase results data were derived from cohort 1 (n=374) where patients were randomised to vedolizumab or placebo. Cohort 2 (n=521) received open label vedolizumab treatment at week 0 and week 2. For the maintenance phase, patients who were treated with vedolizumab from either cohort 1 (randomised group) or cohort 2 (open-label induction treatment) and responded to treatment were randomised (n=373) to either placebo, or vedolizumab every four weeks or vedolizumab every eight weeks. For the safety analyses, all patients were included (n=895).

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

Comparative effectiveness

Vedolizumab vs. placebo

6.2 At week 6, more patients treated with vedolizumab achieved a response or remission (using the full Mayo score) compared to patients treated with placebo. The number needed to treat at six weeks was 5 (95% CI: 3 to 8) for clinical response and 9 (95% CI: 6 to 19) for clinical remission. Of those patients who achieved a clinical response with vedolizumab at week 6, more patients treated with vedolizumab had durable clinical response at week 6 and 52 (NNT: 3; 95% CI: 2 to 5), clinical remission at week 52 *(*NNT: 4; 95% CI: 3 to 7) or durable clinical remission at week 6 and 52 (NNT 9; 95% CI: 5 to 32). The table in the benefits/harms section summarises the main results from the GEMINI I trial.

6.4 The ESC agreed with the evaluation that as the benefit of vedolizumab at the maintenance phase is for those patients who responded to initial vedolizumab patients, the response and remission rates were potentially overestimated for the vedolizumab and placebo arms.

6.5 The trial design of GEMINI I precluded the assessment of comparative efficacy and safety beyond 6 weeks, as only patients who responded to vedolizumab induction therapy were randomised for maintenance therapy. This meant the outcomes reported at week 6 come from different patient groups to those reported at week 52. Notably, both the 'placebo' and vedolizumab groups reported at week 52 had been classified as 'responders' at week 6 to two doses of vedolizumab received at weeks 0

and 2. This potentially favoured vedolizumab with respect to predicting health status at 52 weeks.

6.6 Follow-up data on the outcomes of the 'true' placebo group as well as the vedolizumab non-responders at week 52 were not provided in the submission or clinical trial report. Whilst not directly informing the reported main outcome, these data may have provided better approximations of both efficacy and safety for use in both the clinical and economic analyses undertaken. In response to the evaluation's observation of an absence of a 'true' placebo arm, the sponsor's Pre-Sub-Committee Response (PSCR) provided additional new comparative data on patients who had been randomised to either 6 weeks induction treatment with vedolizumab or placebo and who had not responded to 6 weeks of vedolizumab treatment. The PSCR (p.3) contended that this new data supported the claim that the efficacy of 52 weeks of placebo treatment is lower than that originally estimated in the submission and that this new data supported the contention that the base case estimate of vedolizumab's cost-effectiveness was underestimated. The ESC noted that new data provided in PSCRs are not formally evaluated. The ESC acknowledged that the PSCR's contention of an underestimate of the base-case cost-effectiveness ratio was plausible but considered that the magnitude of any underestimate was likely to be low.

Vedolizumab vs. adalimumab

6.7 The submission considered that vedolizumab is not statistically significantly different to adalimumab for induction and maintenance therapy for the key outcomes of clinical response and clinical remission. For the indirect comparison, the 95% confidence intervals around the relative risk for the five relevant outcomes included the null.

6.8 The ESC considered that for the week 6-8 results, the results of the indirect comparison should be interpreted with caution because the response and remission rate in the placebo arms appeared quite different. Of the placebo treated patients, 26% in the vedolizumab and [redacted]% in the adalimumab trials had a clinical response whilst 5% in the vedolizumab and [redacted]% in the adalimumab trials had clinical remission. This may have indicated heterogeneity between the patients included in the vedolizumab and adalimumab trials.

6.9 The ESC also agreed with the evaluation that for the 52 week results, a comparison of the outcomes from the vedolizumab trial to the outcomes of the adalimumab trials was difficult. In the adalimumab trials, all randomised patients at week 0 were included in the analysis while patients in GEMINI I were required to have a response at week 6 to be eligible for the maintenance phase.

Vedolizumab vs. infliximab

6.10 Both vedolizumab and infliximab showed statistically significant better response and remission at week 6-8 and 52 compared to placebo. The indirect comparison did not result in statistically significant differences for any of the included outcomes.

6.11 The ESC advised that the analyses provided by the submission should be interpreted with caution, as the analyses included the exploratory subgroup of patients who were TNFα antagonist naïve. However, the ESC noted that using results based on the ITT Population of the GEMINI I trial did not result in differences in the overall conclusions (i.e. vedolizumab is statistically significant better than placebo and not statistically significant different from infliximab, using placebo as the common comparator).

6.12 The ESC further considered that the results of the indirect comparison should be interpreted with caution because:

- As noted above, in GEMINI I, patients were randomised for the maintenance trial only if the patient had a response with vedolizumab at week 6, while in the infliximab trial (ACT 1), patients were randomised to receive induction and maintenance at week 0.
- For the results at week 8, the response rates in the placebo arms were lower in the vedolizumab trial (both ITT and TNFα-antagonist naïve), therefore indicating the exchangeability of the trials may not have been ideal.

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

Comparative harms

Vedolizumab vs. placebo

6.13 The most common AEs for maintenance phase were exacerbations of ulcerative colitis, headache, nasopharyngitis, arthralgia and upper respiratory tract infection. The submission stated that there were no differences for the most common adverse events between the placebo and vedolizumab groups, apart from ulcerative colitis. The safety analyses in the GEMINI I trial were not based on patients randomised to either placebo or vedolizumab at week 0 and then followed for 52 weeks, due to the trial design.

6.14 As noted under '4. Clinical place of the proposed therapy', since vedolizumab is in the same pharmacological class as natalizumab, the PBAC was concerned that vedolizumab may have a theoretical potential to be associated with an increased risk of PML. The PSCR (p.4) noted that "To date no cases of PML have been reported, despite over 3,700 patient years of exposure in the program." However, it was noted that patients were excluded from the key trial (GEMINI I) or extension study (C13008) if they were potentially at risk of PML and that such careful screening may not occur to the same extent in practice by gastroenterologists as compared to neurologists treating multiple-sclerosis patients with natalizumab.

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

Benefits/Harms

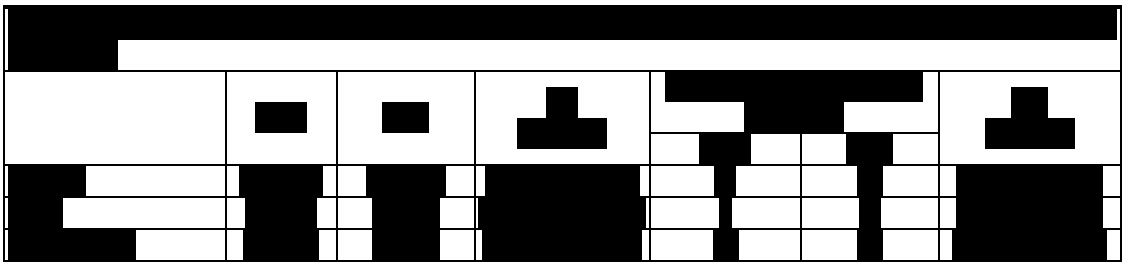
Vedolizumab vs. placebo

6.15 A summary of the comparative benefits and harms for vedolizumab versus placebo is presented in the table below.

Summary of comparative benefits and harms for vedolizumab and PBO in GEMINI I

Trial	VED	PBO	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				VED	PBO	
Benefits						
Week 6 results – induction population (patients randomised at week 0)						
Response	106/225	38/149	[redacted]	47	26	[redacted]
Remission	38/225	8/149	[redacted]	17	8	[redacted]
Week 52 results – maintenance population (patients who responded to OL or DB vedolizumab induction)						
Remission	51/122	20/126	[redacted]	42	16	[redacted]
Durable response (wk 6 + 52)	69/122	30/126	[redacted]	57	24	[redacted]
Durable remission	25/122	11/126	[redacted]	21	9	[redacted]

Trial	VED	PBO	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				VED	PBO	
(wk 6 + 52)						



* For duration provided in the table, i.e. 6 weeks and 52 weeks
PBO = placebo; VED = vedolizumab; RD = risk difference; RR = relative risk; CI = confidence interval; AE = adverse event; SAE = serious adverse event; wk = week;

6.16 On the basis of direct evidence presented by the submission, for every 100 patients treated with vedolizumab in comparison to placebo:

- Approximately 22 additional patients would have clinical response;
- Approximately 12 additional patients would have clinical remission; and
- There is potentially no difference in the number of patients experiencing any adverse event.

Vedolizumab vs. adalimumab

6.17 The table below summarises the results of the indirect comparison to adalimumab.

Indirect comparison summary of comparative benefits and harms for vedolizumab and adalimumab

Trial	VED	Adalimumab	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				VED	Adalimumab	
Benefits						
Indirect comparison – vedolizumab vs. adalimumab						

	VED	PBO	ADA	RR (95% CI)	Event rate/100 patients/duration*			RD (95% CI)
					VED	PBO	ADA	
Clinical response week 6-8								
GEMINI I	106/225	38/149	-		47	26		Not Performed
ADA meta								
Indirect comparison: VED vs. ADA					-			
Clinical remission week 6-8								
GEMINI I	38/225	8/149			17	5		Not Performed
ADA meta								
Indirect comparison: VED vs. ADA								
Clinical remission week 52								
GEMINI I	51/122	20/126			42	16		Not Performed
ULTRA 2		28/342	61/338			8	18	
Indirect comparison: VED vs. ADA								

Harms

Harms
[redacted]

* Duration of exposure as presented in the Table. PBO = placebo; VED = vedolizumab; ADA = adalimumab; RD = risk difference; RR = relative risk; CI = confidence interval; meta = meta-analysis. Source: Compiled during the evaluation. ADA meta-analysis at 8 weeks includes ULTRA 1, ULTRA 2 and Suzuki 2014, the ADA meta-analysis at week 52 includes ULTRA 2 and Suzuki 2014.

6.18 On the basis of the indirect comparison evidence presented by the submission for every 100 patients treated with vedolizumab in comparison to adalimumab for a maximum duration of 52 weeks, approximately the same number of patients would have clinical remission and adverse events.

Vedolizumab vs. infliximab

6.19 The table below summarises the results of the indirect comparison to infliximab.

Indirect comparison summary of comparative benefits and harms for vedolizumab and infliximab

Trial	VED	Comparator	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				VED	Comparator	
Benefits						
Indirect comparison – vedolizumab vs. infliximab						

	VED	PBO	IFX	RR (95% CI)	Event rate/100 patients/duration*			RD (95% CI)
					VED	PBO	IFX	
Clinical response week 6-8								
GEMINI I	106/225	38/149	-	[redacted]	47	26		Not Performed
IFX meta		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	
Indirect comparison: VED vs IFX				[redacted]	-			
Clinical remission week 6-8								
GEMINI I	38/225	8/149		[redacted]	17	5		Not Performed
IFX meta [a]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	
Indirect comparison: VED vs IFX				[redacted]				
Clinical remission week 52								
GEMINI I	51/122	20/126		[redacted]	42	16		Not Performed
ACT 1		20/121	42/121	[redacted]		17	35	
Indirect comparison: VED vs IFX				[redacted]				
Harms								
Indirect comparison – vedolizumab vs. infliximab week 52								

	VED	PBO	IFX	RR (95% CI)	Event rate/100 patients/duration*			RD (95% CI)
Adverse events								
GEMINI I	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		Not Performed
ACT 1		103/121	106/121	[redacted]		85	88	

Trial	VED	Comparator		RR (95% CI)	Event rate/100 patients*		RD (95% CI)
					VED	Comparator	
Indirect comparison: VED vs IFX				[redacted]	-		
Serious adverse events							
GEMINI I	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	Not Performed
ACT 1		31/121	26/121	[redacted]		26	22
Indirect comparison: VED vs IFX				[redacted]			
Infectious adverse events							
GEMINI I	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	Not Performed
ACT 1		47/121	53/121	[redacted]		39	44
Indirect comparison: VED vs IFX				[redacted]			

* Duration of exposure as presented in the Table. PBO = placebo; VED = vedolizumab; IFX = infliximab; RD = risk difference; RR = relative risk; CI = confidence interval; meta = meta-analysis. Source: Compiled during the evaluation. [a] Excludes Probert 2003, due to difference in response definition.

On the basis of the indirect comparison evidence presented by the submission, for every 100 patients treated with vedolizumab in comparison to infliximab over a maximum duration of exposure of 52 weeks, approximately the same number of patients would have clinical remission and adverse events.

Clinical claim

Vedolizumab vs. placebo

6.20 The submission described vedolizumab as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over placebo.

6.21 For safety, the results were not derived from randomised treatment of 52 weeks of placebo or vedolizumab. The ESC considered that it was unclear what the impact of the lack of randomised trial data had on the overall claim for safety.

Vedolizumab vs. adalimumab and vedolizumab vs. infliximab

6.22 The submission described vedolizumab as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over adalimumab as well as infliximab.

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

Economic analysis

6.23 The submission presented two economic analyses versus placebo treatment, based on the two proposed restrictions. In the commentary, the focus was on option 2, as this option uses the partial Mayo score for continuation, which is most likely to reflect clinical practice as it does not require endoscopy. The submission did not present economic analyses comparing vedolizumab with adalimumab and infliximab. Equi-effective doses were estimated by the evaluation.

Summary of model structure and rationale

Component	Summary
Time horizon	30 years in the model base case versus 6 and 52 weeks in trial
Outcomes	Quality adjusted life years (QALYs)
Methods used to generate results	Cohort expected value analysis

Component	Summary
Health states	10 health states, remission (vedolizumab or placebo), mild-moderate (vedolizumab or placebo), moderate-severe (vedolizumab or placebo), surgery, post-surgery remission, post-surgery complication and death
Cycle length	first cycle is 10 weeks, thereafter 8 weeks.
Transition probabilities	Based on GEMINI I. The clinical trial data (beyond first cycle) is different from the patients in the economic model specifically: • For placebo patients, probabilities are derived from patients treated and responded to vedolizumab induction treatment (over- or under-estimate placebo efficacy) • For vedolizumab non-responders, no clinical trial data is provided. In the economic model, placebo response is applied to this arm from the induction ('true placebo', one cycle) and maintenance phase (patients who responded to vedolizumab induction and were randomised to placebo). This is inappropriate and will overestimate the vedolizumab efficacy. Patients who do not respond to vedolizumab treatment are unlikely to achieve a response or remission, eight weeks after discontinuation of vedolizumab treatment.

Source: compiled during the evaluation

6.24 The ESC noted the key disease progression health states in the model were the remission, mild-moderate, and moderate-severe states. The ESC considered the model to have likely overestimated the proportion of vedolizumab patients in remission at 52 weeks as it applied the placebo response rates in the induction and maintenance phases to patients observed not to respond to vedolizumab in the induction phase. Data submitted in the PSCR indicated that the 52 week response and remission rates in this group were overestimated.

6.25 The ESC also considered that the overestimation of remission rates for the intervention groups was likely conflated by the assumptions and data used to model the long-term effects of achieving remission during the maintenance phase. Firstly, patients in remission and on vedolizumab were assumed to discontinue treatment with vedolizumab after 2.5 years. At this time point, over 30% of vedolizumab patients remain in remission and so would be likely to meet the defined criteria for treatment continuation. The PSCR (p.6) contended that "…the incremental treatment benefit for vedolizumab is assumed to be maintained for only 2.5 years. This comprises the observed data from GEMINI I at week 52 (i.e. 1 year) and an extrapolation of 1.5 years. After 2.5 years, all patients in the vedolizumab arm of the model are switched to placebo and hence the hazard ratio between vedolizumab and placebo is set to 1." The ESC disagreed with this approach and considered that for vedolizumab patients in remission at 2.5 years, the economic analysis should capture the impacts of potentially diminishing vedolizumab comparative efficacy through the continuation rule against the backdrop of accumulating vedolizumab treatment costs.

6.26 Secondly, once in remission, the ESC considered the submission's assumption of the probability of staying in remission, was high (99% on vedolizumab, 94% on conventional therapy per 8 week cycle), over the duration of the model's time horizon. This raised concerns with respect to either the validity of the transition probabilities, or the assumption of discontinuation of treatment at 2.5 years.

6.27 On leaving remission, patients quickly transitioned from the mild-moderate state to the moderate-severe state (41% per 8 week cycle for patients not on treatment). Thus, QALY gains were strongly influenced by the difference in QoL between the remission and moderate-severe health states. The model used the utility study showing the greatest difference between these states (0.18, vs. 0.13 and 0.14 in other studies). Therefore, the utility values obtained from post-hoc analysis of the clinical trial data may have overestimated the utility assigned to the remission health state when compared to published Australian utility values.

6.28 The PSCR (p.6) contended that "…using utility values from a population not representative of the PBS population (i.e. Gibson et al, 2013) rather than utility values derived directly from the pivotal study (GEMINI I) is not appropriate. In addition, with nearly double the number of patients (373 patients in GEMINI I vs. 175 in Gibson et al 2013), the precision of estimates is more reliable; as is the fact that GEMINI I was a randomised, blinded study vs. Gibson being an observational study." The ESC nonetheless considered the data from Gibson (2013) should not be disregarded as these data are derived from an Australian population and therefore are likely to provide reasonable applicability to the proposed PBS population. The ESC noted that sensitivity analyses on the ICER indicate that the ICER for vedolizumab treatment was sensitive to the utility values sourced from Gibson (2013).

6.29 There was also some uncertainty regarding the estimated health state costs. An Access Economics study in 2007 estimated a total annual cost per patient with ulcerative colitis of $1,033. The current analysis estimated a cost of between $1,212 and $2,561 per 8 week cycle. The costing study appeared to be reasonable, though it was possible that the recruitment of patients via outpatient clinics biased the cohort to the more severe end of the spectrum, especially for the moderate-severe group.

6.30 The model validity was also impacted by the model-based predictions of surgical intervention, which indicated that, on average, every placebo patient would undergo 1.26 and 4.48 episodes of surgery over 20 and 50 years, respectively.

6.31 The submission estimated an ICER of $15,000 - $45,000 per QALY. The results of the stepped economic evaluation are shown below:

Results of the stepped economic evaluation (partial Mayo)

Step and component	Vedolizumab	Placebo	Increment
Step 1: trial-based costs and outcomes – 10 weeks			
Costs	[redacted]	[redacted]	[redacted]
Clinical response	[redacted]	[redacted]	[redacted]
Clinical remission	[redacted]	[redacted]	[redacted]
Incremental cost/extra clinical response gained			[redacted]
Incremental cost/extra clinical remission gained			[redacted]
Step 2: trial results and pre-modelling (incl surgery and mortality) – 10 weeks			
Costs	[redacted]	[redacted]	[redacted]
Clinical response	[redacted]	[redacted]	[redacted]
Incremental cost/extra clinical response gained			[redacted]
Step 3: modelled evaluation (including utilities) – 54 week time horizon			
Costs	[redacted]	[redacted]	[redacted]
QALY	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			[redacted]
Step 4: modelled evaluation (including utilities + health state costs) – 54 week time horizon			
Costs	[redacted]	[redacted]	[redacted]
QALY	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			[redacted]
Step 5: modelled evaluation (including utilities + health state costs) – 30 year time horizon [a]			
Costs	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALY	[redacted]	[redacted]	[redacted]
Incremental cost/extra life year gained			[redacted]
Incremental cost/extra QALY gained			[redacted]

[redacted]

NC = not calculable, as no differences in life years

[a] *Value in italics is for the respecified base case: No half cycle correction vedolizumab costs, continuation rule at 30 weeks,*

patients loosing response do not get placebo induction ITT response for first cycle

6.32 The PSCR (p.5) further provided an ICER within the range of $15,000 - $45,000 following a sponsor re-specified analysis that involves the use of transition probabilities for both placebo and vedolizumab patients that factor in the existence of a 'true' placebo group. The ESC considered that both ICERs (i.e. $15,000 - $45,000 /QALY gained and $15,000 - $45,000/QALY gained) were likely to be underestimated.

6.33 In sensitivity analyses, the ESC noted that the economic model was sensitive to the model duration, treatment duration, efficacy for non-responders to vedolizumab, and utility values. A multivariate analysis using a 10-year model duration, EQ-5D values from Gibson et al. (2013) and vedolizumab treatment duration of 7.3 years resulted in an ICER of $75,000 - $105,000 per QALY. Notwithstanding the data presented in the PSCR (p.3), the ESC noted that transition probabilities for the period beyond the induction phase had not been modified by the evaluation as values derived from the GEMINI I trial were not available in the submission or clinical study reports.

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

Drug cost/patient/year:

6.34 The drug cost/patient/year was estimated to be $[redacted] in first year, based on 8.0 infusions and a split between public and private hospital of 60.5% vs. 39.5%, [redacted] in following years, based on 6.5 infusions and similar split between public and private hospital.

Estimated PBS usage & financial implications

6.35 This submission was not considered by DUSC.

6.36 The submission presented the estimated use and financial implications as follows:

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated total net cost					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

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

7 PBAC Outcome

7.1 The PBAC rejected the submission to list vedolizumab for the treatment of moderate to severe ulcerative colitis on the basis that the evidence presented did not conclusively establish non-inferiority of vedolizumab to infliximab in terms of comparative safety and effectiveness. Therefore a cost-minimisation listing was not able to be supported. The cost-effectiveness of listing vedolizumab compared to

placebo was unacceptably high. Further, the cost-effectiveness of listing vedolizumab following treatment failure with 5-aminosalicylate therapies, oral immunosuppressive systemic therapies and an anti-TNF alfa inhibitor, was unknown.

7.2 The PBAC noted that the requested listing for vedolizumab differed slightly from that recommended for infliximab in March 2014 in terms of defining moderate to severe disease and defining an adequate or sustained response. The PBAC considered that if vedolizumab was to be PBS-listed for moderate to severe ulcerative colitis, it would be reasonable to expect that the restriction for vedolizumab be aligned with infliximab's restriction for moderate to severe ulcerative colitis as much as practical in terms of defining 'moderate to severe' disease, the use of Mayo and partial Mayo clinic scoring, and, defining an adequate response for continuing treatment. However, in terms of the requested restriction positioning vedolizumab as a monoclonal antibody treatment for use after failure of prior systemic immunosuppressive therapy, the PBAC was concerned that it may not be appropriate at this stage to position vedolizumab in the same clinical place in therapy as existing therapies like infliximab and adalimumab.

7.3 The submission's proposed clinical place in therapy for vedolizumab was as treatment following an inadequate response to 5- aminosalicylate therapies and 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 agreed with the ESC's concern that due to the limited clinical experience with vedolizumab, its clinical position relative to existing anti-TNF alpha drugs is unclear at this stage but may be possibly behind these drugs if they were also PBS-listed for ulcerative colitis (i.e. vedolizumab's use may be reserved for patients who do not initially respond to an anti-TNF alpha drug). The PBAC recalled that it had recommended infliximab for listing earlier in March 2014 for the same indication as that proposed for vedolizumab. Therefore, there appeared to be 2 options for the choice of comparator in the submission.

7.4 The submission's nominated comparator was current standard of care, comprising of 5-ASAs, corticosteroids and immunomodulators as the main comparator. In view of the positive recommendation made for infliximab in March 2014, the PBAC considered that vedolizumab would likely replace infliximab the most in practice if clinicians considered vedolizumab to be in the same clinical place in therapy as infliximab. The other comparator option was best supportive care following treatment failure/inadequate response to infliximab. The PBAC considered this comparison is potentially more relevant given the relatively limited clinical experience with vedolizumab compared to existing anti-TNF alpha inhibitors and a potential small risk of developing PML which both may deter prescribing of vedolizumab in practice. The PBAC noted the main evidence base for the submission was one head-to-head randomised controlled trial comparing vedolizumab to placebo (GEMINI I) in which patients could have previously received anti-TNF alpha inhibitor treatment prior to vedolizumab treatment.

7.5 The PBAC noted the evaluation's concerns that the trial design of GEMINI I (i.e. the exclusion of vedolizumab non-responders after the first 6 weeks of treatment from further maintenance treatment) may have potentially favoured vedolizumab. Follow-up data on the outcomes of the 'true' placebo group as well as the vedolizumab non-responders at week 52 were not provided in the submission or clinical trial report. Whilst not directly informing the reported main outcome, this data may have provided

better approximations of both efficacy and safety for use in both the clinical and economic analyses undertaken. The PSCR provided this new data but it was not formally evaluated. The PBAC further noted that no direct head-to-head randomised controlled trials comparing vedolizumab to infliximab were available.

7.6 For the comparison of vedolizumab to placebo, the PBAC observed that at week 6 in the GEMINI I trial, more patients treated with vedolizumab compared to patients treated with placebo achieved a response (47% vs. 26%) or achieved remission (17% vs. 8%) using the full Mayo score to measure response or remission. Of those patients who achieved a clinical response with vedolizumab at week 6, more patients treated with vedolizumab compared to placebo had a durable clinical response at week 6 and 52 (57% vs. 24%), clinical remission at week 52 *(*42% vs. 16%) or durable clinical remission at week 6 and 52 (21% vs. 9%). Given the absence of a 'true' placebo arm, the PBAC noted the PSCR's additional data on patients who had been randomised to either 6 weeks induction treatment with vedolizumab or placebo and the PSCR's contention that the efficacy of 52 weeks of placebo treatment was underestimated in the submission. Overall, the PBAC accepted that vedolizumab provides a greater response than placebo. However the more relevant comparison is vedolizumab's comparative efficacy and safety compared to infliximab.

7.7 For the comparison of vedolizumab to infliximab, the PBAC observed that both vedolizumab and infliximab showed statistically significant better response rates and remission rates at week 6-8 and 52 compared to placebo. The indirect comparison of infliximab and vedolizumab demonstrated a similar response rate for the two drugs. Noting the ESC's caution on the interpretation of the results, the PBAC considered the results to show that vedolizumab has comparable efficacy to that of infliximab.

7.8 No further comment was made on the indirect comparison of vedolizumab to adalimumab as the PBAC was yet to accept that adalimumab is cost-effective for moderate to severe ulcerative colitis.

7.9 In terms of vedolizumab's comparative safety, although the submission claimed that there were no differences for the most common adverse events between the placebo and vedolizumab groups, the PBAC noted that the results were not derived from randomised treatment of 52 weeks of placebo or vedolizumab. The PBAC therefore agreed that it was unclear what the impact of the lack of randomised trial data had on the overall claim for safety. The PBAC further noted that vedolizumab is in the same pharmacological class as natalizumab and may have the theoretical potential to be associated with an increased risk of PML. The PSCR stated that to date, no cases of PML had been reported, despite over 3,700 patient years of exposure in the program. Despite this reassurance, the PBAC noted that patients were excluded from the key trial (GEMINI I) or extension study (C13008) if they were potentially at risk of PML and agreed that such careful screening may not occur to the same extent in real life practice by gastroenterologists as compared to neurologists treating multiple-sclerosis patients with natalizumab. The PBAC considered that the number of patients enrolled in the clinical trials was unlikely to be adequately powered to detect cases of PML due to the naturally low disease incidence (approximately 1 case in 10,000).

7.10 Therefore, it was the PBAC's view that the non-inferiority of vedolizumab to infliximab in terms of comparative safety had not been conclusively established on the basis of the evidence presented in the submission. In particular, the PBAC was concerned about prescribers in practice having to trade-off the risk of PML against the benefits of vedolizumab treatment.

7.11 The PBAC noted the submission's cost-utility analysis of vedolizumab compared to best supportive care and the submission's claimed ICER of $15,000 - $45,000/QALY gained (or $45,000 - $75,000/QALY gained for the respecified base case). The PBAC agreed with the ESC that the submission's estimate of the ICER is likely to be underestimated, noting that the economic model was sensitive to the model duration, treatment duration, efficacy for non-responders to vedolizumab, and utility values. The PBAC noted that a multivariate analysis using a 10-year model duration, EQ-5D health state values from Gibson et al. (2013) and a vedolizumab treatment duration of 7.3 years produced a plausible ICER within the range of $75,000 - $105,000 per QALY. The PBAC considered this ICER to be unacceptably high.

7.12 As the PBAC had not accepted the claim of non-inferiority of vedolizumab to infliximab in terms of comparative safety, there was no basis for the PBAC to recommend listing vedolizumab on a cost-minimisation basis at this stage. The PBAC further noted that the submission did not present a cost-minimisation analysis of vedolizumab versus infliximab but that the pre-PBAC response had indicated a willingness to accept pricing flexibility. It was noted that the submission's proposed annual drug treatment costs per patient for vedolizumab was higher than that proposed for infliximab and adalimumab.

7.13 The PBAC considered 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 patients, treated patients and number of patients achieving an adequate response to be eligible for continuing treatment. As the estimated uptake rate of vedolizumab was based on the expert opinion of one gastroenterologist and the clinical place of vedolizumab relative to existing anti-TNF alfa inhibitor therapies is still to be determined, the PBAC considered estimates of the uptake rate of vedolizumab and the resulting financial implications to be unreliable.

7.14 The PBAC advised that any future re-submission for vedolizumab should account for the PBAC's positive recommendation to list infliximab for moderate to severe ulcerative colitis and give consideration to positioning vedolizumab as treatment of patients who have not responded to infliximab. This could be by revising the proposed restriction and/or the economic analysis. The PBAC considered that vedolizumab's comparative safety to existing anti-TNF alfa inhibitors would also need to be established as non-inferior or accounted for in an economic analysis. Any re-submission should take the form of a major submission.

7.15 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

The sponsor notes that vedolizumab for the treatment of patients with moderate to severe ulcerative colitis received full approval from the TGA, with registration occurring on 26 June 2014 just prior to the PBAC's July meeting. The sponsor also notes that no cases of PML were seen in the extensive GEMINI clinical program for inflammatory bowel disease, both for ulcerative colitis and Crohn's disease. Whilst disappointed by the PBAC's decision, the sponsor is actively working with the Department and the clinical community to address the PBAC's concerns in order to secure a positive recommendation for the listing for vedolizumab for the treatment of ulcerative colitis on the PBS.