

6.05 VEDOLIZUMAB, Powder for injection 300 mg, Entyvio[®], Takeda Pharmaceuticals Australia Pty. Ltd.

1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for initial treatment and an Authority Required (Telephone/Online) listing for continuing treatment of chronic pouchitis.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care (SOC).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adult patients with moderate to severe chronic pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis (IPAA) for ulcerative colitis (UC) and either: have had an inadequate response with or lost response to antibiotic therapy; or are antibiotic dependent for this condition (clarified in the Pre-Sub-Committee Response).
Intervention	Vedolizumab intravenous (IV) infusion plus standard of care
Clinical comparator	Placebo plus standard of care
Outcomes	Primary endpoint: <ul style="list-style-type: none"> • Clinically relevant modified Pouchitis Disease Activity Index (mPDAI) remission ^a Secondary endpoints ^b : <ul style="list-style-type: none"> • PDAI remission • Time to Pouchitis Disease Activity Index) PDAI remission. • Partial mPDAI response • Change from baseline in mPDAI Total score • Change from baseline in PDAI Total score • Change from baseline in PDAI symptom subscore • Change from baseline in PDAI endoscopic subscore • Change from baseline in PDAI histologic subscore • Change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) • Clinically meaningful improvement in IBDQ • IBDQ remission • Change from baseline in Cleveland Global Quality of life (CGQL) • Safety
Clinical claim	Superior effectiveness vs placebo with inferior safety
Economic evaluation	Cost-effectiveness (cost-utility) analysis

Source: Table10of the submission.

Abbreviations: CGQL, Cleveland Global Quality of life; IBDQ, Inflammatory Bowel Disease Questionnaire; IPAA, ileal pouch anal anastomosis; IV, intravenous; mPDAI, modified Pouchitis Disease Activity Index; PDAI, Pouchitis Disease Activity Index; UC, ulcerative colitis.

^a The primary endpoint included in the clinical trial was mPDAI remission at Week 14. The clinical trial also included mPDAI remission at Week 34 as a secondary endpoint, which is not included in this table.

^b The secondary points included in the clinical trial were measured at Week 14 and Week 34.

2 Background

Registration status

- 2.1 Vedolizumab for IV injection was TGA registered on 29 June 2023 for the treatment of adult patients with moderate to severe chronic pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis (IPAA) for UC, and have had an inadequate response with or lost response to antibiotic therapy.
- 2.2 Vedolizumab is also registered for the following indications:
- Treatment of adult patients with moderate to severe ulcerative colitis (UC) 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 (27 Jun 2014).
 - 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 TNF α antagonist (27 Jun 2014).
- 2.3 Issues with the clinical data that were raised in the TGA Delegate's Overview for this indication included (of TGA Delegate's overview):
- "The trial included multiple secondary endpoints for analysis and is unlikely to have been adequately powered to prove reliable evidence of statistical significance for endpoints other than the primary efficacy endpoint of clinical remission according to mPDAI after 14 weeks."
 - "It is not clear whether significant concomitant use of (prohibited) antibiotics before Week 14 in both treatment arms may have influenced the clinical outcomes. Some 20% of participants in both study groups were receiving antibiotics at Week 14".
 - "The analyses provide reasonable evidence of efficacy at Week 14, but higher frequency of relapses following remission in the vedolizumab treatment arm, and less convincing evidence of efficacy at Week 34 could suggest that the effect of vedolizumab may not be sustained."

Previous PBAC consideration

- 2.4 Vedolizumab IV has previously been considered by the PBAC in July 2014 and March 2015 for the treatment of moderate to severe UC and severe CD in adult patients. Vedolizumab IV was recommend for both indications in March 2015. A subcutaneous formulation of vedolizumab (pre-filled pen and syringe) was also considered by PBAC in November 2020 and was recommended for the same indications as the IV formulation. The subcutaneous formulation is not currently TGA approved for the treatment of pouchitis.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	AEMP	Dispensed Price for Max. Qty		Available brands
					Public	Private	
VEDOLIZUMAB							
Vedolizumab, 300 mg powder for injection for intravenous infusion; in a single-use vial	Initial			Published: \$2,949.93 Effective: \$ Pre-PBAC response: \$	Published: \$2,949.93 Effective: \$	Published: \$2,998.30 Effective: \$5	Entyvio, Takeda Pharmaceuticals Australia Pty. Ltd.
	1	1	2				
Continuing			Published: \$2,949.93 Effective: \$ Pre-PBAC response: \$	Published: \$2,949.93 Effective: \$	Published: \$2,998.30 Effective: \$		
1	1	2					

Category / Program	S100 HSD
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition	Pouchitis in patients who have undergone ileal pouch anal anastomosis (IPAA) for ulcerative colitis (UC)
Severity	Moderate to severe
Restriction type	<input checked="" type="checkbox"/> Authority Required – In writing (initial treatment)
Treatment phase	Initial treatment
Treatment criteria	Must be treated by a gastroenterologist, OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology]. AND Treatment must be initiated in parallel with standard of care antibiotic
Clinical criteria	Patient must have a history of IPAA for UC that was created at least 1 year previously AND The condition must be confirmed based on the patient's symptoms, treatment history and baseline endoscopic examination of the pouch (pouchoscopy) AND Patient must have a Modified Pouchitis Disease Activity Index (mPDAI) score of at least 5 AND Patient must have a minimum endoscopic mPDAI sub-score of at least 2 AND Patient must have had at least 3 recurrent episodes of pouchitis within the previous year each of which was treated with at least 2 weeks of antibiotic or other prescription therapy, OR The condition must have required maintenance antibiotic therapy taken continuously for at least 4 weeks AND Patient must not receive more 3 doses to be administered at weeks 0, 2 and 6 under this treatment phase. Patient must be aged 18 years or older AND

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	<p>Patient must not have previously received PBS-subsidised treatment with this drug for this condition for this treatment cycle/current pouchitis episode, AND</p> <p>Application for authorisation of initial treatment must be in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Pouchitis PBS Authority Application - Supporting Information Form which includes the following:</p> <p>(i) the completed current Modified Pouchitis Disease Activity Index (mPDAI) calculation sheet including the date of assessment of the patient's condition; and</p> <p>(ii) details of prior drug therapy for the condition [dosage, date of commencement and duration of therapy].</p> <p>A maximum quantity and number of repeats to provide for an initial course of this drug consisting of one vial of 300 mg per dose, with one dose to be administered at weeks 0, 2 and 6, will be authorised.</p> <p>Up to a maximum of 2 repeats will be authorised.</p> <p>The endoscopic assessment contributing to the Modified Pouchitis Disease Activity Index score to confirm the patient's condition at baseline must have been performed no more than 4 weeks prior to the application.</p>
<p>Prescribing instructions</p>	<p>Applications for treatment of this condition must be received within 4 weeks of the endoscopy to confirm diagnosis</p> <p>Prescriber must exclude secondary causes of pouchitis, for example:</p> <ul style="list-style-type: none"> • Ischaemia • Crohn's disease (CD) or CD of the pouch • Irritable pouch syndrome • Predominant cuffitis • Pouch stricture or pouch fistula • Active infection • NSAIDs • Celiacs disease

Source: Table 13, p14-16 of submission.

Abbreviations: CD, Crohn's disease; HSD, Highly Specialised Drug; IPAA, ileal pouch anal anastomosis; mPDAI, modified Pouchitis Disease Activity Index; NSAIDs, non-steroidal anti-inflammatory drugs; PBS, Pharmaceutical Benefits Scheme, UC, ulcerative colitis.

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Category /Program	S100 HSD
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition	Pouchitis in patients who have undergone ileal pouch anal anastomosis (IPAA) for ulcerative colitis (UC)
Severity	Moderate to severe
Restriction type	<input checked="" type="checkbox"/> Authority Required – Immediate/real time assessment telephone (continuing treatment)
Treatment phase	Continuing treatment
Treatment criteria	Must be treated by a gastroenterologist; OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology]. AND
Clinical criteria	Patient must have previously received PBS-subsidised initial treatment with this drug for this condition, AND Patient must have demonstrated or sustained an adequate response to the most recent PBS-subsidised treatment with this drug for this condition. Note: Patient must be discontinued from receiving PBS-subsidised treatment with this drug for this condition if no evidence of therapeutic benefit is observed by 14 weeks of treatment with vedolizumab
Notes	<ul style="list-style-type: none"> • Patients who have failed to maintain an adequate response compared to baseline with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug for this treatment cycle/pouchitis episode. • Patients are eligible to receive continuing treatment with this drug in courses up to 24 weeks providing they continue to sustain a response. • At the time of the authority application, medical practitioners should request the appropriate number of vials, to provide for a single infusion of 300 mg per dose. • Up to a maximum of 2 repeats will be authorised. • An application for the continuing treatment must be accompanied with the assessment of response following a minimum of 12 weeks of therapy with this drug and submitted no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment. • Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment. • If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within this treatment cycle. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.

Source: Table 14 of submission.

Abbreviations: HSD, Highly Specialised Drug; IPAA, ileal pouch anal anastomosis; mPDAI, modified Pouchitis Disease Activity Index; NSAIDs, non-steroidal anti-inflammatory drugs; PBS, Pharmaceutical Benefits Scheme; UC, ulcerative colitis.

3.1 The submission proposed a special pricing arrangement (SPA) with an effective price of \$| per 300 mg vial, consistent with the effective price for vedolizumab IV for UC (though lower than the effective price of vedolizumab IV for Crohn’s disease at the time the submission was made). The pre-PBAC response proposed a revised price of \$| to align with a recent (June 2024) change to the price in Crohn’s disease, which was the lowest indication-specific vedolizumab price on the PBS at the time of PBAC consideration.

3.2 The proposed restriction stated the condition must be moderate to severe, however this was not explicitly defined in the proposed restriction, which instead relied on the modified Pouchitis Disease Activity Index (mPDAI) as a clinical criterion for initial treatment. The mPDAI is a modified version of the PDAI. As outlined in Table 2, the PDAI is an 18-point overall score calculated from 3 separate 6-point scales based on clinical symptoms (0-6), endoscopic findings (0-6) and histologic findings (0-6), whereas the mPDAI is a 12-point overall score that excludes histologic findings. The evaluation and the ESC considered there is a lack of validation of the mPDAI for pouchitis disease activity, it was developed in very small patient samples, the clinical remission cut-off is arbitrarily defined, and there is a lack of psychometric evidence (e.g. lack of good inter-rater reliability of the overall total score between the PDAI and mPDAI and poor correlation with stool and blood markers of inflammation, and lack of predictability for therapeutic response^{1,2,3,4}).

Table 2: Pouchitis Disease Activity Index (PDAI). The mPDAI omits the histology component.

Criteria	Score
Clinical	
Stool frequency	
Usual postoperative stool frequency	0
1-2 stools/day > postoperative usual	1
3 or more stools/day > postoperative usual	2
Rectal bleeding	
None or rare	0
Present daily	1
Fecal urgency or abdominal cramps	
None	0
Occasional	1
Usual	2
Fever (temperature > 37.8° C)	
Absent	0
Present	1
Endoscopic inflammation	
Edema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucous exudates	1
Ulceration	1
Acute histologic inflammation	
Polymorphic nuclear leukocyte infiltration	
Mild	1
Moderate + crypt abscess	2
Severe + crypt abscess	3
Ulceration per low-power field (mean)	
>25%	1
25-50%	2

Source: www.yumpu.com/en/document/read/4702016/modified-pouchitis-disease-activity-index-a-cleveland-clinic

3.3 The evaluation stated that, from a consultation with clinicians (gastroenterologists), the Pouchitis Disease Activity Index (PDAI) appeared to be used more commonly than

¹ Kohyama et al, (2009), 'Pouchitis disease activity index (PDAI) does not predict patients with symptoms of pouchitis who will respond to antibiotics', *Surgery Today*, 39(11), pp962-968.

² Sedano et al, (2022), 'Disease activity indices for pouchitis: a systematic review', *Inflammatory Intestinal Diseases*, 28, pp622-638

³ Donet et al, (2020), '#MondayNightIBD: Management of chronic #pouchitis', *Crohns Colitis* 360, 2(4): otaa071

⁴ Ardalan et al, (2020), 'When less is more and more is less: The interrater reliability of the endoscopic findings of pouchitis', *Journal of Gastroenterology and Hepatology*, 35, pp139.

mPDAI in clinical practice. Although several instruments exist to measure pouchitis disease activity (including PDAI and mPDAI), none have been fully validated or deemed reliable or responsive.⁵

- 3.4 The Pre-Sub-Committee Response (PSCR) argued that whilst the PDAI and mPDAI scales are not fully validated, they remain the most commonly used pouchitis assessment tools and are recognised by the European Crohn’s and Colitis Organisation (ECCO), and that the mPDAI instrument has shown similar sensitivity and specificity to the PDAI scale⁶.
- 3.5 The proposed initial PBS restriction requires patients to have an mPDAI total score ≥ 5 with a minimum endoscopic sub-score of 2, consistent with the eligibility criteria for the clinical trial. In the clinical trial, total mPDAI score < 5 was considered quiescent disease; 5 to 8 was moderately active; and a score 9 to 12 was severely active. Overall, the ESC considered that the mPDAI score is not well validated for assessing severity, is subjective in the way it reports symptoms, and patients can achieve scores ≥ 5 with relatively mild symptoms. The ESC considered that while it was unclear whether the PDAI and/or mPDAI scores are routinely recorded by clinicians in current practice, the symptom-based components underpinning the scores are likely to be routinely assessed (e.g. changes to stool frequency, rectal bleeding, faecal urgency and abdominal cramps) with endoscopy actively considered by clinicians.
- 3.6 The proposed restriction for continuing treatment states that the “patient must have demonstrated or sustained an adequate response” with vedolizumab to continue treatment with vedolizumab. However, the proposed restriction did not define “adequate response” nor specify how it should be demonstrated, sustained or objectively assessed. In the clinical trial: remission was defined as a total score of < 5 and decrease of ≥ 2 points from baseline; and partial response as a decrease of ≥ 2 points from baseline.
- 3.7 The submission stated that the continuing restriction did not include a requirement for endoscopic examination to assess response “to avoid the burden on patients”. However, the evaluation considered that endoscopic examinations are regularly used to assess response to treatment and these examinations are generally accepted by patients. The evaluation considered that the inclusion of a diagnostic tool (e.g., endoscopy) in the proposed continuing treatment restriction would be important to confirm sustained adequate response to treatment. Additionally, the results from the clinical trial in achieving mPDAI-defined remission at Week 14 were driven by changing endoscopic appearances rather than symptoms (paragraph 6.30). The criteria to

⁵ Sedano, R, et al. (2022). ‘Disease Activity Indices for Pouchitis: A Systematic Review’. *Inflamm Bowel Dis*, 28(4), 622-638. <https://doi.org/10.1093/ibd/izab124>

⁶ Shen. B., et al. (2003b). Modified pouchitis disease activity index: a simplified approach to the diagnosis of pouchitis. *Diseases of the colon and rectum*, 46(6), 748–753. <https://doi.org/10.1007/s10350-004-6652->

determine remission or response to treatment had a significant impact on the results of the economic model and financial estimates.

- 3.8 The PSCR acknowledged the proposed restriction relies on a clinician’s judgement to continue treatment, however argued the risk of treating some patients on the basis of symptomatic response alone should not detract from the importance of having a treatment option available for this condition given its rarity. However, the PSCR also stated the Sponsor is open to suggestions from the PBAC regarding the proposed restriction, alignment with the clinical trial data and measures of remission and/or response for continuing treatment. The ESC considered that, in the absence of a more objective assessment of continuing response, it was likely that many patients would receive long-term vedolizumab treatment despite the lack of clinical data to support use beyond Week 34 for this condition. However, the ESC also considered it was unclear whether repeat endoscopies are routinely performed, on an ongoing basis (every six months), to assess treatment response in current clinical practice.
- 3.9 As outlined in paragraph 6.38, there is no clinical data to support continuing use of vedolizumab beyond Week 34 for this condition. This was also raised as a concern in the TGA Delegate’s overview (TGA Delegate’s overview).
- 3.10 The submission’s proposed 14-week timepoint for first assessing response was consistent with the TGA product information (PI), economic model and financial estimates. Further, the 14-week time point is consistent with response assessment in patients with moderate or severe ulcerative colitis. However, it was inconsistent with the clinical trial which allowed patients to remain on treatment up to Week 30.
- 3.11 The submission requested (although did not propose restriction wording for) a provision for initial treatment (recommencement of treatment after a break) to allow patients who have previously initiated vedolizumab on the PBS for pouchitis but who ceased for a reason other than failure to maintain an adequate treatment response. This would allow recommencement of vedolizumab in these patients if they experience a re-emergence of chronic pouchitis symptoms. This patient population was excluded from the clinical trial (EARNEST). There is currently no clinical evidence to support re-treatment after a break. Further, the proposed restriction would not preclude patients who had previously failed vedolizumab for pouchitis (or ulcerative colitis) from re-trialling vedolizumab for subsequent episodes, and these patients were included in the financial estimates (refer to paragraph 6.78). The ESC considered it would not be reasonable to allow re-treatment with vedolizumab for chronic pouchitis if it was previously ineffective, but considered that it may be reasonable to allow re-treatment after a treatment break or cessation of treatment for non-efficacy reasons.
- 3.12 The submission also requested a grandfathering provision and stated that there are 10 patients in the Patient Access Program.

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

4 Population and disease

- 4.1 Pouchitis is a rare condition characterised by inflammation of a surgically constructed pouch. Restorative proctocolectomy with IPAA is a surgical procedure performed to restore gastrointestinal continuity after removal of the colon and rectum, by creating an ileal pouch reservoir to aid stool retention.⁷ The aim of the IPAA surgery is to definitively cure disease and prevent malignant degeneration, while maintaining continence and avoiding a permanent stoma. The ESC noted the number of proctocolectomies and IPAAs for UC performed in Australia may have decreased over time (refer to Table 15), which may be due to the availability of effective biologics for earlier stages of ulcerative colitis.
- 4.2 Pouchitis is the most common complication in patients with UC who have undergone the IPAA procedure.⁸ Among patients who have undergone an IPAA, the reported incidence of pouchitis ranges from 20 to 50%.^{9,10 11,12} The reported rate of acute pouchitis from a single Australian institution study was 42.3% among patients who have undergone an IPAA, with 8.7% of patients developing chronic pouchitis.¹³
- 4.3 Pouchitis is characterised by frequent, watery, sometimes bloody stools associated with urgency, incontinence, abdominal cramps, malaise, and fever.^{2,14} Disease activity is difficult to classify but has been described as (1) remission (no active pouchitis), (2) mildly to moderately active (increased stool frequency, urgency, infrequent incontinence), or (3) severely active (hospitalisation for dehydration, frequent incontinence).¹⁵
- 4.4 Pouchitis has also been classified based on duration of pouch-related symptoms as either acute (<4 weeks) or chronic (≥4 weeks). Acute pouchitis develops in up to 50%

⁷ Sofo, L., et al., (2016), 'Restorative proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis: A narrative review', *World journal of gastrointestinal surgery*, 8(8), 556–563. <https://doi.org/10.4240/wjgs.v8.i8.556>

⁸ Shen, B., & Lashner, B. A. (2008), 'Diagnosis and treatment of pouchitis'. *Gastroenterology & hepatology*, 4(5), 355–361.

⁹ Fazio, V. W., et al., (2013), 'Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients', *Annals of surgery*, 257(4), 679–685. <https://doi.org/10.1097/SLA.0b013e31827d99a2>

¹⁰ Ikeuchi, H., et al., (2018), 'Long-term outcomes following restorative proctocolectomy ileal pouch-anal anastomosis in pediatric ulcerative colitis patients: Multicenter national study in Japan'. *Annals of gastroenterological surgery*, 2(6), 428–433. <https://doi.org/10.1002/ags3.12198>

¹¹ Penna, C., et al., (1996), 'Pouchitis after ileal pouch-anal anastomosis for ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis'. *Gut*, 38(2), 234–239. <https://doi.org/10.1136/gut.38.2.234>

¹² Ferrante, M., et al., (2008), 'Outcome after proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis', *Inflammatory bowel diseases*, 14(1), 20–28. <https://doi.org/10.1002/ibd.20278>

¹³ Lim MH, et al., (2021), 'Ileal Pouch-Anal Anastomosis for Ulcerative Colitis: An Australian Institution's Experience', *Ann Coloproctol*, 37(5):318-325. doi: 10.3393/ac.2020.08.26

¹⁴ Shen, B., et al., (2021), 'Diagnosis and classification of ileal pouch disorders: consensus guidelines from the International Ileal Pouch Consortium'. *The lancet. Gastroenterology & hepatology*, 6(10), 826–849. [https://doi.org/10.1016/S2468-1253\(21\)00101-1](https://doi.org/10.1016/S2468-1253(21)00101-1)

¹⁵ Sandborn, W. J., & Pardi, D. S., (2004), 'Clinical management of pouchitis', *Gastroenterology*, 127(6), 1809–1814. <https://doi.org/10.1053/j.gastro.2004.10.011>

of patients within 10 years of undergoing the IPAA procedure.¹⁶ Acute pouchitis usually responds to a single or several courses of antibiotic therapy, however 10% to 20% of patients with acute pouchitis may subsequently develop chronic pouchitis.¹⁷ Pouchitis can develop, based on the number of episodes and response to antibiotics, from acute antibiotic-responsive to chronic antibiotic-dependent pouchitis (CADP) (defined as ≥ 3 antibiotic-responsive episodes a year). In some patients, if the symptoms persist despite a course of more than four weeks of antibiotic therapy, pouchitis can become chronic antibiotic-refractory pouchitis (CARP).^{13,18}

- 4.5 The SOC treatment of chronic pouchitis generally includes antibiotics with a combination of 2 antibiotics agents (e.g., ciprofloxacin and metronidazole for over 4 weeks). Short-term corticosteroids followed by biologic agents in combination with antibiotics are proposed for patients who are intolerant to antibiotics or who are concerned about the risks of long-term antibiotic therapy and for patients with CARP. The American Gastroenterological Association (AGA)¹⁹ guidelines mention use of advanced immunosuppressive therapies, including TNF- α antagonists (i.e., infliximab, adalimumab, golimumab, certolizumab pegol), vedolizumab, ustekinumab, ozanimod, tofacitinib, and upadacitinib, that can be used alone or in combination with antibiotics for CADP and CARP patients. The guidelines conditional recommendation described vedolizumab as low certainty of evidence and very low for other advanced immunosuppressive therapies. Vedolizumab is the only biologic that is TGA-approved for the treatment of pouchitis, though others may be used off-label in clinical practice (e.g. adalimumab and infliximab).
- 4.6 Vedolizumab is proposed to be used in combination with SOC, which includes antibiotics. Vedolizumab is a gut-selective monoclonal antibody that specifically targets the $\alpha 4\beta 7$ integrin. Vedolizumab blocks the interaction of $\alpha 4\beta 7$ integrin with the mucosal addressin cell adhesion molecule-1, thereby inhibiting the migration of gut-homing T lymphocytes across the intestinal vascular endothelium and consequently reducing intestinal inflammation.

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

¹⁶ Magro, F., et al., (2017), 'Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders', *Journal of Crohn's and colitis*, 11(6), 649–670. <https://doi.org/10.1093/ecco-jcc/jjx008>

¹⁷ Quinn, K. P., & Raffals, L. E., (2020), 'An Update on the Medical Management of Inflammatory Pouch Complications', *The American journal of gastroenterology*, 115(9), 1439–1450. <https://doi.org/10.14309/ajg.0000000000000666>

¹⁸ Outtier, A., & Ferrante, M., (2021), 'Chronic Antibiotic-Refractory Pouchitis: Management Challenges', *Clinical and experimental gastroenterology*, 14, 277–290. <https://doi.org/10.2147/CEG.S219556>

¹⁹ Barnes, E. L., et al. (2024). 'AGA Clinical Practice Guideline on the Management of Pouchitis and Inflammatory Pouch Disorders'. *Gastroenterology*, 166(1), 59-85. <https://doi.org/10.1053/j.gastro.2023.10.015>

5 Comparator

- 5.1 The submission nominated standard of care (SOC) as the main comparator. SOC includes the use of antibiotic therapy (additional to the companion antibiotic with the initiation of vedolizumab), as required, for the treatment of flares. The submission stated that additional supportive therapies for pouchitis may include the use of probiotics and anti-diarrheal treatments. Other supportive therapies (not identified in the submission) that may also comprise SOC include corticosteroids and advanced immunosuppressive therapies. There are currently no TGA approved therapies specific for the treatment of chronic pouchitis other than vedolizumab.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician outlined the significant impact that chronic pouchitis can have on patient quality of life, and that the condition generally affects younger adults consistent with the median age of patients recruited in the EARNEST trial being 44 years. The clinician discussed the management of pouchitis including that vedolizumab is the only biologic agent with randomised controlled trial evidence for this condition. In response to questions, the clinician outlined that in current practice, patients are monitored for response based on their symptoms. Endoscopy is performed to confirm remission, then used less frequently on an on-going basis for monitoring (e.g. generally every three years thereafter depending on other risk factors). The clinician outlined that vedolizumab would likely be used long-term in those patients who respond. Treatment breaks (with close monitoring) may be offered to patients who achieve histological remission. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon condition.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from a health care professional and an organisation via the Consumer Comments facility on the PBS website. The health care professional described the significant morbidity associated with chronic pouchitis and outlined that there are a proportion of patients who do not respond to current treatments. The comments also described the known and favourable safety profile of vedolizumab and the potential for improved quality of life and increased productivity with vedolizumab.
- 6.3 The PBAC noted the advice received from Crohn's and Colitis Australia that was supportive of the evidence provided in the submission. Evidence provided from a person living with pouchitis described the burden of symptoms on everyday life (e.g.

increased bowel motions, urgency, fatigue and lack of energy) and the need for alternative effective treatment options.

Clinical trials

6.4 The submission was based on one head-to-head trial comparing VEDO + SOC to PBO + SOC (N=102): EARNEST.

6.5 Details of the trial presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
EARNEST NCT02790138	A Randomized, Double-Blind, Placebo-Controlled Phase 4 Study to Evaluate the Efficacy and Safety of ENTYVIO (Vedolizumab IV) in the Treatment of Chronic Pouchitis (EARNEST). Travis S, Silverberg MS, Danese S et al. Vedolizumab for the treatment of chronic pouchitis.	June 2021 NEJM 2023; 388(13), 1191-1200

Source: Table 19 of the submission.

Abbreviation: IV, intravenous; NEJM, New England Journal of Medicine.

6.6 The key features of the direct randomised trial are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes ^a	Use in modelled evaluation
VEDO + SOC vs. PBO + SOC						
EARNEST (Travis 2023)	102	R, DB, PC, MC, MN 34 weeks	High ^b	Patients who had undergone a proctocolectomy and IPAA for UC ^c and had chronic pouchitis	<ul style="list-style-type: none"> mPDAI-defined clinical remission^d PDAI-defined clinical remission Partial mPDAI-defined response Clinically meaningful improvement in IBDQ score Change from baseline in mPDAI total score Change from baseline in PDAI total score, and clinical, endoscopic and histologic sub-score Change from baseline in IBDQ score Change from baseline in CGQL Fazio score 	mPDAI clinical remission, change from baseline in IBDQ score

Source: Table 19 of the submission.

Abbreviations: CGQL, Cleveland Global Quality of Life; DB, double-blind; IBDQ, Inflammatory Bowel Disease Questionnaire; IPAA, ileal pouch anal anastomosis; MC, multi-centre; MN, multi-national; mPDAI, modified Pouchitis Disease Activity Index; PBO, placebo; PC, placebo-controlled; PDAI, Pouchitis Disease Activity Index; R, randomised; SOC, standard-of-care; UC, ulcerative colitis; VEDO, vedolizumab.

^a All outcomes were assessed at the Week 14 and 34 endpoints.

^b Risk of bias has been raised from 'low' in the submission to high based on the high attrition rate, use of the last observation carried forward imputation method and the large number of protocol deviations.

^c History of IPAA for UC demonstrated at least 1 year prior to randomisation.

^d Only the mPDAI clinical remission at Week 14 was considered the primary outcome. All other outcomes were secondary and considered patient-relevant.

- 6.7 The EARNEST trial was a multicentre, randomised, placebo-controlled trial to assess the efficacy and safety of vedolizumab in adults with moderate to severe pouchitis inadequately responding to antibiotic therapy. Patients were randomly assigned in a 1:1 ratio to either vedolizumab or placebo. All patients received the SOC antibiotic therapy with ciprofloxacin for the first four weeks from randomisation. Additional courses of antibiotics were permitted after Week 14 as needed for the management of disease flares. Final efficacy assessments were conducted at Week 34, which was 4 weeks after the last dose of study drug administered at Week 30. A final safety follow-up visit was conducted at Week 48. The primary efficacy outcome of mPDAI-defined clinical remission was assessed at Week 14. All other secondary outcomes including mPDAI-defined clinical remission and response were assessed at Week 34.
- 6.8 The submission claimed that there was an overall low risk of bias from the EARNEST trial. However, the evaluation and the ESC considered an overall high risk of bias was more appropriate for the following reasons: due to substantial treatment and study discontinuation, use of LOCF imputation methods, and large number of protocol deviations. This attrition bias likely favours the intervention.
- There was a high proportion of treatment discontinuation before the 30-week treatment period; 29.4% in the VEDO + SOC vs 37.3% in the PBO + SOC. Reasons included voluntary withdrawal and lack of efficacy (23.5% vs. 27.4% respectively), and adverse events (3.9% vs. 9.8% respectively).
 - At Week 14, study discontinuation was 9.8% in the VEDO + SOC group and 15.7% in the PBO + SOC group. The submission did not describe the reasons for study discontinuation before Week 14 (primary efficacy outcome endpoint). By Week 34, study discontinuation increased to 27.5% in the VEDO + SOC group and 37.3% in the PBO + SOC group. Reasons for study discontinuation before Week 34 included lack of efficacy (15.7% in each treatment arm), adverse events and significant protocol deviations (5.0% vs. 9.8%, respectively).
 - There was a high proportion of patients with at least one study-specific significant protocol deviation; 37.3% in VEDO + SOC vs 39.2% in PBO + SOC. Study procedure deviations, such as missing Week 14 endoscopies or poor-quality endoscopy recordings, were less common in the VEDO + SOC group (7.8%) compared to the PBO + SOC group (19.6%).
 - 15.7% of patients in the VEDO + SOC group and 25.5% in the PBO + SOC group reported at least one major protocol violation. This was mainly due to more patients in the PBO + SOC group having missing mPDAI at Week 14 (21.6% vs. 6% in the VEDO + SOC group).
- 6.9 The evaluation considered the higher frequency of study discontinuation at Week 14 in the VEDO + SOC arm (versus the PBO + SOC arm) was further exacerbated by the imputation of missing data for withdrawn patients, which could favour VEDO + SOC. While completely missing data for mPDAI clinical remission scores was addressed by

non-response imputation, partially missing data were addressed by LOCF based on baseline data and unscheduled data visits.

- 6.10 Using the LOCF imputation method could favour vedolizumab and was not the most conservative approach as some patients withdrew due to lack of efficacy, which was not reflected in the imputed data. The evaluation considered that additional information would be required to understand how many patients withdrew or were discontinued by the investigator due to lack of efficacy before Week 14, and if these withdrawals, both before and after Week 14, were classified as non-responders.
- 6.11 These issues regarding LOCF imputation were also identified by the TGA where the evaluators requested that “the sponsor apply a more comprehensive approach to imputing missing data, including imputing missing data as non-response in some analyses (rather than LOCF) and a jump-to-reference imputation with tipping point analysis” (TGA Delegate’s Overview; paragraph 6.23).
- 6.12 The ESC considered the issues raised in paragraphs 6.8 – 6.11 were substantial sources of uncertainty when interpreting the outcomes of the EARNEST trial, however acknowledged the challenges in generating robust randomised controlled trial evidence in the context of the rarity of chronic pouchitis.
- 6.13 The primary efficacy outcome of the EARNEST trial was mPDAI-defined clinical remission at Week 14 defined as an mPDAI total score <5 (considered quiescent disease) with a ≥ 2 point reduction from baseline.
- 6.14 The submission stated that there is no established minimally clinically important difference (MCID) for mPDAI but applied an assumed treatment difference effect size of at least 25 percentage point to be a “clinically significant” for the mPDAI at Week 14 for sample size calculations (described in the statistical analysis plan (SAP) of the EARNEST trial). The rationale for selecting this was not adequately justified nor validated.
- 6.15 The submission included several secondary efficacy outcomes, including mPDAI clinical remission at Week 34, changes from baseline in PDAI total score and its clinical, endoscopic, and histologic sub-scores, as well as changes from baseline in IBDQ score. The IBDQ instrument is a validated tool for inflammatory bowel disease (not pouchitis). Secondary outcomes were not controlled for multiplicity and concerns were raised in the TGA Delegate’s Overview regarding the reliability of these endpoints (paragraph 2.3).
- 6.16 All patients randomised into the study had prior medications for treating pouchitis initiated post-colectomy. 94.1% of patients in the VEDO + SOC group had prior antibiotic treatment with ciprofloxacin compared to 82.4% of patients in the PBO + SOC group. 72.5% of patients in the VEDO + SOC group had prior antibiotic treatment with metronidazole, compared to 64.7% of patients in the PBO + SOC group. Higher prior antibiotic usage in the VEDO + SOC arm could favour VEDO + SOC because

patients in this arm had a higher level of pre-treatment without a washout period before commencing investigational therapy.

- 6.17 Concomitant medications were defined as any medications that were ongoing at or started on/after the start of study medication including medication given after Week 34, excluding the companion antibiotics that were administered from Day 1 through Week 4 per protocol. Almost all patients in both the VEDO + SOC (98.0%) and PBO + SOC (96.1%) groups were treated with a concomitant medication throughout the study, and the majority of patients were taking concomitant medication specifically for pouchitis (84.3% vs. 80.4%, respectively).
- 6.18 There was a higher proportion of concomitant antibiotic usage observed in the VEDO + SOC group (58.8%) compared to the PBO + SOC group (37.3%). This was evident at both the Week 14 (22.2% vs. 20.0%, respectively) and Week 34 (21.2% vs. 12.5%) study endpoints, coinciding with the assessment of mPDAI and other secondary outcomes. The greater proportion of concomitant antibiotic including additional ciprofloxacin courses for the management of flares in the VEDO + SOC group, particularly at Week 14 and Week 34, could potentially confound and overestimate the treatment effect of vedolizumab. Therefore, the treatment effect observed in the EARNEST trial with VEDO + SOC should be interpreted with caution, in the context of the additional doses of antibiotics beyond the four weeks of ciprofloxacin. Additionally, this affects the generalisability of the trial results to routine clinical use, where antibiotic use may be more common. The TGA Delegate's Overview raised similar concerns (paragraph 2.3).

Comparative effectiveness

- 6.19 The full analysis set (FAS) population was the primary analysis set for efficacy. The FAS population was defined as all randomised participants who received at least 1 dose of the study drug medication. An intention-to-treat (ITT) analysis was not conducted. The FAS approach appears reasonable since all randomised patients received at least 1 dose of the study medication.
- 6.20 Table 5 presents the results of the mPDAI-defined clinical remission for the primary outcome endpoint of Week 14 and secondary (and exploratory) outcomes at Week 34.

Table 5: mPDAI-defined remission at Week 14 and 34 in the EARNEST trial, FAS

Endpoint	VEDO + SOC (N=51)	PBO + SOC (N=51)	Treatment difference (95% CI)	RR (95% CI)
mPDAI remission at Week 14 ^{a, d}	16/51 (31.4)	5/51 (9.8)	21.6 (4.9, 37.5)	3.20 (1.27, 8.08)
mPDAI remission at Week 34 ^{b, d}	18/51 (35.3)	9/51 (17.6)	17.6 (0.3, 35.1)	2.00 (0.99, 4.03)
Sustained mPDAI remission (i.e. at both Week 14 and 34) ^{c, d}	14/51 (27.5)	3/51 (5.9)	21.6 (6.5, 37.0)	4.67 (1.43, 15.3)

Source: Table 30 of the submission and calculated during evaluation.

Abbreviations: CI, confidence interval; FAS, full analysis set; mPDAI, modified Pouchitis Disease Activity Index; PBO, placebo; RR, risk ratio; SOC, standard of care; VEDO, vedolizumab.

Bold indicates statistically significant primary outcome results.

^a Primary outcome

^b Secondary outcome

^c Additional exploratory analysis showing the number of patients who achieved mPDAI-defined remission measured at both Weeks 14 and 34

^d Outcome used in the economic model to calculate transition probabilities

- 6.21 At Week 14, there were more patients who had mPDAI-defined clinical remission in the VEDO + SOC group (31.4%) compared to PBO + SOC group (9.8%) with a treatment difference of 21.6 percentage points (95% CI: 4.9, 37.5). The EARNEST trial did not achieve a 25 percentage point difference in the remission rate for the mPDAI-defined clinical remission at Week 14, used for the purpose of sample size calculation (albeit unvalidated). The reported 95% confidence intervals for the treatment differences reported were wide. At Week 34, the treatment difference effect decreased to 17.6 percentage points (95% CI: 0.3, 35.1).
- 6.22 The submission included additional (exploratory) efficacy analyses based on the outcome of sustained mPDAI remission defined as mPDAI remission at both Week 14 and 34. Sustained mPDAI remission was observed in 27.5% of VEDO + SOC patients and 5.9% of PBO + SOC patients, with a 21.6 percentage point treatment difference (95% CI: 6.5, 37.0) between groups. Further, at Week 34 remission was achieved by 11.4% of VEDO + SOC patients and 13.0% of PBO + SOC patients who were not in remission at Week 14. The ESC considered that the outcome of ‘sustained remission’ reported in the trial may not be indicative of long-term remission as it was based solely on a patient achieving mPDAI-assessed remission at two discrete time points (Weeks 14 and 34) with no requirement for remission to be maintained between or beyond these two timepoints. Overall, there was no evidence suggesting that prolonged VEDO + SOC treatment induces more mPDAI-defined remissions compared to placebo after 14 weeks.
- 6.23 The submission performed sensitivity analysis to assess the impact of study discontinuation using two methods: a full LOCF approach; and a hybrid approach. The hybrid method imputed interim missing data (e.g., missing data at Week 14 but present at Week 34) with LOCF, while missing data after discontinuation of the study drug were imputed based on the primary reason for discontinuation, using non-

response imputation for adverse events or lack of efficacy and LOCF for other reasons. The TGA Delegate's Overview concluded that the statistical superiority was supported by sensitivity analyses, and numerically but not statistically in the per-protocol set analysis, where participants with missing data were imputed as not achieving remission (TGA Delegate's Overview). However, the evaluation considered: (a) imputing all discontinuations as non-responders would be a more conservative approach; (b) a sensitivity analysis imputing as per TGA Delegate's Overview recommendations (paragraph 6.11) would be informative; and (c) given the high rates of discontinuation (hence imputation), presenting results based on complete case analyses would also be informative. The PSCR re-iterated the results of the sensitivity analyses conducted on the per-protocol set which found numerically but not statistically significant increases in mPDAI-remission at Week 14 (clinical remission rates of 32.6% (14/43) in the vedolizumab arm and 13.2% (5/38) in the placebo arm at 14 weeks, with a 19.4 percentage point difference (p=0.064)). The PSCR argued the results of the full analysis set are supported by the per-protocol analysis.

- 6.24 In an additional sensitivity analysis where patients who received concomitant antibiotics before Week 14 were imputed as non-responders, the results indicated a smaller treatment difference of 15.7 percentage points between VEDO + SOC and PBO + SOC at Week 14. The use of concomitant antibiotic including additional ciprofloxacin is a potential confounder of the efficacy results.
- 6.25 These results also raise concern that flares should be treated as an efficacy outcome rather than safety (as presented in the submission, refer to paragraph 6.34). The trial indicated that flares are associated with worsening pouchitis symptoms and include patient-perceived clinical symptoms of the disease, such as faecal urgency and abdominal cramps. Therefore, patients might perceive flares as being related to their disease rather than as a side effect of the treatment.
- 6.26 Table 6 presents the secondary efficacy outcomes in the EARNEST trial.

Table 6: Secondary outcomes in the EARNEST trial, FAS

Endpoint	VEDO + SOC n/N (%)	PBO + SOC n/N (%)	Treatment difference (95% CI)	RR (95% CI)
CATEGORISED OUTCOMES				
PDAl-defined clinical remission				
Week 14	18/51 (35.3)	5/51 (9.8)	25.5 (8.0, 41.4)	3.60 (1.45, 8.96)
Week 34	19/51 (37.2)	9/51 (17.6)	19.6 (1.9, 37.0)	2.11 (1.06, 4.22)
Sustained PDAl remission ^{a, b}	16/51 (31.4)	4/51 (7.8)	23.5 (8.0, 38.8)	4.00 (1.44, 11.1)
Partial mPDAl-defined response				
Week 14 ^a	32/51 (62.7)	17/51 (33.3)	29.4 (8.0, 47.6)	1.88 (1.21, 2.93)
Week 34 ^a	26/51 (51.0)	15/51 (29.4)	21.6 (1.9, 39.8)	1.73 (1.05, 2.87)
IBDQ remission				
Week 14	20/51 (39.2)	16/51 (31.4)	7.8 (-11.0, 26.3)	1.25 (0.74, 2.12)
Week 34	22/51 (43.1)	10/51 (19.6)	23.5 (4.9, 40.7)	2.20 (1.16, 4.17)
Clinically meaningful improvement in IBDQ				
Week 14	25/51 (49.0)	25/51 (49.0)	0.0 (-20.1, 20.1)	1.00 (0.67, 1.49)
Week 34	23/51 (45.1)	18/51 (35.3)	9.8 (-9.6, 28.7)	1.28 (0.79, 2.06)
OUTCOMES BASED ON RAW SCORES				
Endpoint	VEDO + SOC (N=51), mean change from baseline (SD)	PBO + SOC (N=51), mean change from baseline (SD)	Mean change difference (95% CI)	
Change from baseline in mPDAl Total score				
Week 14	-2.7 (2.6)	-1.3 (1.8)	-1.4 (-2.3, -0.5)	
Week 34	-3.5 (2.9)	-2.0 (2.4)	-1.5 (-2.8, -0.2)	
Change from baseline in PDAl Total score				
Week 14	-3.1 (3.9)	-1.4 (2.7)	-1.7 (-3.2, -0.3)	
Week 34	-3.9 (4.2)	-2.1 (3.5)	-1.7 (-3.7, 0.2)	
RAW SCORES				
Change from baseline in PDAl clinical sub-score				
Week 14	-1.4 (1.4)	-1.1 (1.1)	-0.3 (-0.8, 0.2)	
Week 34	-1.7 (1.6)	-1.2 (1.2)	-0.5 (-1.2, 0.2)	
Change from baseline in PDAl endoscopic sub-score				
Week 14	-1.2 (1.6)	-0.1 (1.2)	-1.1 (-1.8, -0.5)	
Week 34	-1.7 (2.1)	-0.9 (1.9)	-0.8 (-1.8, 0.2)	
Change from baseline in PDAl histologic sub-score				
Week 14	-0.5 (2.1)	-0.1 (1.5)	-0.4 (-1.1, 0.4)	
Week 34	-0.4 (1.9)	-0.1 (1.6)	-0.3 (-1.2, 0.6)	
Change from baseline in IBDQ score				
Week 14	21.1 (29.0)	16.7 (27.0)	4.4 (-7.4, 16.2)	
Week 34	33.1 (34.4)	23.1 (21.6)	9.9 (-4.8, 24.6)	
Change in CGQL Fazio score				
Week 14	0.11 (0.17)	0.07 (0.16)	0.04 (-0.03, 0.11)	
Week 34	0.13 (0.18)	0.10 (0.14)	0.03 (-0.05, 0.11)	

Source: Table 31, p57; Table 32; Table 33, p58; Table 34, p59; Table 35, p59; Table 36, p61, Table 37, p62; Table 38, p62; Table 39, p63 of the submission and calculated during evaluation.

Abbreviations: CGQL, Cleveland Global Quality of Life; CI, confidence interval; FAS, full analysis set; IBDQ, Inflammatory Bowel Disease Questionnaire; mPDAl, modified Pouchitis Disease Activity Index; PBO, placebo; PDAl, Pouchitis Disease Activity Index; RR, risk ratio; SD, standard deviation; SOC, standard-of-care; VEDO, vedolizumab.

^a Outcome used in the economic model to calculate transition probabilities

^b Additional exploratory analysis showing the number of patients who achieved PDAl-defined remission measured at both Weeks 14 and 34

- 6.27 There were higher proportions of patients for categorised outcomes such as PDAI-defined remission (at Week 14 and 34), partial mPDAI-defined response (at Week 14 and 34), and IBDQ remission (at Week 34 only) in the VEDO + SOC group compared to the PBO + SOC group. Statistically significant changes were also observed for outcomes based on raw scores or raw scores such as change from baseline in mPDAI total score (at Week 14 and 34), change from baseline in PDAI total score (at Week 14 only), change from baseline in PDAI endoscopic sub-score (at Week 14 only). The trial reported a hazard ratio for achieving PDAI remission by Week 34 of 3.95 times higher in the VEDO + SOC group than in the PBO + SOC group (95% CI: 1.7, 9.4). These results should be interpreted with caution given the validity issues of the mPDAI, PDAI and IBDQ instruments and the arbitrary and unvalidated definitions for clinical remission and response cut-off (paragraphs 3.2 and 6.15).
- 6.28 The economic model used the outcome of partial mPDAI-defined response to determine the proportion of patients in the 'response (without remission)' health state. This was defined solely as a decrease of ≥ 2 points from the baseline mPDAI total score (while mPDAI-defined clinical remission was defined as an mPDAI score of <5 and a reduction of ≥ 2 points in the baseline mPDAI total score). At Week 14 there were 29.4% more patients with partial mPDAI-defined response in the vedolizumab arm compared with the placebo arm (62.7% versus 33.3%, respectively with a treatment difference of 29.4% (95% CI: 8.0, 47.6).
- 6.29 No statistically significant improvements were reported for change from baseline in PDAI total score (at Week 34 only), change from baseline in PDAI clinical (Week 14 and 34), endoscopic (Week 34) and histologic sub-score (Week 14 and 34), IBDQ remission (at Week 14 only), clinically meaningful IBDQ improvement and change from baseline in IBDQ score (at Week 14 and 34) and change in CGQL Fazio score (at Week 14 and 34). The PSCR argued both the clinical and HRQoL measures showed consistent numerical differences in favour of vedolizumab, including a statistically significant increase in IBDQ remission at Week 34 (with 43.1% of patients in the vedolizumab group identified as achieving IBDQ remission compared to 19.6% in the placebo group at Week 34). However, the ESC considered the IBDQ scale was of uncertain applicability to a post-operative population.
- 6.30 Across the three PDAI sub-scores, only the PDAI endoscopic sub-score at Week 14 showed a statistically significant difference from baseline compared to PBO + SOC. This difference decreased and was no longer significant at Week 34. None of the other sub-scores (clinical or histologic) indicated statistically significant differences at Week 14 and Week 34. The evaluation and ESC considered that the overall mPDAI and PDAI total scores were driven by observed difference in the change from baseline in the PDAI endoscopic sub-score at Week 14.
- 6.31 Other results included reported changes of inflammatory markers including faecal calprotectin and C-reactive protein (CRP) at Week 14 and 34 from baseline. While faecal calprotectin reduction was comparable between groups, the proportion of

patients with faecal calprotectin of ≤ 250 $\mu\text{g/g}$ (indicative of disease remission)²⁰ was not reported. Additionally, it is unclear whether the patients with levels < 250 $\mu\text{g/g}$ at baseline were the same as those with low levels at Week 14 and 34. If these patients are the same, it would suggest that VEDO + SOC did not induce remission as assessed by faecal calprotectin levels.

- 6.32 Results of pre-specified subgroup analyses suggest that treatment benefit is driven by specific patient characteristics such as patients with recurrent, severe disease, prior anti-TNF exposure for UC or pouchitis, high inflammatory markers, or with treatment started post-colectomy. However, the ability to draw meaningful conclusions from these analyses are limited by small patient numbers.

Comparative harms

- 6.33 Table 7 presents the safety outcomes of the EARNEST trial.

²⁰ 'Faecal calprotectin in inflammatory bowel disease', <https://www.nps.org.au/bdmards/gastroenterology/resources/faecal-calprotectin-in-inflammatory-bowel-disease>, accessed 11 April 2024.

Table 7: Summary of key adverse events in the randomised trials, SAF

	VEDO + SOC (N=51), n (%)	PBO + SOC (N=51), n (%)
TEAEs	47 (92.2)	44 (86.3)
Mild	15 (29.4)	11 (21.6)
Moderate	29 (56.9)	28 (54.9)
Severe	3 (5.9)	5 (9.8)
Related	12 (23.5)	11 (21.6)
Not related	35 (68.6)	33 (64.7)
Leading to study drug discontinuation	1 (2.0)	5 (9.8)
Related TEAEs	12 (23.5)	11 (21.6)
Mild	8 (15.7)	6 (11.8)
Moderate	4 (7.8)	3 (5.9)
Severe	0	2 (3.9)
Serious TEAEs	3 (5.9)	4 (7.8)
Related	0	1 (2.0)
Not related	3 (5.9)	3 (5.9)
Leading to study drug discontinuation	0	0
Summary of most frequently reported TEAEs (≥5% patients in any treatment group of any grade)		
Pouchitis ^a	24 (47.1)	20 (39.2)
Arthralgia	7 (13.7)	9 (17.6)
Headache	10 (19.6)	3 (5.9)
Nasopharyngitis	6 (11.8)	6 (11.8)
Nausea	5 (9.8)	5 (9.8)
Abdominal pain	4 (7.8)	3 (5.9)
Back pain	2 (3.9)	5 (9.8)
Frequent bowel movements	4 (7.8)	2 (3.9)
Upper respiratory tract infection	5 (9.8)	1 (2.0)
Gastroenteritis	2 (3.9)	3 (5.9)
Influenza	4 (7.8)	1 (2.0)
Dyspnea	0 (0)	3 (5.9)
Summary of drug-related TEAEs (≥2.0% patients in any treatment group of any grade)		
Patients with any drug-related TEAE	12 (23.5)	11 (21.6)
Infections and infestations	8 (15.7)	4 (7.8)
Nasopharyngitis	3 (5.9)	1 (2.0)
Upper respiratory tract infection	2 (3.9)	0
Gastrointestinal disorders	1 (2.0)	2 (3.9)
Pouchitis	1 (2.0)	2 (3.9)
Musculoskeletal and connective tissue disorders	0	3 (5.9)
Arthralgia	0	2 (3.9)
AESIs	5 (9.8)	7 (13.7)
Deaths	0	0

Source: Table 40, p65; Table 41Table 42, p69 of the submission.

Abbreviations: AESI, adverse events of special interest; PBO, placebo; SAF, safety analysis set; SOC, standard of care; TEAE, treatment-emergent adverse event; VEDO, vedolizumab.

^a Reported as related to a flare or worsening of pouchitis

6.34 Pouchitis as related to a flare or worsening of pouchitis was the most frequently reported TEAE and was more common in the VEDO + SOC group (47.1%) compared to the PBO + SOC group (39.2%). Adverse events of special interests (AESIs) were observed in 9.8% of patients in the VEDO + SOC group and 13.7% of patients in the PBO + SOC group. There were no deaths reported in the trial. Given that treatment with vedolizumab was expected to treat chronic pouchitis, the evaluation and ESC

considered the increased incidence of pouchitis flare or worsening in the VEDO + SOC group raises concerns.

6.35 Table 8 summarises the TEAEs and serious TEAEs related to flare.

Table 8: TEAEs and serious TEAEs related to a flare, SAF

	VEDO + SOC (N=51)		PBO + SOC (N=51)	
	n (%)	# Events	n (%)	# Events
TEAEs related to a flare^a	29 (56.9)	51	24 (47.1)	32
Mild	13 (25.5)	22	4 (7.8)	7
Moderate	14 (27.5)	27	18 (35.3)	23
Severe	2 (3.9)	2	2 (3.9)	2
Related	1 (2.0)	1	3 (5.9)	3
Not related	28 (54.9)	50	21 (41.2)	29
Leading to study drug discontinuation	1 (2.0)	1	2 (3.9)	2
Serious TEAEs related to a flare	2 (3.9)	2	1 (2.0)	1
Related	0 (0)	0	1 (2.0)	1
Not related	2 (3.9)	2	0 (0)	0
Leading to study drug discontinuation	0 (0)	0	0 (0)	0
Deaths	0 (0)	0	0 (0)	0

Source: Table 43 of the submission

Abbreviations: PBO, placebo; SAF, safety analysis set; SOC, standard-of-care; TEAE, treatment-emergent adverse event; VEDO, vedolizumab.

^a TEAEs related to a flare were pre-specified in study protocol but no formal definition provided.

6.36 TEAEs related to a flare was more common in the VEDO + SOC group (56.9%) compared to the PBO + SOC group (47.1%). There were two (3.9%) serious TEAEs related flare in the VEDO + SOC group and one (2.0%) in the PBO + SOC group. The greater use of concomitant antibiotics in the VEDO + SOC group compared to the PBO + SOC group was likely to treat flares.

Benefits/harms

6.37 On the basis of direct evidence presented by the submission, for every 100 patients treated with VEDO + SOC in comparison with PBO + SOC:

- Approximately 22 additional patients will achieve mPDAI-defined remission at 14 weeks (Table 5).
- Approximately 8 additional patients would experience a pouchitis flare or worsening of pouchitis (Table 7).

Clinical claim

6.38 The submission described VEDO + SOC as superior in terms of effectiveness compared with PBO + SOC. The evaluation considered the claim was not adequately supported because:

- There is a high overall risk of bias arising from attrition bias due to substantial treatment discontinuations and protocol deviations. This in turn has an impact on

the amount of missing data that requires imputation. The LOCF approach applied likely favours vedolizumab.

- The definitions for remission and response were based on mPDAI and PDAI instruments that lack validation and relied on arbitrary definitions for clinical remission cut-off.
 - The primary outcome (mPDAI-defined remission) at Week 14 did not achieve a 25 percentage point difference in the remission rate, the difference used for the trial sample size calculation. Although a statistically significant treatment difference of 21.6% (95% CI: 4.9, 37.5) was reported at Week 14, this was likely driven by the endoscopic sub-score (paragraph 6.30). The observed treatment difference decreased to 17.6% (95% CI: 0.3, 35.1) at Week 34. It was unclear if this is a clinically meaningful difference given there is no established MCID, and in the context of higher rates of flares and more concomitant antibiotic use reported in the VEDO + SOC group compared with the PBO + SOC group.
 - Apart from the statistically significant difference in the PDAI endoscopic sub-score at Week 14, most other secondary outcome measures failed to show statistically significant differences at Week 14 and 34.
 - No clinical data were presented to support continued treatment beyond six doses (30 weeks) or for re-treatment (after a break or following non-response with vedolizumab). The PSCR acknowledged the lack of data beyond 34 weeks in chronic pouchitis, however contended the available long-term evidence and post-marketing for vedolizumab in ulcerative colitis (and other conditions) demonstrates the efficacy and safety of vedolizumab over the longer term. The ESC considered the longer-term efficacy of vedolizumab for this condition is unclear, and considered this was a particular issue given there would likely be a proportion of patients who would continue vedolizumab long-term (even with more objective response assessment criteria in the restriction).
 - The high proportion of concomitant antibiotic use to manage the higher incidence of flares in the VEDO + SOC group compared to the PBO + SOC group could confound and overestimate the observed treatment effect at Weeks 14 and 34.
- 6.39 The ESC considered the claim of superior comparative effectiveness versus SoC to be uncertain. The ESC considered the trial results were difficult to interpret given the issues identified in the paragraph above, and considered the treatment effect reported in the trial appeared modest and was associated with wide confidence intervals (treatment difference in mPDAI remission at Week 14: 21.6% (95% CI: 4.9, 37.5)).
- 6.40 The submission described VEDO + SOC as non-inferior in terms of safety compared to PBO + SOC. The evaluation considered this claim was adequately supported. The ESC considered that whilst the definition of pouchitis events as safety events was not well

justified, the claim of non-inferior comparative safety was, on balance, likely to be reasonable.

- 6.41 The PBAC considered that the claim of superior comparative effectiveness versus SOC alone was reasonable, though the magnitude of benefit was uncertain and likely modest.
- 6.42 The PBAC considered that the claim of non-inferior comparative safety versus SOC was reasonable.

Economic analysis

- 6.43 The submission presented a stepped economic evaluation of vedolizumab + SOC compared to SOC, including cost-effectiveness and cost-utility analyses based on the results from the EARNEST trial. Steps 1 and 2 of the stepped economic evaluation were trial-based analyses and Steps 3 and 4 were modelled.
- 6.44 A summary of the key components of the economic evaluation is presented in Table 9.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	VEDO + SOC vs SOC
Time horizon	10.4 years in the model base case versus 34 weeks in trial (EARNEST)
Outcomes	Trial-based economic analysis: remission, response and quality-adjusted life years (QALYs); Modelled evaluation: QALYs
Methods used to generate results	A Markov model was used to estimate the costs and outcomes over the proposed time horizon.
Health states	Five: Remission; Response (w/o remission); No response; Pouch Failure; Death The response-based health states were split by treatment to allow for the incorporation of treatment discontinuation, thus resulting in a total of eight health states. Treatment discontinuation (other than the proposed PBS continuing criteria) was not applied in the base case.
Cycle length	Trial-period: Cycle 1 = 14 weeks; Cycle 2 = 24 weeks. Post-trial period: 24 weeks cycles Cycle lengths were varied to align with timing of outcomes and dosing schedule of vedolizumab. The timing of the Week 34 outcome was applied at Week 38 in the model because of the proposed cycle length. The submission claimed that differences in remission and response rates at Weeks 34 and 38 were marginal.
Transition probabilities	Transition probabilities for the response-based health states were largely informed by the observed data for remission (mPDAI-defined remission) and response (mPDAI-defined response) at Weeks 14 and 34 from the EARNEST trial and assumptions made for the proportion of patients transitioning between health states. Pouch failure transitions were informed by Alsafi (2022). Background mortality was informed by the ABS lifetables.
Extrapolation method	Transition probabilities estimated for the period between Weeks 14 and 38 were applied to the remaining time horizon. The submission assumed that the treatment effect observed at the end of Week 34 is constant over time and would carry across the 10-year time horizon. The submission also assumed that the patients would remain on vedolizumab as long as they were in the Remission health state and assumed a 100% compliance despite the inferior safety claims.

Component	Summary
	95% of QALYs (and 96% of costs) occur in the extrapolated period.
Health related quality of life	<p>Utilities (EQ-5D) estimated using the IBDQ scores reported from the EARNEST trial were used to inform the response-based health states. The same utility values were applied for both the intervention and comparator arms. Remission – 0.784; Response (w/o remission) – 0.754; No response – 0.672.</p> <p>Utility for pouch failure (0.550) was based on the post-surgery complications health state from Tsai (2008).</p> <p>Sensitivity analyses were based on published results (Arsenau (2006), Tsai (2008) and Park (2012)).</p>
Costs	<p>The model included: Treatment costs (vedolizumab only), health states costs, pouch failure event cost and costs for managing treatment-emergent adverse events.</p> <p>For base case, the submission used the resource use reported for the post-surgery remission and post-surgery complication health states from Tsai (2008) to inform the Remission and No response health states costs in the model. Tsai (2008) is a cost-effectiveness study which reported resource use from six UK gastroenterologist for health states relating to moderate-to-severe ulcerative colitis.</p> <p>For the Response (without remission) health state, the submission assumed this cost be the average of the Remission and No response health states.</p>

Source: Table 46 of the submission

Abbreviations: ABS, Australia Bureau of Statistics; PBS, Pharmaceutical Benefit Scheme; EQ-5D, EuroQol 5 Dimension; IBDQ, Inflammatory Bowel Disease Questionnaire; mPDAI, modified Pouchitis Disease Activity Index; QALY, quality-adjusted life years; SOC, standard-of-care; UK, United Kingdom; VEDO, vedolizumab; w/o, without

- 6.45 The submission stated that the economic model consisted of five mutually exclusive health states: Remission; Response (without remission); No response; Pouch Failure and Death. However, three of the health states (Remission, Response (without remission), No response) were further split by treatment (on VEDO and on SOC) resulting in a total of eight health states. The ESC considered that given the VEDO arm was divided into VEDO and SOC treatment states, the model could be described as having 11 health states. Patients begin the model in the 'No response' health state. At Week 14, patients in the vedolizumab treatment group could transition into the 'VEDO: Remission' health state based on the primary outcome of the EARNEST trial (mPDAI-defined remission at Week 14). All other patients would transition into the 'SOC: Response (without remission)' or 'SOC: No response' health states based on calculated patient proportions from the secondary outcome (partial mPDAI-defined response). 'Response (without remission)' was based on partial mPDAI-defined response. Across both treatment arms, patients in the SOC health states can remain in the same health state or transition into any SOC health states. Patients in the 'Remission', 'Response (without remission)', 'No response' health states are susceptible to pouch failure and could transition to the 'Pouch failure health state. Dead is an absorbing health state for deaths from any cause.
- 6.46 The evaluation and the ESC considered that applicability issues with respect to the clinical evidence included:

- It is unknown whether the mPDAI-defined remission and response criteria used in the clinical trial would be applied in the same way in the PBS clinical setting (e.g. given there is subjectivity around some of the criteria in the mPDAI scale).
 - Patients in the EARNEST trial could be treated with anti-TNF biologics (adalimumab and infliximab) as prior, concomitant and/or subsequent medications. In the Australian setting, these biologics are not currently PBS-listed for the treatment of pouchitis and patients may be biologic naïve. As no other biologics are TGA registered or PBS subsidised for chronic pouchitis, the potential confounding effect and impact on the reliability of the effect estimate of vedolizumab to the economic model is unknown. The ESC considered the model could have included the cost of other biologic treatments (especially anti-TNF biologics) given these may be used off-label in Australian clinical practice (e.g. supplied through public hospitals).
 - The proposed PBS continuing restriction requires that patients demonstrate adequate or sustained response at Week 14 to continue treatment. This does not align with the study design which allowed patients to continue treatment up to Week 30.
- 6.47 The submission extrapolated the treatment effect from Week 34 over a 10.4 year time horizon. This is long relative to the EARNEST trial duration of 34 weeks. The ESC considered a shorter time horizon may have been more appropriate given the lack of trial data beyond 34 weeks; however acknowledged that given the nature of chronic pouchitis, a 10 year time horizon may be reasonable for an economic model for this condition if longer-term data were available.
- 6.48 The trial results observed from Week 14 to 34 were assumed to continue repeatedly, each model cycle, throughout the 10.4 year time horizon. For example, in the trial, 14 of the 16 (87.5%) patients in the vedolizumab arm who were in remission at Week 14 remained in remission at Week 34. Thus, this proportion (converted to a transition probability and to reflect the 24-week cycle length) was applied to VEDO+SOC patients in remission every model cycle for the remainder of the model time horizon. Similarly, in the placebo arm of the trial, 3 of the 5 (60%) patients who were in remission at Week 14 remained in remission at Week 34. Thus, this proportion (converted to a transition probability) was applied to SOC patients in remission every model cycle for the remainder of the model time horizon. This transition probability was also applied to the patients in the VEDO+SOC group who had been assumed to cease vedolizumab due to loss of mPDAI-remission.
- 6.49 The PSCR argued that in the absence of longer-term data, this was the only evidence-based approach to the extrapolation, and the issues identified reflected the clinical data limitations, rather than methodological issues with the model. The PSCR represented sensitivity analyses in which alternative extrapolation assumptions were applied with a constant proportion of patients assumed to lose remission per cycle (proportions of 2.5%, 5% or 10% were applied, although no justification for these

percentages was provided), as outlined in Table 12. The PSCR argued that the ICER did not increase beyond \$45,000 to < \$55,000 per QALY for the alternative scenarios presented. However, the ESC considered the sensitivity analyses applied in the PSCR were blunt (e.g. constant proportions continued to be applied each cycle). Overall, the ESC considered the assumption that the 34-week trial results would be constant over 10 years was highly optimistic.

- 6.50 Further, the ESC noted that some of the transition probabilities applied in the model relied heavily on outcomes from a very small number of patients in the trial (as outlined in paragraph 6.48) plus assumptions (as outlined in paragraph 6.52) and also reflected the limitations of the clinical data and the poorly validated nature of the indexes used in the trial (as seen in the Markov traces, refer to paragraph 6.60).
- 6.51 In the model, the vedolizumab treatment group was split into two further treatment arms (VEDO and SOC), that is when patients in the vedolizumab group ceased vedolizumab (due to not meeting the mPDAI-remission criteria required for ongoing treatment in the model) the transition probabilities for the SOC were applied, which was associated with a large placebo effect.
- 6.52 For transitions between Weeks 14 and 38, data on an exploratory outcome, sustained clinical (mPDAI) remission, were used to inform the transition probabilities for remaining in the Remission health state. Concerns relating to this exploratory outcome were described in paragraph 6.22. Other transitions between health states were based on limited data on the number of patients achieving the remission or response outcome at Week 34 and assumptions made. These assumptions included:
- For the VEDO + SOC arm, among those who did not achieve sustained remission at Week 38, patients would be split equally (50%/50%) between the Response (without remission) and No response health states. However, for the PBO + SOC arm, all patients who did not achieve sustained remission were assumed to transition into the No response health state. This assumption favoured vedolizumab.
 - In the EARNEST trial, at Week 34, there were 4 additional patients in the VEDO + SOC arm that achieved remission who did not demonstrate remission at Week 14. The model assumed that half of these patients were previously from the Response (without remission) state and half were from the No response health state. Given the proposed PBS continuing criteria, patients who did not achieve remission at Week 14 would not have been allowed to continue treatment, thus these patients should have been excluded.
 - The timing of the second cycle of the model (Week 38) did not align with the end of the trial period (Week 34) when outcomes were measured. The submission stated that differences in remission and response rates would be marginal and Week 38 would be considered a more appropriate time point reflecting the proposed PBS continuing criteria. This assumption could favour vedolizumab because the treatment effect attenuates over time. The EARNEST trial treatment

difference for the mPDAI remission outcome between the VEDO + SOC and PBO + SOC groups reduced from 22% (95% CI: 5, 38) at Week 14 to 18% (95% CI: 0.3, 35) at Week 34.

- 6.53 The ESC noted that the model base case assumed that patients would only continue vedolizumab if they experienced mPDAI-defined remission. This was inconsistent with the requested restriction, which would allow vedolizumab to be continued based on a clinical assessment of response (no criteria or definition of response was specified in the proposed restriction). Therefore, the ESC considered it would be more appropriate for the model to assume patients in the 'Response (without remission)' health state (which was based on the outcome of partial mPDAI-defined response, paragraph 6.28) would also continue treatment with vedolizumab to better align with the proposed restriction, and noted this change increased the ICER by 90% to \$55,000 to < \$75,000 per QALY. With this assumption applied, the model estimated an average of 13.3 vedolizumab doses per patient (versus 9.2 in the base case).
- 6.54 Further, the submission assumed 100% compliance with vedolizumab i.e. all patients in the VEDO+SOC group were assumed to receive three doses of vedolizumab in the first model cycle, then all patients in VEDO+SOC group who remained in the 'remission' health state were assumed to continue vedolizumab treatment with 100% compliance. This was inconsistent with the trial which reported that 70.6% of patients in the VEDO + SOC group in the EARNEST trial completed all six doses (i.e. 29.4% of patients in the VEDO + SOC group discontinued the trial before the 30-week treatment period), with some discontinuations due to reasons other than lack of efficacy (e.g. due to adverse events and voluntary withdrawal). The ESC considered the assumption of 100% compliance with vedolizumab was conservative (potentially underestimated vedolizumab treatment costs).
- 6.55 The submission estimated utilities for the response-based health states by converting IBDQ scores to EQ-5D utility values using a published mapping algorithm (Buxton et al. 2007). The submission applied several steps for this translation. IBDQ scores for the proposed health states were reported in the trial CSR. It is unclear why the submission did not apply the observed IBDQ scores, and instead estimated the health state values by adding the change from baseline scores to averaged baseline scores. The extra steps applied another level of uncertainty the utility value estimates. The resulting utility estimates are higher than other published estimates and are an important driver of the ICER.
- 6.56 The base case health state costs applied in the model were from a UK study (Tsai, 2008) for the post-surgery remission and complications for moderate-to-severe UC. These costs were lower than those reported in two US-based studies (Holubar (2012) and Barnes (2022)) which were more recent and specific to the proposed population (IPAA with pouchitis). No Australian costs were available, and the model was sensitive to this parameter.
- 6.57 A summary of the key drivers of the model is presented in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case: \$11/QALY gained		
Outcome applied to demonstrate remission or response	The submission applied mPDAI-defined remission at Weeks 14 and 34 from the EARNEST trial to inform on the proportion of patients that would be eligible to continue treatment with vedolizumab, while the PBS restriction did not define response (paragraph 3.7).	High, favours vedolizumab. The use of the mPDAI-defined response outcome from 14 weeks (an example of a different response criteria) increased the ICER to \$21/QALY gained (+10%).		
Health state costs	Costs applied in the model are presented in the table below.			
	Health state	Base case	Applied in sensitivity analyses	
		Tsai (2008)	Holubar (2012)	Barnes (2022)
	Remission	\$2,753	\$5,818	\$20,336
	Response (w/o remission)	\$7,415	\$11,154	\$26,216
	No response	\$12,078	\$16,489	\$32,096
Post-pouch failure	\$12,078	\$16,489	\$32,096	
Utilities	Base case utility values estimated from IBDQ scores from the EARNEST trial. Remission: 0.784; Response (w/o remission): 0.754; No response: 0.672; Pouch failure: 0.550 (from Tsai, 2008).			
Extrapolation of treatment effect	The treatment effect from Week 34 observed in the EARNEST trial for mPDAI-defined remission was extrapolated over the proposed time horizon and assumed to be constant over time.			

Source: Compiled during the evaluation

Abbreviations: IBDQ; Inflammatory Bowel Disease Questionnaire; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; mPDAI, modified Pouchitis Disease Activity Index.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$55,000 to < \$75,000

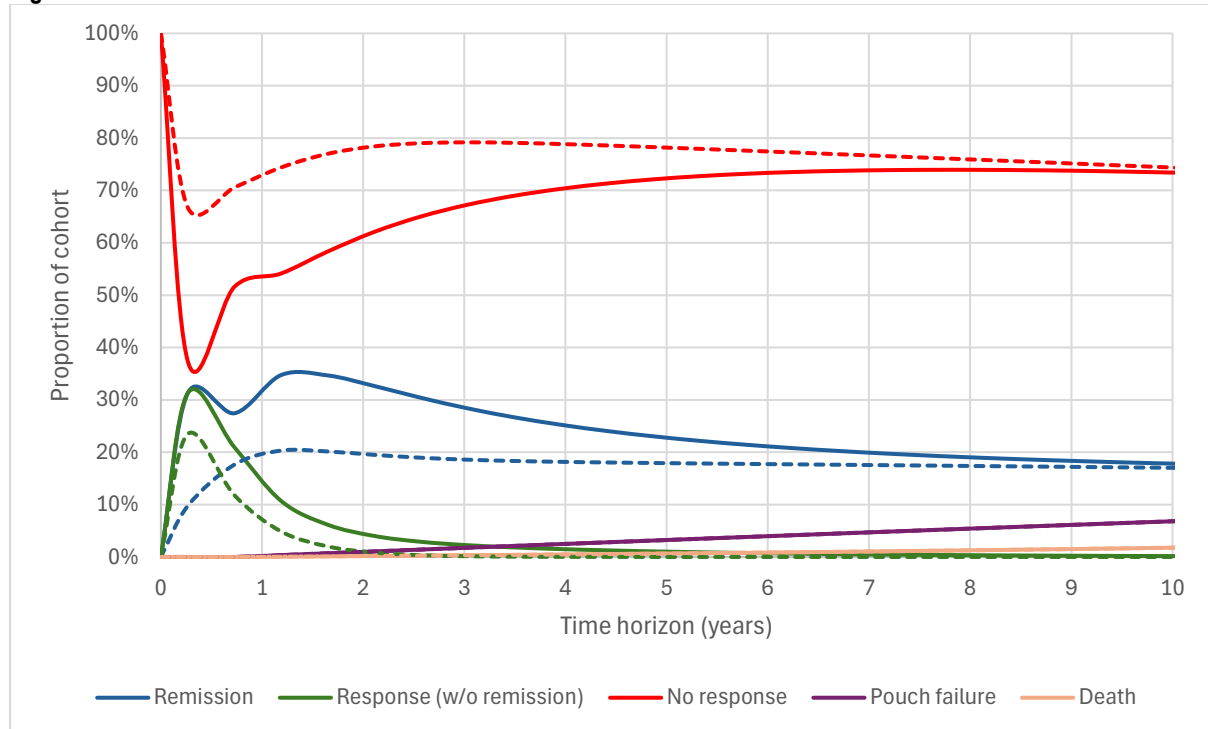
³ \$75,000 to < \$95,000

⁴ \$15,000 to < \$25,000

\$45,000 to < \$55,000

6.58 Figure 1 shows the Markov traces to illustrate the proportion of patients in each of the health states over time.

Figure 1: Markov traces – Solid lines for VEDO + SOC and dashed lines for SOC



Source: Generated from data sourced from tab 'Model' of the PBAC_Economicmodel_VEDO of the submission
 Abbreviations: SOC, standard of care; VEDO, vedolizumab; w/o, without.

6.59 The Markov trace showed that, in the vedolizumab arm, more patients were in the remission health state at 1.5 years than at 14 weeks. The Markov trace for the Remission health state of the VEDO + SOC arm suggests that up to 35% of patients would achieve remission (23% on VEDO + 11% on SOC) and this is higher compared to data from the EARNEST trial, which reported that 27% of patients in the VEDO + SOC arm achieved sustained remission. Patients on the VEDO + SOC arm in the EARNEST trial were on SOC concurrently therefore assuming a separate (SOC) group of patients in addition to the VEDO within the VEDO + SOC arm implies an additive effect that will overestimate the combined treatment effect. This is likely related to the structure of the model which splits health states of the vedolizumab treatment group into two further treatment arms (VEDO and SOC).

6.60 The PSCR argued that in the absence of longer-term data, the model used the best evidence-based approach to the extrapolation, and stated the higher proportion of patients in remission at 1.5 years compared to 14 weeks “was an unfortunate artefact of the repeated application of the week 14 to 34 transition probability matrix, which includes a placebo effect that is then applied to the vedolizumab non-responders”. The ESC considered these results in the model trace were not clinically plausible and

noted that many of the patients in the vedolizumab group who are in the remission health state at 1.5 years are not accruing vedolizumab costs (as they are assumed to have moved to SOC treatment after they fail to achieve remission with vedolizumab). Further, the ESC noted there is a ‘long tail’ to the Markov traces for the remission health states for both groups, though after five years fewer than 5.2% of patients in the vedolizumab group are accruing vedolizumab costs.

6.61 Table 11 shows the results of the stepped economic evaluation.

Table 11: Results of the stepped economic evaluation

Step and component	Proposed medicine	Comparator	Increment
Step 1: Trial-based analysis			
Cost: Treatment cost (drug and administration)			
Outcomes: Remission and response			
Time horizon: 34 weeks ^a			
No discounting applied			
Costs	\$█	\$0	\$█
Outcome: Remission ^b	27.5%	5.9%	21.6%
Incremental cost/extra remission gained			1
Step 2: Trial-based analysis			
Cost: As per Step 1			
Outcomes: Quality-adjusted life years (QALYs)			
Time horizon: 34 weeks ^a			
No discounting applied			
Costs	\$█	\$0	\$█
Outcome: QALYs	0.457	0.424	0.032 ^d
Incremental cost/extra QALY gained			2
Step 3: Modelled evaluation			
Costs: As per Step 1			
Outcomes: Quality-adjusted life years (QALYs)			
Time horizon: 10 years			
Discounting applied at 5% per annum			
Costs	\$█	\$0	\$█
QALY	5.850	5.767	0.083
Incremental cost/extra QALY gained			3
Step 4: Modelled evaluation			
Costs: As per Step 1 plus health state, safety and pouch failure costs			
Outcomes: Quality-adjusted life years (QALYs)			
Time horizon: 10 years			
Discounting applied at 5% per annum			
Costs	\$█	\$88,324	\$█
QALY	5.850	5.767	0.083
Incremental cost/extra QALY gained			4

Source: Table 82 of the submission and corrected during the evaluation to use trial data at Step 1 and 2.

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

^a Based on timing of the outcome as per trial

^b Based on sustained remission (mPDAI) outcome data at Week 34 from the EARNEST trial (Table 2.5.1)

^c Calculated based on public/private weighted DPMQ + administration cost for 6 doses at a compliance rate of 70.6% as per EARNEST trial

^d Calculated based on observed baseline and Week 34 IBDQ scores converted to EQ-5D utility values as reported for each of the treatment arms in EARNEST. Should be interpreted with caution as these were based on small numbers (n=35 for VEDO + SOC and n=30 for PBO + SOC) and the difference between the two arms were not statistically significant.

The redacted values correspond to the following ranges:

1 \$15,000 to < \$25,000

2 \$135,000 to < \$155,000

3 \$95,000 to < \$115,000

4 \$35,000 to < \$45,000

- 6.62 Given the key concerns with the extrapolation, the evaluation considered the trial-based analyses (Steps 1 and 2) of the cost per remission gained may provide a more reliable basis for decision making. However, the evaluation considered these results should also be interpreted with caution as the clinical evidence and clinical significance of remission as defined in the trial was uncertain. Further, these analyses were based on a maximum vedolizumab treatment duration of 34 weeks, while some patients will continue for longer. The ESC noted that the incremental cost per responder approach can be more difficult to justify and value for a chronic therapy. Further, the ESC noted the value of a remission was unclear given the issues with the mPDAI scale.
- 6.63 The ESC noted that the vial price proposed in the submission was the same as the current vial price in ulcerative colitis (noting a revised price was proposed in the pre-PBAC response, per paragraph 3.1). In the context of the small financial spend, the ESC considered this may provide a frame of reference for interpreting the cost-effectiveness results.
- 6.64 The results of key univariate sensitivity analyses are summarised in Table 12.

Table 12: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER (\$/QALY)	Change to ICER
Base case		0.083	█ ¹	-
Discount rate (base case 5% costs and outcomes)				
• 0% costs and outcomes		0.085	█ ¹	-█%
• 3.5% costs and outcomes		0.092	█ ²	-█%
Time horizon (base case 10 years)				
• 3 years		0.056	█ ³	█%
• 5 years		0.073	█ ¹	█%
• 15 years		0.084	█ ¹	-█%
• 20 years		0.084	█ ¹	-█%
Continuing criteria (base case required to demonstrate remission at Week 14) ^a				
• Response from 14 weeks ^a		0.091	█ ³	█%
• Remission from 38 weeks ^a		0.100	█ ⁴	█%
• Response from 38 weeks ^a		0.101	█ ⁵	█%
Assumptions applied for extrapolations (base case data from EARNEST extrapolated over time horizon ^c)				
• On VEDO: 2.5% lose remission (to SOC response) per cycle On SOC: 5% lose remission (to response) and response (to no response) per cycle		0.137	█ ¹	█%
• On VEDO: 5% lose remission per cycle On SOC: 10% lose remission (to response) and response (to no response) per cycle		0.124	█ ¹	-█%
• On VEDO: 5% lose remission per cycle On SOC: 5% lose remission (to response) and response (to no response) per cycle		0.121	█ ⁴	█%
• On VEDO: 10% lose remission per cycle On SOC: 10% lose remission (to response) and response (to no response) per cycle		0.096	█ ⁴	█%
Utility values (base case estimated based on changes at Week 34)				
• Week 14 trial data – treatment arm specific		0.059	█ ⁴	█%
• Week 34 trial data – treatment arm specific		0.077	█ ¹	█%
• Week 14 trial data – pooled		0.075	█ ¹	█%
• Arsenau 2006		0.270	█ ⁶	-█%
• Tsai 2008		0.042	█ ⁵	█%
• Park 2012		0.208	█ ⁷	-█%
Health state costs (base case ^b)				
• Halved (x50%)		0.083	█ ⁵	█%
• Doubled (x200%)	-	0.083	Dominant	-
• Holubar 2012 ^b		0.083	█ ²	-█%
• Barnes 2022 ^b		0.083	█ ⁷	-█%

Source: Tables 87, 88, 89 and 90 of the submission and added to during the evaluation

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SOC, standard-of-care; VEDO, vedolizumab

^a Remission = applying mPDAl remission outcome data from the EARNEST trial and response = applying mPDAl response outcome data

^b As described in Table 3.6.3

^c; i.e. assumes treatment effect carried and remains constant over time horizon

The redacted values correspond to the following ranges

1 \$35,000 to < \$45,000

2 \$25,000 to < \$35,000

3 \$55,000 to < \$75,000

4 \$45,000 to < \$55,000

5 \$75,000 to < \$95,000

6 \$5,000 to < \$15,000

7 \$15,000 to < \$25,000

6.65 The ESC considered the economic model presented may not be informative for decision-making. In particular, the ESC considered the key issues with the economic model were that it:

- was based on the EARNEST trial results and thus the model inherits the highly uncertain treatment effect from the trial. Further, the model relied on measurement instruments that are not well validated. The ESC acknowledged, however, that it was unlikely that further evidence will be forthcoming in the foreseeable future;
- assumed the trial results observed from Week 14 to 34 continue repeatedly, each model cycle, throughout the 10.4 year time horizon. The ESC considered a shorter time horizon may be more appropriate given the lack of data beyond 34 weeks and noted that a 5 year time horizon increased the ICER by 14% (from \$35,000 to < \$45,000 per QALY to \$35,000 to < \$45,000 per QALY).
- assumed patients would only continue vedolizumab if they experienced mPDAI-defined remission, which was inconsistent with the requested restriction which allowed vedolizumab to be continued in patients experiencing an “adequate response” (no criteria or definition of response was specified in the proposed restriction). The ESC considered that, unless a more objective response assessment was included in the continuing restriction, the model should assume patients in the ‘Response (without remission)’ health state (which was based on the outcome of partial mPDAI-defined response) are also allowed to continue vedolizumab. This increased the ICER by 90% to \$55,000 to < \$75,000 per QALY.
- The vedolizumab group was split into two further treatment arms (VEDO and SOC), i.e. when patients in the vedolizumab group cease treatment with vedolizumab (due to not meeting the mPDAI-remission criteria) the transition probabilities for the SOC group are applied, which is associated with a large placebo effect (as shown in the Markov trace). The ESC advised a simpler model that did not apply a placebo effect to the vedolizumab non-responders would likely be more informative.

6.66 The pre-PBAC response proposed a revised price (paragraph 3.1), which reduced the base case ICER from \$35,000 to < \$45,000 per QALY to \$25,000 to < \$35,000 per QALY.

6.67 As shown in Table 13, the pre-PBAC response also presented multivariate sensitivity analyses that included the revised price and addressed some of the key issues raised by the ESC including the: lack of long-term data (addressed by applying a shorter time horizon of five years); continuation criteria applied in the model (based on ‘partial mPDAI-defined response’ rather than ‘mPDAI-defined remission’); and extrapolation method (by assuming either no transitions beyond the trial period or that 5% of patients worsen by one health state per cycle).

Table 13: Sensitivity analyses presented in the pre-PBAC response

Analyses		Incremental cost	Incremental QALY	ICER (\$/QALY)	Change to ICER
Base case in submission			0.083	█ ¹	-
Apply revised price (\$951.33)			0.083	█ ²	-█%
Apply response-based continuation criteria			0.091	█ ³	-█%
Scenario analyses					
Time horizon	Extrapolation method				
5	Repeat trial data		0.077	█ ³	-█%
10	Repeat trial data		0.091	█ ³	-█%
5	No transitions beyond trial period		0.162	█ ⁴	-█%
10	No transitions beyond trial period		0.097	█ ⁴	-█%
5	5% of patients worsen by one health state per cycle		0.089	█ ⁴	-█%
10	5% of patients worsen by one health state per cycle		0.132	█ ⁴	-█%

Source: Table 1, pre-PBAC response

The redacted values correspond to the following ranges

1 \$35,000 to < \$45,000

2 \$25,000 to < \$35,000

3 \$55,000 to < \$75,000

4 \$95,000 to < \$115,000

6.68 The pre-PBAC response stated the ICERs from the multivariate sensitivity analyses presented ranged from \$55,000 to < \$75,000 to \$95,000 to < \$115,000 per QALY.

Drug cost/patient

Table 14: Drug cost per patient for vedolizumab, as proposed in the submission

	Vedolizumab Trial dose and duration	Vedolizumab Model	Vedolizumab Financial estimates
Dosing frequency	300 mg IV at Weeks 0, 2, 6 and at 8-week intervals thereafter	Same as in trial	Same as in trial
Duration of treatment	Up to six doses (Week 30)	Ongoing as long as patient remains in remission.	Ongoing as long as patient remains in remission.
Mean duration of exposure (days)	297 ^a	NR	NR
Compliance	70.6% ^b	100%	100%
Number of doses administered in the first (initiating) year (in responding patients)	NR	7.75 ^d	7.75 ^d
Cost/patient/year (initiating year)	\$█ ^c	\$█ ^d	\$█ ^d
Average number of doses over time horizon	NR	9.2 ^e	6.7 ^f
Cost/patient/year (averaged over proposed time horizon)	\$█ ^c	\$█ ^e	\$█ ^f

Source: Compiled during the evaluation

Abbreviations: NR, Not reported

^a Duration of exposure to vedolizumab IV is defined as date of last dose – date of first dose + 1 + 126 to account for 5*half-life of vedolizumab and duration of exposure to placebo is defined as date of last dose – date of first dose + 1.

^b Proportion of patients completing six doses

^c Calculated based on weighted DPMQ, 6 doses and compliance of 70.6%

^d Calculated based on recommended dose and compliance of 100%

^e Based on outputs from the model (undiscounted) over a 10-year time horizon

^f Calculated based on weighted DPMQ, 6.7 vials (7.75 in year 1 and 6.5 for subsequent years), compliance of 100% over a 6-year time horizon

- 6.69 The drug cost per patient for vedolizumab is presented in Table 14, based on the price proposed in the submission. A lower price (1% reduction) was proposed in the pre-PBAC response.
- 6.70 The average number of doses per patient was different between the economic model and the financial estimates.
- 6.71 The higher cost per patient per year in both the economic model and the financial estimates is due to the submission’s assumption that patients on vedolizumab would continue to remain on treatment as long as patient remained in remission and a 100% compliance.

Estimated PBS usage & financial implications

- 6.72 This submission was not considered by DUSC.
- 6.73 The submission used a mixed incidence-prevalence approach to estimate the financial implications associated with the proposed listing of vedolizumab.
- 6.74 The key inputs in the financial analysis are summarised in Table 15.

Table 15: Key inputs for financial estimates

Data	Value applied and source	Comment
Eligible population		
Number of proctocolectomies and IPAAAs for UC	179 applied each year based on AIHW data	This source is appropriate. The submission used the average number of procedures undertaken between 2018 and 2022 and assumed the estimates beyond 2022 remain constant. The evaluation considered this approach may be reasonable based on the 2018-2022 data, however, the submission also included data from 2013 in the financial model and a downward trend was observed from 2013 to 2022, with 248 procedures in 2013 and 159 procedures in 2022. While the evaluation considered that the number of proctocolectomies and IPAAAs may have been overestimated, the ESC considered the number of procedures may be gradually decreasing over time due to the availability of effective biologics for earlier stages of ulcerative colitis.
Patients with pouchitis from proctocolectomies and IPAAAs for UC	50% applied annually based on Nguyen et al. 2019, Yu et al. 2007	The evaluation considered this was reasonable, although slightly higher than the incidence of pouchitis reported in an Australian study (42.3%). ²¹

²¹ Lim MH, et al., (2021), 'Ileal Pouch-Anal Anastomosis for Ulcerative Colitis: An Australian Institution's Experience', Ann Coloproctol, 37(5):318-325. doi: 10.3393/ac.2020.08.26

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Data	Value applied and source	Comment
New patients with chronic pouchitis	20% applied annually based on Travis et al. 2023, Rabbenou & Chang 2021	Based on the annual rates applied in the submission (50% x 20%), this appeared to be slightly higher than the chronic pouchitis rate reported in an Australian study (8.7%). ²² This population appeared to be broader than the proposed patient population as it included all chronic pouchitis (rather than moderate and severe) while the proposed population was a subset that have had an inadequate response with or lost response to antibiotic therapy.
Prevalent pool (previous patients)	450 patients, based on assumption (25 years)	The evaluation considered this was highly uncertain. The prevalent pool was based on the estimated incident patients and applied over a 25-year period. The number of these procedures fluctuated over the last 25 years. This could underestimate or overestimate the prevalent pool.
Previous non-responding patients (previously exposed to vedolizumab)	0 in Year 1, increasing to 408 in Year 6, estimated based on uptake, response and discontinuation rates.	The submission described these patients as previous patients with prior failures who re-trial vedolizumab. These estimates imply that patients previously treated with vedolizumab will be eligible for re-treatment despite not responding to the previous course of vedolizumab treatment. The PBAC considered that patients who had previously failed vedolizumab for pouchitis should not be permitted to re-trial PBS-subsidised vedolizumab.
Treatment utilisation		
New patient's uptake rate	█% in Year 1, increasing to █% in Year 6, based on assumption.	The evaluation considered that the uptake rate may be an overestimate given the uncertainty in the superior effectiveness of vedolizumab, or on the other hand may be reasonable given that vedolizumab is the only biologic that is TGA approved for the treatment of chronic pouchitis. Overall, the ESC considered this uptake rate may be reasonable given vedolizumab was unlikely to be the first choice of biologic agent for all patients with pouchitis, particularly those who experienced prior treatment failure with vedolizumab for earlier stage UC (e.g. these patients may receive treatment with other biologics through public hospital programs, albeit outside the TGA-registered indications).
Prevalent patient's cumulative uptake rate	█% in Year 1, █% in Year 2, █% in Year 3 and █% in Years 4-6, based on assumption.	This assumption implies a large prevalent pool waiting to be treated with vedolizumab. This is uncertain considering the uncertainty in the superior effectiveness of vedolizumab and the inferior safety claim, and it may overestimate the financial estimates. The financial model is sensitive to this parameter.
Previous non-responding patient's uptake rate	█% in Years 1-2 and █% in Years 3-6, based on assumption.	As outlined above, the PBAC considered that patients who had previously failed vedolizumab for pouchitis should not be permitted to re-trial PBS-subsidised vedolizumab. Thus, the PBAC considered the uptake rate in previous non-responders should be 0%.

²² Lim MH, et al., (2021), 'Ileal Pouch-Anal Anastomosis for Ulcerative Colitis: An Australian Institution's Experience', Ann Coloproctol, 37(5):318-325. doi: 10.3393/ac.2020.08.26

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Data	Value applied and source	Comment
Response rate (for continuing patients within the year)	31.37% applied annually, based on primary endpoint of mPDAI-defined remission at Week 14 from EARNEST trial.	The evaluation and the ESC considered that 'response' was not objectively defined in the continuing PBS restriction, so higher rates of treatment continuation may be observed in PBS practice. The PBAC considered that it would be more appropriate for continuation to be based on the proportion of patients in the trial who experienced 'partial mPDAI-defined response' at Week 14 (62.7%), rather than 'mPDAI-defined remission'.
Discontinuation rate (for continuing patients within the first year and in subsequent years)	29.33% applied in the first year and 14.67% in subsequent years. Assumptions based on sustained mPDAI remission from EARNEST trial.	The evaluation considered these assumptions were uncertain. The discontinuation rate of 29.33% was estimated based on the proportion of patients in remission at Week 14 who maintained remission to Week 34 (14/16=87.5%) in the EARNEST trial with a 20-week maintenance of remission scaled up to 52 weeks. The submission also assumed that long-term discontinuation rate (after Year 1) to be half of the discontinuation of the first year (14.67%). The evaluation considered that continuation rates may be higher as the proposed PBS continuing restriction was subjective and did not rely on mPDAI-defined remission. The PBAC considered there was a lack of long-term data to inform the discontinuation rate beyond the trial period, but considered that it would be more appropriate for long-term continuation to be based on the proportion of patients in the trial who experienced 'partial mPDAI-defined response' at Week 34 (51.0%), per Table 6 (i.e. a discontinuation rate of 49% applied every 34 weeks, on-going).
Number treated	█ ¹ in Year 1, decreasing to █ ¹ in Year 6.	The evaluation considered that the number of treated patients may be overestimated because of the assumptions made relating to the incident, prevalent and previous non-responding populations, and the proposed uptake and discontinuation rates.
Scripts dispensed	█ ² in Year 1, decreasing to █ ² █ in Year 6. Product of each treated patient group by corresponding scripts use based on assumptions.	The submission applied 7.75 scripts (initiating year) and 6.5 scripts (subsequent years) for patients completing treatment for the whole year, calculated based on recommended dose. Patients were assumed to stop treatment halfway if discontinued; 5.38 scripts (initiating year) and 3.25 scripts (subsequent years) applied.
Costs		
Proposed medicine	\$█ – Effective AEMP	The pre-PBAC response proposed a revised effective AEMP of \$█.
MBS costs	\$84.35 (80%=\$67.48) MBS item number 116	The submission did not include the MBS costs related to IV administration in the financial estimates, but it was included in the economic model. This was added to the financial estimates during the evaluation.

Source: Compiled during the evaluation based on information source from Section 4.1, 4.2 and 4.3 of the submission.

Abbreviations: AEMP, approved ex-manufacturer price; AIHW, Australian Institute of Health and Welfare; DPMQ, dispensed price for maximum quantity; IPAA, proctocolectomy and ileal pouch anal anastomosis; IV, intravenous; MBS, Medicare Benefits Schedule; mPDAI, modified Pouchitis Disease Activity Index; PBS, Pharmaceutical Benefits Scheme; PI, product information; SPA, special pricing arrangements; TGA, Therapeutic Goods Administration; UC, ulcerative colitis.

The redacted values correspond to the following ranges

1 < 500

2 500 to < 5,000

6.75 The estimated use and financial implications for the PBS listing of vedolizumab are summarised in Table 16.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use – number of patients						
1 st year responders continuing till end of the year	1	1	1	1	1	1
1 st year responders discontinue by end of the year	1	1	1	1	1	1
15 Subsequent years – full year of treatment	1	1	1	1	1	1
Subsequent years – discontinue during the year	1	1	1	1	1	1
Vedolizumab non-responders	1	1	1	1	1	1
Total number of patients treated	1	1	1	1	1	1
Estimated extent of use – number of prescriptions						
Total number of scripts	2	2	2	2	2	2
Estimated financial implications of vedolizumab – estimated in the submission						
Cost to PBS/RPBS less copayments	3	3	3	3	3	3
Net financial implications – estimated in the submission						
Net cost to PBS/RPBS	3	3	3	3	3	3
Net cost to MBS (80%) ^a	3	3	3	3	3	3
Net cost to Australian Government health budget	3	3	3	3	3	3
Net financial implications – based on revised vial price in the pre-PBAC response						
Net cost to PBS/RPBS with revised vial price ^b	3	3	3	3	3	3

Source: Compiled and calculated during the evaluation, based on Table 105 and Table 106 submission and MBS online April 2024.

Abbreviations: MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

^a Based on 80% rebate fee for MBS item code 116 and estimated number of packs/scripts by the submission. The 80% benefit is in line with the User Manual for the Utilisation and Cost Model Workbook for PBAC Submissions (version 1.4, updated in June 2021.)

^b Based on the spreadsheet provided with the submission, with the revised AEMP applied.

Note: Discrepancies between the values presented in the submission and those calculated during the evaluation were due to the application of PBS/RPBS split and co-payments. Numbers may not add up due to rounding

The redacted values correspond to the following ranges

1 < 500

2 500 to < 5,000

3 \$0 to < \$10 million

6.76 The submission estimated the total cost to the PBS/RPBS of listing vedolizumab for this indication would be \$0 to < \$10 million in Year 1 and \$0 to < \$10 million in Year 6, and a total of \$0 to < \$10 million in the first 6 years of listing. With the revised vial price proposed in the pre-PBAC response, the submission’s estimate of the total cost to the PBS/RPBS would be \$0 to < \$10 million in the first 6 years of listing.

6.77 The submission did not include the MBS costs related to IV administration in the financial estimates, but it was included in the economic model as MBS item 116. This cost was included in financial estimates during the evaluation.

- 6.78 The evaluation and the ESC considered that the financial estimates presented in the submission could be overestimated due to:
- Use of a large prevalent pool of patients with chronic pouchitis over a 25-year period.
 - The inclusion of a previous non-responding population (with prior failure of vedolizumab for chronic pouchitis). The ESC considered that it would not be reasonable to allow re-treatment with vedolizumab if it was previously ineffective for chronic pouchitis.
 - High uptake rates assumed for new patients and prevalent patients despite the uncertainty in the superior effectiveness of vedolizumab.
 - The submission also assumed that patients would remain on vedolizumab with 100% compliance as long as they were demonstrating remission. There is currently no effectiveness data beyond that reported in the EARNEST trial at Week 34 to support prolonged use of vedolizumab.
- 6.79 On the other hand, the ESC considered that the financial estimates presented in the submission could be underestimated due to the continuation and discontinuation rates being based on the mPDAI-defined remission and sustained remission outcomes, which was inconsistent with the proposed PBS restriction in which continuation was based on a patient demonstrating “adequate response” (which was not defined in the restriction).
- 6.80 The submission stated that 10 patients were expected to be grandfathered based on the Sponsor’s patient access program. Grandfathered patients were not added into the estimated number of treated patients, which appeared reasonable given these patients would likely already be included in the prevalence estimates.
- 6.81 The PSCR acknowledged the financial estimates were uncertain, however stated the approach incorporated all possible eligible patients, as well as uptake and discontinuation rates that were consistent with the pivotal trial and which took into account the lack of alternative treatments. The PSCR reiterated that the estimated budget impact was less than \$0 to < \$10 million per year over the first 6 years of listing, and would be even lower if utilisation were lower than expected.
- 6.82 The ESC advised that the methods used to derive the utilisation and financial estimates and the structure of the financial estimates model were generally reliable for decision-making, with sources of uncertainty outlined in paragraph 6.78.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program – Public and Private Hospital) listing of vedolizumab for the treatment of patients with chronic

pouchitis. The PBAC considered there was a high unmet need for additional treatment options in this small group of patients. The PBAC was satisfied that vedolizumab provides, for some patients, a significant improvement in efficacy over standard of care (SOC) alone. However, the PBAC considered the magnitude of benefit was uncertain and likely modest in most patients. The PBAC's recommendation for listing was based on, among other matters, its assessment that in the context of the high clinical need and small patient population, vedolizumab was likely cost-effective at the price proposed in the pre-PBAC response.

- 7.2 The PBAC welcomed the consumer input received for this submission. The input described the significant impact that chronic pouchitis can have on quality of life and outlined that there are a proportion of patients who do not adequately respond to current treatments. Overall, the PBAC considered there is a high unmet need for effective therapies to treat this rare condition.
- 7.3 The PBAC considered the nominated comparator of standard of care (SOC), comprising antibiotic treatment (as required), probiotics and anti-diarrheal medications was reasonable.
- 7.4 The PBAC considered the claim that vedolizumab plus SOC has superior efficacy compared with SOC alone was reasonable based on the results of the randomised controlled trial, EARNEST. However, the PBAC considered the magnitude of benefit was uncertain given the trial had a high overall risk of bias due to protocol deviations and a substantial number of patients prematurely discontinuing the trial. The impact of the discontinuations was exacerbated by the use of the last observation carried forward imputation method for missing data, which could favour the vedolizumab treatment arm. Further, the PBAC noted the key outcomes, the modified Pouchitis Disease Activity index (mPDAI) and Pouchitis Disease Activity index (PDAI) measured at Weeks 14 and 34, were poorly validated surrogate outcomes.
- 7.5 The EARNEST trial found a statistically significant difference in the primary outcome of mPDAI-defined remission at Week 14, with 31.4% of patients in the vedolizumab arm achieving this outcome versus 9.8% in the placebo arm (treatment difference of 21.6 percentage points, 95% CI: 4.9%, 37.5%). However, the PBAC noted: the trial did not achieve the 25 percentage point difference that was considered meaningful when the sample size for the trial was calculated; the 95% confidence intervals were wide; and at Week 34 the treatment difference decreased to 17.6 percentage points (95% CI: 0.3%, 35.1%). Overall, the PBAC considered that the treatment effect of vedolizumab is likely to be modest in this condition.
- 7.6 Further, the PBAC considered that the outcome of 'sustained remission' reported in the trial may not be indicative of long-term remission as it was based solely on a patient achieving mPDAI-assessed remission at two discrete time points (Weeks 14 and 34) with no requirement for remission to be maintained between these two timepoints. In addition, the PBAC noted that no clinical data were presented regarding the efficacy of vedolizumab for chronic pouchitis beyond 34 weeks, despite there

being a proportion of patients who would likely continue treatment long-term.

- 7.7 The PBAC noted the safety data appeared to be consistent with the established profile of vedolizumab in other gastrointestinal conditions. Overall, the PBAC considered that the claim of non-inferior comparative safety versus SOC was reasonable.
- 7.8 The PBAC noted the base case ICER presented in the submission was \$35,000 to < \$45,000 per QALY, and this reduced to \$25,000 to < \$35,000 per QALY with the revised price proposed in the pre-PBAC response.
- 7.9 The PBAC noted that the ESC had raised the following issues with the economic model:
- the trial results observed from Week 14 to 34 were assumed to continue repeatedly, each model cycle, throughout the 10.4 year time horizon. The ESC considered a shorter time horizon may be more appropriate given the lack of data beyond 34 weeks.
 - in the model, patients only continued vedolizumab if they experienced mPDAI-defined remission. However, the requested restriction was broader with patients able to continue vedolizumab if they experienced an “adequate response” (no definition was specified in the proposed restriction). The ESC considered that, given the proposed continuing restriction, it would be more appropriate for the model to assume that patients with ‘partial mPDAI-defined response’ would also continue vedolizumab.
 - The vedolizumab group was split into two further treatment arms (VEDO and SOC). When patients in the vedolizumab group ceased vedolizumab, the transition probabilities for the SOC group were applied, which was associated with a large placebo effect.
- 7.10 The PBAC noted that the pre-PBAC response presented a range of multivariate sensitivity analyses that included the revised price and addressed the three key issues raised by ESC by: applying a shorter time horizon (five years); adjusting the continuation criteria applied in the model (to be based on ‘partial mPDAI-defined response’ rather than ‘mPDAI-defined remission’); and applying alternative extrapolation methods which removed the issues associated with patients ceasing vedolizumab experiencing a placebo effect. The PBAC also noted the revised price proposed in the pre-PBAC response was lower than the price of vedolizumab for Crohn’s disease. Overall, in the context of the high clinical need and small patient population, the PBAC considered vedolizumab was likely cost-effective at the price proposed in the pre-PBAC response.
- 7.11 The PBAC considered the financial estimates were generally reasonable but that the following assumptions would be more appropriate:
- patients who previously failed vedolizumab for pouchitis should not be permitted to re-trial PBS-subsidised vedolizumab.

- the continuation rate at 14 weeks (i.e. after the initial treatment period) should be based on the proportion of patients in the trial who experienced ‘partial mPDAI-defined response’ at Week 14 (62.7%), rather than ‘mPDAI-defined remission’.
 - long-term continuation (beyond 14 weeks) should be based on the proportion of patients in the trial who experienced ‘partial mPDAI-defined response’ at Week 34 (51.0%), in the absence of more reliable long-term data.
- 7.12 The PBAC noted that, with the revised price proposed in the pre-PBAC response and the combined impact of the above changes, the estimated financial impact to the PBS/RPBS would be around \$0 to < \$10 million to \$0 to < \$10 million over the first six years of listing.
- 7.13 With regard to the restriction, the PBAC considered:
- the initial PBS restriction should require patients to have an mPDAI total score of 5 or more with a minimum endoscopic sub-score of 2, as proposed in the submission and consistent with the clinical trial.
 - the continuing PBS restriction should require patients to demonstrate or sustain a partial or complete response, as determined by the treating clinician. As proposed in the submission, the PBAC considered that response should not be defined in the restriction and should instead rely on the clinician’s judgement. The PBAC considered it would be reasonable for decisions around continuation of therapy to be based on symptoms alone, without the need for six-monthly endoscopies given these are likely performed less frequently in routine clinical practice.
 - the restriction should allow recommencement of vedolizumab (initial 2 treatment phase) following a treatment break in those patients who would have ceased due to reasons other than failure to maintain an adequate treatment response. The PBAC considered that there should be no requirement for these patients to re-trial antibiotics prior to re-initiating vedolizumab, but that vedolizumab should be recommenced in combination with standard of care antibiotic therapy (given the Product Information states ‘vedolizumab should be initiated in parallel with standard of care antibiotic’). In addition, the PBAC considered there should not be a requirement for patients recommencing therapy following a treatment break to have a mPDAI total score of 5 or more with a minimum endoscopic sub-score of 2.
 - the restriction should not allow recommencement of vedolizumab if it was previously ineffective for this condition (i.e. in patients who previously failed, or ceased to respond to, PBS-subsidised treatment with vedolizumab for this condition).

- the restriction should not include an age restriction (i.e. remove the following population criteria proposed in the submission: ‘Patient must be aged 18 years or older’).
- grandfather and balance of supply (for initial 1 and 2 treatment) restrictions would be appropriate.

7.14 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for vedolizumab:

- The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity over alternative therapies, as the treatment effect of vedolizumab appears to be modest;
- The treatment is not expected to address a high and urgent unmet clinical need as alternative medical interventions are available;
- It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed OR

7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item and new indication:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Manufacturer	Name and
VEDOLIZUMAB						
vedolizumab 300 mg injection, 1 vial	NEW (HSD Public) NEW (HSD Private) MP	1	1	2	Entyvio®	Takeda Pharmaceuticals Pty Ltd

Restriction Summary [new 1] / Treatment of Concept: [new 2]

Concept ID	Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private Hospitals)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – In Writing/HPOS
	Authority type: required for s100 HSD <input checked="" type="checkbox"/> Complex Authority Required (CAR)
	Administrative Advice:

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	No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Episodicity: Chronic
	Severity: Moderate to severe
	Condition: Pouchitis
	Indication: Moderate to severe chronic pouchitis
	Treatment Phase: Initial 1 treatment (new patient)
	Clinical criteria: Patient must have undergone ileal pouch anal anastomosis (IPAA) due to ulcerative colitis (UC) at least one year previously
	AND
	Clinical criteria: Patient must not have previously received PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria: The condition must be confirmed based on the patient's symptoms, treatment history and baseline endoscopic examination of the pouch (pouchoscopy)
	AND
	Clinical criteria: Patient must have a Modified Pouchitis Disease Activity Index (mPDAI) score of at least 5
	AND
	Clinical criteria: Patient must have a minimum endoscopic mPDAI sub-score of at least 2
	AND
	Clinical criteria: Patient must have had at least 3 recurrent episodes of pouchitis within the previous year each of which was treated with at least: (i) 2 weeks of antibiotic, (ii) other prescription therapy; OR
	The condition must have required maintenance antibiotic therapy taken continuously for at least 4 weeks before commencing treatment with this drug.
	AND
	Clinical criteria: Patient must not receive more than 14 weeks of treatment under this restriction.
	AND
	Treatment criteria: Must be treated by a gastroenterologist, OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
	AND
	Clinical criteria: The treatment must be initiated in combination with standard of care antibiotic
	AND
	Prescribing Instructions: <i>The assessment of a patient's response to this initial course of treatment must be made after the third dose of vedolizumab so there is an adequate time for a response to be demonstrated. The assessment must be made prior to obtaining a PBS authority for continuing treatment from the dose at week 14. Where a response assessment is not conducted within this timeframe, the patient will be deemed to have failed to respond to treatment with this drug.</i>
	Prescribing Instructions: Application for authorisation of initial treatment must be in writing and must include: (a) details of the proposed prescription; and (b) a completed <i>authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)</i> which includes the following: (i) <i>The patient's baseline Modified Pouchitis Disease Activity Index (mPDAI) score and endoscopic mPDAI subscore; and</i> (ii) <i>details of prior drug therapy for this condition [dosage, date of commencement and duration of therapy].</i>

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	Prescribing Instructions: The endoscopic assessment contributing to the Modified Pouchitis Disease Activity Index score to confirm the patient's condition at baseline must have been performed no more than 4 weeks prior to the application.
	Prescribing Instructions: Applications for treatment of this condition must be received within 4 weeks of the endoscopy to confirm diagnosis. The prescriber must exclude secondary causes of pouchitis, for example: (a) Ischaemia (b) Crohn's disease (CD) or CD of the pouch (c) Irritable pouch syndrome (d) Predominant cuffitis (e) Pouch stricture or pouch fistula (f) Active infection (g) NSAIDs (h) Coeliac disease
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

Restriction Summary [new] / Treatment of Concept: [new]

Concept ID	Category / Program: Section 100 – Highly Specialised Drugs Program {Public/Private Hospitals}
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – In Writing/HPOS (Complex Authority Required)
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Episodicity: Chronic
	Severity: Moderate to severe
	Condition: Pouchitis
	Indication: Moderate to severe chronic pouchitis
	Treatment Phase: Initial 2 treatment (Recommencement of treatment after a break in biological medicine)
	Clinical criteria: Patient must have previously received PBS subsidised treatment with this drug for this condition.
	AND
	Clinical criteria: Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria: Patient must not receive more than 14 weeks of treatment under this restriction.
	AND
	Treatment criteria: Must be treated by a gastroenterologist, OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
	AND
	Clinical criteria:

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	The treatment must be initiated in combination with standard of care antibiotic
	Prescribing Instructions: <i>The assessment of a patient's response to this initial course of treatment must be made after the third dose of vedolizumab so there is adequate time for a response to be demonstrated. The assessment must be made prior to obtaining a PBS authority for continuing treatment from the dose at week 14.</i>
	Prescribing Instructions: <i>Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.</i>
	Prescribing Instructions: Application for authorisation of initial treatment must be in writing and must include: (a) details of the proposed prescription; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) which includes the following: (i) <i>The patient's baseline Modified Pouchitis Disease Activity Index (mPDAI) score and minimum endoscopic mPDAI sub-score;</i> and (ii) details of prior biological medicine therapy for this condition, [date of commencement and duration of therapy]
	Prescribing Instructions: The endoscopic assessment contributing to the Modified Pouchitis Disease Activity Index score to confirm the patient's condition at baseline must have been performed no more than 4 weeks prior to the application.
	Prescribing Instructions: Applications for treatment of this condition must be received within 4 weeks of the endoscopy to confirm diagnosis. The prescriber must exclude secondary causes of pouchitis, for example: a. Ischaemia b. Crohn's disease (CD) or CD of the pouch c. Irritable pouch syndrome d. Predominant cuffitis e. Pouch stricture or pouch fistula f. Active infection g. NSAIDs h. Coeliac disease
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

Restriction Summary [new] / Treatment of Concept: [new]

Concept ID	Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private Hospitals)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic (Complex Authority Required)
	Episodicity: Chronic
	Severity: Moderate to severe
	Condition: Pouchitis
	Indication: Moderate to severe chronic pouchitis
	Treatment Phase: Balance of Supply – Initial 1 treatment (new patient) and Initial 2 treatment (recommencement of treatment after a break in biological medicine)
	Clinical criteria:
	Patient must have received insufficient therapy with this drug under the Initial 1 treatment (new patient) restriction to complete 14 weeks of treatment; or
	Patient must have received insufficient therapy with this drug under the Initial 2 treatment (recommencement of treatment after a break in biological medicine) to complete 14 weeks of treatment.
	AND

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Clinical criteria:
The treatment must provide no more than the balance of up to 14 weeks treatment available under the above treatment phases
AND
Treatment criteria:
Must be treated by a gastroenterologist, OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Manufacturer	Name and
VEDOLIZUMAB						
vedolizumab 300 mg injection, 1 vial	NEW (HSD Public) NEW (HSD Private) MP	1	1	2	Entyvio®	Takeda Pharmaceuticals Pty Ltd

Restriction Summary [new] / Treatment of Concept: [new]

Concept ID	Category / Program: Section 100 – Highly Specialised Drugs Program {Public/Private Hospitals}
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic
	Authority type: required for s100 HSD <input checked="" type="checkbox"/> Complex Authority Required (CAR)
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Episodicity: Chronic
	Severity: Moderate to severe
	Condition: Pouchitis
	Indication: Moderate to severe chronic pouchitis
	Treatment Phase: Continuing treatment
	Clinical criteria: Patient must have previously received this drug as their most recent course of PBS-subsidised biological medicine for this condition,
	AND
	Clinical criteria: Patient must have demonstrated or sustained a partial or complete response, as determined by the treating clinician, to the most recent PBS-subsidised course of treatment with this drug for this condition.
	AND
	Treatment criteria: Must be treated by a gastroenterologist, OR

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	Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
	Prescriber Instructions: Patients who have failed to demonstrate a partial or complete response with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.
	Prescriber Instructions: Patients are eligible to receive continuing treatment with this drug in courses up to 24 weeks providing they continue to sustain a response.
	Prescriber Instructions: An application for the continuing treatment must be made following the third dose with this drug and requested no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment. Where an application is not made within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.
	Prescriber Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicessaustralia.gov.au/HPOS) or by telephone by contacting the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Restriction Summary [new] / Treatment of Concept: [new]

Concept ID	Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private Hospitals)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – In Writing
	Authority type: required for s100 HSD <input checked="" type="checkbox"/> Complex Authority Required (CAR)
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Episodicity: Chronic
	Severity: Moderate to severe
	Condition: Pouchitis
	Indication: Moderate to severe chronic pouchitis
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – Grandfather arrangements
	Clinical criteria: Patient must have received treatment with this drug for this PBS indication prior to [PBS listing date]
	AND
	Clinical criteria: Patient must be receiving treatment with this drug for this condition at the time of application
	AND
	Clinical criteria: Patient must have undergone ileal pouch anal anastomosis (IPAA) due to ulcerative colitis at least one year prior to initiating non-PBS subsidised treatment with this drug for this condition
	AND
	Clinical criteria: The condition must be confirmed based on the patient's symptoms, treatment history and baseline endoscopic examination of the pouch (pouchoscopy)
	AND
	Clinical criteria: Patient must have had a Modified Pouchitis Disease Activity Index (mPDAI) score of at least 5 at the time of initiating treatment with this drug for this condition
	AND
	Clinical criteria:

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	Patient must have a minimum endoscopic mPDAI sub-score of at least 2 at the time of initiating treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have had at least 3 recurrent episodes of pouchitis within the year prior to initiating treatment with this drug for this condition, each of which was treated with at least 2 weeks of antibiotic or other prescription therapy; OR
	The condition must have required maintenance antibiotic therapy taken continuously for at least 4 weeks before commencing treatment with this drug.
	AND
	Clinical criteria:
	Patient must not receive more than 24 weeks of treatment under this restriction.
	AND
	Clinical criteria:
	The treatment must have been initiated in combination with standard of care antibiotic
	AND
	Clinical criteria:
	Patient must have demonstrated a partial or complete response to treatment with this drug as determined by the treating clinician, for this condition if the patient has received non-PBS-subsidised treatment for the first three doses of induction.
	AND
	Treatment criteria:
	Must be treated by a gastroenterologist, OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
	Prescribing Instructions: The assessment of a patient's response to this course of treatment must be made after the third dose of vedolizumab so there is adequate time for a response to be demonstrated. The assessment must be made prior to obtaining a PBS authority for continuing treatment from the dose at week 14.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug.
	Prescribing Instructions: The application for authorisation of treatment must be in writing and must include: (a) details of the proposed restriction; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) which includes the following: (i) The patient's baseline Modified Pouchitis Disease Activity Index (mPDAI) score and minimum endoscopic mPDAI sub-score; and (ii) details of prior drug therapy for the condition [dosage, date of commencement and duration of therapy]; and (iii) the date of commencement of this drug for this condition.
	Prescribing Instructions: The endoscopic assessment contributing to the Modified Pouchitis Disease Activity Index score to confirm the patient's condition at baseline must have been performed no more than 4 weeks prior to initiation with non-PBS subsidised treatment with this drug.
	Prescribing Instructions: The prescriber must have excluded secondary causes of pouchitis, for example: (a) Ischaemia (b) Crohn's disease (CD) or CD of the pouch (c) Irritable pouch syndrome (d) Predominant cuffitis (e) Pouch stricture or pouch fistula (f) Active infection (g) NSAIDs (h) Coeliac disease
	Prescribing Instructions: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
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These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.