

6.14 VEDOLIZUMAB,

**Injection 108 mg in 0.68 mL single use pre-filled pen;
Powder for injection 300 mg,
Entyvio[®],
Takeda Pharmaceuticals Australia Pty. Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested a new listing to allow for an additional dose of vedolizumab 300 mg at week 10 for the initial treatment of severe Crohn disease (CD) for patients who have not responded to therapy after the existing three dose induction therapy.
- 1.2 The submission also requested the removal of requirement to assess the risk of developing progressive multifocal leukoencephalopathy (PML) during this treatment from all Pharmaceutical Benefits Scheme (PBS) listings for vedolizumab.
- 1.3 Listing was requested based on a cost-minimisation approach of vedolizumab intravenous (IV) under the current PBS restriction versus vedolizumab IV under the proposed PBS restriction with a two-year time horizon for continuing therapy of the IV formulation at a lower proposed, weighted, effective price per vial.

2 Background

Registration status

- 2.1 Vedolizumab is Therapeutic Goods Administration (TGA) registered for the treatment of:
 - adult patients with moderate to severe ulcerative colitis who have had an inadequate response to, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNF- α) antagonist.
 - adult patients with moderate to severe Crohn's disease who have had an inadequate response with, lost response to, or are intolerant to, either conventional therapy or a tumour necrosis factor-alpha (TNF- α) antagonist.

Induction doses

- 2.2 The existing PBS regimen of three induction doses of vedolizumab 300 mg IV at weeks 0, 2, and 6 aligns with the recommended dosing in the TGA-approved Product Information (PI).
- 2.3 In June 2017, the sponsor applied to the TGA to amend the PI to allow for an additional induction dose at week 10. The delegate requested consideration by the Advisory Committee on Medicines (ACM), who stated that the sponsor's submission did not

satisfactorily establish the safety and efficacy of administering an additional induction dose at week 10 for patients with CD who have not responded to the 0, 2 and 6 week regimen.

- 2.4 Following the ACM advice, the TGA requested further data from the sponsor. The Delegate considered these data and approved the variations to the PI to state that *‘Some patients with Crohn’s disease who have not shown a response may benefit from a dose at week 10’*.

PML Clinical Criteria

- 2.5 On 27th September 2023, the TGA Risk Management Plan (RMP) evaluator accepted the updated EU-RMP v8.1 and Australian Specific Annex (ASA) v7.0 (dated September 2023) for vedolizumab, whereby a specific adverse event follow-up check list for PML is no longer required as an Additional Risk Minimisation Measures (ARMMS). A Healthcare Professional (HCP) brochure and Patient Alert Card for vedolizumab as an ARMMS is also no longer required for PML or other serious infections.
- 2.6 On 18 December 2023, the TGA approved an amendment to the PI for vedolizumab. The following two sentences were amended in the special warnings and precautions section of the PI under PML:

~~‘Patients should be advised of this potential risk for PML and that they should carry a Patient Alert Card at all times. The Alert Card reminds patients that they must contact their doctor if they have unusual or prolonged new neurological symptoms or if they have severe or prolonged symptoms of infection.’~~

- 2.7 The revised PI continues to contain the following section regarding PML:

Progressive Multifocal Leukoencephalopathy

Some integrin antagonists and some systemic immunosuppressive agents have been associated with progressive multifocal leukoencephalopathy (PML), which is a rare and often fatal opportunistic infection of the central nervous system (CNS) caused by the John Cunningham (JC) virus. Vedolizumab has no known systemic immunosuppressive activity.

In ENTYVIO clinical trials, patients were screened for PML prior to enrolment and actively monitored during participation, with evaluations of any new, unexplained neurological symptoms as necessary. While no cases of PML were identified among patients with at least 24 months of exposure, a risk of PML cannot be ruled out.

Patients should be monitored for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

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Patients should be advised of this potential risk for PML and that they should contact their doctor if they have unusual or prolonged new neurological symptoms or if they have severe or prolonged symptoms of infection. Healthcare professionals should monitor patients on vedolizumab for any new signs or symptoms that may be suggestive of serious infection including PML. Vedolizumab dosing should be withheld immediately at the first signs or symptoms suggestive of PML, and patients should be referred to a neurologist. If PML is confirmed, treatment must be permanently discontinued.

Previous PBAC consideration

- 2.8 At its March 2015 meeting, the PBAC recommended the listing of vedolizumab IV for the treatment of moderate to severe ulcerative colitis (MSUC) and severe CD. Vedolizumab IV was first listed on the PBS on 1 August 2015.
- 2.9 At its November 2020 meeting, the PBAC recommended the listing of vedolizumab subcutaneous (SC) administration as maintenance treatment for patients with MSUC and severe CD on a cost minimisation basis to vedolizumab IV.
- 2.10 The PBAC has not previously considered the listing of an additional dose of vedolizumab IV 300 mg at week 10 for the initial treatment of severe CD.

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

3 Requested listing

3.1 Suggested additions are in italics and deletions are in strikethrough.

Additional induction dose:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
VEDOLIZUMAB					
vedolizumab 300 mg injection, 1 vial	NEW (Public) NEW (Private) MP	1	1	0	Entyvio
Restriction Summary [new 1] / Treatment of Concept: [new 2]					
Concept ID (for internal Dept. use)	Category / Program Section 100 – Highly Specialised Drugs Program				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
Prescribing rule level	<p>Administrative Advice: SEVERE CROHN DISEASE - TREATMENT PHASES AND CYCLES</p> <p><i>The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of benefits that contain the words: 'severe Crohn disease' in the stated PBS indication. Some of these benefits are not biological medicines, but are small molecules (e.g. a Janus-kinase inhibitor). Where the term 'biological medicine' appears in the restriction, it includes such benefits for PBS administrative purposes.</i></p>				

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	<p>A patient is eligible for PBS-subsidised treatment with only one PBS-subsidised biological medicine at any one time.</p> <p><i>Treatment cycle:</i> A treatment cycle begins when an authority application is approved under an Initial 1 or Initial 3 type restriction. Once commenced, where biological medicine fails to provide the patient with an adequate response on 3 occasions, the current treatment cycle ends and there must be an absence of PBS-subsidy for a period of 5 years. The 5 year break is measured from the date of the last approval for PBS-subsidised biological medicine treatment in the most recent cycle to the date of the first application for initial treatment with a biological medicine under the new treatment cycle.</p> <p>An exception to this 5 year break clause applies where:</p> <ul style="list-style-type: none">(i) since the commencement of the break, an additional biological medicine has since become PBS-listed with a different pharmacological mechanism of action (i.e. the newly listed biological medicine) relative to those available on the PBS at the time of commencing the 5 year break; and(ii) the patient has never been prescribed the newly listed biological medicine; and(iii) the prescribed biological medicine is the newly listed biological medicine. <p>Prescribing of the newly listed biological medicine is to occur through the 'Initial 2' treatment phase listing and the patient will not be in a new treatment cycle (i.e. where this newly listed biological medicine fails to provide an adequate response, the current treatment cycle ends and there must be an absence of PBS-subsidised biological medicine for a period of 5 years unless the exception outlined above is triggered again).</p> <p>Within the same treatment cycle, the same PBS-subsidised biological medicine cannot continue to be subsidised where it has resulted in an inadequate response. An inadequate response is one which does not meet the minimum improvements in disease measures stated in the Continuing treatment restriction. A serious adverse reaction leading to treatment discontinuation will be exempted from being counted as an inadequate response.</p> <p>There is no limit to the number of treatment cycles a patient may undertake in their lifetime.</p> <p><i>Treatment phases:</i></p> <ul style="list-style-type: none">(a) Initial 1 Apply through this treatment phase where the patient has never been treated with PBS-subsidised biological medicine for this indication.(b) Initial 2 Apply through this treatment phase where the prescribed treatment is changing (other than dose/form), or, where there has been a break in therapy of less than 5 years and treatment is resuming; authority applications through this treatment phase do not require prior response to conventional therapies to be re-established and do not require baseline disease activity to be re-demonstrated. An assessment of response to the preceding supply must be provided - where it is not, it will be assumed that the preceding supply provided an inadequate response.(c) Initial 3 Apply through this treatment phase where treatment is resuming after an absence of PBS-subsidy for at least 5 years; authority applications through this treatment phase do not require a re-trial of conventional therapies.(e) Continuing treatment Apply through this treatment phase where an adequate response to the preceding supply is observed (or where the dose is increasing where multiple strengths exist). It is recommended that a patient be reviewed in the 4 weeks prior to exhausting the current supply to ensure uninterrupted supply.
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	<p>Continuing treatment authority applications are not to be made on the same day as Initial treatment authority applications.</p> <p>(f) Balance of supply Apply through this type of treatment phase only where the benefit was not requested in the full amount available in the preceding supply - this may be because the maximum quantity was not prescribed and/or the full number of repeat prescriptions was not prescribed. The intent of this treatment phase listing is to: (i) provide the balance of what could have been obtained had the full quantity and number of repeats been prescribed in the preceding authority application, (ii) allow further time for an adequate response to treatment to be demonstrated where it may not have already, and (iii) provide more immediate access to PBS-subsidy via a telephone/online authority application relative to an 'in-writing only' application where the preceding supply was obtained through such.</p>
	<p>Administrative Advice: Special Pricing Arrangements apply.</p>
	<p>Indication: Severe Crohn disease</p>
	<p>Treatment Phase: Initial 4 (additional dose at week 10)</p>
	<p>Treatment criteria:</p>
	<p>Must be treated by a gastroenterologist (code 87); or</p>
	<p>Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or</p>
	<p>Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)]</p>
	<p>Clinical criteria:</p>
	<p>Patient must have received prior PBS-subsidised treatment with this drug for this condition in this treatment cycle</p>
	<p>Clinical criteria:</p>
	<p>Patient must have received 3 doses of initial treatment under Initial 1 (new patient) restriction (the initial infusion regimen at 0, 2 and 6 weeks); OR Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) restriction (the initial infusion regimen at 0, 2 and 6 weeks); OR Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) restriction to complete the 3 doses (the initial infusion regimen at 0, 2 and 6 weeks); OR Initial 1 or 2 or 3 with a Balance of supply</p> <p>Patient must have received 3 doses of initial treatment under either (i) initial 1, (ii) initial 2, (iii) initial 3</p>
	<p>Clinical criteria:</p>
	<p>Patient must not have achieved an adequate response to this drug after a total of 3 doses of initial treatment under either (i) initial 1, (ii) initial 2, (iii) initial 3 under this restriction minimum of 6 weeks of treatment.</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>The treatment must not exceed a total of 4 doses to be administered at weeks 0,2,6 and 10 under this restriction</p>
	<p>AND</p>
	<p>Clinical criteria</p>
	<p>Patient must have an adequate response to this drug defined as a reduction in Crohn Disease Activity Index (CDAI) Score to a level no greater than 150 if assessed by CDAI or if affected by extensive small intestine disease; or</p>

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	Patient must have an adequate response to this drug defined as (a) an improvement of intestinal inflammation as demonstrated by: (i) blood: normalisation of the platelet count, or an erythrocyte sedimentation rate (ESR) level no greater than 25 mm per hour, or a C-reactive protein (CRP) level no greater than 15 mg per L; or (ii) faeces: normalisation of lactoferrin or calprotectin level; or (iii) evidence of mucosal healing, as demonstrated by diagnostic imaging findings, compared to the baseline assessment; or (b) reversal of high faecal output state; or (c) avoidance of the need for surgery or total parenteral nutrition (TPN), if affected by short gut syndrome, extensive small intestine or is an ostomy patient
	AND
	Clinical criteria
	Patient must be appropriately assessed for the risk of developing progressive multifocal leukoencephalopathy whilst on this treatment
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing Instructions: Patient must not receive more than one dose at 10 weeks under this restriction A maximum quantity and number of repeats to provide for an additional dose of this drug consisting of one vial of 300 mg, with one dose to be administered at week 10, will be authorised.
	Prescribing Instructions: The assessment of the patient's response to the initial course of treatment must be conducted prior to 10 weeks and a second assessment must be conducted following a minimum of 12 weeks of treatment and no later than 4 weeks from the cessation of that treatment course. If the response assessment is not conducted within these timeframes, the patient will be deemed to have failed this course of treatment in this treatment cycle.
	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, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing 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 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.
	Administrative Advice: Patient must be assessed as having an inadequate response to the drug after completing an initial infusion regimen at 0, 2, and 6 weeks and prior to 10 weeks.
	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).

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Amendment of clinical criteria:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
VEDOLIZUMAB					
vedolizumab 300 mg injection, 1 vial	10384M	1	1	0	Entyvio
	10390W				
	10398G				
	10415E				
vedolizumab 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	12620F	1	2	0	
	12638E				
	12644L				
	12647P				
	12369F	1	2	5	
12654B					
Clinical Criteria:					
Patient must be appropriately assessed for the risk of developing progressive multifocal leukoencephalopathy whilst on this treatment					

Flow on changes:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
VEDOLIZUMAB					
vedolizumab 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	12638E	1	2	0	
Prescribing Instructions:					
Where four initial doses of vedolizumab (at weeks 0, 2, 6 and 10) is administered via intravenous infusion, initial treatment with subcutaneous form will commence at week 14 (4 weeks after the fourth dose). A maximum quantity with no repeats should be requested to provide for weeks 14 and 16.					

- 3.2 The proposed effective approved ex-manufacturer price (AEMP) for vedolizumab 300 mg IV for the treatment of severe CD was \$ I . This is a weighted average AEMP of the current AEMP (\$ I) for the I % of patients who do not require an additional dose at week 10 and the AEMP of \$ I that is obtained from the cost minimisation analysis (CMA) for the I % of patients who may derive additional benefit from the week 10 dose ($(\text{I}\% \times \$\text{I}) + (\text{I}\% \times \$\text{I}) = \$\text{I}$). Following the suggested alternative approach to achieve cost-neutrality, the Pre-Sub-Committee Response (PSCR) considered that the weighted AEMP for the initiating treatment phase would be determined as follows: (I x % patients who do NOT require an additional dose) + (I x % patients who DO require the additional dose at Week 10). This was calculated to be \$ I ($(\text{I}$ x I) + (I x I)).
- 3.3 The evaluation noted that the alternative approach to achieving cost neutrality for the financials would require that initial and continuing restrictions be separated into different item codes.

- 3.4 Vedolizumab 300 mg IV is currently listed with a special pricing arrangement. The sponsor requested that this arrangement and the published AEMP of \$2,949.93 are maintained.

Monitoring for PML

- 3.5 The December 2023 TGA-approved amendment to the PI removed the need for patient to carry a patient alert card, though it still maintains the need for healthcare professionals to monitor for signs of PML. See PI amendments below:

Patients should be monitored for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

Patients should be advised of this potential risk for PML and that they should ~~carry a Patient Alert Card at all times. The Alert Card reminds patients that they must~~ contact their doctor if they have unusual or prolonged new neurological symptoms or if they have severe or prolonged symptoms of infection.

Healthcare professionals should monitor patients on vedolizumab for any new signs or symptoms that may be suggestive of serious infection including PML. Vedolizumab dosing should be withheld immediately at the first signs or symptoms suggestive of PML, and patients should be referred to a neurologist. If PML is confirmed, treatment must be permanently discontinued.

- 3.6 The administrative advice included for all listings for vedolizumab for severe CD maintains a note about PML. The submission has not requested amendment to this administrative advice:

A serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment, including serious infusion or injection related reactions, Steven's Johnson Syndrome, development of a demyelinating lesion, progressive multifocal leukoencephalopathy and malignancy related to treatment with the biological medicine, is not considered as a treatment failure.

- 3.7 It is noted that natalizumab for the treatment of clinically definite relapsing-remitting multiple sclerosis includes only a caution note related to PML. The PI for natalizumab still requires patients to carry a patient alert card.

Progressive multifocal leukoencephalopathy has been reported with this drug.

- 3.8 In its PSCR, the sponsor stated that while it is common for a PI to suggest monitoring for adverse events or other parameters that may be suggestive of risks of an AE (e.g., blood pressure, cardiac parameters etc), these do not appear in PBS restrictions, even in cases of medicines with black box warnings, such as upadacitinib. Following the removal of the requirement for a Patient Alert Card for PML, PML is subject to standard monitoring, and the PSCR considered it is reasonable that the monitoring of signs and symptoms suggestive of adverse events for vedolizumab not be treated differently to that of any other medicine.

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

4 Population and disease

- 4.1 Australia has one of the highest incidence and prevalence rates of inflammatory bowel disease (IBD) in the world. CD and ulcerative colitis (UC) are the two most common types of IBD. It is estimated that approximately 100,000 Australians are living with IBD¹.
- 4.2 CD is typically characterised by transmural inflammation of the intestine and can affect any part of the gastrointestinal tract from mouth to perianal area, although it most commonly affects the small intestine and/or the colon. Patients with CD usually present with abdominal pain, weight loss, fever, anaemia and clinical signs of bowel obstruction or diarrhoea with passage of blood, mucous, or both (vedolizumab Public Summary Document (PSD), November 2020 PBAC Meeting).
- 4.3 In both UC and CD, treatment guidelines recommend a step-up treatment strategy. For patients with MSUC and CD, conventional therapies, including 5-aminosalicylic acid (5-ASA) preparations, corticosteroids, and immunomodulators (e.g. azathioprine, 6-mercaptopurine, and methotrexate) are given as first-line therapies. If a patient has inadequate response to, or is unable to tolerate conventional therapy, biologic or targeted synthetic disease modifying anti-rheumatic drugs (b/tsDMARDs) are initiated (vedolizumab PSD, November 2020 PBAC Meeting).

5 Comparator

- 5.1 The submission nominated vedolizumab's current induction regimen (300 mg IV at weeks 0, 2 and 6) as the comparator to the proposed induction regimen (300 mg IV at weeks 0, 2, 6 and 10) for those patients who have not yet had a response. This was appropriate, however, as detailed below, there may be additional relevant comparators.
- 5.2 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.
- 5.3 While not directly applicable to the nature of this submission, the circumstances of infliximab subcutaneous injection (IFX SC) are noteworthy. When first recommended for rheumatoid arthritis, CD and ulcerative colitis in November 2020, the PBAC recommended IFX SC (maintenance therapy only) on a cost minimisation basis with infliximab IV, on the basis that while there are alternative therapies which may be less

¹ Crohns & Colitis Australia (CCA); <https://crohnsandcolitis.org.au/>. 2023

costly, a switch from those alternative agents to IFX SC for maintenance therapy is less likely (paragraph 7.12, infliximab PSD, November 2020 PBAC meeting with addendum). However, when IFX SC was recommended for induction therapy in rheumatoid arthritis in 2022, the PBAC considered IFX SC may replace any of the currently listed alternatives, therefore the listing should be on a cost minimisation basis with the lowest cost alternative treatment (paragraph 6.4, infliximab PSD, November 2022 PBAC meeting).

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from one organisation via the Consumer Comments facility on the PBS website. Crohn's and Colitis Australia supported the listing of an additional dose of vedolizumab at week 10 for the initial treatment of severe Crohn disease. The input stated it understood that this is the evidence-based clinical practice for initial treatment experienced by people with IBD. The input further noted that reliance on full payment of compassionate access to the additional dose creates uncertainty and sometimes financial burden for people in the early stages of potentially successful treatment.

6.3 The input also provided quotes from patients who are using vedolizumab for the treatment of IBD with a four-weekly dosing regimen as opposed to the currently listed 8-weekly dosing regimen. The PBAC acknowledged this input, though noted that this request was outside the consideration of the current submission.

Clinical studies

6.4 The submission was based on the two pivotal vedolizumab randomised, placebo-controlled trials, GEMINI 2 (C13007) and GEMINI 3 (C13011) previously considered by the PBAC that formed the clinical evidence for the basis of listing vedolizumab 300 mg for IV infusion for the treatment of CD.

6.5 Details of the trials presented in the submission are provided in Table 1.

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Table 1: Trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
GEMINI II	Clinical Study Report C13007. A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients With Moderate to Severe Crohn's Disease Sandborn, W. J., Feagan, B. G., Rutgeerts, P., Hanauer, S., Colombel, J. F., Sands, B. E., Lukas, M., Fedorak, R. N., Lee, S., Bressler, B., Fox, I., Rosario, M., Sankoh, S., Xu, J., Stephens, K., Milch, C., and Parikh, A. Vedolizumab as induction and maintenance therapy for Crohn's disease.	2012 New England Journal of Medicine. 2013; 369 (8): 711- 721
GEMINI III	Clinical Study Report C13011. A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicenter Study of the Induction of Clinical Response and Remission by Vedolizumab in Patients with Moderate to Severe Crohn's Disease	2012

Source: vedolizumab Public Summary Document March 2015

- 6.6 Patients in GEMINI 2 received two doses of induction treatment at week 0 and 2 with clinical remission assessed at week 6. Patients randomised to GEMINI 3 received three doses of induction treatment at week 0, 2 and 6 and clinical remission was assessed at week 6 and 10. Clinical remission was defined as a Crohn's Disease Activity Index (CDAI) < 150 points and corresponds to the criterion for eligibility for continuing (i.e., maintenance) treatment for CD on the PBS.
- 6.7 The clinical evidence provided to support an additional induction dose at week 10 is derived from a subgroup of GEMINI 2. Patients in GEMINI 3 did not receive any doses beyond week 6.
- 6.8 The submission was based on analysis of the results of a subgroup of patients who were deemed to be non-responders at week 6 in the GEMINI 2 trial following two induction doses at weeks 0 and 2. These patients were moved into an open label, non-randomised arm of the trial and provided vedolizumab 300 mg IV every 4 weeks, beginning week 6. These patients did not form part of the ITT population in the trial and were excluded from the maintenance study and analysis. The evaluation noted that none of the clinical data provided includes patients provided with 4 induction doses followed by 8-weekly continuing therapy, per the requested PBS restriction. While there is a risk that some patients who achieve response with a 4-dose induction regimen and Q4W continuation may not maintain response under a Q8W continuation regimen, the financial risk is partially mitigated by the requirement for patients to demonstrate response prior to each continuing therapy prescription (i.e., required to demonstrate response after 14 weeks of continuing treatment, which is week 24 of treatment).

- 6.9 The submission provided a review article on the predictors of response to vedolizumab and ustekinumab in inflammatory bowel disease (Barré, et al., 2018²). The review article referenced a prospective study from 2 French hospitals that included patients with CD or UC receiving induction therapy with vedolizumab (Williet, et al., 2017³). Williet used low trough levels of vedolizumab at week 6 (< 19.0 mg/mL) following standard induction doses at weeks 0, 2 and 6, as a measure to determine whether patients would be placed onto optimised therapy (additional doses of vedolizumab given at week 10 and then every 4 weeks). The observational study consisted of 47 consecutive patients with CD [n=31] or UC [n=16] who had not responded to 2 previous treatment regimens with antagonists of tumour necrosis factor. Of the 47 patients included in the study, 27 patients achieved clinical remission at week 6, and 20 patients required an additional dose at week 10. Of the 20 patients receiving an additional dose, 15 achieved clinical remission at week 10 (75%). The evaluation noted that the study is limited by its small cohort size, and it did not differentiate patients by inflammatory disease in its results, making it unclear how applicable these results would be to the severe CD population.
- 6.10 Barré, et al., also noted patients who achieved early response to vedolizumab are more likely to have a long-term response, which may indicate patients requiring a week 10 dose are less likely to maintain a clinical response and remain in remission. The evaluation noted that there was insufficient data provided to draw any clear conclusions, although the committee may wish to consider the difference in response between patients who had previously failed TNF α therapy and those who did not, presented in Tables 2 and 3, and the risk that some of these patients may be treatment resistant.
- 6.11 The evaluation conducted an abbreviated literature search (PubMed; Cochrane Library) that identified one additional induction trial of note which was not included in the submission: Watanabe 2020⁴, a Japanese study of vedolizumab with a comparable design to GEMINI 2; however, given the trial was limited to a Japanese population, it is unlikely to be generalisable to the Australian population. The

² Barré A, Colombel J-F, Ungaro R. Review article: predictors of response to vedolizumab and ustekinumab in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2018;47:896–905. <https://doi.org/10.1111/apt.14550>

³ Williet N, Boschetti G, Fovet M, Di Bernado T, Claudez P, Del Tedesco E, Jarlot C, Rinaldi L, Berger A, Phelip JM, Flourie B, Nancey S, Paul S, Roblin X. Association Between Low Trough Levels of Vedolizumab During Induction Therapy for Inflammatory Bowel Diseases and Need for Additional Doses Within 6 Months. *Clin Gastroenterol Hepatol.* 2017 Nov;15(11):1750-1757.e3. doi: 10.1016/j.cgh.2016.11.023. Epub 2016 Nov 24. PMID: 27890854.

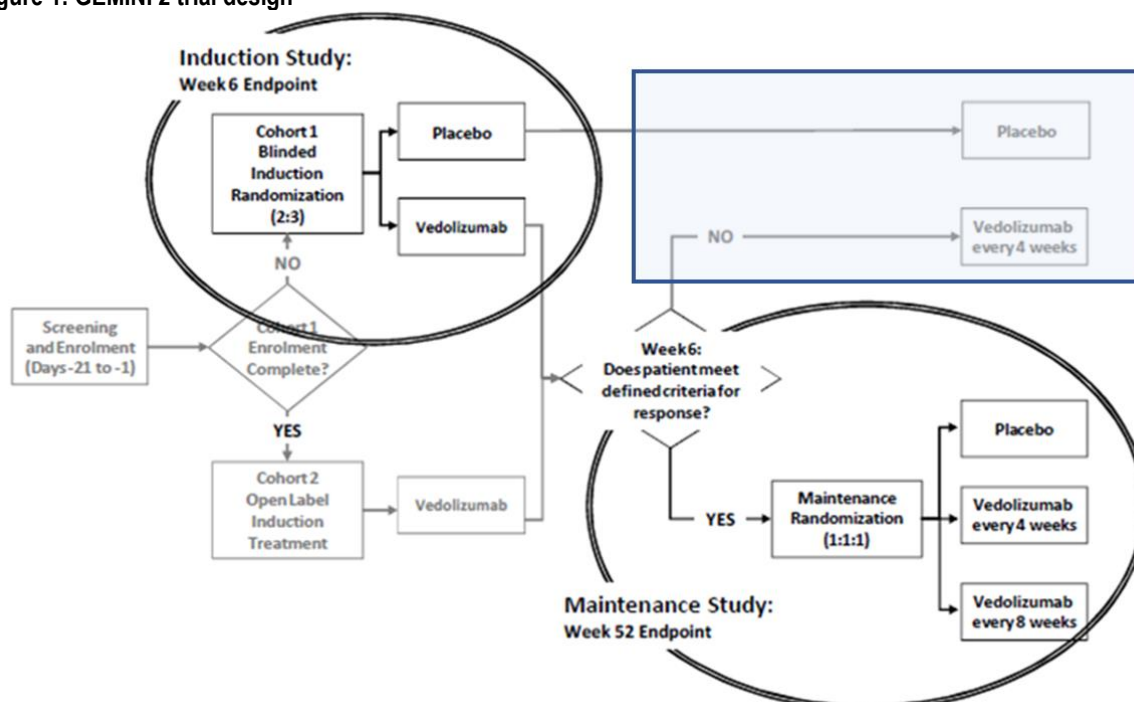
⁴ Watanabe K, Motoya S, Ogata H, Kanai T, Matsui T, Suzuki Y, Shikamura M, Sugiura K, Oda K, Hori T, Araki T, Watanabe M, Hibi T. Effects of vedolizumab in Japanese patients with Crohn's disease: a prospective, multicenter, randomized, placebo-controlled Phase 3 trial with exploratory analyses. *J Gastroenterol.* 2020 Mar;55(3):291-306. doi: 10.1007/s00535-019-01647-w. Epub 2019 Dec 13. PMID: 31836930; PMCID: PMC7026209.

Cochrane Library search identified one additional study (Feagan 2008⁵) within a review of vedolizumab for Crohn's disease⁶; however, this study used both weight-based dosing and a different dosing regimen and was considered not relevant to the current submission.

Comparative effectiveness

6.12 GEMINI 2 included an induction and maintenance phase. A schematic of the clinical trial design of GEMINI 2 is presented in Figure 1. The circles highlight the induction and maintenance intend-to-treat (ITT) populations. The evaluation noted that results from these populations were considered by the PBAC in its March 2015 recommendation. Patients received two induction doses (week 0 and 2) and those who demonstrated a clinical response (CDAI-70) at week 6 for the maintenance ITT population. The maintenance ITT population received a third dose at week 6 and every 8 weeks (i.e., week 14, 22 etc.).

Figure 1: GEMINI 2 trial design



Source: Submission main body p11

Black circles indicate the induction and maintenance ITT population. Blue square indicates the maintenance non-ITT population.

⁵ Feagan BG, Greenberg GR, Wild G, Fedorak RN, Paré P, McDonald JW, Cohen A, Bitton A, Baker J, Dubé R, Landau SB, Vandervoort MK, Parikh A. Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin. *Clin Gastroenterol Hepatol*. 2008 Dec;6(12):1370-7. doi: 10.1016/j.cgh.2008.06.007. Epub 2008 Oct 1. Erratum in: *Clin Gastroenterol Hepatol*. 2009 Apr;7(4):494. PMID: 18829392.

⁶ Hui S, Sinopoulou V, Gordon M, Aali G, Krishna A, Ding NS, Boyapati RK. Vedolizumab for induction and maintenance of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2023, Issue 7. Art. No.: CD013611. DOI: 10.1002/14651858.CD013611.pub2. Accessed 16 January 2024.

- 6.13 The sponsor stated that the justification for an additional induction dose at week 10 is derived from the response to vedolizumab in the delayed response population (i.e., vedolizumab non-ITT maintenance population). These patients received two induction doses (week 0 and 2), did not demonstrate a clinical response and received vedolizumab every 4 weeks (i.e., at week 6, 10, etc.) (Figure 1, blue rectangle). The evaluation noted that as the patients deemed not to have met criteria for response at week 6 were not included in the maintenance study component of the GEMINI 2 trial or the analyses presented to the PBAC in the March 2015 submission, this population was not previously considered by the PBAC as part of the ITT population in its 2015 recommendation.
- 6.14 The submission claimed the response to treatment in the vedolizumab non-ITT population can also be compared with the patients who did not achieve a response to two doses of placebo at week 6 and continued to receive placebo (i.e., a subgroup of the placebo non-ITT maintenance population). The evaluation noted that this proposal does not reflect the proposed comparator regimen of a three-dose induction regimen.
- 6.15 The submission stated patients who had not achieved a clinical response (CDAI-70) at week 6 after receiving two doses of vedolizumab (week 0 and 2) benefited from an additional dose of vedolizumab at week 6 with 16.0% of patients achieving an enhanced clinical response (CDAI-100) at week 10. This was a combination of patients from Cohorts 1 and 2 combined. An additional dose of vedolizumab at week 10 increased the proportion of patients who achieved an enhanced clinical response (CDAI-100) to 21.7% at week 14. The enhanced clinical response rate among placebo-treated subjects who had not responded at week 6 and continued placebo in the maintenance phase was 7.2% at week 10 and 11.6% at week 14. The evaluation noted that as the existing induction regimen includes a dose at week 6, the relevant statistic here is the increase in response, within the non-responder group, of 5.7% at week 14 following the additional dose at week 10 compared to those who achieved clinical response at week 10 following 3 doses at weeks 0, 2 and 6.
- 6.16 The proportions of patients who achieved an enhanced clinical response (CDAI-100) also increase with additional vedolizumab doses in the subgroup of patients who had failed TNF α antagonist from week 10 (16.2%) to week 14 (17.1%) as well as those who had not failed (week 10: 15.4%, week 14: 30.8%). The proportion of week 6 responders from the ITT population of Cohort 1 of the GEMINI 2 study have been added for reference in both Tables 2 and 3.

Table 2: Enhanced clinical response (CDAI-100) in the delayed response population

	Vedolizumab*	Placebo*	Vedolizumab Cohort 1 in GEMINI 2 (reference case)**
Delayed response population			Measured at week 6
week 10	N = 351 56 (16.0%)	N = 69 5 (7.2%)	N = 220 69 (31.4%)
week 14	N = 351 76 (21.7%)	N = 69 8 (11.6%)	
Prior TNF α antagonist failure			
week 10	N = 234 38 (16.2%)	N = 31 3 (9.7%)	
week 14	N = 234 40 (17.1 %)	N = 31 6 (19.4%)	
No TNF α antagonist failure			
week 10	N = 117 18 (15.4%)	N = 38 2 (5.3%)	
week 14	N = 117 36 (30.8%)	N = 38 2 (5.3%)	

Source: Submission main body p12

*Patients who had not achieved a response at week 6 to their respective treatments

**Figure 1A from Sandborn et al 2013.

- 6.17 The submission presented corresponding results for clinical remission (CDAI < 150) for the delayed response population (presented in Table 3).
- 6.18 The submission stated an additional dose of vedolizumab at week 10 increased the proportion of patients who achieved clinical remission to 10.5% at week 14. The clinical remission rate among placebo-treated subjects was 4.3% at week 10 and 10.1% at week 14. Patient numbers were small making percentage comparison less reliable. However, the evaluation noted that the increase in percentage of patients achieving clinical remission between weeks 10 and 14 was larger in the placebo group compared to those that received the week 10 dose. As outlined in Table 3, this was largely driven by low response in the prior TNF α antagonist failure subgroup, compared to the TNF α antagonist naïve group where a greater response rate was seen.
- 6.19 The submission claimed the proportions of patients who achieved clinical remission also increased with additional vedolizumab doses in the subgroup of patients who had failed TNF α antagonist failures from week 10 (5.1%) to week 14 (6.4%) as well as those who had not failed (week 10: 10.3%, week 14: 18.8%).
- 6.20 The submission stated the placebo arms in the TNF α antagonist subgroups were small and hence the estimates of response less reliable than in the overall delayed response population.

Table 3: Clinical remission (CDAI < 150) in the delayed response population

	Vedolizumab*	Placebo*	Vedolizumab Cohort 1 in GEMINI 2 (reference case)**
Delayed response population			Measured at week 6
week 10	N = 351 24 (6.8%)	N = 69 3 (4.3%)	N = 220 32 (14.5%)
week 14	N = 351 37 (10.5%)	N = 69 7 (10.1%)	
Prior TNFα antagonist failure subgroup			
week 10	N = 234 12 (5.1%)	N = 31 2 (6.5%)	
week 14	N = 234 15 (6.4%)	N = 31 4 (12.9%)	
No TNFα antagonist failure subgroup			
week 10	N = 117 12 (10.3%)	N = 38 1 (2.6%)	
week 14	N = 117 22 (18.8%)	N = 38 1 (7.9%)	

Source: Submission main body p13

*Patients who had not achieved a response at week 6 to their respective treatments

** Figure 1A from Sandborn et al 2013.

- 6.21 Of the 76 patients who achieved enhanced clinical response with the additional induction dose at week 10 and then continued to receive dosing every four weeks, by week 52, 53 (69.7%) of these patients were in clinical response and 41 (53.9%) were in clinical remission. The evaluation noted that the inclusion of the fourth induction dose at week 10 in the PI was approved by the TGA based on the clinical response/remission following a four weekly continuing dosing regimen. Vedolizumab 300 mg IV for the treatment of severe CD is only PBS listed for eight weekly continuing dosing. The submission did not provide any clinical response/remission data based on the non-response population receiving a fourth dose at week 10, and then continuing vedolizumab at the PBS maintenance regimen.
- 6.22 The PSCR stated that due to the trial design of the GEMINI 2 trial, the cohort of patients presented as evidence for a Week 10 dose improving response rates is derived from patients who did not achieve a response to the induction phase of GEMINI 2 (i.e., non-ITT maintenance phase). These patients received vedolizumab 300 mg every 4 weeks (i.e., non-ITT maintenance phase) rather than vedolizumab 300 mg IV every 8 weeks (i.e., this was the ITT maintenance phase) due to the trial design of GEMINI 2.

Clinical claim

- 6.23 The submission did not make a specific clinical claim. The submission stated that for non-responders in week 6, an additional dose at week 10 may allow an additional proportion of patients to achieve clinical response and/or remission versus no additional dose.

Economic analysis

- 6.24 The submission initially presented a cost minimisation approach (CMA) of vedolizumab IV under the current PBS restriction versus vedolizumab IV under the proposed PBS restriction over a two-year time horizon (104 weeks) resulting in a nil cost to Government.
- 6.25 The submission stated that patients who commence treatment with PBS-subsidised vedolizumab can lodge a request with the sponsor for an additional dose at week 10 as part of its patient access program. The submission presented an analysis of the data from the patient access program and compared this to the number of initiating patients based on the 10% PBS sample data to calculate approximately 1% of patients who initiate PBS-subsidised treatment with vedolizumab for severe CD were receiving the additional dose through the patient access program.
- 6.26 The submission stated that while a CMA is presented, equi-effective doses and/or dosing regimens are not applicable and hence have not been estimated.
- 6.27 The submission did not provide financial estimates to support a claim of cost savings or cost neutrality. The evaluation considered that to assess the financial impact to Government, a new model would need to be provided, considering:
- The proportion of patients receiving a fourth dose that would be expected not to meet the continuation treatment criteria
 - The discontinuation rate of vedolizumab in the continuing phase
 - The proportion of patients switching from IV to SC
 - The additional MBS costs associated with additional testing and specialist visits
- 6.28 The submission stated it requested a lower AEMP to offset any costs of an additional induction dose over a two-year period of continuing treatment. The evaluation considered that a simpler way to introduce a nil cost to Government would be to amend the AEMP at the initiating item codes only. This would require amendment of the restrictions to separate the initiating and continuing phases, and amendment of the current SPA in place to incorporate differing AEMPs for initiating and continuing regimens. This would reduce the risk of cost neutrality not being realised over two years by limiting the impact of patient discontinuations and switching (including from IV to SC).
- 6.29 The PSCR stated that the sponsor was amenable to this suggestion, and based on the updated CMA that considers the initiating treatment phase only, the AEMP for vedolizumab IV for the proportion of patients who require an additional dose at Week 10 is \$1 (Table 6). The PSCR noted this would require amendment of the restrictions to separate the initiation and continuing phases, and amendment of the current SPA to incorporate differing AEMPs for initiating and continuing regimens.

- 6.30 It may also be possible to achieve cost neutrality through the application of a [REDACTED]% rebate for the week 10 dose under the SPA. This approach would require creation of a separate item code for the week 10 dose.
- 6.31 In its pre-PBAC response, the sponsor stated the [REDACTED]% rebate approach to achieving cost neutrality to Government is consistent with the submission's intent and that it is open to considering this approach. The pre-PBAC response noted that in practice a corresponding SPA rebate is likely to be marginally less than [REDACTED]% once the weighted average patient copayment (\$25.24, using Medicare services data Feb23-Jan24) and weighted hospital markup fees (62% public hospitals and 38% private hospitals) are taken into account in the SPA rebate calculation.

Additional costs and/or offsets

- 6.32 The submission considered that the additional prescription for week 10 induction dose will be written on the same day as vedolizumab is dispensed before being administered intravenously. The submission stated that the cost of a health care practitioner writing the prescription is not included separately and is instead assumed to be captured in the additional cost associated with the IV infusion. This consideration formed part of the submission's basis for requesting an Authority Required (Telephone/Online) listing due to the 1-2 week processing time required for Authority Required (Written) listings.
- 6.33 For the existing vedolizumab initial 1, 2 and 3 listings, patients receive the third induction dose in week 6 and an assessment of response is required to be conducted no earlier than week 12. However, for the proposed week 10 dose regimen, patients will need to be assessed prior to or at week 10 to determine eligibility for the week 10 dose and reassessed after week 12 to determine eligibility for continuing therapy. The submission claimed some doctors already organise a visit between weeks 6 and 8 and so this additional assessment would not result in an increase in prescriber appointments. The submission also stated response could also be assessed based on an additional blood test (platelet count, ESR or CRP) or faecal test (calprotectin or lactoferrin), which can be conducted at a local pathology laboratory. The evaluation noted that no data was provided to show the extent to which prescribers routinely schedule appointments for patients in weeks 6 to 8. Given the submission claimed only some doctors undertake this practice, it would be reasonable to anticipate that this would constitute an increase in appointments for patients of the doctors who do not currently organise appointments in weeks 6 to 8. An assessment of response prior to week 12 would not be valid for the purpose of determining eligibility for continuing therapy under the current criteria. It is unclear based on what is provided if any prescribers currently perform assessment prior to week 10. It seems reasonable to assume the proposed listing is likely to incentivise prescribers to perform an additional assessment for a majority, if not all, patients prior to, or at week 10 to determine eligibility for the additional subsidised dose. The cost of any additional health services required to complete assessment, such as blood tests and specialist appointments, were not included in the financial estimates.

- 6.34 The submission noted that the inclusion of the week 10 dose in the PBS restriction is associated with an additional IV infusion. Consistent with previous economic analyses of vedolizumab IV, the cost of this additional IV infusion has been included in the CMA. The submission stated that aside from dosing frequency during the initiation treatment period, there are no other differences in administration for which the resource use and associated cost should be included in the analysis. The cost of the additional IV administration is based on the 85% benefit for MBS item 14245 (i.e., \$91.25); intravenous infusion of an immunomodulating agent for at least 2 hours duration where the agent is provided under Section 100 of the PBS.
- 6.35 The submission stated that the inclusion of an additional dose at Week 10 in the current restriction does not result in additional monitoring requirements or management of adverse events.
- 6.36 The AEMP for vedolizumab was initially established based on a CMA that included an additional cost of approximately \$3.00 per 300 mg vial associated with the monitoring for PML. As the submission has requested removal of the monitoring requirement for PML from all restrictions for vedolizumab, the submission stated that these administration costs could reasonably be added back to the AEMP. However, the submission has not included this cost offset in the CMA.

Vedolizumab subcutaneous form

- 6.37 The submission stated 'The current analysis assumes that patients continue treatment with vedolizumab 300 mg IV when some may prefer vedolizumab 108 mg SC. However, the Services Australia data indicate that most patients receive treatment with vedolizumab 300 mg IV rather than vedolizumab 108 mg SC thereby supporting the approach. Further, vedolizumab 108 mg SC is listed on a CMA-basis to vedolizumab 300 mg when used for continuing treatment and is therefore not expected to impact on the analysis.'
- 6.38 The evaluation noted that vedolizumab SC listings allow for patients to switch to SC therapy after a minimum of two IV induction doses (at week 6) and is then dosed fortnightly. Patients are also able to switch to SC therapy after completion of induction therapy with VDZ IV or following a 24-week continuing therapy prescription. The submission did not consider whether patients who transfer to VDZ SC at weeks 6 or 8 should be eligible for the week 10 IV dose if they meet the criteria.
- 6.39 The PSRC stated that the week 10 dose is solely intended for patients receiving initial treatment with vedolizumab IV. While the initial restriction allows for patients to commence treatment with vedolizumab SC from week 6, the TGA PI clearly describes that the SC form is for maintenance treatment only. Thus, patients who commence treatment with vedolizumab SC from Week 6 must necessarily have achieved a response and the SC form is therefore used to maintain this response.

Cost of medicines

- 6.40 The proposed effective AEMP for vedolizumab 300 mg IV for severe CD is presented in Table 4. The submission stated that because the AEMP for the proposed restriction applies only to the $\frac{1}{2}$ of patients who require an additional dose at week 10, the proposed effective AEMP that accounts for the distribution of patients who do $\frac{1}{2}$ at $\frac{1}{2}$ and do not $\frac{1}{2}$ at $\frac{1}{2}$ require the additional dose at week 10 is therefore $\frac{1}{2}$ (Table 4).
- 6.41 Table 5 presents the PSCR amended proposed effective AEMP based on $\frac{1}{2}$ patients who require an additional dose at week 10 and an effective price of $\frac{1}{2}$ for the induction doses.

Table 4: Cost of medicines at the confidential effective AEMP

	Strength	Max Qty (units)	Max Qty (packs)	Effective AEMP
AEMP for the current restriction				
Vedolizumab 300 mg IV	300 mg	1	1	$\frac{1}{2}$
AEMP for the $\frac{1}{2}$ of patients who may derive benefit from a dose at Week 10				
Vedolizumab 300 mg IV	300 mg	1	1	$\frac{1}{2}$
Weighted average AEMP under the proposed restriction ($\frac{1}{2}$ of patients)				
Vedolizumab 300 mg IV	300 mg	1	1	$\frac{1}{2}$

Source: Submission main body p16

Abbreviations: Max = maximum, Qty = Quantity, AEMP = Approved Ex-manufacture price, IV = intravenous

Table 5: Cost of medicines at the confidential effective AEMP following PSCR

	Strength	Max Qty (units)	Max Qty (packs)	Effective AEMP
AEMP for the current restriction				
Vedolizumab 300 mg IV	300 mg	1	1	$\frac{1}{2}$
AEMP for the $\frac{1}{2}$ of patients who may derive benefit from a dose at Week 10				
Vedolizumab 300 mg IV	300 mg	1	1	$\frac{1}{2}$
Weighted average AEMP under the proposed restriction ($\frac{1}{2}$ of patients)				
Vedolizumab 300 mg IV	300 mg	1	1	$\frac{1}{2}$

Source: Submission main body p16

Abbreviations: Max = maximum, Qty = Quantity, AEMP = Approved Ex-manufacture price, IV = intravenous

- 6.42 Over the 2-year time horizon, patients under the current PBS restriction require a total 14.25 administrations, whereas 15.25 administrations are required under the proposed restriction.

Table 6: Cost minimisation approach – Additional dose at Week 10 versus current PBS dosing schedule

	PBS dosing schedule	Additional dose at Week 10
Initial treatment AEMP	$\frac{1}{2}$	$\frac{1}{2}$
Cost of infusion	\$91.25	\$91.25
Cost per administration	$\frac{1}{2}$	$\frac{1}{2}$
Administration initial treatment period	3	4
Total cost of initial treatment period	$\frac{1}{2}$ (3 x $\frac{1}{2}$)	$\frac{1}{2}$ (4 x $\frac{1}{2}$)

Source: Pre-Sub-Committee Response p3

Table 7: Cost minimisation approach over 2 years

	Current PBS restriction (14.25 * \$)	Proposed PBS restriction incl Week 10 dose (4 * \$ + 11.25 * \$) ^a	Incremental cost
Vedolizumab 300 mg IV	\$	\$	-\$
Administration	\$1,300.31	\$1,391.56	\$91.25
Total cost of treatment	\$	\$	\$

Source: Submission main body p17

^a calculation amended following Pre-Sub-Committee Response

Abbreviations: IV = intravenous; PBS = Pharmaceutical Benefits Scheme

6.43 The submission stated that based on the current and proposed confidential AEMP and the cost of the IV administration, the total cost of treatment with vedolizumab 300 mg IV under the current and proposed PBS restrictions of \$ are identical.

Drug cost/patient/2 years

6.44 Based on the proposed effective AEMP of \$ for the induction doses and maintaining the current AEMP for continuing doses at \$, the drug cost/patient/2 years for patients requiring treatment under the proposed regimen was estimated to be \$ based on 15.25 administrations in 104 weeks of treatment (4 induction doses and 1 dose every 8 weeks thereafter). This is based on the weighted average DPMQ between public and private hospital administration (64.07% public and 35.93% private sourced from Table 8). The treatment is ongoing.

Estimated PBS usage & financial implications

6.45 The Drug Utilisation Sub-Committee (DUSC) did not consider the submission.

6.46 As the initiation and continuing treatment restrictions are combined into a single PBS item code, the submission stated it was not possible to estimate the number of patients who newly commence PBS subsidised treatment with vedolizumab 300 mg IV and require an additional dose at Week 10 from the number of services processed by Services Australia. The submission therefore estimated the predicted use of the additional dose of vedolizumab 300 mg IV at week 10 using an epidemiological approach. The evaluation noted that the approach taken is not a true epidemiological approach, but rather uses PBS data to determine the number of initiating patients and applies the proportion requiring a week 10 dose based on the number of patients in the access program.

6.47 The submission noted that while the additional dose at Week 10 is currently provided by the sponsor through the patient access program, the cost of continuing treatment for this cohort is already captured in the current PBS expenditure.

6.48 The analysis of the predicted use and financial implications is based on the calendar years 2024 to 2029. The variables and associated data sources that were used to determine the predicted use of the additional dose of vedolizumab 300 mg IV at week 10 are summarised in Table 8.

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Table 8: Variables and data sources

Variable	Source
Epidemiology	
Patients newly initiating treatment with vedolizumab	10% PBS sample data
Patients requiring an additional dose of vedolizumab 300 mg IV at Week 10	Takeda patient access program
Utilisation and cost	
Vedolizumab 300 mg IV [proposed] AEMP --- for those who require an additional dose only ---	Published: \$2,949.93 Effective: \$█ ^a
Vedolizumab 300 mg IV [current] AEMP	Published: \$2,949.93 Effective: \$█
Public versus private hospital (%)	Services processed for PBS items 10390W and 10415E in the 2022 calendar year. Public: 64.07% Private: 35.93%
Vedolizumab 300 mg IV administration	MBS item 14245 100% Benefit: \$107.30
Average patient copayments	Distribution of services processed for PBS items 10390W and 10415E in the 2022 calendar year. PBS: \$23.54 RPBS: \$7.06

Source: Submission main body p18, amended during evaluation to reflect updated proposed AEMP

^a price amended following PSCR

Abbreviations: MBS = Medicare Benefits Schedule PBS = Pharmaceutical Benefits Scheme, RPBS = repatriation Pharmaceutical Benefits Schedule, IV = intravenous, AEMP = Approved Ex-Manufacturer Price

6.49 The number of patients that commence treatment with vedolizumab was sourced from the 10% PBS sample data. Over the period August 2021 to June 2023, approximately 30 patients with severe CD newly commenced treatment with vedolizumab on the PBS each month.

6.50 The modelled number of patients that are expected to newly commence treatment with vedolizumab in each year of the analysis was estimated by applying the percent change in the number of initiations from the trendline analysis to the observed initiations in the 2022 calendar year. The predicted number of patients with severe CD that are expected to newly commence treatment with vedolizumab in each year over the period 2023 to 2029 is presented in Table 9.

Table 9: Patients with severe CD newly initiating treatment with vedolizumab

	2022	2023	2024	2025	2026	2027	2028	2029
Analysis year	Reference	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Predicted patients initiating treatment with vedolizumab								
Predicted initiations	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Change vs prior year		%	%	%	%	%	%	%
Modelled patients initiating treatment with vedolizumab								
Observed initiations	█ ¹	-	-	-	-	-	-	-
Modelled initiations	-	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Initiations/month	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹

Source: Entyvio (vedolizumab) - CD - UCM.xlsx, worksheet Initiations - 10% PBS

The redacted values correspond to the following ranges:

¹ < 500

6.51 An analysis of the supply of the IV form of vedolizumab was undertaken during the evaluation. Data extracted from the PBS, Authorities and Date of Death databases

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maintained by Department of Health and Aged Care, processed by Services Australia were used for analyses.

- 6.52 Data were extracted for all supplies of the powder for injection 300 mg for vedolizumab for the treatment of severe CD from the date of first listing (1 October 2017) to 30 November 2023. The data were extracted based on the date of supply. Supplies for subcutaneous injections of vedolizumab were excluded. The PBS prescriptions data were linked to the Authorities data to identify supplies for new patients (i.e. the Initial 1 authority).
- 6.53 The number of new patients supplied vedolizumab was counted by listing year (i.e. Oct-Sep) commencing from 1 October 2017, presented in Table 10.

Table 10: Number of new patients supplied IV vedolizumab for severe Crohn disease under an Initial 1 treatment authority

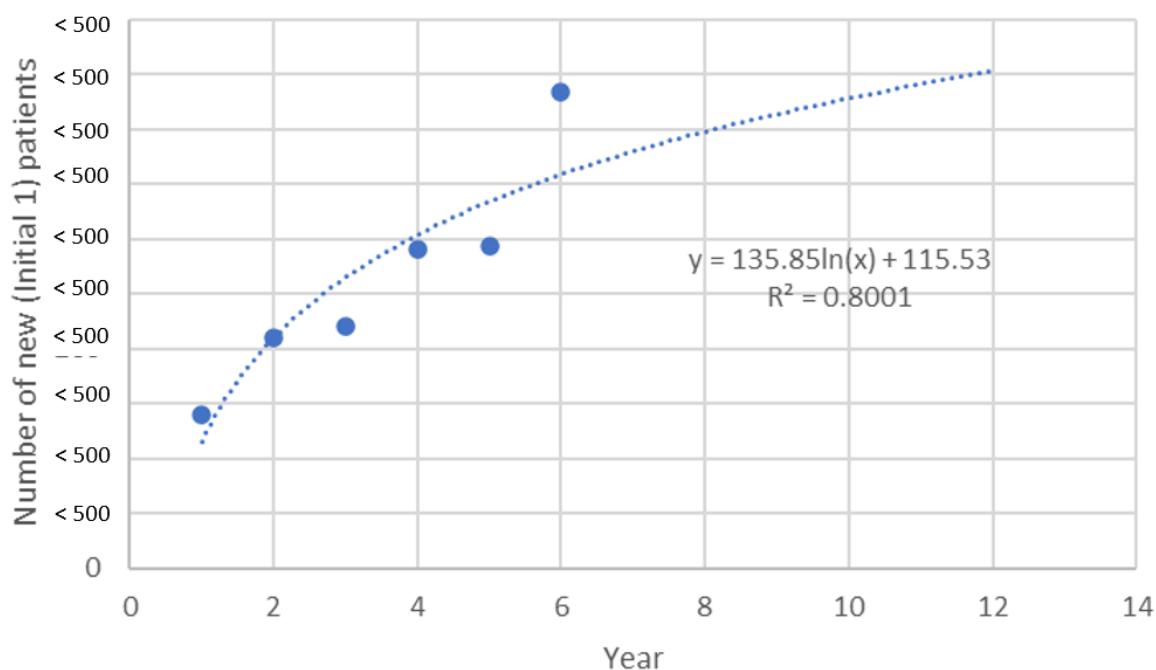
Listing year	New patients
Year 1 (Oct 2017 - Sep 2018)	1
Year 2 (Oct 2018 - Sep 2019)	1
Year 3 (Oct 2019 - Sep 2020)	1
Year 4 (Oct 2020 - Sep 2021)	1
Year 5 (Oct 2021 - Sep 2022)	1
Year 6 (Oct 2022 - Sep 2023)	1

The redacted values correspond to the following ranges:

1 < 500

- 6.54 Consistent with the approach used in the submission, a logarithmic trendline was applied to forecast the number of new IV patients based on the actual utilisation over the first 6 years of listing as shown in Figure 2.

Figure 2: Logarithmic forecast of the number of new (Initial 1) patients with severe Crohn disease supplied IV vedolizumab



6.55 The number of forecasted new patients supplied 3 IV doses is presented in Table 11.

Table 11: Number of projected new patients supplied 3 doses of IV vedolizumab for severe Crohn disease

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients newly initiating treatment						
March 2024 submission based on 10% PBS sample ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Evaluation forecast based on 100% PBS sample matched to Initial 1 authorities	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹

¹ Figures sourced from the main March 2024 submission, Table 4.3-3 page 21.

The redacted values correspond to the following ranges

¹ < 500

6.56 The evaluation noted there was limited detail provided in the submission about the 10% PBS sample, including whether the data are based on the date of processing, or the date of supply and which PBS item codes were used for the data extraction. It is unclear how patients who newly commenced vedolizumab were identified as the PBS 10% sample does not contain the written authority approval data which is required to distinguish between treatment phase within individual item codes.

6.57 The submission presented the number of patients for whom the prescriber requested an additional dose via the sponsor’s patient access program at week 10 over the period August 2021 to September 2023 (Table 12). The submission assumed that all eligible patients are utilising the sponsor’s patient access program.

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Table 12: Patients with severe CD requiring an additional dose of vedolizumab IV at Week 10

Month	Patients requiring an additional dose at Week 10	Patients newly commencing treatment with vedolizumab (from submission)	Patients newly commencing treatment with vedolizumab (from Department)
Aug-21	1	1	1
Sep-21	1	1	1
Oct-21	1	1	1
Nov-21	1	1	1
Dec-21	1	1	1
Jan-22	1	1	1
Feb-22	1	1	1
Mar-22	1	1	1
Apr-22	1	1	1
May-22	1	1	1
Jun-22	1	1	1
Jul-22	1	1	1
Aug-22	1	1	1
Sep-22	1	1	1
Oct-22	1	1	1
Nov-22	1	1	1
Dec-22	1	1	1
Jan-23	1	1	1
Feb-23	1	1	1
Mar-23	1	1	1
Apr-23	1	1	1
May-23	1	1	1
Jun-23	1	1	1
Jul-23	1	No data	1
Aug-23	1	No data	1
Sep-23	1	No data	1
Total	1	2	2
August 2021 to June 2023	1%	1/2	1%
July 2022 to June 2023	1%	1/1	1%

Source: Entyvio (vedolizumab) - CD - CMA.xlsx; Evaluation sourced patient data

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 1,000

6.58 The submission concluded that these data together with the total number of patients who newly commence treatment with vedolizumab from the 10% sample data show that 1% of patients required an additional dose of vedolizumab at Week 10 in the most recent 12-month period (July 2022 to June 2023). The evaluation noted the percentage was calculated based on the number of patients to whom the sponsor claimed it has supplied an additional week 10 dose under its patient access program. No evidence was supplied to enable validation of this patient number. No information was supplied as to the criteria used by the sponsor in assessing applications for the patient access program or whether the patients receiving the week 10 dose went on

to achieve a clinical response sufficient to enable them to access vedolizumab under the continuing PBS restriction. No information was provided as to whether any applications to the patient access program for the week 10 dose were rejected by the sponsor based on any eligibility criteria. It is therefore unclear if there are any patients who did not achieve response by week 10 and were ineligible under the sponsor program who may be eligible under the proposed listing or vice versa (eligible under sponsor program but ineligible under the proposed PBS listing).

- 6.59 The PSCR provided an extract of the patient access program reports to assist in validating the number of patients who have been supplied with an additional dose at Week 10. The PSCR stated that the only eligibility criteria applied when assessing requests from prescribers for an additional dose at Week 10 through the patient access program was that patients must be receiving PBS-subsidised treatment with vedolizumab for severe CD. As such, no request for an additional dose at Week 10 has been rejected to date. The PSCR stated that in terms of the number of patients who received the additional dose at Week 10 and subsequently went on to achieve a response and met the criteria for continuing treatment with vedolizumab, this information is not collected via the patient access program; however, it reiterated the claim the evidence from GEMINI 2 showed that the additional dose at Week 10 increased the proportion of patients who achieved clinical remission by 3.7%.
- 6.60 The evaluation presented alternate patient numbers based on data extracted from the PBS, Authorities and Date of Death databases maintained by Department of Health and Aged Care, processed by Services Australia. The PBS prescriptions data was linked to the Authorities data to identify supplies for new patients (i.e., the Initial 1 authority). The sponsor's patient access program data together with the total number of patients who newly commence treatment with vedolizumab from the analysis shows that $\frac{1}{2}$ % of patients required an additional dose of vedolizumab at Week 10 in the 12-month period July 2022 to June 2023. This is higher than the submission calculated $\frac{1}{2}$ %. Alternate proposed weighted AEMPs were calculated using the various estimated utilisation of the fourth dose and presented in Table 13.
- 6.61 The PSCR stated that the estimates from the 100% PBS sample are more reliable and therefore appropriate to inform the estimation of the proportion of patients who require an additional dose at Week 10. Based on the total number of patients who had been supplied an additional dose at Week 10 through the patient access program, the recalculated proportion of patients who are expected to require an additional dose at Week 10 is $\frac{1}{2}$ %.

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Table 13: Estimated utilisation of fourth vedolizumab dose based on varying time periods of patient data

Period	Submission		Evaluation	
	Estimated utilisation of fourth dose	Weighted average AEMP	Estimated utilisation of fourth dose	Weighted average AEMP
Jul-22 to Jun-23	█ %	\$ █	█ %	\$ █
Aug-21 to June-23	█ %	\$ █	█ %	\$ █
Recent 12-months (Oct22-Sep23)	Not provided	-	█ %	\$ █
Recent 24-months (Oct21-Sep23)	Not provided	-	█ %	\$ █
All available data (Aug21-Sep23)	Not provided	-	█ %	\$ █

Source: Entyvio (vedolizumab) - CD - CMA.xlsx; Evaluation sourced patient data

6.62 The ESC advised that all available data (Aug21-Sep23) should be used to estimate percentage of newly initiating patients requiring a fourth dose at week 10, providing as estimated utilisation of a fourth dose at █% of initiating patients. The PSCR supported this request for advice from the ESC.

6.63 The resulting number of patients with severe CD who are expected to require an additional dose of vedolizumab 300 mg IV at Week 10, based on the estimates provided in the submission, is therefore < 500 in Year 1 increasing to < 500 patients in Year 6 (Table 14).

Table 14: Patients with severe CD requiring an additional dose at Week 10

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Newly initiating treatment	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Additional Week 10 dose (%)						
Additional Week 10 dose (n)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹

Source: Entyvio (vedolizumab) - CD - UCM.xlsx, worksheet 2a. Patients – incident

The redacted values correspond to the following ranges

¹ < 500

6.64 Based on the evaluation forecast on new initiating treatment patient numbers and the █% calculation from the evaluation and the sponsor’s patient access program data, the number of patients with severe CD requiring an additional dose at week 10 was recalculated (see Table 15).

Table 15: Evaluation estimate of patients with severe CD requiring an additional dose at Week 10

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Newly initiating treatment (n)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Additional Week 10 dose (%)						
Additional Week 10 dose (n)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹

Source: Evaluation analyses with sponsor patient access program data

The redacted values correspond to the following ranges

¹ < 500

6.65 The PSCR stated that the final proposed weighted AEMP for vedolizumab IV for the initiating treatment phase can be provided in the pre-PBAC response based on the ESC’s advice on the proportion of patients who require the Week 10 dose. The PSCR considered that the weighted AEMP for the initiating treatment phase would be determined as follows: (\$█ x % patients who do not require an additional dose) + (\$█ x % patients who do require the additional dose at Week 10). The PSCR provided a table

summarising the estimated net financial impact which it now estimated to be a small net save, but did not provide a revised model supporting this.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of an additional dose of vedolizumab 300 mg at week 10 for the initial treatment of severe CD for patients who have not responded to therapy after the existing three dose induction therapy, provided that it is cost-neutral to Government.
- 7.2 The PBAC noted that the additional dose is currently provided to eligible patients through the sponsor's compassionate access program. The PBAC also noted advice from specialists that this approach is being used in clinical practice.
- 7.3 The PBAC noted input from Crohn's and Colitis Australia stating that it understood that administration of a fourth dose at week 10 is evidence-based clinical practice for initial treatment experienced by people with IBD.
- 7.4 The PBAC noted the clinical trials presented, GEMINI 2 (C13007) and GEMINI 3 (C13011), were previously considered by the PBAC in its consideration of listing vedolizumab 300 mg for IV infusion for the treatment of CD.
- 7.5 The PBAC noted that patient numbers of the GEMINI II trial were small making percentage comparison less reliable. The PBAC noted that an additional dose of vedolizumab at week 10 increased the proportion of patients who achieved clinical remission to 10.5% at week 14. The clinical remission rate among placebo-treated subjects was 4.3% at week 10 and 10.1% at week 14. The PBAC noted that the submission claimed the proportions of patients who achieved clinical remission also increased with additional vedolizumab doses in the subgroup of patients who had failed TNF α antagonist from week 10 (5.1%) to week 14 (6.4%) as well as those who had not failed (week 10: 10.3%, week 14: 18.8%).
- 7.6 The PBAC considered the listing of the additional dose as an Authority Required (Telephone/Online) item, rather than as an Authority Required (Written) item, was appropriate to allow sufficient time between assessment of an inadequate response after 6 weeks and the additional dose at week 10.
- 7.7 The PBAC considered that it would be appropriate for the criteria to require patients to be assessed after 6 weeks and prior to 10 weeks from the initial dose.
- 7.8 The PBAC also recommended the removal of the requirement to assess the risk of developing PML during this treatment from all PBS listings for vedolizumab, following the updates for the RMP ASA and the PI where the need for a patient alert card has been removed. The PBAC acknowledged that whilst it is common for a PI to suggest monitoring for adverse events or other parameters that may be suggestive of risks of an AE (e.g., blood pressure, cardiac parameters etc), these are not generally included

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as clinical criteria in the PBS listing.

- 7.9 The PBAC noted minor flow-on restriction changes to the prescribing instructions of the subcutaneous form of vedolizumab for severe CD.
- 7.10 The PBAC recommended the listing of the additional dose be cost-neutral to the Government and noted that the sponsor had proposed this in its submission.
- 7.11 The PBAC noted that the evaluation and the ESC had provided different options to achieve cost-neutrality, including offsetting the additional cost in the initial treatment phase only, or providing the additional dose with the application of a 10% rebate. The PBAC advised that the sponsor work with the Department on an appropriate pricing approach for vedolizumab in severe CD to achieve cost neutrality.
- 7.12 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 an additional induction dose and the amendment of the current clinical criteria, the treatment is not expected to address a high and urgent unmet clinical need.
- 7.13 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:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
VEDOLIZUMAB					
vedolizumab 300 mg injection, 1 vial	NEW (Public) NEW (Private) MP	1	1	0	Entyvio
Restriction Summary [new 1] / Treatment of Concept: [new 2]					
Concept ID (for internal Dept. use)	Category / Program Section 100 – Highly Specialised Drugs Program				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
Prescribing rule level	<p>Administrative Advice: SEVERE CROHN DISEASE - TREATMENT PHASES AND CYCLES</p> <p>The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of benefits that contain the words: 'severe Crohn disease' in the stated PBS indication. Some of these benefits are not biological medicines, but are small molecules (e.g. a Janus-kinase inhibitor). Where the term 'biological medicine' appears in the restriction, it includes such benefits for PBS administrative purposes.</p> <p>A patient is eligible for PBS-subsidised treatment with only one PBS-subsidised biological medicine at any one time.</p>				

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	<p><i>Treatment cycle:</i> A treatment cycle begins when an authority application is approved under an Initial 1 or Initial 3 type restriction. Once commenced, where biological medicine fails to provide the patient with an adequate response on 3 occasions, the current treatment cycle ends and there must be an absence of PBS-subsidy for a period of 5 years. The 5 year break is measured from the date of the last approval for PBS-subsidised biological medicine treatment in the most recent cycle to the date of the first application for initial treatment with a biological medicine under the new treatment cycle.</p> <p>An exception to this 5 year break clause applies where:</p> <ul style="list-style-type: none">(i) since the commencement of the break, an additional biological medicine has since become PBS-listed with a different pharmacological mechanism of action (i.e. the newly listed biological medicine) relative to those available on the PBS at the time of commencing the 5 year break; and(ii) the patient has never been prescribed the newly listed biological medicine; and(iii) the prescribed biological medicine is the newly listed biological medicine. <p>Prescribing of the newly listed biological medicine is to occur through the 'Initial 2' treatment phase listing and the patient will not be in a new treatment cycle (i.e. where this newly listed biological medicine fails to provide an adequate response, the current treatment cycle ends and there must be an absence of PBS-subsidised biological medicine for a period of 5 years unless the exception outlined above is triggered again).</p> <p>Within the same treatment cycle, the same PBS-subsidised biological medicine cannot continue to be subsidised where it has resulted in an inadequate response. An inadequate response is one which does not meet the minimum improvements in disease measures stated in the Continuing treatment restriction. A serious adverse reaction leading to treatment discontinuation will be exempted from being counted as an inadequate response.</p> <p>There is no limit to the number of treatment cycles a patient may undertake in their lifetime.</p> <p><i>Treatment phases:</i></p> <p>(a) Initial 1 Apply through this treatment phase where the patient has never been treated with PBS-subsidised biological medicine for this indication.</p> <p>(b) Initial 2 Apply through this treatment phase where the prescribed treatment is changing (other than dose/form), or, where there has been a break in therapy of less than 5 years and treatment is resuming; authority applications through this treatment phase do not require prior response to conventional therapies to be re-established and do not require baseline disease activity to be re-demonstrated. An assessment of response to the preceding supply must be provided - where it is not, it will be assumed that the preceding supply provided an inadequate response.</p> <p>(c) Initial 3 Apply through this treatment phase where treatment is resuming after an absence of PBS-subsidy for at least 5 years; authority applications through this treatment phase do not require a re-trial of conventional therapies.</p> <p>(e) Continuing treatment Apply through this treatment phase where an adequate response to the preceding supply is observed (or where the dose is increasing where multiple strengths exist). It is recommended that a patient be reviewed in the 4 weeks prior to exhausting the current supply to ensure uninterrupted supply. Continuing treatment authority applications are not to be made on the same day as Initial treatment authority applications.</p>
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	<p>(f) Balance of supply Apply through this type of treatment phase only where the benefit was not requested in the full amount available in the preceding supply - this may be because the maximum quantity was not prescribed and/or the full number of repeat prescriptions was not prescribed. The intent of this treatment phase listing is to: (i) provide the balance of what could have been obtained had the full quantity and number of repeats been prescribed in the preceding authority application, (ii) allow further time for an adequate response to treatment to be demonstrated where it may not have already, and (iii) provide more immediate access to PBS-subsidy via a telephone/online authority application relative to an 'in-writing only' application where the preceding supply was obtained through such.</p>
	<p>Administrative Advice: Special Pricing Arrangements apply.</p>
	<p>Indication: Severe Crohn disease</p>
	<p>Treatment Phase: Initial 4 (additional dose at week 10)</p>
	<p>Treatment criteria:</p>
	<p>Must be treated by a gastroenterologist (code 87); or</p>
	<p>Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or</p>
	<p>Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)]</p>
	<p>Clinical criteria:</p>
	<p>Patient must have received prior PBS-subsidised treatment with this drug for this condition in this treatment cycle</p>
	<p>Clinical criteria:</p>
	<p>Patient must have received 3 doses of initial treatment under Initial 1 (new patient) restriction (the initial infusion regimen at 0, 2 and 6 weeks); OR Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) restriction (the initial infusion regimen at 0, 2 and 6 weeks); OR Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) restriction to complete the 3 doses (the initial infusion regimen at 0, 2 and 6 weeks); OR Initial 1 or 2 or 3 with a Balance of supply</p> <p>Patient must have received 3 doses of initial treatment under either (i) initial 1, (ii) initial 2, (iii) initial 3</p>
	<p>Clinical criteria:</p>
	<p>Patient must not have achieved an adequate response to this drug after a total of 3 doses of initial treatment under either (i) initial 1, (ii) initial 2, (iii) initial 3 under this restriction. minimum of 6 weeks of treatment.</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>The treatment must not exceed a total of 4 doses to be administered at weeks 0,2,6 and 10 under the initial treatment phase</p>
	<p>AND</p>
	<p>Clinical criteria</p>
	<p>Patient must have an adequate response to this drug defined as a reduction in Crohn Disease Activity Index (CDAI) Score to a level no greater than 150 if assessed by CDAI or if affected by extensive small intestine disease; or</p>
	<p>Patient must have an adequate response to this drug defined as (a) an improvement of intestinal inflammation as demonstrated by: (i) blood: normalisation of the platelet count, or an erythrocyte sedimentation rate (ESR) level no greater than 25 mm per hour, or a C reactive protein (CRP) level no greater than 15 mg per L; or (ii) faeces: normalisation of lactoferrin or calprotectin level; or (iii) evidence of mucosal healing, as demonstrated by diagnostic imaging findings, compared to the baseline assessment; or (b) reversal of high faecal output state; or (c) avoidance of the need for surgery or total parenteral nutrition (TPN), if affected by short gut syndrome, extensive small intestine or is an ostomy patient</p>

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	AND
	Clinical criteria
	Patient must be appropriately assessed for the risk of developing progressive multifocal leukoencephalopathy whilst on this treatment
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing Instructions: Patient must not receive more than one dose at 10 weeks under this restriction A maximum quantity and number of repeats to provide for an additional dose of this drug consisting of one vial of 300 mg, with one dose to be administered at week 10, will be authorised.
	Prescribing Instructions: The assessment of the patient's response to the initial course of treatment must be conducted prior to 10 weeks and a second assessment must be conducted following a minimum of 12 weeks of treatment and no later than 4 weeks from the cessation of that treatment course. If the response assessment is not conducted within these timeframes, the patient will be deemed to have failed this course of treatment in this treatment cycle.
	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, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing 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 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.
	Prescribing instructions: An adequate response to this drug defined as A reduction in Crohn Disease Activity Index (CDAI) Score to a level no greater than 150 if assessed by CDAI or if affected by extensive small intestine disease; or (a) an improvement of intestinal inflammation as demonstrated by: (i) blood: normalisation of the platelet count, or an erythrocyte sedimentation rate (ESR) level no greater than 25 mm per hour, or a C-reactive protein (CRP) level no greater than 15 mg per L; or (ii) faeces: normalisation of lactoferrin or calprotectin level; or (iii) evidence of mucosal healing, as demonstrated by diagnostic imaging findings, compared to the baseline assessment; or (b) reversal of high faecal output state; or (c) avoidance of the need for surgery or total parenteral nutrition (TPN), if affected by short gut syndrome, extensive small intestine or is an ostomy patient
	Administrative Advice: Patient must be assessed as having an inadequate response to the drug after completing an initial infusion regimen at 0, 2, and 6 weeks and prior to 10 weeks.
	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).

8.2 Amendment of clinical criteria:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
VEDOLIZUMAB					

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vedolizumab 300 mg injection, 1 vial	10384M	1	1	0	Entyvio
	10390W				
	10398G				
	10415E				
vedolizumab 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	12620F	1	2	0	
	12638E				
	12644L				
	12647P	1	2	5	
	12369F				
12654B					
Clinical Criteria:					
Patient must be appropriately assessed for the risk of developing progressive multifocal leukoencephalopathy whilst on this treatment					

8.3 Flow on changes:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
VEDOLIZUMAB					
vedolizumab 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	12638E	1	2	0	
Prescribing Instructions: Where four initial doses of vedolizumab (at weeks 0, 2, 6 and 10) is administered via intravenous infusion, initial treatment with subcutaneous form will commence at week 14 (4 weeks after the fourth dose). A maximum quantity with no repeats should be requested to provide for weeks 14 and 16.					

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.