

**5.11 VEDOLIZUMAB,
Injection 108 mg in 0.68 mL pre-filled syringe,
Injection 108 mg in 0.68 mL pre-filled pen,
Entyvio®,
Takeda Pharmaceuticals Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The submission requested Section 85, Authority Required listings for a subcutaneously administered formulation of vedolizumab (VDZ SC), (i) as maintenance treatment for patients with moderate to severe ulcerative colitis (MSUC) and (ii) as maintenance treatment for patients with severe Crohn’s disease (CD). Vedolizumab for intravenous infusion (VDZ IV) is currently listed on the PBS for both initial and continuing treatment of MSUC and severe CD.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis (CMA) between VDZ SC and VDZ IV. The key components of the clinical issue addressed by the submission are summarised below.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	<ul style="list-style-type: none"> Patients with moderate or severe ulcerative colitis (MSUC) who have responded to induction treatment with VDZ IV. Patients with severe Crohn’s disease (CD) who have responded to induction treatment with VDZ IV.
Intervention	VDZ SC, 108 mg pre-filled pen or pre-filled syringe every two weeks, as maintenance therapy following induction treatment with VDZ IV.
Comparator	VDZ IV, 300 mg infusion every 8 weeks, as maintenance therapy following induction treatment with VDZ IV.
Outcomes	MSUC: Clinical remission, mucosal healing, durable clinical response, durable clinical remission, corticosteroid-free remission Severe CD: Clinical remission, enhanced clinical response, corticosteroid-free remission
Clinical claim	<ul style="list-style-type: none"> In patients with MSUC who have responded to VDZ IV induction treatment, VDZ SC maintenance treatment is as effective as VDZ IV maintenance treatment for clinical remission. In patients with severe CD who have responded to VDZ IV induction treatment, VDZ SC maintenance treatment is as effective as VDZ IV maintenance treatment for clinical remission. VDZ SC is associated with a similar safety and tolerability profile to that seen with VDZ IV.

Source: Table 1.1-1, p 6 of the submission.

IV = intravenous; SC = subcutaneous; VDZ= vedolizumab

2 Background

Registration status

- 2.1 Two presentations of VDZ SC (vedolizumab 108 mg/0.68 mL solution for injection prefilled syringe and VDZ 108 mg/0.68 mL solution for injection pre-filled pen) were TGA registered on 12 May 2020 for the following indications:

- i) Treatment of adult patients with moderate to severe ulcerative colitis 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; and
- ii) Treatment of adult patients with moderate to severe Crohn’s disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNF- α) antagonist.

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

3 Requested listings

3.1 The requested listings for MSUC and severe CD are presented below. Suggested additions are in italics and deletions are in strikethrough.

Moderate to severe ulcerative colitis

NEW Initial treatment

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL syringes	NEW NEW	1	2	1	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	NEW NEW	1	2	1	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd

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Category / Program: GENERAL – General Schedule (Code GE)
Prescriber Type(s): Medical Practitioners
PBS Indication: Moderate to severe ulcerative colitis
Treatment phase : Initial treatment with subcutaneous form at weeks 6, 8, 10 and 12
Restriction Type: Authority required - immediate/real time assessment by Medicare (telephone/online/emergency)
<p>Treatment criteria: Must be treated by a gastroenterologist (code 87); 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)]</p>
<p>Clinical criteria Patient must have received insufficient therapy with this drug for this condition under the Initial 1 (new patient) restriction to complete 14 weeks treatment if the patient wants to switch to the subcutaneous form at week 6 dose (the initial infusion regimen at 0 and 2); or Patient must have received insufficient therapy with this drug for this condition under the Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) restriction to complete 14 weeks treatment if the patient wants to switch to the subcutaneous form at week 6 dose (the initial infusion regimen at 0 and 2); or Patient must have received insufficient therapy with this drug for this condition under the Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) restriction to complete 14 weeks treatment if the patient wants to switch to the subcutaneous form at week 6 dose (the initial infusion regimen at 0 and 2) AND The treatment must provide no more than the balance of up to 4 doses of subcutaneous form to complete 14 weeks of therapy available under Initial 1, 2 or 3 treatment AND Patient must be appropriately assessed for the risk of developing progressive multifocal leukoencephalopathy whilst on this treatment</p>
<p>Prescriber Instructions At least two initial doses of vedolizumab (at weeks 0 and 2) must be administered via intravenous infusion.</p>
<p>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 Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL syringes	NEW NEW	1	2	5	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	NEW NEW	1	2	5	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd

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Category / Program: GENERAL – General Schedule (Code GE)
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
Restriction Type – <input checked="" type="checkbox"/> Authority Required – telephone
Severity: Moderate to severe
Condition: Ulcerative colitis
Indication: Moderate to severe ulcerative colitis
Treatment Phase: Continuing – subcutaneous form
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 treatment with this drug for this condition,
AND
Clinical criteria:
Patient must have demonstrated or sustained an adequate response to treatment by having a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 while receiving treatment with this drug,
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 aged 18 years or older.
Prescribing Instructions:
Two initial doses of vedolizumab must be administered with vedolizumab intravenous infusion. Subsequent doses may be administered with either intravenous or subcutaneous vedolizumab.
Patients who have failed to maintain a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug.
Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain the response.
At the time of the authority application, medical practitioners should request sufficient quantity for up to 24 weeks of treatment under this restriction.
Up to a maximum of 5 repeats will be authorised.
An application for the continuing treatment must be accompanied with the assessment of response conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from cessation of the most recent course 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 this 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. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological medicine was approved in this cycle and the date of the first application under a new cycle under the Initial 3 treatment restriction.
Note
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 Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Public Summary Document – November 2020 PBAC Meeting

Severe Crohn's disease

NEW initial treatment

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL syringes	NEW NEW	1	2	1	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	NEW NEW	1	2	1	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber Type(s): Medical Practitioners
PBS Indication: Severe Crohn disease
Treatment phase : Initial treatment with subcutaneous form at weeks 6, 8, 10 and 12
Restriction Type: Authority required - immediate/real time assessment by Medicare (telephone/online/emergency)
Treatment criteria Must be treated by a gastroenterologist (code 87); 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)]
Clinical criteria Patient must have received insufficient therapy with this drug for this condition under the Initial 1 (new patient) restriction to complete 14 weeks treatment if the patient wants to switch to the subcutaneous form at week 6 dose (the initial infusion regimen at 0 and 2); or Patient must have received insufficient therapy with this drug for this condition under the Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) restriction to complete 14 weeks treatment if the patient wants to switch to the subcutaneous form at week 6 dose (the initial infusion regimen at 0 and 2); or Patient must have received insufficient therapy with this drug for this condition under the Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) restriction to complete 14 weeks treatment if the patient wants to switch to the subcutaneous form at week 6 dose (the initial infusion regimen at 0 and 2) AND The treatment must provide no more than the balance of up to 4 doses of subcutaneous form to complete 14 weeks of therapy available under Initial 1, 2 or 3 treatment AND Patient must be appropriately assessed for the risk of developing progressive multifocal leukoencephalopathy whilst on this treatment
<i>At least two initial doses of vedolizumab (at weeks 0 and 2) must be administered via intravenous infusion.</i>
[19606] Authority approval for sufficient therapy to complete the balance of supply may be requested by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL syringes	NEW NEW	1	2	5	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	NEW NEW	1	2	5	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
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
Restriction Type – <input checked="" type="checkbox"/> Authority Required – in writing
Severity: Severe
Condition: Crohn's disease
Indication: Severe Crohn's disease
Treatment Phase: Continuing
Treatment criteria:

Public Summary Document – November 2020 PBAC Meeting

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 this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition
AND
Clinical criteria:
Patient must not receive more than 24 weeks of treatment under this restriction
AND
Clinical criteria:
Patient must be appropriately assessed for the risk of developing progressive multifocal leukoencephalopathy whilst on this treatment,
AND
Clinical criteria:
Patient must have an adequate response to this drug defined as a reduction in Crohn's 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
Clinical criteria:
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 disease or is an ostomy patient.
Population criteria:
Patient must be aged 18 years or older.
Prescribing Instructions:
Applications for authorisation must be made in writing and must include:
(a) a completed authority prescription form; and
(b) a completed Crohn Disease PBS Authority Application - Supporting Information Form which includes the following:
(i) the completed Crohn Disease Activity Index (CDAI) Score calculation sheet including the date of the assessment of the patient's condition, if relevant; or
(ii) the reports and dates of the pathology test or diagnostic imaging test(s) used to assess response to therapy for patients with short gut syndrome, extensive small intestine disease or an ostomy, if relevant; and
(iii) the date of clinical assessment.
Two initial doses of vedolizumab must be administered with vedolizumab intravenous infusion. Subsequent doses may be administered with either intravenous or subcutaneous vedolizumab.
An application for the continuing treatment must be accompanied with the assessment of response conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from cessation of the most recent course 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 this 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. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological medicine was approved in this cycle and the date of the first application under a new cycle under the Initial 3 treatment restriction.
Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain the response.

At the time of the authority application, medical practitioners should request sufficient quantity for up to 24 weeks of treatment under this restriction.

Up to a maximum of 5 repeats will be authorised.

If fewer than 5 repeats are requested at the time of the application, authority approvals for sufficient repeats to complete 24 weeks treatment may be requested by telephone and authorised through the Balance of Supply treatment phase PBS restriction. Under no circumstances will telephone approvals be granted for continuing authority applications, or for treatment that would otherwise extend the continuing treatment period.

Note

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. EST 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

- 3.2 The submission proposed that the current special pricing arrangement (SPA) for VDZ IV be extended to VDZ SC.
- 3.3 As patients must receive initial treatment with VDZ IV to be eligible for continuing therapy with VDZ SC, it is the restriction for initial treatment with VDZ IV that will effectively restrict eligibility for VDZ SC to the proposed PBS population.
- 3.4 The submission did not include a restriction for balance of supply for continuing treatment with VDZ SC for either MSUC or severe CD. The submission also did not provide a restriction for grandfathering treatment despite requesting a grandfathering clause for 12 patients currently enrolled in an extension study of the key trials for VDZ SC.
- 3.5 The restriction for initial treatment with VDZ IV, for both MSUC and severe CD, states that an application for continuing treatment must be accompanied by the assessment of response following a minimum of 12 weeks of therapy with this drug (i.e. doses at Week 0, 2 and 6); patients who fail to demonstrate a response to treatment will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. In contrast:
 - The TGA recommended dosage regimen for VDZ SC states that maintenance treatment with VDZ SC should be initiated following at least 2 intravenous infusions (i.e. at 0 and 2 weeks), with the first dose administered in place of the next scheduled IV dose (i.e. patients can receive the SC formulation from Week 6); and
 - In the key clinical trials for VDZ SC for the treatment of patients with MSUC (VISIBLE 1) and severe CD (VISIBLE 2), patients received induction treatment with

VDZ IV at Weeks 0 and 2, and only those who had achieved a clinical response at Week 6 were randomised into the maintenance phase of the trial.

- 3.6 The Sponsor stated in their pre-PBAC response that allowing for a switch from the IV to SC formulation during the induction phase of treatment increases the administrative burden for an inflammatory bowel disease (IBD) clinic to ensure patients have sufficient injections and are appropriately trained to self-inject prior to the 12 to 14 week response assessment window. The Sponsor maintained that VDZ SC should only become a treatment option once a patient has qualified for maintenance treatment under the current PBS criteria.
- 3.7 The CD trials (VISIBLE 2 and GEMINI 2) included patients with moderate to severe disease (moderate defined as a CD Activity Index (CDAI) score of 220 to 450). However, the PBS population for initiation of VDZ induction therapy are patients with severe CD (defined as a CDAI score of ≥ 300 or CDAI ≥ 220 with extensive intestinal inflammation ≥ 50 cm or short gut syndrome). The mean baseline CDAI scores were 318.3-320.0 in VISIBLE 2 and 325.2-325.5 in GEMINI 2. The proportions of patients by disease severity status were not provided for the trials.

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 IBD in the world. Crohn's disease and UC are the two most common types of IBD. It is estimated that approximately 75,000 Australians are living with IBD and over 1,622 new cases are diagnosed every year: 846 with UC and 776 with CD.
- 4.2 Ulcerative colitis characteristically involves the large bowel. Patients usually present with diarrhoea, which is commonly associated with blood in the stool. Bowel movements are frequent and small in volume as a result of rectal inflammation. Associated symptoms include abdominal pain, urgency, tenesmus and incontinence. Patients with mainly distal disease may have constipation accompanied by frequent discharge of blood and mucous.
- 4.3 Crohn's disease 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.
- 4.4 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, biological

disease modifying drugs (bDMDs) are initiated. There is currently limited data to determine the optimal sequencing of biological therapies for these conditions.¹

- 4.5 VDZ is a humanised monoclonal antibody that binds to the $\alpha 4\beta 7$ integrin, a receptor which is expressed on the surface of various leukocytes, including T lymphocytes, preventing adhesion of these cells to mucosal addressing cell adhesion molecule-1 (MAdCAM-1). A subset of memory T lymphocytes preferentially migrates into the gastrointestinal tract and causes inflammation that is characteristic of UC and CD.

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

5 Comparator

- 5.1 The submission nominated VDZ 300 mg for IV injection as the comparator. VDZ IV was recommended for listing for the treatment of MSUC on a cost-minimisation basis with infliximab, and for severe CD on a cost-minimisation basis with infliximab and adalimumab, at the March 2015 PBAC Meeting (paragraph 7.2, 7.06 vedolizumab Public Summary Document (PSD) and paragraph 7.2, 5.25 vedolizumab PSD, March 2015 PBAC Meeting).
- 5.2 As discussed above, the availability of a subcutaneously administered formulation of VDZ may result in VDZ replacing other currently used bDMDs listed on the PBS for the treatment of MSUC and severe CD. These are summarised in Table 2.

¹ Gastroenterology Society of Australia (GESA). Clinical Update for General Practitioners and Physicians - Inflammatory Bowel Disease, 2018.

Lamb CA, Kennedy NA, *et al.* British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019; 68 (Suppl 3):s1-s106.

Harbord M, Eliakim R, *et al.* Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *J Crohns Colitis*. 2017; 11 (7):769-84.

Torres J, Bonovas S, *et al.* ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *J Crohns Colitis*. 2020; 14 (1):4-22.

Table 2: Comparison of bDMDs listed on the PBS for the treatment of MSUC and severe CD

	VDZ IV/SC	Infliximab^d	Adalimumab	Ustekinumab	Golimumab
Pharmacological action	α4β7 integrin monoclonal antibody	TNFα inhibitor	TNFα inhibitor	IgG1κ monoclonal antibody	IgG1κ monoclonal antibody
PBS indication					
MSUC	✓	✓	✓	✗	✓
Severe CD	✓	✓	✓	✓	✗
Dose regimen ^a					
Induction	300 mg IV at 0 and 2 weeks ± 6 weeks ^b	5 mg/kg IV at 0, 2 and 6 weeks	160 mg SC Day 0 ^e 80 mg SC Day 14	Single IV infusion (tiered dose), then 90 mg SC Q8W from Week 8	200 mg SC Week 0 100 mg at Week 2
Maintenance	300 mg IV Q8W, commencing 8 weeks after last induction dose, OR 108 mg SC Q2W, commencing in place of the next scheduled IV dose ^c	5 mg/kg IV Q8W, commencing 8 weeks after last induction dose.	40 mg SC Q2W from Day 28		100 mg SC Q4W from Week 6

Source: compiled during the evaluation based on the PBS listings and the Product Information documents.

bDMD = biological disease modifying drug; CD = Crohn's disease; IV = intravenous; MSUC = moderate to severe ulcerative colitis; Q2W = every 2 weeks; Q8W = every 8 weeks; SC = subcutaneous; TNF = tumour necrosis factor.

^a TGA-recommended dose for adult patients.

^b The TGA recommends three IV infusions (at 0, 2 and 6 weeks) prior to maintenance with VDZ IV, while maintenance therapy with VDZ SC may be commenced following a minimum of 2 IV infusions (i.e. at 0 and 2 weeks).

^c The TGA dosage recommendations indicate that VDZ SC may be commenced from week 6 (following IV infusions at 0 and 2 weeks). In contrast, as the PBS listing for VDZ IV for both MSUC and severe CD states that an application for continuing treatment must be accompanied by an assessment of response following a minimum of 12 weeks of therapy, patients would only be eligible for PBS-subsidised VDZ SC from week 12.

^d Currently, the only formulation of infliximab on the PBS is for IV infusion. A submission for a subcutaneous formulation of infliximab for the treatment of both MSUC and CD will be considered at the November 2020 PBAC meeting.

^e The initial 160 mg dose may be administered in one day or over two days.

- 5.3 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.
- 5.4 For the populations for which listing of VDZ SC is requested, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: (i) infliximab, adalimumab and golimumab for the treatment of MSUC, and (ii) infliximab, adalimumab and ustekinumab for the treatment of severe CD. Some of these alternative therapies may be less costly than initial treatment with VDZ IV followed by continuing treatment with VDZ SC.
- 5.5 The Sponsor argued in the Pre-Sub-Committee Response (PSCR) and pre-PBAC response that the treatment choices for MSUC and CD are based on the drug class (e.g. TNF-α antagonists [adalimumab, golimumab, infliximab], anti-interleukin-12/23

antibody [ustekinumab], anti- $\alpha 4\beta 7$ integrin antibody [VDZ]) rather than the route of administration, and that the availability of VDZ SC will not change clinical decision making with respect to drug selection. The PSCR further stated that VDZ SC is solely for use in patients who achieve a response to VDZ IV in the induction phase and can only substitute for VDZ IV as maintenance treatment. The PSCR stated that patients will be unable to switch to maintenance treatment with VDZ SC directly from alternative bDMDs. The ESC noted that, notwithstanding the comments in the PSCR, VDZ IV followed by VDZ SC may also replace the alternative therapies identified in Table 2. The PBAC considered that the relevant alternative therapy is VDZ IV, noting that for patients who had already received initial VDZ IV, transfer to VDZ SC for maintenance therapy is likely to deliver improved outcomes, for some patients, compared with a switch to an alternative agent. The PBAC noted that VDZ acts selectively on the intestine, unlike other bDMDs approved for these conditions, and that VDZ SC is the only SC formulation in the $\alpha 4\beta 7$ integrin monoclonal antibody class of drugs.

- 5.6 For MSUC, there are two tiers of relativity for bDMDs. Tier 1 (more effective) comprises VDZ IV (nominated comparator) and infliximab IV. Tier 2 (less effective) comprises adalimumab SC and golimumab SC. The ESC noted the submission did not provide any clinical evidence to support the superiority of VDZ IV followed by VDZ SC versus adalimumab and golimumab. The Sponsor stated in their pre-PBAC response that the VARSITY study of VDZ versus adalimumab in MSUC (Sands et al 2019²) showed that VDZ IV was superior to adalimumab SC in achieving clinical remission (primary endpoint), mucosal healing and the absence of active histologic disease at Week 52. However, this trial did not investigate the combination of VDZ IV followed by VDZ SC [versus adalimumab]. The PBAC acknowledged that non-inferiority of VDZ IV followed by VDZ SC [versus VDZ IV] should be adequately supported by superiority of VDZ IV followed by VDZ SC compared to adalimumab and golimumab, for the purposes of Section 101(3B) of the National Health Act 1953 (paragraph 5.3). However, as noted above for patients who had already received initial VDZ IV, the PBAC considered that transfer to VDZ SC for maintenance therapy is likely to deliver improved outcomes, for some patients, compared with a switch to an alternative agent.

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.

² Sands B, Peyrin-Biroulet L, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *NEJM* 2019; 381:1215-26.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (HCPs; 3) and organisation (1) via the Consumer Comments facility on the PBS website. The comments from HCPs described a range of benefits of treatment with VDZ SC including patient convenience and reduced cost associated with decreased hospital infusion requirements. A HCP commented that once available, the SC formulation is likely to be the usual mode of prescribing VDZ.
- 6.3 The organisation Crohn’s and Colitis Australia stated that it supports the listing of the self-injectable SC form of VDZ because, in addition to the points mentioned by HCPs, patients will be able to avoid work absences and travel associated with infusions in a medical facility.

Clinical trials

Moderate and severe ulcerative colitis (MSUC)

- 6.4 The submission was based on a post-hoc analysis of the VDZ SC and IV arms in the VISIBLE 1 trial. This trial was a phase 3, multicentre, randomised, double blind, double-dummy, controlled trial in patients with MSUC. All patients received open label VDZ IV 300 mg at Weeks 0 and 2. At Week 6, the patients were assessed for clinical response (defined as a reduction in complete Mayo score of ≥ 3 points and $\geq 30\%$ from baseline (Week 0)). Only patients who achieved a clinical response to induction therapy at Week 6 were randomised into the double-blind maintenance phase at a ratio of 2:1:1 to VDZ SC 108 mg every 2 weeks (Q2W), VDZ IV 300 mg every 8 weeks (Q8W) and placebo.
- 6.5 Details of the included trial are summarised in the Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Ulcerative colitis trials – Direct comparison between VDZ SC and VDZ IV		
VISIBLE 1	Clinical Study Report/Protocol A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study, with a Vedolizumab IV Reference Arm, to Evaluate the Efficacy and Safety of Vedolizumab Subcutaneous as Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy.	7 February 2019
	Sandborn et al. Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis.	Gastroenterology 2020; 158 (3): 562-572.e12.

Source: Table 2.2.3, p28 of the main submission

- 6.6 The key features of the included trial are summarised in Table 4.

Table 4: Key features of the included evidence for MSUC

Trial	N	Design/ duration	Risk of bias in the individual trials	Patient population	Outcomes	Use in cost- minimisation
VISIBLE 1	216 ^a	R, DB, DD/ 52 weeks ^b	Low	Adult patients with MSUC who had inadequate response to, loss of response to or intolerance of at least one of an immunomodulator, TNF α antagonist or corticosteroid	Clinical remission at Week 52	Yes

Source: Generated during the evaluation using data from section 2.3 and 2.4 of the submission

DB = double blind; DD= double dummy; R = randomised; MSUC= moderate or severe ulcerative colitis; NR= not reported; TNF = tumour necrosis factor;

^aNumber of patients representing the ITT population for the maintenance phase of VISIBLE 1

^bDuration of follow up was not reported in VISIBLE 1 trial

6.7 The evidence was derived from the comparison between the VDZ SC arm and the VDZ IV arm in the VISIBLE 1 trial. Overall, the baseline demographics and disease characteristics were well balanced between the VISIBLE 1 trial arms suggesting successful randomisation.

6.8 Note that VISIBLE 1 trial was not powered to detect a difference between VDZ SC and IV arms. Also, while the submission claimed non-inferiority of the VDZ SC compared to VDZ IV, the VISIBLE 1 trial was not a non-inferiority designed trial. In addition, no non-inferiority margin was pre-specified for the interpretation of this post-hoc analysis.

Crohn's disease

6.9 The submission was based on an adjusted indirect comparison between VDZ SC (Phase III VISIBLE 2 trial: VDZ SC 108 mg Q2W maintenance therapy versus placebo), and VDZ IV (Phase III GEMINI 2 trial: VDZ IV 300 mg Q8W maintenance therapy versus placebo), using placebo as the common reference, in moderately to severely active Crohn's disease. Details of the trials included for the indirect comparison are provided in the Table 5.

Table 5: Crohn's disease - Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
VDZ 108 mg SC Q2W maintenance therapy versus placebo		
VISIBLE 2	Clinical Study Report/Protocol A Phase 3 Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vedolizumab Subcutaneous as Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy.	2 October 2019
	Protocol A Phase 3 Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Vedolizumab Subcutaneous as Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Achieved Clinical Response Following Open-Label Vedolizumab Intravenous Therapy. Amendment 6	24 August 2017
VDZ 300 mg IV Q8W maintenance therapy versus placebo		
GEMINI 2	Clinical study report A Phase 3, Randomised, Placebo-Controlled, Blinded, Multicentre Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients With Moderate to Severe Crohn's Disease. Sandborn et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease. Sands et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease in Patients Naïve to or Who Have Failed Tumor Necrosis Factor Antagonist Therapy. Feagan et al. Efficacy of Vedolizumab in Fistulising Crohn's Disease: Exploratory Analyses of Data from GEMINI 2.	10 October 2012 New England Journal of Medicine 2013; 369 (8): 711-721. Inflammatory Bowel Disease 2017; 23 (1): 97-106. Journal of Crohn's and Colitis 2018;12(5):621-626

Source: Table 2.2.3, p28 and Table 2.2-34, p71 of the main submission

SC = subcutaneous; IV = intravenous; Q2W = every 2 weeks; Q8W = every 8 weeks.

6.10 The key features of the trials included for the indirect comparison are summarised in Table 6.

Table 6: Key features of the evidence included for the indirect comparison

	VISIBLE 2 (VDZ N = 275; PBO N = 134)	GEMINI 2 (VDZ N = 154; PBO N = 153)
Design	R, DB. VDZ SC vs. PBO as maintenance therapy after clinical response to VDZ IV induction	Induction phase: Cohort 1 - R, DB, VDZ IV 300 mg vs PBO IV at Week 0 and 2. Cohort 2 – OL, single arm, VDZ IV 300 mg at Week 0 and 2 Maintenance phase: VDZ SC vs. PBO as maintenance therapy after clinical response to VDZ IV induction
Compared interventions (drug, dose, frequency)	Induction phase: non-randomised, OL, VDZ IV 300 mg at Week 0 and 2	Induction phase <u>Cohort 1</u> (R, DB) VDZ IV 300 mg at Week 0 and 2 Placebo IV at Week 0 and 2 <u>Cohort 2</u> (non-randomised, OL) VDZ IV 300 mg at Week 0 and 2
	Maintenance phase: R, DB, VDZ SC 108 mg Q2W from Week 6 (N = 275) Placebo SC Q2W from Week 6 (N = 134) Median VDZ treatment duration, 68.1 weeks	Maintenance phase R, DB VDZ IV 300 mg Q8W from Week 6 (N = 154) VDZ IV 300 mg Q4W from Week 6 (N = 154) Placebo IV Q4W from Week 6 (N = 153) Median VDZ Q8W treatment duration, 48.0 weeks
Eligibility criteria	Age 18-80 years CD ≥ 3 months CDAI score of 220-450 One of following: CRP > 2.87 mg/L Ileocolonoscopy (≥ 3 non-anastomotic ulcers or ≥ 10 aphthous ulcers), Faecal calprotectin > 250 mcg/g Inadequate or loss of response to ≥ one of the following: Immunomodulators, Corticosteroids, TNF-α antagonists	Age 18-80 years CD ≥ 3 months CDAI score of 220–450 points One of the following: CRP > 2.87 mg/L Colonoscopy (≥ 3 large ulcers or ≥ 10 aphthous ulcers) Faecal calprotectin > 250 mcg/g Inadequate or loss of response to ≥ one of the following: Immunomodulators, Corticosteroids, TNF-α antagonists
Primary outcomes	Clinical remission at Week 52	Clinical remission at Week 52
Secondary outcomes	Enhanced clinical response (i.e. CDAI-100 response) at Week 52 Corticosteroids-free remission at Week 52 Clinical remission in TNF-α antagonist naïve patients at Week 52	CDAI-100 response at Week 52 Corticosteroid-free remission at Week 52 Durable clinical remission
Risk of bias in individual trials	Generally low (possibility of unmasking unclear)	Generally low (possibility of unmasking unclear)
Risk of bias in the indirect comparison	High due to heterogeneity (direction of impact unclear). Results also have limited precision	

Source: Tables 2.2-35, 2.2-36, (pp75-8 of the main submission) and Table 2.3.1 of the evaluation.

R = randomised; DB = double blind; OL = open label; CD = Crohn's disease; CDAI = Crohn's disease activity index; CRP = C-reactive protein; IV = intravenous; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous; TNF = tumour necrosis factor; VDZ = vedolizumab.

6.11 Table 7 summarises heterogeneity between the trials used for the indirect comparison.

Table 7: Heterogeneity between the VISIBLE 2 and GEMINI 2 trials.

Characteristic	VISIBLE 2	GEMINI 2	Comment
Period of study conduct	2015-2019	2008-2012	Possible differences in standard of care (SOC), including increased frequency of study visits in more recent studies and increased patient expectations may increase the placebo response rate ^a . Remains unclear whether different monitoring frequencies (Q4W in GEMINI 2 versus Q2W in VISIBLE 2) may influence disease course to favour one formulation over the other. See placebo rates further below.
Gender and smoking	The proportion of males ranged from 44.2% in GEMINI 2 to 57.1% in VISIBLE 2. The % of current smokers was much lower in VISIBLE 2 (19.4-19.6%) compared with GEMINI 2 (31.2-31.4%).		Information on the influence of gender on disease course, and response to biologics is conflicting ^b . Time until loss of response appears shorter in males treated with some biologics and dose intensification was more often required in men than in women ^c . Male gender together with smoking and family history appear to be predictors of loss of response to treatments for Crohn's disease ^d Smoking is a predictor of non-adherence to therapies for Crohn's disease, and is associated with more severe disease ^e
Duration of Crohn's disease	A higher proportion of patients had disease duration of ≥ 7 years in the placebo group of GEMINI 2 (50.3%) compared with that in VISIBLE 2 (41.8%)		Shorter disease duration is associated with higher rates of response to vedolizumab in patients with Crohn's disease (but not in ulcerative colitis).
Pro-inflammatory markers	Baseline median faecal calprotectin levels were higher for VISIBLE 2 (736.0-870.5 mcg/g) compared with GEMINI 2 (583.5-683.7 mcg/g).		The submission noted that faecal calprotectin is positively correlated with other pro-inflammatory markers, which suggests that patients in VISIBLE 2 may have had greater levels of inflammation at baseline compared with those in GEMINI 2 ^g .
Sites of disease involvement	The proportion of patients whose disease involved both the ileum and colon was lower in VISIBLE 2 (44.4-55.2%) compared to GEMINI 2 (55.9-63.6%)		Whether this will substantially favour the SC formulation in VISIBLE 2 is unclear.
Prior surgery for Crohn's disease	The proportion of patients with prior surgery for Crohn's disease was lower in the VISIBLE 2 trial (25.4% to 27.6%) than in the GEMINI 2 trial (~37%). This was a similar trend for patients with a history of fistulising disease (VISIBLE 2: 19.5-25.4%; GEMINI 2 30.5-37.3%).		The submission noted that ileocolonic involvement, penetrating disease and previous surgical resection were associated with greater disease severity in Crohn's disease ³ . This suggested that patients in VISIBLE 2 may have had less severe disease at baseline compared to those in GEMINI 2. This may have favoured the SC formulation in VISIBLE 2.

³ Peyrin-Biroulet L et al. Defining disease severity in inflammatory bowel diseases: current and future directions. *Clinical Gastroenterology and Hepatology*. 2016;14(3):348-54. e17

Characteristic	VISIBLE 2	GEMINI 2	Comment
Failure to prior therapies at baseline	The frequency of failure to prior immunomodulators was much lower in VISIBLE 2 (4.5- 5.1%) than in GEMINI 2 (18.8-22.2%). The frequency of failure to prior corticosteroid due to inadequate response was balanced in GEMINI 2 (12.3-14.4%). However, the frequency in the placebo group of VISIBLE 2 was almost twice that in the VDZ SC group (14.2% versus 7.3%).		Whether this may significantly favour the SC formulation in VISIBLE 2 over the IV formulation is unclear
Median duration of treatment	There was a longer median (or mean) duration of treatment in VISIBLE 2 (~68 weeks) than in GEMINI 2 (42-48%).		The influence on the indirect estimate of efficacy is unclear but is likely to favour the IV formulation of GEMINI 2 in terms of safety.
Placebo response rates	Placebo response rates were higher in VISIBLE 2 than in GEMINI 2 for most of the outcomes (see comparative effectiveness results below).		This may favour the IV formulation

Source: Information on trial characteristics was sourced from the individual CSRs, Sections 2.4-2.6 of the main submission, and literature searches conducted during the evaluation

^aGallahan W et al. An analysis of the placebo effect in Crohn's disease over time. *Alimentary pharmacology & therapeutics*. 2010;31(1):102-7 and Su C et al. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. *Gastroenterology*. 2004; 126(5):1257-69.

^bMazor Y, Maza I, Kaufman E, Ben-Horin S, Karban A, Chowers Y, et al. Prediction of disease complication occurrence in Crohn's disease using phenotype and genotype parameters at diagnosis. *Journal of Crohn's and Colitis*. 2011; 5(6):592-7.

^cBillioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. *American Journal of Gastroenterology*. 2011;106(4):674-84.

^dGreuter T, Manser C, Pittet V, Vavricka SR, Biedermann L. Gender Differences in Inflammatory Bowel Disease. *Digestion*. 2020:1-7.

^eLopez A et al. Adherence to anti-TNF therapy in inflammatory bowel diseases: a systematic review. *Inflammatory Bowel Diseases*. 2013; 19(7):1528-33 AND Parkes GC et al. Smoking in inflammatory bowel disease: impact on disease course and insights into the aetiology of its effect. *Journal of Crohn's and Colitis*. 2014;8(8):717-25.

^fFaleck DM et al. Shorter disease duration is associated with higher rates of response to vedolizumab in patients with Crohn's disease but not ulcerative colitis. *Clinical Gastroenterology and Hepatology*. 2019; 17(12):2497-505. e1.

^gBourgonje AR, von Martels JZ, de Vos P, Faber KN, Dijkstra G. Increased fecal calprotectin levels in Crohn's disease correlate with elevated serum Th1-and Th17-associated cytokines. *PLoS One*. 2018;13(2):e0193202

6.12 The relevant assessment of the risk of bias/confounding associated with the indirect comparison was considered high. The strength of inference associated with the indirect comparison was limited given the high uncertainty regarding whether any of the observed heterogeneity between the trials could have influenced the indirect comparative treatment effect.

6.13 A non-inferiority margin was not provided to support the submission's claim of non-inferiority of VDZ SC to VDZ IV.

Ulcerative colitis

Comparative effectiveness

- 6.14 The primary outcome of the VISIBLE 1 trial was to show the difference in clinical remission between VDZ SC and the placebo arm, with VDZ IV arm included as an active comparator. Results for the primary outcome showed that patients in the VDZ SC arm were more likely to develop clinical remission at week 52 compared to placebo (RR= 3.24, 95%CI [1.65, 6.35]).
- 6.15 Table 8 summarises the results of the comparison between the VDZ SC and the VDZ IV arms. No statistically significant difference was observed between the two arms in terms of the primary outcome (clinical remission) or the secondary outcomes (mucosal healing, durable clinical response, durable clinical remission and corticosteroid-free remission). In addition, no statistically significant difference was observed between VDZ SC and IV in terms of improvement of patient reported outcomes.

Table 8: Comparison of efficacy outcomes at week 52 between VDZ SC and IV

VISIBLE 1 trial	VDZ SC N = 106	VDZ IV N = 54	VDZ SC vs VDZ IV	
			RR (95% CI) ^a	RD (95% CI) ^a
Primary efficacy outcome				
Clinical remission ^b , n (%)	49 (46.2)	23 (42.6)	1.09 (0.75, 1.57) p = 0.67	0.04 (-0.13, 0.20) p = 0.66
Secondary efficacy outcomes				
Mucosal healing ^c , n (%)	60 (56.6)	29 (53.7)	1.05 (0.78, 1.42) p = 0.73	0.03 (-0.13, 0.19) p = 0.73
Durable clinical response ^d , n (%)	68 (64.2)	39 (72.2)	0.89 (0.71, 1.10) p = 0.29	-0.08 (-0.23, 0.07) p = 0.29
Durable clinical remission ^e , n (%)	16 (15.1)	9 (16.7)	0.91 (0.43, 1.91) p = 0.80	-0.02 (-0.14, 0.10) p = 0.80
Corticosteroid-free remission ^f , n (%)	N = 45 13 (28.9)	N = 21 6 (28.6)	1.01 (0.45, 2.29) p = 0.98	0.00 (-0.23, 0.24) p = 0.98

Source: Table 2.2.23, p54 of the submission

CI = confidence interval; IV = intravenous; OR = odds ratio; RD = risk difference; RR = relative risk; SC = subcutaneous; SD = standard deviation; VDZ = vedolizumab

a Treatment effect and confidence intervals were calculated using RevMan v5.3

b Clinical remission was defined as a complete Mayo score of ≤ 2 points and no individual subscore > 1 point

c Mucosal healing, defined as a Mayo endoscopic subscore of ≤ 1 point, at Week 52 was the first secondary efficacy outcome

d Durable clinical response, defined as response at both Weeks 6 and 52. Clinical response is defined as a reduction in complete Mayo score of ≥ 3 points and $\geq 30\%$ from baseline (Week 0) (or partial Mayo score of ≥ 2 points and $\geq 25\%$ from baseline, if the complete Mayo score was not performed at the visit) with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point

e Durable clinical remission, defined as remission at both Weeks 6 and 52

f Corticosteroid-free remission, defined as patients using oral corticosteroids at baseline (determined by interactive voice response system at time of randomisation) who have discontinued oral corticosteroids and were in clinical remission based on the complete Mayo score at Week 52, was the fourth secondary efficacy outcome

Comparative harms

- 6.16 No statistically significant difference was observed between the VDZ SC arm and the placebo arm in terms of safety or adverse events, however, there were numerically

higher rates of gastrointestinal disorders, colitis ulcerative and infections in the placebo arm.

- 6.17 Summary of the safety comparison between VDZ SC and IV is presented in Table 9. Overall, no statistically significant differences were observed between the two arms in terms of total adverse events, drug related adverse events, serious adverse events or adverse events leading to discontinuation of treatment. As mentioned previously, these results should be considered in the context that the VISIBLE 1 trial was not powered to detect a difference between the SC and the IV VDZ treatment arms.

Table 9: Comparison of safety outcomes and AESIs between VDZ SC and IV

Adverse events, n (%)	VDZ SC N = 106	VDZ IV N = 54	VDZ SC vs VDZ IV		
			RR (95% CI) ^a	RD (95% CI) ^a	OR (95% CI) ^a
Any AEs	69 (65.1)	41 (75.9)	0.86 (0.70, 1.05) p = 0.14	-0.11 (-0.25, 0.04) p = 0.15	0.59 (0.28, 1.24) p = 0.16
Drug-related	28 (26.4)	9 (16.7)	1.58 (0.81, 3.12) p = 0.18	0.10 (-0.03, 0.23) p = 0.14	1.79 (0.78, 4.14) p = 0.17
Leading to discontinuation	5 (4.7)	2 (3.7)	1.27 (0.26, 6.35) p = 0.77	0.01 (-0.05, 0.07) p = 0.76	1.29 (0.24, 6.86) p = 0.77
SAEs	10 (9.4)	7 (13.0)	0.73 (0.29, 1.81) p = 0.49	-0.04 (-0.14, 0.07) p = 0.51	0.70 (0.25, 1.95) p = 0.50
Drug-related	1 (0.9)	1 (1.9)	0.51 (0.03, 7.99) p = 0.63	-0.01 (-0.05, 0.03) p = 0.66	0.50 (0.03, 8.23) p = 0.63
Leading to discontinuation	1 (0.9)	2 (3.7)	0.25 (0.02, 2.75) p = 0.26	-0.03 (-0.08, 0.03) p = 0.31	0.25 (0.02, 2.79) p = 0.26
AESIs					
Infections	39 (36.8)	20 (37.0)	0.99 (0.65, 1.52) p = 0.98	-0.00 (-0.16, 0.16) p = 0.98	0.99 (0.50, 1.95) p = 0.98
Hypersensitivity ^b	16 (15.1)	7 (13.0)	1.16 (0.51, 2.66) p = 0.72	0.02 (-0.09, 0.13) p = 0.71	1.19 (0.46, 3.10) p = 0.72
Malignancy	0	1 (1.9)	0.17 (0.01, 4.14) p = 0.28	-0.02 (-0.06, 0.03) p = 0.42	0.17 (0.01, 4.18) p = 0.28
Liver injury	2 (1.9)	4 (7.4)	0.25 (0.05, 1.35) p = 0.11	-0.06 (-0.13, 0.02) p = 0.15	0.24 (0.04, 1.36) p = 0.11
PML	0	0	-	-	-

Source: Table 2.2.24, p56 and Table 2.2.25, p57 of the submission

AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; IV = intravenous; OR = odds ratio; PML = progressive multifocal leukoencephalopathy; RD = risk difference; RR = relative risk; SAE = serious adverse event; SC = subcutaneous; VDZ = vedolizumab

^a Treatment effect and confidence intervals were calculated using RevMan v5.3

^b Hypersensitivity TEAEs criteria included SMQs for anaphylactic/anaphylactoid shock conditions, angioedema, and hypersensitivity

Benefits/harms

- 6.18 The submission claimed that VDZ 108 mg SC Q2W was non-inferior to VDZ 300 mg IV Q8W, as maintenance therapy. Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.19 The submission described VDZ SC (108 mg Q2W) as non-inferior in terms of effectiveness and safety compared with VDZ IV (300 mg Q8W) in the maintenance

treatment of patients with MSUC who had achieved a clinical response to induction therapy with VDZ IV.

- 6.20 This claim was based on the results of the VISIBLE 1 trial which showed no statistically significant difference between the VDZ SC and IV arms at week 52 in terms of clinical remission, durable clinical remission, durable response, patient-reported outcomes and safety.
- 6.21 The results of the VISIBLE 1 trial and the claim of the submission should be interpreted in the context of the following:
- VISIBLE 1 trial was not powered to detect a difference between VDZ SC and VDZ IV arms. The PSCR argued that as the VISIBLE 1 trial was powered to detect a difference between VDZ SC and placebo, with VDZ IV as an active comparator, it provides a direct comparison of VDZ SC and VDZ IV.
 - VISIBLE 1 trial was not designed to establish non-inferiority. No non-inferiority margin was pre-specified before performing the post-hoc analysis between the SC and the IV arms. The Sponsor stated in both the PSCR and pre-PBAC response that the submission did not nominate a non-inferiority margin because none was identified in the published literature for the outcome of clinical remission, nor is there a recommendation for an accepted MCID for clinical remission. The PSCR stated that in the absence of a MCID [and non-inferiority margin], the PBAC has previously recommended bDMDs for MSUC based on the absence of statistically significant differences between the intervention and comparator (paragraph 6.15, VDZ PSD for MSUC, March 2015).
 - There were inconsistencies in the timing of continuing/maintenance treatment after induction therapy, between the requested PBS listing criteria for VDZ IV (induction at week 0, 2, 6 and assessment of response at weeks 12 - 14), and the key clinical trials for VDZ SC (induction at week 0, 2 and assessment of response at week 6). The PSCR acknowledged that while the timing of the response assessment in the trials is different from the PBS listing criteria, it is consistent across the clinical trials for both VDZ SC and VDZ IV (VISIBLE 1, VISIBLE 2, and GEMINI 2) as maintenance treatments.
 - There were also differences between VISIBLE 1 trial and the PBS restrictions in terms of how the response was defined (clinical response versus clinical remission) and the use of prior biological agents before the initiation of the VDZ induction phase.
- 6.22 The PBAC considered that while the claim of non-inferior comparative effectiveness in MSUC was uncertain, it acknowledged it is likely that maintenance therapy with VDZ SC delivers similar outcomes to continuation of VDZ IV after a 12-14 week assessment point.

6.23 The PBAC considered that the claim of non-inferior comparative safety in MSUC was reasonable.

Crohn's disease

Comparative effectiveness

6.24 Table 10 summarises the indirect comparisons for the outcomes of clinical remission (primary), enhanced clinical response, corticosteroid-free remission, and durable remission. All efficacy outcomes were analysed at Week 52 for both trials.

Table 10: Indirect comparison of the effectiveness of VDZ 108 mg SC Q2W versus VDZ 300 mg IV Q8W as maintenance therapy for moderate to severe Crohn's disease

	VDZ n (%)	PBO n (%)	RR (95% CI) ^a p-value	RD (95% CI) ^a p-value
Clinical remission at Week 52				
VISIBLE-2 (VDZ SC vs PBO)	N = 275 132 (48.0)	N = 134 46 (34.3)	1.40 (1.07, 1.82); p = 0.001	0.14 (0.04, 0.24); p = 0.007
GEMINI-2 (VDZ IV vs PBO)	N = 154 60 (39.0)	N = 153 33 (21.6)	1.81 (1.26, 2.59); p = 0.001	0.17 (0.07, 0.27); p = 0.0007
Indirect comparison (VDZ SC vs VDZ IV)			0.77 (0.49, 1.21); p = 0.2607	-0.03 (-0.17, 0.11); p = 0.6776
Enhanced clinical response at Week 52				
VISIBLE-2 (VDZ SC vs PBO)	N = 275 143 (52.0)	N = 134 60 (44.8)	1.16 (0.93, 1.45); p = 0.18	0.07 (-0.03, 0.18); p = 0.17
GEMINI-2 (VDZ IV vs PBO)	N = 154 67 (43.5)	N = 153 46 (30.1)	1.45 (1.07, 1.96); p = 0.02	0.13 (0.03, 0.24); p = 0.01
Indirect comparison (VDZ SC vs VDZ IV)			0.80 (0.55, 1.16); p = 0.2440	-0.06 (-0.21, 0.09); p = 0.4284
Corticosteroid-free remission at Week 52				
VISIBLE-2 (VDZ SC vs PBO)	N = 95 43 (45.3)	N = 44 8 (18.2)	2.49 (1.28, 4.84); p = 0.007	0.27 (0.12, 0.42); p = 0.0005
GEMINI-2 (VDZ IV vs PBO)	N = 82 26 (31.7)	N = 82 13 (15.9)	2.00 (1.11, 3.61); p = 0.02	0.16 (0.03, 0.29); p = 0.02
Indirect comparison (VDZ SC vs VDZ IV)			1.25 (0.51, 3.03); p = 0.6289	0.11 (-0.09, 0.31); p = 0.2774
Durable clinical remission				
VISIBLE-2 (VDZ SC vs PBO)	N = 275 86 (31.3)	N = 134 34 (25.4)	1.23 (0.88, 1.73); p = 0.23	0.06 (-0.03, 0.15); p = 0.21
GEMINI-2 (VDZ IV vs PBO)	N = 154 33 (21.4)	N = 153 22 (14.4)	1.49 (0.91, 2.43); p = 0.11	0.07 (-0.01, 0.16); p = 0.11
Indirect comparison (VDZ SC vs VDZ IV)			0.83 (0.45, 1.50); p = 0.5284	-0.01 (-0.13, 0.11); p = 0.8742

Sources: Table 2.2-60 to 2.2-63, pp100-102 of the main submission

Placebo rates shaded

^a Calculated in the submission using RevMan v5.3

Definitions: Clinical remission = a CDAI score ≤150 at Week 52; Enhanced clinical response = ≥100-point decrease in CDAI score from baseline (Week 0), at Week 52; Corticosteroid-free remission = Patients using oral corticosteroids at baseline who discontinued oral corticosteroids and were in clinical remission at Week 52; Durable clinical remission = Clinical remission at ≥ 80% of study visits including the final visit.

CDAI = Crohn's disease activity index; CI = confidence interval; IV = intravenous; OR = odds ratio; PBO = placebo; RD = risk difference; RR = relative risk; SC = subcutaneous; VDZ = vedolizumab

- 6.25 There were no statistically significant differences for any of the effectiveness outcomes, between the 108 mg SC Q2W and 300 mg IV Q8W formulations of VDZ maintenance therapy, in moderate to severe CD.
- 6.26 The indirect comparison results however had very wide confidence intervals with exchangeability issues. The direction of any potential bias remains unclear.
- 6.27 Both VDZ trials enrolled patients with moderate to severe CD (CDAI score 220 to 450). However, the PBS population for initiation of VDZ induction therapy are those with severe disease (CDAI ≥ 300 or CDAI ≥ 220 and extensive intestinal inflammation ≥ 50 cm or short gut syndrome). The submission argued that the mean baseline CDAI scores were >300 in both VISIBLE 2 (318.3-320.0) and GEMINI 2 (325.2-325.5), and that GEMINI 2 was previously accepted as evidence by the PBAC for the listing of VDZ IV as induction and maintenance therapy in this population (Appendix 2, Vedolizumab PSD, March 2015).
- 6.28 An updated European Public Assessment Report (EPAR) for VDZ⁴ provided some information on the pharmacology of the SC and IV formulations of VDZ.
- 6.29 The EPAR noted that Exposure-response (E-R) analyses at Week 6 showed that for all the exposure parameters considered, quartiles of higher exposure were associated with greater probability of week 6 clinical remission and week 6 clinical response. In addition, SC treatment, as compared with IV treatment, resulted in a higher exposure to VDZ. Based on analyses of exposure quartiles within treatment arm, and relating them to probability of week 52 clinical remission and mucosal healing, it was apparent that in most cases, the probability of week 52 clinical remission and the rate of week 52 mucosal healing were higher for the SC treatment.
- 6.30 Overall, the EPAR concluded that a general trend of increased rate of response for patients with higher VDZ exposure was observed, and that the SC administration appeared to result in slightly higher exposure parameters compared to IV administration.

Comparative harms

- 6.31 The indirect comparison for safety is presented in the Table 11.

⁴ Entyvio Assessment Report EMA/220524/2020. Last updated 18/05/2020. Available from <https://www.ema.europa.eu/en/medicines/human/EPAR/entyvio#assessment-history-section>

Table 11: Indirect comparison of the safety of VDZ 108 mg SC Q2W versus VDZ 300 mg IV Q8W as maintenance therapy for moderate to severe CD

Proportion of patients, n (%)	VDZ	Placebo	RR (95% CI) ^a , p-value	RD (95% CI) ^a , p-value
Drug-related TEAEs				
VISIBLE 2 (VDZ SC vs PBO)	N = 275 53 (19.3)	N = 134 20 (14.9)	1.29 (0.81, 2.07); p = 0.29	0.04 (-0.03, 0.12); p = 0.26
GEMINI 2 (VDZ IV vs PBO)	N = 154 63 (40.9)	N = 153 51 (33.3)	1.23 (0.91, 1.65); p = 0.17	0.08 (-0.03, 0.18); p = 0.17
Indirect comparison (VDZ SC vs VDZ IV)			1.05 (0.60, 1.83); p = 0.8666	-0.04 (-0.17, 0.09); p = 0.5435
AEs leading to discontinuation				
VISIBLE 2 (VDZ SC vs PBO)	N = 275 11 (4.0)	N = 134 11 (8.2)	0.49 (0.22, 1.10); p = 0.08	-0.04 (-0.09, 0.01); p = 0.11
GEMINI 2 (VDZ IV vs PBO)	N = 154 12 (7.8)	N = 153 15 (9.8)	0.79 (0.38, 1.64); p = 0.53	-0.02 (-0.08, 0.04); p = 0.53
Indirect comparison (VDZ SC vs VDZ IV)			0.62 (0.21, 1.84); p = 0.3892	-0.02 (-0.10, 0.06); p = 0.6157
SAEs				
VISIBLE 2 (VDZ SC vs PBO)	N = 275 23 (8.4)	N = 134 14 (10.4)	0.80 (0.43, 1.51); p = 0.49	-0.02 (-0.08, 0.04); p = 0.50
GEMINI 2 (VDZ IV vs PBO)	N = 154 28 (18.2)	N = 153 23 (15.0)	1.21 (0.73, 2.00); p = 0.46	0.03 (-0.05, 0.11); p = 0.46
Indirect comparison (VDZ SC vs VDZ IV)			0.66 (0.30, 1.48); p = 0.3139	-0.05 (-0.15, 0.05); p = 0.3271
Drug-related SAEs				
VISIBLE 2 (VDZ SC vs PBO)	N = 275 4 (1.5)	N = 134 2 (1.5)	0.97 (0.18, 5.25); p = 0.98	-0.00 (-0.03, 0.02); p = 0.98
GEMINI 2 (VDZ IV vs PBO)	N = 154 5 (3.2)	N = 153 4 (2.6)	1.24 (0.34, 4.54); p = 0.74	0.01 (-0.03, 0.04); p = 0.74
Indirect comparison (VDZ SC vs VDZ IV)			0.78 (0.09, 6.56); p = 0.8210	-0.01 (-0.05, 0.03); p = 0.6486
SAEs leading to discontinuation				
VISIBLE 2 (VDZ SC vs PBO)	N = 275 5 (1.8)	N = 134 5 (3.7)	0.49 (0.14, 1.65); p = 0.25	-0.02 (-0.05, 0.02); p = 0.29
GEMINI 2 (VDZ IV vs PBO)	N = 154 9 (5.8)	N = 153 7 (4.6)	1.28 (0.49, 3.34); p = 0.62	0.01 (-0.04, 0.06); p = 0.62
Indirect comparison (VDZ SC vs VDZ IV)			0.38 (0.08, 1.83); p = 0.2285	-0.03 (-0.09, 0.03); p = 0.3353

Source: Table 2.2-64, pp103-4 of the main submission

Placebo events shaded.

^aCalculated in the submission using RevMan v5.3

AE = adverse event; CI = confidence interval; IV = intravenous; NE = not estimable; PBO = placebo; RD = risk difference; RR = relative risk; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event; VDZ = vedolizumab

- 6.32 There were no statistically significant differences in adverse events between VDZ 108 mg SC Q2W and VDZ 300 mg IV Q8W. Headache, nasopharyngitis, anaemia, and upper respiratory tract infections were the most common AEs across the trials.
- 6.33 The design of the VISIBLE 2 and GEMINI 2 trials was primarily based on efficacy and were not adequately powered to detect differences in AE rates between their randomised groups. Of note is that AEs across the VISIBLE 2 and GEMINI 2 trials were coded using different MedDRA versions (Version 22.0 and Version 14.0, respectively). In addition, the duration of treatment exposure was longer in VISIBLE 2 compared to

GEMINI 2 (VISIBLE 2: median of VDZ SC 68.1 weeks; GEMINI 2: median of VDZ IV 48.0 weeks).

- 6.34 Recognising the limitations of the indirect comparisons, the safety profile of VDZ SC as maintenance therapy in CD would be expected to be consistent with that of IV administration. However, injection site reactions would be expected to be more frequent with the more frequently administered SC formulation.
- 6.35 There was no observed case of progressive multifocal leukoencephalopathy (PML) in the trials. However, VDZ may be associated with an increased risk of PML based on its mechanism of action and pharmacological class. The safety data do not reflect this risk partly because the trials excluded patients who were potentially at risk of PML. This issue is more relevant to other potential comparators such as infliximab, rather than to VDZ IV.

Benefits/harms

- 6.36 The claim in the submission was that VDZ 108 mg SC Q2W was non inferior to VDZ 300 mg IV Q8W, as maintenance therapy. Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.37 The submission described VDZ SC (108mg Q2W) as non-inferior in terms of effectiveness and safety compared with VDZ IV (300mg Q8W), in the maintenance treatment of patients with severe CD.
- 6.38 While VDZ SC demonstrated efficacy as maintenance therapy, versus placebo, in moderate to severe CD, the evaluation considered there was uncertainty regarding the claim of non-inferiority for the indirect comparison with VDZ IV.
- 6.39 The indirect estimates of treatment effect had wide confidence intervals. Furthermore, no non-inferiority margin was provided in the submission to support a non-inferiority claim. The Sponsor stated in the PSCR and pre-PBAC response that the submission did not nominate a non-inferiority margin because none was identified in the published literature for the outcome of clinical remission. The PSCR further stated that, as for MSUC, the PBAC has previously recommended bDMDs for CD based on the absence of statistically significant differences between the intervention and comparator(s) (paragraph 7.8, VDZ PSD for CD, March 2015). The pre-PBAC response argued that the wide confidence intervals are more likely to reflect the lack of statistical power rather than true differences in treatment effect.
- 6.40 There was also apparent heterogeneity between the trials, which decreases the level of confidence in the indirect estimates of treatment effect. Differences between the trials included the age of the studies (VISIBLE 2: 2015-2019; GEMINI 2: 2008-2012), disease characteristics (duration of CD, inflammatory markers, number of sites of disease involvement, prior surgery/inadequate or loss of response to prior corticosteroids), study treatment exposure/durations, and placebo response rates.

The net influence of these differences, in terms of the direction and magnitude of the indirect estimates of treatment effect, is unknown.

- 6.41 The PBAC considered that while the claim of non-inferior comparative effectiveness in severe CD was uncertain, it acknowledged it is likely that maintenance therapy with VDZ SC delivers similar outcomes to continuation of VDZ IV after a 12-14 week assessment point.
- 6.42 The PBAC considered that the claim of non-inferior comparative safety in severe CD was reasonable.

Economic analysis

- 6.43 The submission presented a cost-minimisation analysis of VDZ SC compared to VDZ IV based on a non-inferiority claim.
- 6.44 The equi-effective doses were estimated as VDZ 108 mg subcutaneous injection every two weeks (Q2W) and VDZ 300 mg intravenous infusion every eight weeks (Q8W), based on clinical trials VISIBLE 1, VISIBLE 2 and GEMINI 2. The PBAC considered this is reasonable based on the maintenance dosing regimen selected for VDZ SC 108 mg Q2W to provide similar steady-state exposure to that for VDZ IV 300 mg Q8W as employed in these three clinical trials.
- 6.45 The submission presented a CMA over a 2-year time-horizon (excluding the initiation treatment phase) and assumed 13 administrations for VDZ IV per patient and 52 administrations for VDZ SC per patient over this time horizon. The PBAC considered this is reasonable and agreed with the Sponsor and the evaluation that the cost minimisation should be calculated from the point of patients starting VDZ SC following IV induction.
- 6.46 In addition to the cost of medicines, the submission included costs associated with VDZ IV administration. The submission applied the cost of IV infusion as MBS item 14245 (Schedule fee, \$101). The submission justified the choice of this MBS item based on bringing VDZ IV to room temperature before administration and observation of patients for adverse reactions after the infusion. MBS item 14245 is for an IV infusion of at least 2 hours duration. However, VDZ IV is administered over 30 minutes, and it does not appear reasonable to include the time associated with waiting for the infusion bag to warm up, or post infusion observation in the 'infusion duration time' claimable on the MBS. During the evaluation the cost-minimisation analysis was revised, replacing the administration cost with MBS item 116 (Schedule fee, \$79.05). MBS item 116 was considered the appropriate item for VDZ IV in previous considerations (5.19 vedolizumab, July 2014 PBAC Meeting). The PSCR stated that the Sponsor acknowledged that a cost offset equivalent to the schedule fee of MBS item 116 may be more suitable for use in the economic evaluation.
- 6.47 The results of the CMA for MSUC and severe CD as presented by the submission and revised during the evaluation are presented in Table 12 and Table 13.

Table 12: Results of the cost-minimisation analysis for MSUC maintenance treatment over two-year period at effective AEMP

	Description	VDZ SC (108 mg, 2 pre-filled syringes or pens/pack)	VDZ IV (300 mg, 1 vial/pack)
A	Number of administrations over two-years -Section 100 (Public & Private) - Section 85	- 52	13 -
B	Cost per dose (effective AEMP) - Public hospital - Private hospital - Section 85	- - \$ [redacted] / 2 = \$ [redacted]	- \$ [redacted] -
C	Drug costs over two-years [A x B]	\$ [redacted]	\$ [redacted]
D	Cost per administration (MBS 14245) Revised (MBS item 116)	\$0.00	\$101.0 ^a \$79.05 ^b
E	Administration costs over two-years [A x D] Revised	\$0.00	\$1,313.00 \$1,027.65
F	Total Cost over two-years [C + E] Revised	\$ [redacted]	\$ [redacted]
G	Difference in cost over two-years Revised	Equal cost VDZ SC is \$ [redacted] more costly	

Source: Compiled during evaluation based on information presented in Tables 3.4.1 -3.4.3, pp124-125 and Table 3.4.5, p 126 of the submission.

MSUC = moderate to severe ulcerative colitis AEMP = approved ex-manufacturers price, SPA = special pricing arrangement SC = subcutaneous IV = intravenous, VDZ= vedolizumab

^a Fee for MBS Item code 14245, source MBS online July 2020

^b Fee for MBS item code 116, source MBS online July 2020

Table 13: Results of the cost-minimisation analysis for severe CD maintenance treatment over two-year period at effective AEMP

	Description	VDZ SC (108 mg, 2 pre-filled syringes or pens/pack)	VDZ IV (300 mg, 1 vial/pack)
A	Number of administrations over two-years -Section 100 (Public & Private) - Section 85	- 52	13 -
B	Cost per dose (effective AEMP) - Public hospital - Private hospital - Section 85	- - \$ [redacted] / 2 = \$ [redacted]	\$ [redacted] \$ [redacted] -
C	Drug costs over two-years [A x B]	\$ [redacted]	\$ [redacted]
D	Cost per administration (MBS 14245) Revised (MBS item 116)	\$0.00	\$101.0 ^a \$79.05 ^b
E	Administration costs over two-years [A x D] Revised	\$0.00	\$1,313.00 \$1,027.65
F	Total Cost over two-years [C + E] Revised	\$ [redacted]	\$ [redacted]
G	Difference in cost over two-years Revised	Equal cost VDZ SC is \$ [redacted] more costly	

Source: Compiled during evaluation based on information presented in Tables 3.4.1 -3.4.3, pp124-125 and Table 3.4.5, p 126 of the submission.

AEMP = approved ex-manufacturers price, SPA = special pricing arrangement SC = subcutaneous IV = intravenous, VDZ= vedolizumab

^a Fee for MBS Item code 14245, source MBS online July 2020

^b Fee for MBS item code 116, source MBS online July 2020

6.48 The analysis inappropriately assumed there is no administration cost for VDZ SC because all patients will self-inject. This assumption is not reasonable given a proportion of patients will be unable to self-inject and require assistance. The PBAC had previously accepted that 10% of patients require assistance with injections involving ‘a visit to a doctor’ (paragraph 10, golimumab PSD for RA, March 2010). The Sponsor argued in the pre-PBAC response that while including doctor assistance in the CMA for golimumab may be appropriate, as it is only available as a SC injection, it is not required for VDZ SC, as patients and clinicians will have the flexibility to choose IV or SC administration, as is most appropriate for the patient. Nevertheless, the PBAC considered that it is reasonable to assume 10% of patients will require assistance and that this cost should be included in the CMA.

6.49 The submission cost-minimised the VDZ SC using the indication-specific effective approved ex-manufacturer price (AEMP) for VDZ IV. Given the IV formulation is dispensed through S100 and the SC formulation will be dispensed through S85, the PBAC noted that the incremental cost of VDZ SC is driven by the more frequent administration of S85 items.

Drug cost/patient/2-years for MSUC maintenance treatment

6.50 The expected cost per patient of VDZ SC over two-year period, as estimated in the submission was \$ [redacted] for MSUC treatment. This was based on a proposed

indication-specific approved effective ex-manufacturer price (AEMP). When cost per patient over 2 years is calculated on the basis of the proposed dispensed price, expected cost is \$ [REDACTED].

Table 14: Drug cost per patient for VDZ SC and VDZ IV MSUC maintenance treatment

MSUC	VDZ SC			VDZ IV		
	Trial dose and duration	Cost minimization analysis	Financial estimates ^a	Trial dose and duration	Cost minimization analysis	Financial estimates ^a
Mean dose	108 mg Q2W	As in the trials	As in the trials	300 mg Q8W	As in the trials	As in the trials
Mean duration	52 weeks	2 years	Not estimated	52 weeks	2 years	Not estimated
<i>Cost/patient/ 2-years</i>						
Effective AEMP		\$ [REDACTED]	Not estimated		\$ [REDACTED]	Not estimated
Effective DPMQ		\$ [REDACTED]	Not estimated		\$ [REDACTED]	Not estimated

Source: Table compiled during the evaluation, based on Table 3.4.1, p124, and Table 3.4.3, p125 of the submission. Italicised values have been calculated.

SC = subcutaneous, IV = intravenous, Q2W = every 2 weeks, Q8w = every 8 weeks, VDZ= vedolizumab

^a Financial estimates are based on prescription numbers and market share, not a per patient or epidemiological approach.

Drug cost/patient/2-years for severe CD maintenance treatment

6.51 The expected cost per patient of VDZ SC over two-year period, as estimated in the submission was \$ [REDACTED] for severe CD treatment. This was based on a proposed indication specific effective AEMP. When cost per patient over 2 years is calculated based on the proposed dispensed price, expected cost is \$ [REDACTED].

Table 15: Drug cost per patient for VDZ SC and VDZ IV CD maintenance treatment

Severe CD	VDZ SC			VDZ IV		
	Trial dose and duration	Cost minimization analysis	Financial estimates ^a	Trial dose and duration	Cost minimization analysis	Financial estimates ^a
Mean dose	108 mg Q2W	As in the trials	As in the trials	300 mg Q8W	As in the trials	As in the trials
Mean duration	52 weeks	2 years	Not estimated	52 weeks	2 years	Not estimated
<i>Cost/patient/ 2-years^g</i>						
Effective AEMP		\$ [REDACTED]	Not estimated		\$ [REDACTED]	
Effective DPMQ		\$ [REDACTED]			\$ [REDACTED]	

Source: Table compiled during the evaluation, based on Table 3.4.1, p124, and Table 3.4.4, p126 of the submission. Italicised values have been calculated.

CD = Crohn's disease, SC = subcutaneous, IV = intravenous, Q2W = every 2 weeks, Q8W = every 8 weeks, VDZ= vedolizumab

^a Financial estimates are based on prescription numbers and market share, not a per patient or epidemiological approach.

Estimated PBS usage & financial implications

6.52 This submission was not considered by DUSC. The submission used a market-share approach to predict the likely use and financial impact of listing of VDZ subcutaneous on the PBS.

Table 16: Key inputs for financial estimates

Parameter	Value applied	Source	Comment														
Size of the market																	
Distribution of initiation vs maintenance scripts for PBS Items for MSUC and CD. MSUC maintenance treatment (2014-2019): Adalimumab: 10960W and 10961W Golimumab 11381B. CD maintenance treatment (2007-2019): Adalimumab (9189P and 9191R) All data extrapolated to 2020-2025.	See Figure 4.2.1 and 4.2.2 for initiation prescriptions of adalimumab for MSUC and CD	Services Australia PBS statistics	This data source was appropriate. It could be supplemented by 2017 DUSC reports for MSUC and CD to reflect market overview for all bDMDs used in MSUC & CD treatment. Infiximab is not included in calculations/projections since PBS item codes for infiximab did not allow separation of initiation vs continuing treatment scripts prior to October 2019.														
Estimated number of maintenance prescriptions for VDZ IV	<table border="0"> <tr> <td>MSUC:</td> <td>CD:</td> </tr> <tr> <td>Yr 1: [redacted] 1</td> <td>Yr 1: [redacted] 3</td> </tr> <tr> <td>Yr 2: [redacted] 1</td> <td>Yr 2: [redacted] 3</td> </tr> <tr> <td>Yr 3: [redacted] 2</td> <td>Yr 3: [redacted] 1</td> </tr> <tr> <td>Yr 4: [redacted] 2</td> <td>Yr 4: [redacted] 1</td> </tr> <tr> <td>Yr 5: [redacted] 2</td> <td>Yr 5: [redacted] 1</td> </tr> <tr> <td>Yr 6: [redacted] 2</td> <td>Yr 6: [redacted] 1</td> </tr> </table>	MSUC:	CD:	Yr 1: [redacted] 1	Yr 1: [redacted] 3	Yr 2: [redacted] 1	Yr 2: [redacted] 3	Yr 3: [redacted] 2	Yr 3: [redacted] 1	Yr 4: [redacted] 2	Yr 4: [redacted] 1	Yr 5: [redacted] 2	Yr 5: [redacted] 1	Yr 6: [redacted] 2	Yr 6: [redacted] 1	Observed/predicted distributions of other bDMDs (for MSUC adalimumab and golimumab and for CD adalimumab) applied to the aggregated VDZ IV prescription volumes, adjusted for time of listing.	These estimates appeared reasonable. However, PBS 10% sample for all patients treated with PBS script for VDZ IV could present a more accurate estimation for breakdown of patients (initiation, switch in/out, continuation, discontinuation, etc).
MSUC:	CD:																
Yr 1: [redacted] 1	Yr 1: [redacted] 3																
Yr 2: [redacted] 1	Yr 2: [redacted] 3																
Yr 3: [redacted] 2	Yr 3: [redacted] 1																
Yr 4: [redacted] 2	Yr 4: [redacted] 1																
Yr 5: [redacted] 2	Yr 5: [redacted] 1																
Yr 6: [redacted] 2	Yr 6: [redacted] 1																
Expected substitution rates																	
Proportion of VDZ IV scripts replaced by VDZ SC	<table border="0"> <tr> <td>MSUC:</td> <td>CD:</td> </tr> <tr> <td>Yr 1: [redacted] %</td> <td>Yr 1: [redacted] %</td> </tr> <tr> <td>Yr 2: [redacted] %</td> <td>Yr 2: [redacted] %</td> </tr> <tr> <td>Yr 3: [redacted] %</td> <td>Yr 3: [redacted] %</td> </tr> <tr> <td>Yr 4: [redacted] %</td> <td>Yr 4: [redacted] %</td> </tr> <tr> <td>Yr 5: [redacted] %</td> <td>Yr 5: [redacted] %</td> </tr> <tr> <td>Yr 6: [redacted] %</td> <td>Yr 6: [redacted] %</td> </tr> </table>	MSUC:	CD:	Yr 1: [redacted] %	Yr 1: [redacted] %	Yr 2: [redacted] %	Yr 2: [redacted] %	Yr 3: [redacted] %	Yr 3: [redacted] %	Yr 4: [redacted] %	Yr 4: [redacted] %	Yr 5: [redacted] %	Yr 5: [redacted] %	Yr 6: [redacted] %	Yr 6: [redacted] %	Assumption	The sponsor did not provide any rationale for this assumption.
MSUC:	CD:																
Yr 1: [redacted] %	Yr 1: [redacted] %																
Yr 2: [redacted] %	Yr 2: [redacted] %																
Yr 3: [redacted] %	Yr 3: [redacted] %																
Yr 4: [redacted] %	Yr 4: [redacted] %																
Yr 5: [redacted] %	Yr 5: [redacted] %																
Yr 6: [redacted] %	Yr 6: [redacted] %																
Scripts dispensed for VDZ SC	<table border="0"> <tr> <td>MSUC:</td> <td>CD:</td> </tr> <tr> <td>Yr 1: [redacted] 3</td> <td>Yr 1: [redacted] 3</td> </tr> <tr> <td>Yr 2: [redacted] 1</td> <td>Yr 2: [redacted] 3</td> </tr> <tr> <td>Yr 3: [redacted] 1</td> <td>Yr 3: [redacted] 1</td> </tr> <tr> <td>Yr 4: [redacted] 1</td> <td>Yr 4: [redacted] 1</td> </tr> <tr> <td>Yr 5: [redacted] 2</td> <td>Yr 5: [redacted] 1</td> </tr> <tr> <td>Yr 6: [redacted] 2</td> <td>Yr 6: [redacted] 1</td> </tr> </table>	MSUC:	CD:	Yr 1: [redacted] 3	Yr 1: [redacted] 3	Yr 2: [redacted] 1	Yr 2: [redacted] 3	Yr 3: [redacted] 1	Yr 3: [redacted] 1	Yr 4: [redacted] 1	Yr 4: [redacted] 1	Yr 5: [redacted] 2	Yr 5: [redacted] 1	Yr 6: [redacted] 2	Yr 6: [redacted] 1	MSUC: PBS item codes for VDZ IV do not differentiate between initiation and maintenance treatment. Observed/predicted distributions of adalimumab and golimumab are applied to the aggregated VDZ IV prescription volumes, adjusted for time of listing. Linear and logarithmic trend analysis using MS Excel built-in function is applied to estimate projected number of maintenance prescriptions for VDZ IV. CD:	PBS 10% sample for all patients treated with PBS script for VDZ IV could present a more accurate estimation for breakdown of patients (initiation, switch in/out, continuation, discontinuation, etc). This data could be supplemented by 2017 DUSC reports for MSUC and CD.
MSUC:	CD:																
Yr 1: [redacted] 3	Yr 1: [redacted] 3																
Yr 2: [redacted] 1	Yr 2: [redacted] 3																
Yr 3: [redacted] 1	Yr 3: [redacted] 1																
Yr 4: [redacted] 1	Yr 4: [redacted] 1																
Yr 5: [redacted] 2	Yr 5: [redacted] 1																
Yr 6: [redacted] 2	Yr 6: [redacted] 1																

Public Summary Document – November 2020 PBAC Meeting

Parameter	Value applied	Source	Comment
		Same methodology and calculations used for VDZ IV prescription predictions based on observed/predicted distributions of adalimumab only.	
Number of injections per patient year	VDZ SC: 52 pen or PFS (equals to 26 pack)	PI	This is reasonable.
Public : Private split	MSUC: 61.9% : 38.1% CD: 64.7% : 35.3%	PBS statistics from Jan 2019 to Dec 2019 for VDZ IV items for: MSUC: 10384M and 10398G CD: 10390W and 10415E	This is reasonable.

Source: Table 4.1.1, pp128-9, Table 4.2.2, pp 135-6, Table 4.2.3, p 135 Table 4.2.4, p 137 of the submission.

PBS = Pharmaceutical Benefits Scheme, MSUC = Moderate to Severe Ulcerative Colitis, CD = Crohn's Disease, DUSC = Drug utilisation sub-committee, bDMDs = biologic disease modifying drugs, VDZ SC = vedolizumab subcutaneous, VDZ IV = vedolizumab intravenous, PFS = pre-filled syringe, AEMP = Approved Ex-Manufacturer Price, DPMQ = Dispensed Price for Maximum Quantity, PI = product information, MBS = Medicare Benefits Schedule

The redacted values correspond to the following ranges:

¹10,000 to <20,000

²20,000 to <30,000

³5,000 to <10,000

- 6.53 The total cost to the PBS/RPBS of listing VDZ SC was estimated to be \$0 to <\$10 million in Year 6, and a total of \$20 to <\$30 million in the first 6 years of listing. This was based on the indication-specific proposed effective DPMQs for VDZ SC and indication-specific effective DPMQs for VDZ IV, which were known by the submission. Calculation errors were identified in the financial analysis Excel workbook, which results in different utilisation rates across beneficiary types. In addition, an (average) 80% rebate rate for the MBS 116 cost offset was included in the revised calculations during the evaluation. The PSCR (p stated that revising the subtotal to include the December 2019 figures only impacts the distribution of prescriptions by beneficiary type and thus the patient co-payments, but not the total number of prescriptions for VDZ SC. The net cost to the PBS/RPBS was marginally underestimated; the revised numbers in the PSCR were \$0 to <\$10 million to \$0 to <\$10 million higher over Years 1 to 6, respectively. It is noted that no Excel workbook was supplied with the PSCR and these results could not be replicated based on the Utilisation and Cost Model workbook received during submission.
- 6.54 The financial impact of listing VDZ SC is underestimated as the cost-offsets are calculated based on full schedule fee of MBS item 14245, rather than MBS item 116. The PSCR noted that the financial analysis was revised during the evaluation using an average 80% benefit for MBS item 116. The Sponsor considered that the 85% MBS benefit should be applied, and revised the analysis accordingly in the PSCR. However, it is the 80% benefit that should be applied, as it is in line with the User Manual for the Utilisation and Cost Model Workbook: "The Workbook calculates the financial impact at 80% of the Schedule fee and is indicative only" (Section 12.1.1.1, pg 47) and a footnote states "This figure [80%] is the average between the 75% and 85% rebate rate".

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of vedolizumab (VDZ) subcutaneous (SC) on the General Schedule (Section 85), for the treatment of moderate to severe ulcerative colitis (MSUC) and severe Crohn's disease (CD) on a cost minimisation basis to VDZ intravenous (IV). The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of VDZ SC would be acceptable if it were cost-minimised against VDZ IV.
- 7.2 The PBAC advised that the listing of VDZ SC should be based on the equi-effective dose of VDZ SC 108 mg Q2W and VDZ IV 300 mg Q8W.
- 7.3 The PBAC considered that there is a clinical need for effective therapies in MSUC and severe CD, and the availability of a SC formulation would provide an additional, potentially patient-relevant option for maintenance therapy.
- 7.4 The PBAC noted that the requested authority level for the treatment of MSUC and severe CD is aligned with the other PBS listed drugs for the corresponding treatments.
- 7.5 The PBAC considered that the current PBS listing for VDZ IV will provide for the supply of the initial IV induction doses, and that new PBS item codes for this purpose are not necessary for VDZ IV.
- 7.6 The PBAC noted that the proposed maximum quantities of 2 x 108 mg injection with 5 repeats, for both MSUC and CD, will supply 24 weeks of SC treatment for each indication for continuing treatment. This is appropriate and consistent with existing listings for continuing treatment for alternative SC-administered bDMDs for MSUC and severe CD, which all supply up to 24 weeks of therapy.
- 7.7 The PBAC advised that a restriction for Balance of Supply for continuing treatment with VDZ SC for MSUC and severe CD should be included, in line with the listings of other PBS listed drugs for the corresponding treatments.
- 7.8 The PBAC noted that although a Grandfather clause was requested, a restriction summary was not provided. The Sponsor will be required to work with the Secretariat to finalise the Grandfather clause.
- 7.9 The PBAC considered that the restrictions should be aligned with the PI to allow patients to resume VDZ SC after a treatment break without the need of a re-induction of VDZ IV.
- 7.10 The PBAC noted that the TGA recommended dosage regimen and the key clinical trials for VDZ SC allowed patients to receive SC maintenance treatment after at least 2 doses of induction treatment with the IV formulation. The PBAC advised that it would be appropriate to allow VDZ IV patients to switch to VDZ SC after at least 2 doses of induction treatment. Assessment of response at 12 to 14 weeks should be bridged by a Balance of Supply restriction, if required. This allows patients the flexibility to access

the SC formulation from Week 6 or alternatively use the IV formulation until assessment at 12 to 14 weeks. The PBAC considered that this option would assist patients in remote areas who may have difficulty in accessing the VDZ IV induction treatment.

- 7.11 The PBAC advised that patients should be able to switch back to VDZ IV after receiving VDZ SC, and that this should not be considered a treatment failure. Flow-on changes to the VDZ IV continuing treatment restriction will be required.
- 7.12 The PBAC considered that the nomination of VDZ IV as comparator is appropriate. The PBAC considered that while there are alternative bDMDs which may be less costly, a switch from those alternative agents to VDZ SC for maintenance treatment is less likely, in particular where an assessment of response defined at 12 to 14 weeks makes it inappropriate and/or when re-induction with VDZ IV would be required. The PBAC further considered that VDZ IV followed by VDZ SC is likely to deliver improved outcomes, for some patients, compared with a switch to an alternative agent.
- 7.13 The PBAC noted that in relation to MSUC, the VISIBLE 1 trial was not powered to detect a difference between VDZ SC and VDZ IV, however considered that the results were consistent with a conclusion of no difference. The PBAC considered that although there are uncertainties in the direct clinical evidence for MSUC, VDZ SC may deliver similar outcomes to VDZ IV during the maintenance phase after a 12 to 14 week assessment point.
- 7.14 The PBAC considered that in relation to severe CD, there were no differences identified in the indirect analysis of VDZ SC compared to VDZ IV. The PBAC noted that heterogeneity between the VISIBLE 2 and GEMINI 2 trials, including differences in the treatment durations and placebo response rates, raised concerns regarding the indirect estimates of treatment effect. However, the PBAC considered that a claim of non-inferior efficacy compared with VDZ IV is reasonable, noting that there is greater patient exposure to VDZ in the SC form and there is an association between exposure and its effect.
- 7.15 The PBAC considered that there are no overall differences in the safety profile between VDZ SC and VDZ IV for both MSUC and severe CD, however noted that the discontinuation rates favour VDZ SC.
- 7.16 The PBAC considered it is reasonable to conduct the CMA of VDZ SC over a 2-year time horizon that is calculated from the point of patients starting VDZ SC following IV induction. The PBAC also considered that the CMA should ensure there is no additional cost to the government at the effective price, noting that different fees and mark-ups apply for VDZ IV (\$100) and VDZ SC (\$85). The PBAC considered that it is reasonable to assume 10% of patients will require medical assistance with injections and that this cost should be included in the CMA as a visit to a doctor.
- 7.17 Consistent with the cost-minimisation basis of the listing, the PBAC expected the listing of VDZ SC to be approximately cost neutral.

- 7.18 The PBAC recommended that the Early Supply Rule should apply.
- 7.19 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because VDZ SC is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over VDZ IV, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.20 The PBAC advised that VDZ SC is not suitable for prescribing by nurse practitioners.
- 7.21 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:

Moderate to severe ulcerative colitis

NEW Initial treatment

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL syringes	NEW NEW	1	2	0	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	NEW NEW	1	2	0	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber Type(s): Medical Practitioners
PBS Indication: Moderate to severe ulcerative colitis
Treatment phase : Initial treatment with subcutaneous form
Restriction Type: Authority required - non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart)
Treatment criteria: Must be treated by a gastroenterologist (code 87); 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)]
Clinical criteria: Patient must have received at least 2 of the 3 initial intravenous infusions with this drug for this condition at weeks 0, 2 and 6 under Initial 1 (new patient); OR
Clinical criteria: Patient must have received at least 2 of the 3 initial intravenous infusions with this drug for this condition at weeks 0, 2 and 6 under Initial 2 (change or re-commencement of treatment after a break in biological medicine of less than 24 months); OR
Clinical criteria: Patient must have received at least 2 of the 3 initial intravenous infusions with this drug for this condition at weeks 0, 2 and 6 under Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years);
AND
Population criteria: Patient must be aged 18 years or older

Public Summary Document – November 2020 PBAC Meeting

AND
Clinical criteria:
Patient must be appropriately assessed for the risk of developing progressive multifocal leukoencephalopathy whilst on this treatment
Prescribing Instructions:
Where two initial doses of vedolizumab (at weeks 0 and 2) is administered via intravenous infusion, initial treatment with subcutaneous form will commence at week 6. A maximum quantity and number of repeats to provide for weeks 6, 8, 10, 12, 14 and 16 will be authorised.
Prescribing Instructions:
Where three initial doses of vedolizumab (at weeks 0, 2 and 6) is administered via intravenous infusion, initial treatment with subcutaneous form will commence at week 14 (8 weeks after the third dose). A maximum quantity to provide for weeks 14 and 16 will be authorised.
Prescribing Instructions:
Applications for authorisation must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Ulcerative Colitis PBS Authority Application Form
Prescribing Instructions:
An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 12 weeks of therapy. An application for the continuing treatment must be accompanied with the assessment of response and submitted no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
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 in 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: No increase in the maximum quantity or number of units may be authorised.
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. EST 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

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL syringes	NEW NEW	1	2	5	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	NEW NEW	1	2	5	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
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
Restriction Type – <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Medicare (telephone/online/emergency)
Severity: Moderate to severe
Condition: Ulcerative colitis
Indication: Moderate to severe ulcerative colitis

Public Summary Document – November 2020 PBAC Meeting

Treatment Phase: Continuing treatment with subcutaneous form or switching from intravenous form to subcutaneous form
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 received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition, OR
Clinical criteria:
Patient must have received this drug in the intravenous form as their most recent course of PBS-subsidised biological medicine for this condition under the vedolizumab intravenous form continuing restriction
AND
Clinical criteria:
Patient must not receive more than 24 weeks of treatment under this restriction
AND
Clinical criteria:
Patient must have demonstrated or sustained an adequate response to treatment by having a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 while receiving treatment with this drug,
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 aged 18 years or older.
Prescribing Instructions:
Patients who have failed to maintain a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug.
Prescribing Instructions:
Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain the response.
Prescribing Instructions:
At the time of the authority application, medical practitioners should request sufficient quantity for up to 24 weeks of treatment under this restriction.
Prescribing Instructions:
Up to a maximum of 5 repeats will be authorised.
Prescribing Instructions:
An application for the continuing treatment must be accompanied with the assessment of response conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from cessation of the most recent course the date of completion of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
Prescribing Instructions:
Where a response assessment is not conducted within this 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 in 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:
A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological medicine was approved in this cycle and the date of the first application under a new cycle under the Initial 3 treatment restriction.
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:

Public Summary Document – November 2020 PBAC Meeting

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 Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL syringes	NEW NEW	1	2	0	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	NEW NEW	1	2	0	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
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
Restriction Type – <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Medicare (telephone/online/emergency)
Severity: Moderate to severe
Condition: Ulcerative colitis
Indication: Moderate to severe ulcerative colitis
Treatment Phase: Initial treatment or continuing treatment with subcutaneous form - Balance of supply
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 received insufficient therapy with this drug under the Initial treatment with subcutaneous form to complete 14 to 16 weeks treatment; OR
Clinical criteria:
Patient must have received insufficient therapy with this drug under the Continuing treatment to complete 24 weeks of treatment;
AND
Clinical criteria:
The treatment must provide no more than the balance of doses up to 14 to 16 weeks therapy available under Initial treatment – subcutaneous form; OR
Clinical criteria:
The treatment must provide no more than the balance of up to 24 weeks therapy available under Continuing treatment – subcutaneous form
AND
Population criteria:
Patient must be aged 18 years or older.
Prescribing Instructions:
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
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 Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Public Summary Document – November 2020 PBAC Meeting

Severe Crohn's disease

NEW initial treatment

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL syringes	NEW NEW	1	2	0	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	NEW NEW	1	2	0	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber Type(s): Medical Practitioners
PBS Indication: Severe Crohn disease
Treatment phase : Initial treatment with subcutaneous form
Restriction Type: Authority required - non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart)
Treatment criteria Must be treated by a gastroenterologist (code 87); 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)]
Clinical criteria: Patient must have received at least 2 of the 3 initial intravenous infusions with this drug for this condition at weeks 0, 2 and 3 under Initial 1 (new patient); OR
Clinical criteria: Patient must have received at least 2 of the 3 initial intravenous infusions with this drug for this condition at weeks 0, 2 and 3 under Initial 2 (change or re-commencement of treatment after a break in biological medicine of less than 24 months); OR
Clinical criteria: Patient must have received at least 2 of the 3 initial intravenous infusions with this drug for this condition at weeks 0, 2 and 3 under Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years); AND
Population criteria: Patient must be aged 18 years or older AND
Clinical criteria: Patient must be appropriately assessed for the risk of developing progressive multifocal leukoencephalopathy whilst on this treatment
Prescribing Instructions: Applications for authorisation must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Crohn Disease PBS Authority Application Form
Prescribing Instructions: Where two initial doses of vedolizumab (at weeks 0 and 2) is administered via intravenous infusion, initial treatment with subcutaneous form will commence at week 6. A maximum quantity and number of repeats to provide for weeks 6, 8, 10, 12, 14 and 16 will be authorised.
Prescribing Instructions: Where three initial doses of vedolizumab (at weeks 0, 2 and 6) is administered via intravenous infusion, initial treatment with subcutaneous form will commence at week 14 (8 weeks after the third dose). A maximum quantity to provide for weeks 14 and 16 will be authorised.
Prescribing Instructions: An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 12 weeks of therapy. An application for the continuing treatment must be accompanied with the assessment of response and submitted no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
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:

Public Summary Document – November 2020 PBAC Meeting

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 in 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: No increase in the maximum quantity or number of units may be authorised.

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. EST 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

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL syringes	NEW NEW	1	2	5	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd
VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	NEW NEW	1	2	5	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
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
Restriction Type – <input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart)
Severity: Severe
Condition: Crohn's disease
Indication: Severe Crohn's disease
Treatment Phase: Continuing treatment with subcutaneous form or switching from intravenous form to subcutaneous form
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 received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition; OR
Clinical criteria:
Patient must have received this drug in the intravenous form as their most recent course of PBS-subsidised biological medicine for this condition under the vedolizumab intravenous form continuing restriction
AND
Clinical criteria:
Patient must not receive more than 24 weeks of treatment under this restriction
AND
Clinical criteria:
Patient must be appropriately assessed for the risk of developing progressive multifocal leukoencephalopathy whilst on this treatment,
AND
Clinical criteria:
Patient must have an adequate response to this drug defined as a reduction in Crohn's 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
Clinical criteria:
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 disease or is an ostomy patient.
Population criteria:
Patient must be aged 18 years or older.
Prescribing Instructions:
Applications for authorisation must be made in writing and must include:
(a) a completed authority prescription form; and (b) a completed Crohn Disease PBS Authority Application Form which includes the following: (i) the completed Crohn Disease Activity Index (CDAI) Score calculation sheet including the date of the assessment of the patient's condition, if relevant; or (ii) the reports and dates of the pathology test or diagnostic imaging test(s) used to assess response to therapy for patients with short gut syndrome, extensive small intestine disease or an ostomy, if relevant; and (iii) the date of clinical assessment.
Prescribing Instructions:
An application for the continuing treatment must be accompanied with the assessment of response conducted following a minimum of 12 weeks of therapy and 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.
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 in 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:
Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain the response.
Prescribing Instructions:
A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological medicine was approved in this cycle and the date of the first application under a new cycle under the Initial 3 treatment restriction.
Prescribing Instructions:
At the time of the authority application, medical practitioners should request sufficient quantity for up to 24 weeks of treatment under this restriction.
Prescribing Instructions:
Up to a maximum of 5 repeats will be authorised.
Prescribing Instructions:
If fewer than 5 repeats are requested at the time of the application, authority approvals for sufficient repeats to complete 24 weeks treatment may be requested by telephone and authorised through the Balance of Supply treatment phase PBS restriction. Under no circumstances will telephone approvals be granted for continuing authority applications, or for treatment that would otherwise extend the continuing treatment period.
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: 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. EST Monday to Friday).

Public Summary Document – November 2020 PBAC Meeting

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:
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Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
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VEDOLIZUMAB 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices	NEW NEW	1	2	0	Entyvio® Takeda Pharmaceuticals Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
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
Restriction Type – <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Medicare (telephone/online/emergency)
Severity: Severe
Condition: Crohn's disease
Indication: Severe Crohn's disease
Treatment Phase: Initial treatment or continuing treatment with subcutaneous form - Balance of supply
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 received insufficient therapy with this drug under the Initial treatment with subcutaneous form to complete 14 to 16 weeks treatment; OR
Clinical criteria:
Patient must have received insufficient therapy with this drug under the Continuing treatment to complete 24 weeks of treatment;
AND
Clinical criteria:
The treatment must provide no more than the balance of doses up to 14 to 16 weeks therapy available under Initial treatment – subcutaneous form; OR
Clinical criteria:
The treatment must provide no more than the balance of up to 24 weeks therapy available under Continuing treatment – subcutaneous form
AND
Population criteria:
Patient must be aged 18 years or older.
Prescribing Instructions:
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.

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 Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

This restriction 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

Takeda Australia welcomes the PBAC's decision to recommend the subcutaneously administered formulation of vedolizumab as maintenance treatment for patients with moderate to severe ulcerative colitis and patients with severe Crohn's disease