

**7.06 VEDOLIZUMAB
300mg vial;
Entyvio®, Takeda Pharmaceutical Australia.**

1 Purpose of Application

1.1 The re-submission requested a Section 100, Authority Required, listing for vedolizumab for the treatment of moderate to severe ulcerative colitis. The first submission was March 2014.

2 Requested listing

2.1 Presented below is the proposed restriction.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
VEDOLIZUMAB 300mg injection, 1 X 300mg vial		1	0 \$ [REDACTED]	Entyvio® Pharmaceuticals Takeda Australia

Section 100 Highly Specialised Drug, public hospital Authority required

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
VEDOLIZUMAB 300mg injection, 1 X 300mg vial		1	0 \$ [REDACTED]	Entyvio® Pharmaceuticals Takeda Australia

Section 100 Highly Specialised Drug, private hospitals Authority required

Authority Required (written approval)

Initial treatment of moderate to severe ulcerative colitis in a patient assessed by Mayo score.

Patient must have confirmed ulcerative colitis, defined by standard clinical, endoscopic and/or imaging features, including histological evidence, and being treated by a gastroenterologist or a consultant physician.

Patient must have failed to achieve an adequate response or have intolerance necessitating permanent treatment withdrawal to prior systemic therapy including:

i. a 5-aminosalicylate oral preparation in standard dose for induction of remission for 3 or more months; AND

ii. azathioprine at a dose of at least 2 mg/kg daily for 3 or more months,

OR

iii. 6-mercaptopurine at a dose of at least 1 mg/kg daily for 3 or more months,

OR

iv. a tapered course of oral steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period.

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

Patients who fail to achieve a partial Mayo score ≤ 2 , with no subscore > 1 , within the first 12 weeks of receiving vedolizumab for ulcerative colitis, or have failed to maintain a partial Mayo score ≤ 2 , with no subscore > 1 , with continuing vedolizumab treatment will not be eligible to receive PBS-subsidised treatment with this drug within 12

months of the date on which treatment was ceased.

The patient must sign 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, as outlined in the restriction for continuing treatment.

Authority Required (telephone approval)

Continuing treatment of ulcerative colitis in patients assessed by Mayo score.

The adult patient must have partial Mayo score ≤ 2 , with no subscore > 1 while receiving vedolizumab.

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

Maximum Quantity: 1 vial (all restrictions)

Number of Repeats: 0 (all restrictions) (p.18 of the re-submission)

- 2.2 The previous requested restriction included two options of assessment of initiation and continuation – Option 1 assessed by complete Mayo score and Option 2 assessed by partial Mayo score. The requested PBS restriction in the re-submission is similar to that for infliximab for moderate to severe ulcerative colitis. The following sentences from the infliximab restriction are missing from the proposed vedolizumab restriction and may be of relevance.
- Must be treated by a gastroenterologist (code 87) or a consultant physician [internal medicine specialising in gastroenterology (code 81)] or a consultant physician [general medicine specialising in gastroenterology (code 82)]
 - All tests and assessments should be performed preferably whilst still on treatment, but no longer than 1 month following cessation of the most recent prior treatment. The most recent Mayo clinic, partial Mayo clinic or PUCAI score must be no more than 1 month old at the time of application.
 - Patients may qualify for PBS-subsidised treatment under this restriction once only.
 - Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain the response.
- 2.3 The requested PBS restriction is not in line with the TGA indication: the PBS restriction also allows for the treatment of children. The re-submission requested the same restriction as infliximab 'i.e. as an alternative biological agent after conventional therapies have failed or when the patient is intolerant to treatment with the TNF- α antagonists'. The ESC noted the TGA indication seemed to suggest vedolizumab could be used as second line therapy. The ESC considered that the clinical place of vedolizumab needs to be defined and whether 'adults' and 'failure of a TNF- α antagonist' should be added to the proposed PBS restriction.
- 2.4 The basis for listing is cost-minimisation against infliximab.

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

3 Background

- 3.1 Vedolizumab is TGA registered for the treatment of adult patients with moderate to severe ulcerative colitis who have had an inadequate response to, lost response to,

or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNF- α) antagonist.

3.2 A summary of the previous submission and current re-submission is presented below.

Summary of the previous submission and current re-submission

	Vedolizumab March 2014 submission	Current re-submission
Requested PBS listing	Two options for assessment of initiation and continuation based on complete Mayo score (Option 1) and partial Mayo score (Option 2) PBAC Comment: ‘...expect that the restriction for vedolizumab be aligned with infliximab’s restriction...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.’[7.2, July 2014 PBAC Minutes]	Same as infliximab
Requested price	DPMQ \$ [REDACTED] (Public) effective price DPMQ \$ [REDACTED] (Private) effective price	Effective price DPMQ \$ [REDACTED] (Public) DPMQ \$ [REDACTED] (Private) Published price DPMQ \$ [REDACTED] (Public) DPMQ \$ [REDACTED] (Private)
Main comparator	Standard of care, comprising 5-aminosalicylates, corticosteroids and immunomodulators PBAC Comment: ‘. the ESC advised that this was the appropriate comparator on the assumption that adalimumab and infliximab are not PBS listed for ulcerative colitis.’ 5.3, July 2014 PBAC Minutes	Infliximab as it was listed on the PBS on 1 December 2014
Clinical evidence	One vedolizumab trial n=747 (374 induction and 373 maintenance) Adalimumab – three trials, n=940 (260+494+186) Infliximab – three trials, n=529 (242+244+43)	Same trials (adalimumab in Appendix)
Key effectiveness data	•Clinical response at week 6 RD 21.7 (11.6, 31.7) compared to placebo •Clinical remission at week 52 RD 26.1 (14.9, 37.2) compared to placebo PBAC Comment: ‘Overall, the PBAC accepted that vedolizumab provides a greater response than placebo’ 7.6, July 2014 PBAC Minutes	Indirect comparison - IFX •Clinical response, induction RR [REDACTED] •Clinical response, induction RR [REDACTED] •Clinical remission, maintenance [REDACTED]
Key safety data	•Lack of randomised trial data due to trial design •Due to the pharmacological class, vedolizumab may be associated with an increased risk of PML PBAC Comment: ‘...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.’7.9, March 2014 PBAC Minutes	•Same
Clinical claim	•The submission describes vedolizumab as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over placebo. •The submission describes vedolizumab as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over adalimumab. •The submission describes vedolizumab as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over infliximab.	•Vedolizumab is non-inferior to infliximab both in terms of efficacy and safety •Adalimumab indirect comparison in Appendix

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	Vedolizumab March 2014 submission	Current re-submission
	<p>PBAC Comment: ‘...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’. [Item 7.7, March 2014 PBAC Minutes]</p>	
Economic evaluation	<p>•Cost-utility model: \$ [REDACTED] /QALY against standard of care. PBAC Comment: re-specified base case \$ [REDACTED] /QALY, [7.11, July 2014 PBAC Minutes] ‘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. [Item 7.12, July 2014 PBAC Minutes]</p>	<p>•Cost-minimisation with equi-effective dose \$ [REDACTED] annual cost per maintenance year ([REDACTED] doses)</p>
Number of patients	<p>• [REDACTED] in Year 1 increasing to [REDACTED] in Year 5. PBAC Comment: ‘...the PBAC considered estimates of the uptake rate of vedolizumab and the resulting financial implications to be unreliable.’ [7.14, July 2014 PBAC Minutes]</p>	<p>•Scenario 1: [REDACTED] in Year 1 decreasing to [REDACTED] in Year 5. •Scenario 2: [REDACTED] in Year 1 decreasing to [REDACTED] in Year 5.</p>
Estimated cost to PBS	<p>\$ [REDACTED] in Year 1 increasing to \$ [REDACTED] in Year 5 for a total of \$ [REDACTED] over the first 5 years of listing.</p>	<p>•\$ [REDACTED] in Year 1 increasing to \$ [REDACTED] in Year 5 for a total of \$ [REDACTED] over the first 5 years of listing.</p>
PBAC decision	<p>Reject. ‘.. 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...’ [7.1, July 2014 PBAC Minutes]</p>	-

IFX = infliximab

Source: 5.19, July 2014, PBAC Minutes. Compiled during the evaluation.

4 Clinical place for the proposed therapy

- 4.1 Treatment of moderate to severe ulcerative colitis after failure of conventional agents (5-ASAs, corticosteroids, and immunomodulators), as per that for infliximab (i.e. first-line biologic therapy).
- 4.2 The clinical management algorithm for the intended use of vedolizumab was based on:
- the Australian Guidelines developed by the Gastroenterological Society of Australia (GESA)
 - expert advice from the Sponsor's Advisory Board and,
 - the survey of members of the Australian Inflammatory Bowel Disease Association (AIBDA, n=12 specialist gastroenterologists). All 12 respondents were Code 87 prescribers and represent >97% of the current specialists authorised to prescribe the TNF α antagonists for Crohn disease on the PBS).
- 4.3 The ESC considered that the clinical place of vedolizumab remains to be resolved. The ESC noted the submission argued that, based on the opinion of 12 gastroenterologists, vedolizumab should be an alternative first line biologic rather than restricted to use in patients who have failed infliximab. However, as the TGA indication suggests vedolizumab could be used as second line, a decision needs to be made about the appropriate clinical place for vedolizumab. The trials included patients with TNF- α failure and the PBAC previously considered that a second line listing may be more appropriate.

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

5 Comparator

- 5.1 The re-submission nominated infliximab as the main comparator. This was different from the previous submission's main comparator which was placebo or standard of care. The re-submission also presented a supplementary indirect comparison with adalimumab.
- 5.2 The ESC considered that the comparator was appropriate. However, the ESC also considered that related to the clinical place, vedolizumab may also be administered after treatment failure with infliximab (i.e. second line biologic therapy), rather than replace the use of infliximab. Infliximab was listed for moderate to severe ulcerative colitis on 1 December 2014. The ESC advised that the PBAC would need to consider whether an appropriate comparator is best supportive care in patients who had failed TNF- α antagonist.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician addressed the main issues raised by the ESC regarding the clinical place of vedolizumab in the treatment of ulcerative colitis, relevance of clinical response versus clinical remission, concerns around the non-inferiority claim and theoretical risk for PML. The clinician advised that clinical remission is a more relevant outcome than clinical response as the continuation rules for treatment will depend more on remission in clinical practice.
- 6.2 The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this condition.

Consumer comments

- 6.3 The PBAC noted and welcomed the input from individuals (98), health care professionals (11) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with vedolizumab for ulcerative colitis and Crohn disease indication (item 5.25 refers) including the following:
- potential alternative if infliximab becomes ineffective;
 - preferable alternative treatment than surgery i.e. side effects of this drug is more preferable than surgery;
 - reduced hospital costs;
 - shorter time of administration compared with infliximab; and
 - equity of access and affordability.
- 6.4 Representatives of the PBAC met with Crohn's and Colitis Australia prior to the PBAC meeting, and reported the following key points to the PBAC in relation to the agenda items for Crohn's disease and ulcerative colitis :
- Patients place a high value on maximising possible treatment alternatives, as this provides a sense of empowerment and possibility in managing their disease.
 - When weighing the treatment alternatives, the patient perception may not necessarily be that the risks and benefits of vedolizumab are compared with the risks and benefits of another drug. Rather, patients may be comparing the risks and benefits of vedolizumab against the risks and benefits of surgery.
 - Vedolizumab is perceived as an additional option that will allow patients to postpone the need for surgery, and to potentially resume a normal life. Without PBS subsidy access, the cost of vedolizumab would prohibit most patients from accessing the drug.
- The PBAC noted and welcomed this input.

Clinical trials

- 6.5 The re-submission was based on one head-to-head trial comparing vedolizumab to placebo (n=895) and three head-to-head trials comparing infliximab to placebo (n=771). The trials presented were the same as in the previous submission.
- 6.6 Details of the trials presented in the re-submission are provided in the table below.

Trials and associated reports presented in the re-submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
GEMINI I	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 Feagan, B. G., Rutgeerts, P., Sands, B. E., <i>et al.</i> Vedolizumab as induction and maintenance therapy for ulcerative colitis. .	2012 <i>New England Journal of Medicine</i> 2013; 369 (8): 699-710
Probert	Probert, C. S. J., Hearing, S. D., Schreiber, S., <i>et al.</i> Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: A randomised controlled trial.	<i>Gut</i> 2003; 52 (7): 998-1002
ACT1/ ACT 2	Rutgeerts, P., Sandborn, W. J., Feagan, B. G., <i>et al.</i> Infliximab for induction and maintenance therapy for ulcerative colitis	<i>New England Journal of Medicine</i> 2005; 353 (23): 2462-2476

Source: Table B.2-7, p40-42 of the re-submission

- 6.7 The key features of the direct randomised trials are summarised in the table below.

Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
vedolizumab vs. placebo						
GEMINI I Induction ITT (Cohort 1)	374	R, DB, 6 wks	Low	Moderate to severe UC Failed ≥1 of TNF- α antagonist, immunomodulator or corticosteroids	Full Mayo response, remission wk 6	Not used
GEMINI I Maintenance ITT	373	R, DB, 52 wks	Unclear ^a	Response to VED at wk 6 from GEMINI I (OL or DB)	Full Mayo response, remission wk 52	Not used
infliximab vs. placebo						
ACT 1	242	R, DB 54 wks	Unclear ^a	Moderate to severe UC. Prior treatment with a TNF- α antagonist not allowed.	Full Mayo response remission, wk 8, 54	Not used
ACT 2	244	R, DB 30 wks	Unclear ^a		Full Mayo response remission, wk 8, 30	Not used
Probert	53	R, DB 6 wks	Unclear ^a		Remission, wk 6 (ulcerative colitis symptom score)	Not used

^aGEMINI I: In the maintenance phase, there were fewer patients discontinuing vedolizumab than placebo. ACT 1 and ACT 2: high loss-to-follow up and higher discontinuation rate in the placebo arms compared to the infliximab arms. Probert: included no details regarding discontinuation rates

DB=double blind; MC=multi-centre; OL=open label; R=randomised

Source: compiled during the evaluation

Comparative effectiveness

- 6.8 The previous submission only presented the results of the TNF- α antagonist naïve subgroups. The re-submission presented the ITT population results.

Results of clinical response and clinical remission across the GEMINI I trial, ITT

Trial ID	Vedolizumab n with event/N (%)	Placebo n with event/N (%)	Absolute difference RD (95% CI)	RR (95% CI)	NNT
Induction phase					
Clinical response, Induction phase, ITT					
GEMINI I	106/225 (47.1)	38/149 (25.5)	21.61		5
Clinical remission, Induction phase, ITT					
GEMINI I	38/225 (16.9)	8/149 (5.4)	11.52		9
Maintenance phase					
Clinical remission, Maintenance phase, ITT					
GEMINI I	51/122 (41.8)	20/126 (15.9)	25.93		4

Source: Table B.6.2, p.9, Table B.6.3, p.98 and Table B.6.5, p.99 in re-submission and *calculated during the evaluation*

- 6.9 The key outcomes of the indirect comparison with infliximab in the induction phase are presented in the tables below. These results were presented as supplementary comparison in the previous submission.

Summary of results of the indirect comparison – Clinical response, ITT population, Induction Phase

Trial ID	Vedolizumab			Infliximab			Indirect RR (95% CI)
	RR (95% CI)	VDZ n with event/N (%)	PBO n with event/N (%)	PBO n with event/N (%)	IFN n with event/N (%)	RR (95% CI)	
Clinical response							
GEMINI I		106/225 (47.1)	38/149 (25.5)			-	
ACT 1				45/121 (37.2)	84/121 (69.4)		
ACT 2				36/123 (29.3)	78/121 (64.5)		
Pooled ^a				I ² = p-value= chi-square			

CI = confidence interval; n = number with event; N = number in group; RR = relative risk

^a pooled using the random effects model

Source: Table B.6.2, p.97 in re-submission

Summary of results of the indirect comparison – Clinical remission, ITT population, Induction Phase

Trial ID	Vedolizumab			Infliximab			Indirect RR (95% CI)
	RR (95% CI)	VDZ n with event/N (%)	PBO n with event/N (%)	PBO n with event/N (%)	IFN n with event/N (%)	RR (95% CI)	
Clinical remission							
GEMINI I		38/225 (16.9)	8/149 (5.4)				
ACT 1				18/121 (14.9)	47/121 (38.8)		
ACT 2				7/123 (5.7)	41/121 (33.9)		
Probert				6/20 (30.0)	9/23 (39.1)		
Meta-analysis including Probert				I ² = , chi-squared p-value =			
Meta-analysis excluding Probert				I ² = , chi-square p-value =			

CI = confidence interval; n = number with event; N = number in group; RR = relative risk. a pooled using the random effects model

Source: Table B.6.3, p.98 in re-submission

- 6.10 The resubmission claims that overall, vedolizumab was non-inferior compared to infliximab in terms of clinical remission and clinical response in the induction and maintenance phases. The evaluation considered this claim is generally supported, however, noting that for ‘clinical remission’ and ‘clinical response’ in the induction phase there was a non-significant trend towards vedolizumab being inferior. The PSCR disagreed and maintained that the indirect comparisons demonstrate that vedolizumab is statistically non-inferior to infliximab for all patient relevant outcomes, including clinical remission and clinical response for both induction and maintenance phases. The ESC agreed with the evaluation and considered that the point estimates consistently favour the comparator, but with wide confidence intervals. The ESC advised that the PBAC will need to decide whether it is concerned about the direction of the point estimates and not just the wide confidence intervals.

Comparative harms

- 6.11 There were no significant differences in the relative risks of adverse events, serious adverse events, discontinuations due to adverse events, infectious adverse events and serious adverse events between the vedolizumab and infliximab trials.
- 6.12 Vedolizumab is first in class drug for this indication. The re-submission identified the theoretical risk of PML as vedolizumab is in the same class as natalizumab - this risk was also identified in the previous submission.

Clinical claim

- 6.13 The re-submission described that vedolizumab as non-inferior to infliximab both in terms of efficacy and safety. The evaluation considered there are some issues with exchangeability between the vedolizumab (GEMINI I trial) and infliximab trials (ACT 1, ACT 2 and Probert):

- Some patients in the GEMINI I trial received prior treatment with TNF- α antagonists, but this was not allowed in the ACT 1, ACT 2 and Probert trial.
- The loss to follow up was substantially higher in the ACT 1 and ACT 2 trials compared to GEMINI I.
- The Probert trial used a different definition of clinical remission and had a substantially higher clinical remission event rate for the placebo.

The ESC noted that the PSCR responded to the issues raised in the evaluation about exchangeability, but considered that the issues still remain unresolved.

- 6.14 Due to the pharmacological class, vedolizumab may be associated with an increased risk of PML. Patients in the key trial (GEMINI I) and the extension study (C13008) were excluded if they were potentially at risk of PML. The PSCR advised that a risk management plan is already in place for addressing/managing the theoretical risk for PML, as part of the TGA's requirements for registering vedolizumab.
- 6.15 The PBAC considered that the claim of non-inferior comparative effectiveness was probably reasonable. Notwithstanding its preference for direct evidence, the PBAC remained concerned that the submission presented a claim of non-inferiority, in the absence of a pre-specified margin for non-inferiority.
- 6.16 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.17 The re-submission presented a cost-minimisation analysis to infliximab. The previous submission presented a cost-effectiveness analysis to standard of care (conventional therapies).
- 6.18 The equi-effective doses were estimated as: vedolizumab 300mg and infliximab 5mg/kg, based on the trials.
- 6.19 At a DPMQ of \$ [REDACTED] for public hospital patients and \$ [REDACTED] for private hospital patients the net cost impact of treating a patient with either infliximab or vedolizumab is nil. This includes additional offsets for administration costs. The re-submission also conducted sensitivity analysis of the inclusion of costs of PML screening (estimated to be \$ [REDACTED] in addition to including the same MBS item for drug administration as infliximab).

Drug cost/patient/course:

- 6.20 The drug cost/patient/course was estimated to be \$ [REDACTED]. This is the weighted average DPMQ between public and private hospital administration. Each vial provides treatment for 8 weeks in the maintenance phase. The treatment is ongoing.

Estimated PBS usage & financial implications

- 6.21 This re-submission was not considered by DUSC. The re-submission used an epidemiological approach to estimate the use of vedolizumab. Two scenarios were

modelled: Scenario 1 (infliximab listed) and Scenario 2 (both infliximab and vedolizumab listed). The estimated net cost was based on the difference between Scenario 1 and Scenario 2.

Estimated number of prescriptions and authorisations processed by DHS due to the listing of vedolizumab on the PBS.

	Current year	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario 1: infliximab only						
Prescriptions processed	3,194	4,974	5,555	5,691	5,768	5,412
Scenario 2: infliximab and vedolizumab						
Infliximab prescriptions processed						
Vedolizumab prescriptions processed						
Total						
Change in number of authorisations						

Source: Table E.5.1, p.45 of the commentary

- 6.22 The redacted table above shows the estimated total net patient numbers are less than 10,000 over the first five years of listing.

Net financial implications of vedolizumab of Government health budgets

	Year 1	Year 2	Year 3	Year 4	Year 5
Overall Net Cost to PBS ^a	\$	\$	\$	\$	\$
Overall Net Cost to PBS ^{ab}	\$	\$	\$	\$	\$
Cost to Government for MBS	\$	\$	\$	\$	\$
Overall Net cost to Government Health Budget	\$	\$	\$	\$	\$
Overall Net cost to Government Health Budget ^b	\$	\$	\$	\$	\$

^aDPMQ excluding patient co-payments. ^bUpdated co-payments. Source: Table E.5.2, p.45 of the commentary

- 6.23 The redacted table above shows the estimated total net cost to the PBS/RPBS/MBS for the listing of vedolizumab on the PBS is less than \$10 million per year.
- 6.24 Using scenario 2, at year 1, the estimated number of vedolizumab scripts was less than 10,000 and the net cost to the PBS would be less than \$10 million per year. At year 5, the estimated number of vedolizumab scripts was less than 10,000 and the net cost to the PBS would be less than \$10 million per year.
- 6.25 The evaluation noted that re-submission did not include the cost of treating the grandfathered patients. The resubmission only included the cost of screening for PML in the sensitivity analysis. There is uncertainty over the duration of treatment and the discontinuation rate during the maintenance phase of treatment, which may be an under- or over-estimate. There is uncertainty in the uptake rates of infliximab and vedolizumab under each scenario and for vedolizumab after infliximab failure. It may be that the uptake rate of vedolizumab after infliximab failure (either induction or maintenance) will be higher than the estimate presented in the submission because this is likely to represent the last medical option prior to surgery. The PSCR acknowledged that the financial estimates in the re-submission did not take into account grandfathered patients. However, the PSCR argued that the number of grandfathered patients should be (and not) as the remaining Australian patients are Crohn disease patients from the long-term extension study C13008. The

Pre-PBAC Response further clarifies that not all of these ■ patients are likely to seek grandfather access to PBS subsidy.

Financial Management – Risk Sharing Arrangements

- 6.26 The submission proposed a Special Pricing Arrangement whereby the published price of vedolizumab is ■ per vial (ex-manufacturer), which is a weighted average price across Crohn disease and ulcerative colitis (based on ■% of patients have Crohn disease and ■% have ulcerative colitis) (p5 of the submission). The calculation of the number of patients treated does not take into account grandfathered patients. If these patients are included, the split is 69% with Crohn disease and 31% with ulcerative colitis, resulting in a lower price.
- 6.27 The PBAC noted that the submission did not propose a risk sharing arrangement for this indication. The PBAC noted that addition of vedolizumab may expand the market to a small extent. Therefore, the PBAC recommended that vedolizumab should join the existing risk sharing arrangements for infliximab in moderate to severe ulcerative colitis, as both drugs have the same patient population.

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

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7 PBAC Outcome

- 7.1 The PBAC recommended listing of vedolizumab for the treatment of moderate to severe ulcerative colitis in adult patients, on the basis that it should be available only as Authority required under the Section 100 Highly Specialised Drugs Program.
- 7.2 The PBAC recommended the listing of vedolizumab on a cost-minimisation basis with infliximab. The PBAC considered the equi-effective doses are:
- vedolizumab – 300mg administered at week 0, week 2, week 6 and then every 8 weeks thereafter; and
 - Infliximab – 5mg/kg administered at week 0, week 2, week 6 and then every 8 weeks thereafter.
- 7.3 The PBAC noted that the requested listing for vedolizumab had been updated and is similar to that for infliximab. The PBAC agreed that the listing for vedolizumab should be identical to the moderate to severe ulcerative colitis (in adults) restrictions for infliximab. The PBAC also agreed that switching rules (swapping criteria) within a single treatment cycle must be put in place for infliximab and vedolizumab. The Committee agreed that the restriction should allow a total of 3 trials, where a patient cannot trial and fail or, cease to respond to, the same PBS-subsidised bDMARDs (TNF- α antagonist or α 4-integrin inhibitor) more than twice.
- 7.4 The PBAC recommended the inclusion of a 'grandfather' restriction, consistent with the 'grandfather' restriction for infliximab, to enable continuing PBS-subsidised vedolizumab treatment in patients who have been treated with vedolizumab for moderate to severe ulcerative colitis through the long term extension study C13008.

The PBAC noted the sponsor's pre-PBAC advice that fewer than ■ patients are expected to fall into this group.

- 7.5 The PBAC noted the proposed clinical place for vedolizumab in the re-submission was after failure of the conventional agents (5-ASAs, corticosteroids, and immunomodulators), as for infliximab. The PBAC noted the ESC's concern that the TGA indication suggests vedolizumab could be used as second line therapy. Noting the consumer comments about the application, the PBAC considered that the clinical place for vedolizumab would be as alternative treatment to infliximab in adult patients with moderate to severe ulcerative colitis.
- 7.6 The PBAC accepted infliximab as appropriate comparator. The PBAC noted that in the previous submission standard of care comprising 5-aminosalicylates, corticosteroids and immunomodulators was the nominated comparator.
- 7.7 Based on the input from the clinician at the sponsor hearing, consumer comments from the PBS website and the consumer hearing, the PBAC recognised there is perceived to be a clinical need for vedolizumab as alternative treatment in patients with moderate to severe ulcerative colitis following an inadequate response to standard systemic immunosuppressive therapy, given the debilitating nature of the condition.
- 7.8 The PBAC noted the re-submission's claim of non-inferiority in terms of comparative efficacy against infliximab. The PBAC noted that the trials presented in the re-submission for vedolizumab (GEMINI I) and infliximab (Probert, ACT I and ACT II) were the same trials presented in the original submission. The PBAC noted the clinical issues raised by ESC that the non-inferiority claim was not supported and that the point estimates consistently favour the comparator, but with wide confidence intervals. The PBAC considered that the data were of poor quality and that it was difficult to obtain a meaningful interpretation of non-inferiority due to the use of the indirect comparison in the submission. The PBAC also considered that there were exchangeability issues between the vedolizumab and infliximab trials. However, the PBAC recalled its previous consideration of vedolizumab at the July 2014 meeting where, notwithstanding the ESC's caution on the interpretation of the results, it considered it likely that vedolizumab has comparable efficacy to that of infliximab. The PBAC considered that despite the problems in the indirect comparison, the PBAC was satisfied that vedolizumab may be a reasonable alternative to infliximab.
- 7.9 The PBAC noted that in terms of comparative safety, there were no significant differences between the vedolizumab and infliximab trials. The PBAC noted the theoretical risk of developing PML with vedolizumab treatment as this is in the same class as natalizumab. The PBAC noted that the re-submission described the Risk Management Plan used in the GEMINI I trial and the potential screening and monitoring plan for PML risk. The PBAC considered the submission's and sponsor hearing arguments about the risk of PML being very low (given the gut selective mechanism), and acknowledged that no cases of PML have been reported so far. The PBAC accepted the re-submission's request that the restriction includes a requirement for patients to undergo screening and ongoing monitoring for PML.

- 7.10 The PBAC considered the cost-minimisation analysis of vedolizumab against infliximab. The PBAC agreed with ESC that the cost of managing the theoretical risk of PML should be included in the analysis. The PBAC considered that the cost of managing screening and monitoring for PML should be included in calculating the price for vedolizumab. The PBAC noted the Department's advice that infliximab has a published versus effective price for this indication.
- 7.11 The PBAC agreed with the issues regarding the utilisation and financial estimates outlined in paragraph 6.23 and that the up to ■ potential grandfather patients should be included in the financial estimates. The PBAC noted that the financial estimates are based on the published prices of vedolizumab and infliximab, and that the net financial to the Commonwealth will be less than estimated by the submission.
- 7.12 In accordance with subsection 101(3BA) of the Act the PBAC advised that it is of the opinion that, on the basis of the material available to it at its March 2015 meeting, vedolizumab should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.13 The PBAC advised that vedolizumab is not suitable for prescribing by nurse practitioners.
- 7.14 The PBAC recommended that the Safety Net 20 Day Rule should not apply to vedolizumab.
- 7.15 The PBAC noted the flow-on restriction changes to infliximab for the moderate to severe ulcerative colitis in adults. The PBAC noted that this will be a complex restriction.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item. Restriction to be finalised including flow-on changes to current infliximab restriction.

9 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.

10 Sponsor's Comment

Takeda welcomes the PBAC's recommendation for vedolizumab to be made available on the PBS for the treatment of Australian patients with moderate to severe ulcerative colitis. The listing of vedolizumab on the PBS provides these patients with another possible treatment alternative, something upon which patients place a high value (refer Sections 6.3 and 6.4).