

**5.25 VEDOLIZUMAB
300mg vial;
Entyvio®; Takeda Pharmaceuticals Australia.**

1 Purpose of Application

1.1 The submission requested a Section 100, Authority Required listing for vedolizumab for the treatment of moderate to severe Crohn's disease.

2 Requested listing

2.1 The proposed restriction is presented below.

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 300 mg vial	1	0	\$ [REDACTED]	Entyvio Takeda Pharmaceuticals

Section 100 Highly Specialised Drugs Program, public hospitals

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 300 mg vial	1	0	\$ [REDACTED]	Entyvio Takeda Pharmaceuticals

Section 100 Highly Specialised Drugs Program, private hospitals

Authority Required

Initial treatment of Crohn's disease in a patient assessed by Crohn's Disease Activity Index (CDAI).

Initial PBS-subsidised treatment with ~~infliximab~~ vedolizumab by a gastroenterologist or a consultant physician, of a patient with severe refractory Crohn's disease who satisfies the following criteria:

- (a) has confirmed Crohn's disease, defined by standard clinical, endoscopic and/or imaging features, including histological evidence, with the diagnosis confirmed by a gastroenterologist or a consultant physician; and
- (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, as outlined in the restriction for continuing treatment; and
- (c) has failed to achieve an adequate response to prior systemic therapy including:
 - (i) a tapered course of steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period; and
 - (ii) immunosuppressive therapy including:
 - azathioprine at a dose of at least 2 mg per kg daily for 3 or more months; or
 - 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more months; or
 - methotrexate at a dose of at least 15 mg weekly for 3 or more months.

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 CDAI Score greater than or equal to 300 as assessed.

A maximum quantity and number of repeats to provide for an initial course of vedolizumab consisting of 3 doses to be administered at weeks 0, 2 and 6, will be authorised.

NOTE: vedolizumab is not reimbursed for complex refractory Fistulising Crohn's Disease.

Authority required

Continuing treatment of Crohn's disease in a patient assessed by CDAI.

Continuing PBS-subsidised treatment with vedolizumab by a gastroenterologist, a consultant physician or other consultant physician in consultation with a gastroenterologist, of a patient who:

- (a) has a documented history of severe refractory Crohn's disease; and
- (b) has demonstrated or sustained an adequate response to treatment with vedolizumab.

An adequate response to ~~infiximab~~ vedolizumab treatment is defined as a reduction in Crohn's Disease Activity Index (CDAI) Score to a level no greater than 150.

If the application is the first application for continuing treatment with ~~infiximab~~ vedolizumab, a CDAI 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.

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

NOTE: vedolizumab is not reimbursed for complex refractory Fistulising Crohn's Disease.

- 2.2 The requested PBS restriction is similar to that for infliximab for the treatment of Crohn's disease, although the following details are missing:
- For initial treatment: "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 Crohn's Disease Activity Index (CDAI) assessment must be no more than 1 month old at the time of application."
 - For continuing treatment: "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 to 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. Where an assessment is not submitted to Medicare Australia within these timeframes, patients will be deemed to have failed to respond, or to have failed to sustain a response, to treatment with vedolizumab."
- The PBAC considered these restrictions should also be included.
- 2.3 The requested PBS restriction is not in line with the TGA indication as the PBS restriction also allows for the treatment of children aged 0 to 17, while the TGA indication restricts treatment to adults. The ESC noted the TGA indication suggests 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 submission requested the PBAC to consider whether patients with short gut syndrome, or an ostomy or extensive small intestine disease should be included in the restriction for vedolizumab, given that the restrictions for infliximab and adalimumab include these patients. The GEMINI II and III trials excluded these patients.
- 2.5 The submission also requested the PBAC to consider whether a grandfathering provision be included to allow for patients who have started treatment with vedolizumab prior to it being available on the PBS, to continue with subsidised treatment with vedolizumab (N=53). The submission proposed that patients are required to also meet the PBS restrictions (i.e. CDAI \geq 300 prior to commencing treatment, and have demonstrated or sustained an adequate response to treatment with vedolizumab, defined as a reduction in CDAI to \leq 150).

- 2.6 The requested basis for listing is cost-minimisation against two comparators, infliximab and adalimumab.
- 2.7 The submission stated that the restriction includes a requirement for patients to undergo screening and ongoing monitoring for progressive multifocal leukoencephalopathy (PML) however, this was not included in the restriction, economic evaluation and financial implications. The sponsor in its Pre-PBAC Response stated that it is willing to include the cost of managing screening and monitoring for PML (estimated \$█/patient) in the price of vedolizumab. The calculated price will be used in the cost-minimisation analysis against infliximab and adalimumab.

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 Crohn's disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNF- α) antagonist.
- 3.2 The PBAC had not previously considered vedolizumab for the indication of Crohn's disease.

4 Clinical place for the proposed therapy

- 4.1 The submission proposed vedolizumab for the treatment of moderate to severe Crohn's disease after failure of the conventional agents (5-ASAs, corticosteroids, and immunomodulators), as for infliximab and adalimumab (i.e. first line biologic therapy).

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

5 Comparator

- 5.1 Infliximab and adalimumab. The ESC agreed these comparators were appropriate. However, the ESC also considered given that vedolizumab was inferior to a TNF- α antagonist on many outcome measures and that 50% to 76% of patients in the key clinical trials provided had received prior treatment with TNF- α antagonist therapy, the PBAC should consider whether vedolizumab would be used as second-line or third-line therapy and thus whether best supportive care (BSC) would also be an appropriate comparator in this patient population.

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 ESC regarding the clinical place of vedolizumab in the treatment of Crohn's disease, 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 Crohn's and ulcerative colitis indication (item 7.6 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 :
- Crohn's disease severely affects the quality of life of patients and their families in psychological, social and economic terms. This is in the context of a primarily younger patient population that believes there are few treatment options prior to surgery. Patients are willing to tolerate significant hardship in order to postpone or avoid surgery.
 - 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 is 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.
 - The perception of the group of patients that have had access to vedolizumab for Crohn's disease in clinical trials is that the adverse events are less than alternatives.

The PBAC noted and welcomed this input.

Clinical trials

- 6.5 The submission was based on:
- Two head-to-head trials comparing vedolizumab to placebo: GEMINI II and GEMINI III
 - An indirect comparison to infliximab, based on two head-to-head trials comparing

infliximab to placebo: T16 and ACCENT I

- An indirect comparison to adalimumab, based on five head-to-head trials comparing adalimumab to placebo: CLASSIC I, CLASSIC II, GAIN, Watanabe, CHARM

6.6 Details of the trials presented in the submission are provided in the table below.

Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trials of vedolizumab versus placebo		
GEMINI II	Clinical Study Report C13007. 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 Crohn's Disease Sandborn, W. J., Feagan, B. G., Rutgeerts, P., Hanauer, S., Colombel, J. F., Sands, B. E., Lukas, M., Fedorak, R. N., Lee, S., Bressler, B., Fox, I., Rosario, M., Sankoh, S., Xu, J., Stephens, K., Milch, C., and Parikh, A. Vedolizumab as induction and maintenance therapy for Crohn's disease.	2012 New England Journal of Medicine. 2013; 369 (8): 711-721
GEMINI III*	Clinical Study Report C13011. A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction of Clinical Response and Remission by Vedolizumab in Patients with Moderate to Severe Crohn's Disease.	2012
Supplementary randomised trials: infliximab or adalimumab versus placebo		
T16	Targan, S. R., Hanauer, S. B., van Deventer, S. J. H., Mayer, L., Present, D. H., Braakman, T., DeWoody, K. L., Schaible, T. F., and Rutgeerts, P. J. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor (alpha) for Crohn's Disease.	New England Journal of Medicine 1997; 337 (15): 1029-1035
ACCENT I	Hanauer, S. B., Feagan, B. G., Lichtenstein, G. R., Mayer, L. F., Schreiber, S., Colombel, J. F., Rachmilewitz, D., Wolf, D. C., Olson, A., Bao, W., and Rutgeerts, P. Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial	Lancet 2002; 359 (9317): 1541-1549
CLASSIC I	Hanauer, S. B., Sandborn, W. J., Rutgeerts, P., Fedorak, R. N., Lukas, M., MacIntosh, D., Panaccione, R., Wolf, D., and Pollack, P. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: The CLASSIC-I trial	Gastroenterology 2006; 130 (2): 323-332
CLASSIC II	Sandborn, W. J., Hanauer, S. B., Rutgeerts, P., Fedorak, R. N., Lucas, M., MacIntosh, D. G., Panaccione, R., Wolf, D., Kent, J. D., Bittle, B., Li, J., and Pollack, P. F. Adalimumab for maintenance treatment of Crohn's disease: Results of the CLASSIC II trial.	Gut 2007; 56 (9): 1232-1239
GAIN	Sandborn, W. J., Rutgeerts, P., Enns, R., Hanauer, S. B., Colombel, J. F., Panaccione, R., D'Haens, G., Li, J., Rosenfeld, M. R., Kent, J. D., and Pollack, P. F. Adalimumab induction therapy for Crohn's disease previously treated with infliximab: A randomized trial	Annals of Internal Medicine 2007; 146 (12): 829-838
Watanabe	Watanabe, M., Hibi, T., Lomax, K. G., Paulson, S. K., Chao, J., Alam, M. S., and Camez, A. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease	Journal of Crohn's and Colitis 2012; 6 (2): 160-173
CHARM	Colombel, J., Sandborn, W. J., Rutgeerts, P., Enns, R., Hanauer, S. B., Panaccione, R., Schreiber, S., Byczkowski, D., Li, J., Kent, J. D., and Pollack, P. F. Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial	Gastroenterology 2007; 132 (1): 52-65

Trial ID/First Author	Protocol title/ Publication title	Publication citation
	Sandborn, W. J., Colombel, J. F., D'Haens, G., Plevy, S. E., Panes, J., Robinson, A. M., Pollack, P. F., Zhou, Q., Castillo, M., and Thakkar, R. B. Association of baseline C-reactive protein and prior anti-tumor necrosis factor therapy with need for weekly dosing during maintenance therapy with adalimumab in patients with moderate to severe Crohn's disease. ** Loftus, EV, Feagan, B. G., Colombel, J. F., Rubin, D.T., Wu, E.Q., Yu, A. P., Pollack, P. F., Chao, J., Mulani, P. Effects of Adalimumab Maintenance Therapy on Health-Related Quality of Life of Patients With Crohn's Disease: Patient-Reported Outcomes of the CHARM Trial Patient-Reported Outcomes with Adalimumab for Crohn's Disease. December 2008.	Current Medical Research and Opinion 2013; 29 (5): 483-493 The American Journal of Gastroenterology 103, 3132-3141

* Since published as: Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, D'Haens G, Ben-Horin S, Xu J, Rosario M, Fox I, Parikh A, Milch C, Hanauer S. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014 Sep;147(3):618-627.e3.Source:
** Not originally included in table but referred to in Table B(ii).4-3 p187 of the submission.

Source: Table B(i).2-7, p37 and Table B(ii).2-4, p137 of the submission

6.7 The key features of the 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	Outcome(s)	Use in modelled evaluation
Vedolizumab vs. placebo						
GEMINI II	IP: 368 MP: 461	R, DB + OL IP: 6 weeks, MP: 52 weeks	Low	Prior treatment with a TNF α antagonist <u>allowed</u>	Clinical remission*, clinical response** and enhanced clinical response***	Not used
GEMINI III	IP: 416	R, DB IP: 6 weeks	Low			
Infliximab vs. placebo						
T16	IP: 108	R, DB IP: 4 weeks	Low	Prior treatment with a TNF α antagonist <u>not allowed</u>	Clinical remission* and clinical response**	Not used
ACCENT I	MP: 335	R, DB + OL MP: 54 weeks	Low			
Adalimumab vs. placebo						
CLASSIC I	IP: 299	R, DB IP: 4 weeks	Low	Prior treatment with a TNF α antagonist <u>not allowed</u>	Clinical remission*, clinical response** and enhanced clinical response***	Not used
CLASSIC II	MP: 55	R, DB + OL MP: 60 weeks	Low			
GAIN	IP: 325	R, DB IP: 4 weeks	Low	Prior treatment with a TNF α antagonist <u>required</u>		
CHARM	MP: 499	R, DB + OL MP: 56 weeks	Low	Prior treatment with a TNF α antagonist <u>allowed</u>		
Watanabe	IP: 90 MP: 43	R, DB IP: 4 weeks, MP: 56 weeks	Low			

DB=double blind; IP= induction phase; MP = maintenance phase; MC=multi-centre; OL=open-label; R=randomised #When endpoint for efficacy was measured. * CDAl \leq 150 ** CDAl \geq 70 reduction from baseline, *** CDAl \geq 100 reduction from baseline. Source: compiled during the evaluation

Comparative effectiveness

6.8 The tables below present the efficacy from the GEMINI II and GEMINI III (vedolizumab against placebo) trials for the induction and maintenance phase, for the ITT population.

Results in induction phase across the direct randomised trials, ITT

Trial ID	Vedolizumab n/N (%)	Placebo n/N (%)	Absolute difference RD (95% CI)	Relative difference RR (95% CI)	NNT
Clinical remission					
GEMINI II	32/220 (14.5)	10/148 (6.8)	7.79 (1.62, 13.96)	2.15 (1.09, 4.24)	13
GEMINI III	40/209 (19.1)	25/207 (12.1)	7.06 (0.12, 14.00)	1.58 (1.00, 2.51)	14
Pooled result			NA	1.75, (1.19, 2.56)	NA
Chi-square for heterogeneity: P=0.463, I ² statistic with 95% uncertainty interval =0%					
Clinical response					
GEMINI II					9
GEMINI III					6
Pooled result					NA
Chi-square for heterogeneity: P=0.369, I ² statistic with 95% uncertainty interval =0%					

RD = risk difference; RR = relative risk; NA = not available. Source: Table B(i).6-2, p101 and Table B(i).6-3, p102 of the submission and calculated during evaluation.

Results in maintenance phase across the direct randomised trials, ITT

Trial ID	Vedolizumab n/N (%)	Placebo n/N (%)	Absolute difference RD (95% CI)	Relative difference RR (95% CI)	NNT
Clinical remission					
GEMINI II	60/154 (39.0)	33/153 (21.6)	17.39 (7.30, 27.48)	1.81 (1.26, 2.59)	6
Clinical response					
GEMINI II	70/154 (45.5)	54/153 (35.3)	10.16 (-0.76, 21.08)	1.29 (0.98, 1.70)	10

BOLD indicates potentially not more effective than placebo. RD = risk difference; RR = relative risk; NA = not available. Source: Table B(i).6-4, p103 and Table B(i).6-6, p104 of the submission and calculated during evaluation.

6.9 Vedolizumab versus placebo (based on GEMINI II and III):

- Vedolizumab was statistically more effective in terms of clinical remission in the induction and maintenance phase, and in terms of clinical response in the induction phase.
- In GEMINI II vedolizumab was not statistically more effective in terms of clinical response in the maintenance phase.

6.10 The tables below present subgroup analyses of vedolizumab against placebo in TNF- α antagonist naïve and TNF- α antagonist experienced groups.

Results across the direct randomised trials, treatment naïve

Trial ID	Vedolizumab n/N (%)	Placebo n/N (%)	Absolute difference RD (95% CI)	Relative difference RR (95% CI)	NNT
Induction Phase					
Clinical remission					
GEMINI II					-
GEMINI III					5
Pooled result					NA
Chi-square for heterogeneity: , I ² statistic with 95% uncertainty interval =0%					

Trial ID	Vedolizumab n/N (%)	Placebo n/N (%)	Absolute difference RD (95% CI)	Relative difference RR (95% CI)	NNT
Clinical response					
GEMINI II					6
GEMINI III					-
Pooled result					NA
Chi-square for heterogeneity: , I ² statistic with 95% uncertainty interval =0%					
Maintenance Phase					
Clinical remission					
GEMINI II					4
Clinical response					
GEMINI II					4

BOLD indicates potentially not more effective than placebo. RD = risk difference; RR = relative risk; NA = not available. Source: Table B(i).6-8 and Table B(i).6-9 p109, Table B(i).6-4 p107 and Table B(i).6-12 p108 of the submission and calculated during evaluation.

Results across the direct randomised trials, treatment experienced

Trial ID	Vedolizumab n/N (%)	Placebo n/N (%)	Absolute difference RD (95% CI)	Relative difference RR (95% CI)	NNT
Induction Phase					
Clinical remission					
GEMINI II					-
GEMINI III					-
Clinical response					
GEMINI II					-
GEMINI III					5
Maintenance Phase					
Clinical remission					
GEMINI II					15
Clinical response					
GEMINI II					NR

BOLD indicates potentially not more effective than placebo. RD = risk difference; RR = relative risk; NA = not available. Source: Table B(ii).6-15 p226 and Table B(ii).6-17, p227 of the submission, Table 21, p140 of CSR C13007, Table 11-2, p99 of CSR C13007, Table 61, p249 of CSR 13007 and calculated during evaluation.

- 6.11 The ESC noted that at a different baseline risk, treatment experienced patients were less likely to achieve remission and response than treatment naïve patients. The ESC also noted that the relative treatment effect was not statistically significant for a number of measures, however this may be due to smaller sample sizes. Overall, the ESC considered that the sub-group analyses did not suggest a clear difference in treatment effect between TNF- α antagonist naïve patients and TNF- α antagonist experienced patients.
- 6.12 The tables below summarise the main results from the indirect comparisons of vedolizumab against infliximab and adalimumab.

Summary of results of the indirect comparison against infliximab, ITT populations

Trial	Vedolizumab			Infliximab			Indirect estimate of effect ^c RR (95% CI)
	Treatment effect ^a RR (95% CI)	Vedolizumab n/N (%)	Placebo n/N (%)	Placebo n/N (%)	Infliximab n/N (%)	Treatment effect ^b RR (95% CI)	
Clinical remission in induction phase							
GEMINI II	2.15 (1.09, 4.24)	32/220 (14.5)	10/148 (6.8)				
GEMINI III							
T16				1/24 (4.2)	13/27 (48.1)	11.56 (1.63, 81.99)	
Pooled	I ² = p-value=			-	-		
Clinical response in induction phase							
GEMINI II	1.31 (1.00, 1.70)	99/220 (45.0)	51/148 (34.5)				
GEMINI III							
T16				4/24 (16.7)	22/27 (81.5)	4.89 (1.96, 12.18)	
Pooled	I ² = p-value=						
Clinical remission in maintenance phase							
GEMINI II	1.81 (1.26, 2.59)	60/154 (39.0)	33/153 (21.6)				
ACCENT I				15/110 (13.7)	32/113 (28.0)	2.08 (1.19, 3.61)	
Durable Clinical remission in maintenance phase							
GEMINI II	1.49 (0.91, 2.43)	33/154 (21.4)	22/153 (14.4)				
ACCENT I				12/110 (11)	28/113 (25)	2.27 (1.22, 4.24)	
Clinical response in maintenance phase							
GEMINI II							
ACCENT I				17/110 (15.5)	43/113 (38)	2.46 (1.50, 4.04)	

CI = confidence interval; n = number with event; N = number in group; RR = relative risk. ^a vedolizumab over placebo. ^b infliximab over placebo. ^c inferred as vedolizumab over infliximab. ^d pooled using the random effects model. Attachment B of the Commentary, Source: Tables B(i).6-2, B(i).6-3, B(i).6-4, B(i).6-5, B(i).6-6, p101-104 of the submission.

Summary of results of the indirect comparison against adalimumab, ITT populations

Trial ID	Vedolizumab			Adalimumab			Indirect estimate of effect ^c RR (95% CI)
	Treatment effect ^a RR (95% CI)	Vedolizumab n/N (%)	Placebo n/N (%)	Placebo n/N (%)	Adalimumab n/N (%)	Treatment effect ^b RR (95% CI)	
Clinical remission in induction phase							
GEMINI II	2.15 (1.09, 4.24)	32/220 (14.5)	10/148 (6.8)				
GEMINI III	1.58 (1.00, 2.51)	40/209 (19.1)	25/207 (12.1)				
CLASSIC I				9/74 (12)	27/76 (36)	2.92 (1.48, 5.78)	

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Trial ID	Vedolizumab			Adalimumab			Indirect estimate of effect ^c RR (95% CI)
	Treatment effect ^a RR (95% CI)	Vedolizumab n/N (%)	Placebo n/N (%)	Placebo n/N (%)	Adalimumab n/N (%)	Treatment effect ^b RR (95% CI)	
GAIN				12/166 (7)	34/159 (21)	2.96 (1.59, 5.51)	
Watanabe				3/23 (13)	11/33 (33)	2.56 (0.80, 8.15)	
Pooled	I ² =0%, chi-square p-value=0.463		1.75 (1.19, 2.56)	I ² =█%, chi-square p-value=█		█	
Clinical response in induction phase							
GEMINI II	1.31 (1.00, 1.70)	99/220 (45.0)	51/148 (34.5)				
GEMINI III	█	█	█				
CLASSIC I				25/74 (34)	44/76 (58)	1.71 (1.18, 2.49)	█
GAIN				56/166 (34)	82/159 (52)	1.53 (1.18, 1.98)	█
Watanabe				7/23 (30)	23/33 (70)	2.29 (1.19, 4.42)	
Pooled	I ² =0%, chi-square p-value=0.369		1.43 (1.20, 1.71)	I ² =█%, chi-square p-value=█		█	
Enhanced clinical response in induction phase							
GEMINI II	1.23 (0.88, 1.72)	69/220 (31.4)	38/148 (25.7)				
GEMINI III	█	█	█				
CLASSIC I				18/74 (24)	37/76 (49)	2.00 (1.26, 3.18)	█
GAIN				41/166 (25)	61/159 (38)	1.55 (1.12, 2.16)	█
Watanabe				4/23 (17)	15/33 (46)	2.61 (0.99, 6.87)	
Pooled	I ² =55.6%, chi-square p-value=0.133		1.47 (1.05, 2.05)	I ² =█%, chi-square p-value=█		█	
Clinical remission in maintenance phase							
GEMINI II	1.81 (1.26, 2.59)	60/154 (39.0)	33/153 (21.6)				
CHARM				20/170 (12)	62/172 (36)	3.06 (1.94, 4.84)	█
Watanabe				2/22 (9.1)	8/21 (38.1)	4.19 (1.00, 17.50)	█
Pooled				I ² =█%, chi-square p-value=█		█	
Clinical response in maintenance phase							
GEMINI II	█	█	█				
CHARM				30/170 (17.6)	74/172 (43.0)	2.44 (1.69, 3.52)	█
Watanabe				2/22 (10)	9/21 (42.8)	4.71 (1.15, 19.32)	█
Pooled				I ² =█%, chi-square p-value=█		█	
Enhanced clinical response in maintenance phase							

Trial ID	Vedolizumab			Adalimumab			Indirect estimate of effect ^c RR (95% CI)
	Treatment effect ^a RR (95% CI)	Vedolizumab n/N (%)	Placebo n/N (%)	Placebo n/N (%)	Adalimumab n/N (%)	Treatment effect ^b RR (95% CI)	
GEMINI II	1.45 (1.07, 1.96)	67/154 (43.5)	46/153 (30.1)				
CHARM				28/170 (16.5)	71/172 (41.3)	2.51 (1.71, 3.67)	
Watanabe				2/22 (9.1)	8/21 (38.1)	4.19 (1.00, 17.50)	
Pooled				I ² = % , chi-square p-value=			

CI = confidence interval; n = number with event; N = number in group; RR = relative risk. ^a vedolizumab over placebo. ^b adalimumab over placebo. ^c inferred as vedolizumab over adalimumab. ^d pooled using the random effects model. Attachment B of the Commentary, Source: Tables B(ii).6-2, B(ii).6-3, B(ii).6-4, B(ii).6-5, B(ii).6-7, B(ii).6-8, B(ii).6-15 p217-21 of the submission

6.13 Vedolizumab versus infliximab (based on the indirect comparisons):

- Vedolizumab was non-inferior in terms of clinical remission in the induction and maintenance phase, although there is a trend towards vedolizumab being inferior.
- Vedolizumab was statistically inferior in terms of clinical response in the induction phase and maintenance phase.

6.14 Vedolizumab versus adalimumab (based on the indirect comparisons):

- Vedolizumab was non-inferior in terms of clinical remission in the induction and maintenance phase, although there is a trend towards vedolizumab being inferior, and in the maintenance phase the upper 95% confidence interval was very close to 1.
- Vedolizumab was non-inferior in terms of clinical response and enhanced clinical response in the induction phase, although there is a trend towards vedolizumab being inferior.
- Vedolizumab was statistically inferior in terms of clinical response and enhanced clinical response in the maintenance phase.

6.15 The sub-group analysis by prior treatment did not substantially affect the results except that vedolizumab was no longer statistically inferior in terms of clinical response and enhanced clinical response compared to adalimumab in the maintenance phase. The ESC considered this may be because the smaller sample size increased the width of the confidence intervals. There was also no clear trend in that one sub-group was more or less likely to experience clinical remission than the other.

Comparative harms

6.16 There were no significant differences in the relative risks of any adverse events, infectious adverse events, serious infectious adverse events or deaths with vedolizumab compared to infliximab or adalimumab. However there were significantly more serious adverse events with vedolizumab compared to infliximab and adalimumab, and significantly fewer discontinuations due to adverse events with vedolizumab compared to infliximab. The submission identified the theoretical risk of PML as vedolizumab is in the same class as natalizumab. This risk was identified in the March 2014 submission for vedolizumab for the treatment of ulcerative colitis.

Clinical claim

- 6.17 In terms of comparative effectiveness, the submission described vedolizumab as:
- Versus infliximab: non-inferior for induction of clinical remission; inferior for induction of clinical response; non-inferior for maintenance of clinical remission and durable clinical remission; inferior for maintenance of clinical response.
 - Versus adalimumab: non-inferior for induction of clinical remission, enhanced clinical response and clinical response in the ITT populations, TNF- α antagonist naïve patients, and TNF- α antagonist failure/experienced patients; non-inferior in the ITT populations for maintenance of clinical remission and corticosteroid-free clinical remission; inferior for the maintenance of enhanced clinical response and clinical response; and non-inferior in TNF- α antagonist naïve patients and TNF- α antagonist failure/experienced patients for clinical remission and enhanced clinical response.
- 6.18 In terms of comparative safety, the submission described vedolizumab as:
- Versus infliximab: non-inferior for adverse events during the induction phase; non-inferior for adverse events and inferior for serious adverse events during the maintenance phase for the ITT populations and TNF- α antagonist naïve patients; and superior for discontinuation due to adverse events in the ITT populations and TNF- α antagonist naïve patients.
 - Versus adalimumab: non-inferior for adverse events, discontinuation due to adverse events, serious adverse events, infectious adverse events and serious infectious adverse events during the induction phase; non-inferior for adverse events, discontinuation due to adverse events, infectious adverse events and serious infectious adverse events during the maintenance phase; inferior for serious adverse events during the maintenance phase.
- 6.19 The evaluation considered that non-inferiority was not adequately supported. The indirect comparisons were not powered to test for non-inferiority and there was a trend towards vedolizumab being inferior. The PSCR argued that vedolizumab was non-inferior to both infliximab and adalimumab for clinical remission in the induction and maintenance phases (the primary endpoint for the GEMINI II and GEMINI II trials). The ESC agreed with the evaluation and considered that the point estimates consistently favour the comparator. The ESC considered that the non-inferiority claim was not supported by the indirect comparisons.
- 6.20 The evaluation noted there were also some issues with exchangeability between the trials:
- Prior treatment: The GEMINI II, GEMINI III, Watanabe and CHARM trials allowed prior treatment with a TNF- α antagonist. T16, ACCENT I, CLASSIC I and II did not. GAIN required it.
 - Doses in induction phase: Patients in GEMINI II, CLASSIC I, GAIN and Watanabe received 2 doses, but in GEMINI III received 3 doses, and in T16 1 dose. Patients in CHARM trial received adalimumab 80mg week 0 and 40mg week 2 (i.e. a lower dose compared to the other adalimumab trials). The PSCR clarified that although patients in GEMINI III did receive 3 doses, assessment of response was undertaken at the 6 week time point after 2 doses of vedolizumab.
 - Date of trials: The vedolizumab trials were conducted later than the infliximab and adalimumab trials. Improvements in the management of Crohn's disease may have reduced the baseline risk of an event over time.

- Timing of measurement: Clinical remission and response were measured later in the vedolizumab trials than in the infliximab trials and the adalimumab trials in the induction phase, but earlier in the maintenance phase. No adjustment was made for this in the analysis. The PSCR advised that based on the timing of all the assessments conducted in the trials there was insufficient data to allow for adjustments to be made. The ESC considered this could potentially favour vedolizumab.

The ESC noted the comments raised in the PSCR and considered that exchangeability issues still remain.

- 6.21 Due to the pharmacological class, vedolizumab may be associated with an increased risk of PML. Patients in the trials (GEMINI II and III) were excluded if they were potentially at risk of PML. The implication of this perceived risk may be that clinicians' will be reluctant to accept vedolizumab in the same line of therapy as infliximab. The TGA approved PI lists PML as a precaution and that 'patients should be advised of this potential risk for PML and that they should carry a Patient Alert Card at all times'.
- 6.22 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data for response, but may be for remission. 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.
- 6.23 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

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

Economic analysis

- 6.24 The submission presented a cost-minimisation analysis against infliximab and adalimumab. Special pricing arrangements are in place for infliximab and adalimumab for the treatment of Crohn's disease.
- 6.25 The equi-effective doses were estimated as:
- Vedolizumab 300mg administered at week 0, week 2, week 6 and then every 8 weeks.
 - Infliximab 5mg/kg administered at week 0, week 2, week 6 and then every 8 weeks.
 - Adalimumab 160mg at week 0, 80mg at week 2, 40mg at week 4 and then every 2 weeks.

The trials provided the source of the equi-effective doses.

- 6.26 At a DPMQ of \$ [REDACTED] for public hospital patients and \$ [REDACTED] for private hospital patients the net cost impact of treating a patient with adalimumab, infliximab or vedolizumab is nil. This includes additional offsets for administration costs. The 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:

6.27 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

6.28 This submission was not considered by DUSC. The submission used a market share approach to estimate the use of vedolizumab.

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]
Market share	Up to 20.16% of patients currently treated. Plus an additional 2.06% of patients who have discontinued treatment				
Scripts ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

^a Assuming [REDACTED] scripts per patient per quarter as estimated by the submission. Source: Table E.2-5 and E.2-6 p285, Table E.2-11 p288, Table E.2-12 p289, E.2-14 p290, and Table E.3-17 p300 of the submission

6.29 The redacted table above shows:

- The estimated total patient numbers are less than 10,000 over the first five years of listing
- The estimated total net cost to the PBS/RPBS/MBS for the listing of vedolizumab on the PBS is less than \$10 million over the first five years of listing.

6.30 At year 1, the estimated number of patients was [REDACTED] and the net cost to the PBS would be \$[REDACTED]. At year 5, the estimated number of patients was [REDACTED] and the net cost to the PBS would be \$[REDACTED].

6.31 The submission did not take into account the [REDACTED] grandfathered patients or include the cost of screening or treatment of PML. There is uncertainty in the uptake rates of vedolizumab. In first-line currently treated patients, uptake rates may be lower than indicated by the AIBDA survey results ([REDACTED]%), which may be optimistic. Conversely, the uptake rate of vedolizumab after infliximab or adalimumab failure may be higher than that estimated by the submission because vedolizumab would be the last medical option prior to surgery. The PSCR acknowledged that the financial estimates should take into account the [REDACTED] grandfathered patients, but noted that the estimate of [REDACTED] is conservative, anticipating that some patients enrolled in the long-term safety study will discontinue treatment.

Financial Management – Risk Sharing Arrangements

6.32 The submission proposed a Special Pricing Arrangement whereby the published price of vedolizumab is \$[REDACTED] per vial (ex-manufacturer), which is a weighted average price across Crohn’s disease and ulcerative colitis (assuming [REDACTED]% of

patients have Crohn's disease and ■% have ulcerative colitis). The calculation of the number of patients treated does not take into account grandfathered patients. If these patients are included, the split is ■% with Crohn's disease and ■% with ulcerative colitis.

- 6.33 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 currently in place for infliximab and adalimumab in Crohn's disease, as all three drugs have the same patient population.

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

7 PBAC Outcome

- 7.1 The PBAC recommended listing of vedolizumab for the treatment of severe Crohn's disease 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 and adalimumab. The PBAC considered the equi-effective doses are:
- vedolizumab – 300mg administered at week 0, week 2, week 6 and then every 8 weeks thereafter;
 - Infliximab – 5mg/kg administered at week 0, week 2, week 6 and then every 8 weeks thereafter; and
 - adalimumab 160mg at week 0, 80mg at week 2, 40mg at week 4 and then every 2 weeks thereafter.
- 7.3 The PBAC accepted the submission's request to include patients with short gut syndrome, or an ostomy or extensive small intestine disease in the restriction for vedolizumab, given that the restrictions for infliximab and adalimumab include these patients.
- 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 Crohn's disease through the long term extension study C13008. The PBAC noted that fewer than ■ patients are expected to fall into this group
- 7.5 The PBAC noted the proposed clinical place for vedolizumab in the submission was after failure of the conventional agents (5-ASAs, corticosteroids, and immunomodulators), as for infliximab and adalimumab i.e. as first line biologic therapy. The PBAC noted the ESC considered that the TGA indication suggests vedolizumab could be used as second line therapy. Noting the consumer comments, sponsor hearing and consumer hearing about the application, the PBAC recognised there is a perceived clinical need for vedolizumab as alternative treatment in patients with moderate to severe Crohn's disease following an inadequate response to standard systemic immunosuppressive therapy, given the debilitating nature of the condition. The PBAC noted that vedolizumab may be a preferable alternative treatment to surgery and patients would compare the risks and benefits of

vedolizumab to surgery, rather than the alternative PBS-subsidised drugs.

- 7.6 The PBAC agreed that the listing for vedolizumab should be identical to the adult Crohn's disease restrictions for infliximab and adalimumab, and that the switching rules (swapping criteria) within a single treatment cycle should be the same. 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 bDMARD (TNF- α antagonist or α 4-integrin inhibitor) more than twice.
- 7.7 The PBAC accepted infliximab and adalimumab as the appropriate comparators.
- 7.8 The PBAC considered that the claim of non-inferiority in terms of comparative efficacy had not been supported in the submission for the outcome of 'clinical response', although it may be supported for 'clinical remission'. The PBAC noted the results of the indirect comparisons between vedolizumab (GEMINI II and III) and infliximab (T16 and ACCENT I) and against adalimumab (CLASSIC I, CLASSIC II, GAIN, CHARM and Watanabe). The PBAC noted the clinical issues raised by ESC and considered that the trial data for the comparator infliximab had extremely wide confidence intervals and small patient numbers making the indirect comparison unreliable. Further, the PBAC noted 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 noted that there were exchangeability issues between the vedolizumab and infliximab and adalimumab trials. The sponsor in its Pre-PBAC Response and the clinician in the sponsor hearing maintained that vedolizumab is non-inferior in clinical remission and that this was the most relevant patient outcome. The PBAC considered that despite the problems with the indirect comparison, the PBAC was satisfied that, on balance, vedolizumab may be a reasonable alternative to infliximab and adalimumab.
- 7.9 The PBAC also considered the subgroup analyses of vedolizumab against placebo in TNF- α antagonist naïve and TNF- α antagonist experienced groups. The PBAC agreed with ESC that the sub-group analyses did not suggest a clear difference in treatment effect between TNF- α antagonist naïve patients and TNF- α antagonist experienced patients.
- 7.10 The PBAC noted that in terms of comparative safety, serious adverse events were more likely to be experienced in patients treated with vedolizumab than infliximab or adalimumab. 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 submission described the Risk Management Plan used in the GEMINI II and GEMINI III trials 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 recommended that the restriction include a requirement for patients to undergo screening and ongoing monitoring for PML (paragraph 2.7) as proposed in the submission.
- 7.11 The PBAC considered the cost-minimisation analysis of vedolizumab against infliximab and adalimumab. 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.

- 7.12 The PBAC agreed with the issues regarding the utilisation and financial estimates outlined in paragraph 6.30 and that the up to ■ 'grandfathered' patients should be included in the financial estimates.
- 7.13 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.
- 7.14 The PBAC advised that vedolizumab is not suitable for prescribing by nurse practitioners.
- 7.15 The PBAC recommended that the Safety Net 20 Day Rule should not apply to vedolizumab.
- 7.16 The PBAC noted the flow-on restriction changes to infliximab and adalimumab for the severe Crohn's disease 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 and adalimumab restrictions.

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 Crohn's disease. The listing of vedolizumab on the PBS provides these patients with another possible treatment alternative, noting that patients place a high value on maximising possible treatment alternatives (refer Sections 6.3 and 6.4).