

**5.07 MIRIKIZUMAB,
Solution concentrate for I.V. infusion 300 mg in
15 mL,
Solution for injection 100 mg in 1 mL pre-filled pen,
Omvoh[®],
Eli Lilly Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested Section 100 (Highly Specialised Drugs Program) and General Schedule, Authority Required (written (initial)/electronic (continuing)) Pharmaceutical Benefits Scheme (PBS) listings of mirikizumab (MIRI) vial for intravenous (IV) infusion and pre-filled pen for subcutaneous (SC) injection, respectively (Omvoh[®]), for the treatment of moderate to severe ulcerative colitis (MSUC) in adult patients who have had an inadequate response with, lost response to, or were intolerant to conventional therapy.
- 1.2 There are currently eight treatments available on the PBS for MSUC, including three tumour necrosis factor alpha inhibitors (TNFi) – infliximab (IFX), adalimumab (ADA), and golimumab (GOL), two janus kinase (JAK) inhibitors – tofacitinib (TOF) and upadacitinib (UPA), one interleukin 12/23 (IL-12/23) inhibitor – ustekinumab (UST), one sphingosine-1 phosphate (S1P) inhibitor – ozanimod (OZA), and one $\alpha 4\beta 7$ integrin inhibitor – vedolizumab (VDZ). MIRI would be the second drug in the interleukin (IL) proinflammatory class recommended by the PBAC after UST (IL-12/23 inhibitor).
- 1.3 Listing was requested on the basis of a cost-minimisation approach versus VDZ.

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

Component	Description
Population	Treatment of MSUC in adult patients who have had an inadequate response with, lost response to, or were intolerant to conventional therapy.
Intervention	Induction: MIRI 300 mg IV at Week 0, 4, 8 (standard induction, 12 weeks); ± additional doses at Week 12, 16, 20 (extended induction, up to a maximum of 24 weeks). Maintenance: MIRI 200 mg (given as two consecutive SC injections of 100 mg each) every 4 weeks thereafter.
Comparator	Main comparator: VDZ 300 mg IV infusion at Weeks 0, 2, 6 and every 8 weeks thereafter.* Secondary comparator: ADA SC injection, 160 mg at Week 0, 80 mg at Week 2 then 40 mg every 2 weeks thereafter. Near Market Comparator: UST IV infusion (based on body weight [^]) at Week 0, then UST 90 mg SC injection at Week 8 and every 8 or 12 weeks thereafter.
Outcomes	Indirect comparison of MIRI versus VDZ, MIRI versus ADA and MIRI versus UST was conducted for the following outcomes, for induction and maintenance therapy: clinical remission, clinical response.
Clinical claim	Main comparator: MIRI is clinically non-inferior in terms of efficacy and comparable in terms of safety versus VDZ. Secondary comparator: MIRI is clinically superior in terms of efficacy and comparable in terms of safety versus ADA. Near market comparator: MIRI is clinically non-inferior in terms of efficacy and comparable in terms of safety versus UST.

Source: Table 1, p31 of the submission.

ADA=adalimumab, IV=Intravenous, MIRI=mirikizumab, MSUC=moderate to severe ulcerative colitis, SC=Subcutaneous, UST=ustekinumab, VDZ=vedolizumab.

* The submission nominated VDZ IV as the main comparator, but patients can switch to VDZ 108 mg SC injection every 2 weeks from Week 6 after the first two IV infusions (Week 0 and 2).

[^] UST IV 260 mg for weight ≤ 55 kg; UST IV 390 mg for weight > 55 kg to ≤ 85 kg; UST IV 520 mg for weight > 85 kg.

2 Background

Registration status

- 2.1 TGA status at time of PBAC consideration: The Delegate’s Overview and draft Product Information were available. Mirikizumab is under evaluation by Swissmedic as part of the work-sharing initiative of the ACSS (Australia, Canada, Singapore and Switzerland) consortium (now known as ‘Access Consortium’).
- 2.2 The proposed TGA indication is: “OMVOH is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in patients who have had an inadequate response with, lost response to, or were intolerant to conventional therapy or a biologic treatment or a Janus kinase (JAK) inhibitor, or have medical contraindications to such therapies.”
- 2.3 The submission noted that the clinical evaluation report was not provided to sponsors with the Section 31 request for information.

3 Requested listing

- 3.1 The submission requested MIRI solution concentrate for I.V. infusion 300 mg in 15 mL be listed under a Section 100 (Highly Specialised Drugs Program) listing for Initial 1, 2 and 3 for the treatment of MSUC. The minimum treatment period of the Initial listing

requested was 12 weeks and a maximum treatment period of 24 weeks, and a maximum quantity of 1 vial and maximum of 5 repeats. The submission also requested a General Schedule Authority Required (Written) listing for mirikizumab solution for subcutaneous injection 100 mg in 1 mL pre-filled pen for continuing treatment for the treatment of MSUC, with a maximum quantity of 2 pre-filled pens (1 pack) and a maximum of 5 repeats.

- 3.2 The draft Product Information stated ‘The recommended induction dosage regimen of OMVOH is 300 mg infused intravenously for at least 30 minutes at Week 0, Week 4, and Week 8.....Evaluate patients after the 12-week induction dosing, and if there is adequate therapeutic response, transition to maintenance dosing. If patients do not have adequate therapeutic response at Week 12 after induction dosing, consider extended induction dosing by administering 300 mg OMVOH by intravenous infusion at Weeks 12, 16, and 20.....If therapeutic benefit is achieved with the additional intravenous therapy, patients may initiate OMVOH subcutaneous maintenance dosing every 4 weeks. Discontinue OMVOH in patients who do not show evidence of therapeutic benefit to extended induction therapy by Week 24.
- 3.3 The recommended maintenance dosage regimen is 200 mg (given as two consecutive subcutaneous injections of 100 mg each) every 4 weeks after completion of induction dosing.....starting at Week 12.....Patients with loss of therapeutic response during maintenance treatment may receive 300 mg mirikizumab by intravenous infusion every 4 weeks, for a total of 3 doses. If therapeutic benefit is achieved with the additional intravenous therapy, patients may resume subcutaneous maintenance dosing every 4 weeks’.
- 3.4 The submission requested a grandfather listing for MIRI for 9 patients currently enrolled in the LUCENT-3 (NCT02519945) open label extension study. The submission stated that patients enrolled in LUCENT-3 would meet the requirements for the requested PBS listing, and that these patients would transition to accessing MIRI through the PBS.
- 3.5 The Secretariat proposed a maximum of 2 repeats for Initial treatment listings (MIRI 300 mg/15 mL injection) to allow for an initial assessment of response at Week 12. An additional three doses of MIRI 300 mg/15 mL injection could be requested through a Balance of Supply listing if patients require the extended induction dosing. This reduces potential wastage if patients do not require the full six doses under the induction regimen. The Pre-Sub-Committee Response (PSCR) agreed with the proposal of including Balance of Supply listing if patients require the extended induction dosing.
- 3.6 For brevity reasons, an abbreviated version of the requested restrictions is presented below, with suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Public Summary Document – July 2023 PBAC Meeting

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
MIRIKIZUMAB					
mirikizumab 300 mg/15 mL injection, 15 mL vial	NEW	1	1	52	OmvoH
Restriction Summary 12180 / Treatment of Concept: 12080					
Category / Program: Section 100 – Highly Specialised Drugs Program					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)					
Indication: Moderate to severe ulcerative colitis					
Treatment Phase: Initial treatment – Initial 1 (new patient)					
Clinical criteria:					
Patient must have failed to achieve an adequate response to a 5-aminosalicylate oral preparation in a standard dose for induction of remission for 3 or more consecutive months or have intolerance necessitating permanent treatment withdrawal,					
AND					
Clinical criteria:					
Patient must have failed to achieve an adequate response to azathioprine at a dose of at least 2 mg per kg daily for 3 or more consecutive months or have intolerance necessitating permanent treatment withdrawal;					
OR					
Clinical criteria:					
Patient must have failed to achieve an adequate response to 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more consecutive months or have intolerance necessitating permanent treatment withdrawal;					
OR					
Clinical criteria:					
Patient must have failed to achieve an adequate response to a tapered course of oral steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period or have intolerance necessitating permanent treatment withdrawal, and followed by a failure to achieve an adequate response to 3 or more consecutive months of treatment of an appropriately dosed thiopurine agent,					
AND					
Clinical criteria:					
Patient must have a Mayo clinic score greater than or equal to 6;					
OR					
Clinical criteria:					
Patient must have a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo clinic score).					
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)].					
Population criteria:					
Patient must be aged 18 years or older.					
Restriction Summary 12136 / Treatment of Concept: 12179					
Category / Program: Section 100 – Highly Specialised Drugs Program					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)					
Indication: Moderate to severe ulcerative colitis					

Public Summary Document – July 2023 PBAC Meeting

	Treatment Phase: Initial treatment - Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years)
	Clinical criteria:
	Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle,
	AND
	Clinical criteria:
	Patient must not have already failed, or ceased to respond to, PBS -subsidised treatment with this drug for this condition during the current treatment cycle.
	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)].
	Population criteria:
	Patient must be aged 18 years or older.
Restriction Summary 12079 / Treatment of Concept: 12219	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Initial treatment - Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with a biological medicine for this condition,
	AND
	Clinical criteria:
	Patient must have had a break in treatment of 5 years or more from the most recently approved PBS-subsidised biological medicine for this condition,
	AND
	Clinical criteria:
	Patient must have a Mayo clinic score greater than or equal to 6;
	OR
	Clinical criteria:
	Patient must have a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo clinic score).
	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)].
	Population criteria:
	Patient must be aged 18 years or older.
Restriction Summary: modification of / Treatment of Concept: modification of	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required immediate/real time assessment by Services Australia (telephone/online application avenues)
	Indication: Moderate to Severe Ulcerative Colitis

Public Summary Document – July 2023 PBAC Meeting

Treatment Phase: <i>Initial 1 (new patient) or Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) or Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) – Balance of Supply</i>
Clinical criteria:
<i>Patient must have received insufficient therapy with this drug for this condition under the Initial 1 (new patient) restriction to complete 20 weeks of treatment (administered at weeks 0, 4, 8, 12,16 and 20)</i>
<i>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 20 weeks of treatment (administered at weeks 0, 4, 8, 12,16 and 20)</i>
<i>Patient must have received insufficient therapy with this drug for this condition under the Initial 3 (change or recommencement of treatment after a break in biological medicine of more than 5 years) restriction to complete 20 weeks of treatment (administered at weeks 0, 4, 8, 12,16 and 20)</i>
AND
Clinical criteria:
<i>The treatment must provide no more than the balance of up to 20 weeks treatment available under the above restrictions.</i>
Treatment criteria:
<i>Must be treated by a gastroenterologist (code 87); or</i>
<i>Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or</i>
<i>Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)]</i>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
MIRIKIZUMAB					
mirikizumab 100 mg/mL injection 2 x 1 mL pen devices	NEW	1	2	5	OmvoH

Restriction Summary 12181 / Treatment of Concept: 12135

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Indication: Moderate to severe ulcerative colitis
Treatment Phase: Continuing treatment with subcutaneous form
Clinical criteria:
Patient must have previously received this drug administered via intravenous infusion as their most recent course of PBS-subsidised biological medicine 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.
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)].
Population criteria:
Patient must be aged 18 years or older.

Public Summary Document – July 2023 PBAC Meeting

Restriction Summary [new] / Treatment of Concept: [new]	
Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Restriction type:	<input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system) (in writing only via post/HPOS upload)
Indication:	Moderate to severe ulcerative colitis
Treatment Phase:	Transitioning from non-PBS to PBS-subsidised supply - Grandfather treatments arrangements
Clinical criteria:	Patient must have received <i>non-PBS-subsidised treatment</i> with this drug as their most recent course of non-PBS-subsidised biological medicine treatment for this condition prior to [PBS listing date].
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.
	<i>Patient must have had a Mayo clinic score greater than or equal to 6 prior to commencing non-PBS-subsidised treatment with this drug for this condition; or</i>
	<i>Patient must have had a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo clinic score) prior to commencing non-PBS-subsidised treatment with this drug for this condition; or</i>
	<i>Patient must have a documented history of moderate to severe refractory ulcerative colitis prior to having commenced non-PBS-subsidised treatment with this drug for this condition where a Mayo clinic or partial Mayo clinic baseline assessment is not available.</i>
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)].
Population criteria:	
	Patient must be aged 18 years or older.
Prescribing Instructions:	<i>The authority application must be made in writing and must include:</i> <i>(1) a completed authority prescription form; and</i> <i>(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice), which includes:</i> <i>(i) the completed baseline Mayo clinic or partial Mayo clinic calculation sheet prior to initiating treatment (if available) including the date of assessment;</i> <i>(ii) the date of commencement of this drug.</i>
Prescribing Instructions:	<i>A patient may qualify for PBS-subsidised treatment under this restriction once only.</i>
Prescribing Instructions:	<i>For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</i>
Prescribing Instructions:	<i>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.</i>
Prescribing Instructions:	<i>Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain a response.</i>

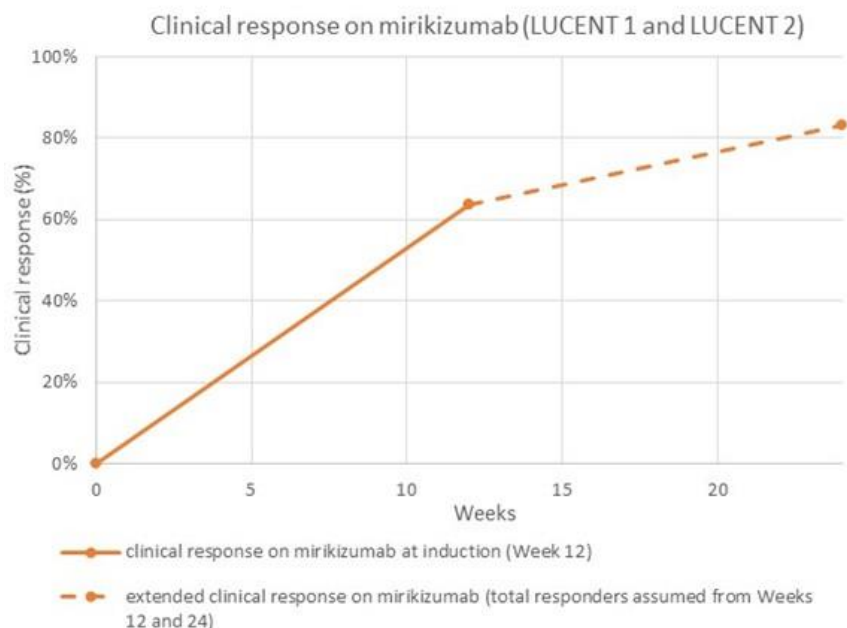
Public Summary Document – July 2023 PBAC Meeting

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:	An application for the continuing treatment must be accompanied with the assessment of response conducted 12 weeks after initial dose 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.
Prescribing Instructions:	<i>The assessment of the patient's response to this PBS-subsidised course of therapy must be conducted no later than 4 weeks from the cessation of the treatment course.</i>
Prescribing Instructions:	Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
Prescribing Instructions:	If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within this treatment cycle. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
Prescribing Instructions:	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:	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).
Administrative Advice:	Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

- 3.7 For initial treatment, the maximum quantity of 1 x 300 mg vials with 5 repeats (total 6 doses) allows for up to a maximum 24 weeks of treatment. This provides all patients with the recommended three doses of induction treatment at Weeks 0, 4 and 8 and for patients who do not have adequate response at Week 12 ('partial responders'), there are an additional three doses for extended induction treatment at Weeks 12, 16 and 20. Patients who demonstrate an adequate therapeutic response at Week 12 (or between Week 16 to 24 for patients treated with extended induction) would switch from the IV formulation to SC formulation for maintenance treatment. The requested maximum quantity of 2 x 100 mg pre-filled pens with 5 repeats (total 6 doses) allows for 24 weeks of maintenance treatment at the recommended dose.

- 3.8 The PSCR did not define the clinical criteria for ‘partial responders’ compared to complete lack of response. The pre-PBAC response stated that the option of the extended induction treatment would be clinically meaningful for patients who do not fully meet the definition of clinical response at the end of the first induction period, but who experience improvements in disease symptoms. The pre-PBAC response stated that clinicians can determine prognostic factors that could indicate if a patient would benefit from extended induction rather than switch to a new treatment class. It further stated that this request is similar to that of upadacitinib, which had an extended induction for patients with an inadequate response after standard induction treatment (paragraph 3.2, upadacitinib (ulcerative colitis), Public Summary Document (PSD), July 2022).
- 3.9 For induction treatment, the main clinical comparisons presented in the submission were based on key clinical outcomes reported at Week 12 for MIRI and Weeks 6 to 10 for the nominated comparators (VDZ, ADA, UST). The requested listing for up to 24 weeks of initial treatment with MIRI was based on the results of a non-randomised cohort of induction non-responders in the LUCENT 2 trial. A total of 272 patients without clinical response at Week 12 following three doses of MIRI 300 mg IV in LUCENT 1, received a further three doses of MIRI 300 mg IV in an open-label extended induction phase in LUCENT 2. The results showed 146 / 272 (53.7%) patients without clinical response at Week 12 had achieved clinical response at Week 24 (i.e. delayed clinical response). Taken together with the results from the LUCENT 1 trial, the submission stated that the (cumulative) response rate for MIRI induction treatment increased from 63.5% at Week 12 to 83.1% at Week 24, illustrated in Figure 1. The submission, however, did not present any evidence to inform the counterfactual at Week 24 (i.e. the incremental benefit of extended induction versus placebo). In the context of alternative treatment options on the PBS, extending the induction period with MIRI from 12 to 24 weeks may also delay induction non-responders from receiving an effective alternative treatment. The requested 24 weeks of initial treatment with MIRI is also longer than the initial treatment period of other treatments currently listed on the PBS (14 to 16 weeks, depending on the treatment). The PSCR suggested that there are only a small number of non-responders who are delayed in receiving an effective alternative treatment by extending the induction period to 24 weeks.

Figure 1: Clinical response at induction (Week 12) and extended induction (Week 24) for mirikizumab treatment



Source: compiled during the evaluation.

- 3.10 From a practical perspective, it was assumed patient response would be assessed at every appointment from Week 12 to Week 24, until the patient meets the eligibility criteria for continuing treatment or completes all six induction doses. The requested Authority Required (electronic) listing for the SC formulation would allow patients who meet the response criteria to initiate continuing treatment immediately, avoiding the need for a further IV infusion.
- 3.11 The submission requested equivalent restriction criteria for MIRI to other PBS-listed treatments (biologic/targeted synthetic disease modifying anti-rheumatic drugs (bDMARDs/tsDMARDs)) for initial and continuing treatment of MSUC. Response to treatment is defined based on Full Mayo Score (FMS), however in the MIRI trials the reported outcomes defined clinical response and remission based on Modified Mayo Score (MMS). The submission proposed that these outcomes based on MMS are consistent with FMS and are clinically relevant for use in clinical trials and clinical practice. See paragraph 4.3.
- 3.12 The submission requested a Special Pricing Arrangement (SPA). The proposed published approved ex-manufacturer price (AEMP) for MIRI (\$1,737.08) is equivalent to the published AEMP for VDZ 300 mg IV for MSUC, and the proposed effective AEMP for MIRI would be based on a cost-minimisation approach with VDZ IV using the effective AEMP. The submission presented a 'hypothetical' cost-minimisation approach using the published price of VDZ and requested an updated analysis using the effective AEMP of VDZ (unknown to the sponsor) following the same methodology. The sponsor also requested a flat pricing structure for the MIRI IV and SC dose forms.

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

4 Population and disease

- 4.1 Ulcerative colitis is a chronic inflammatory bowel disease characterised by continuous mucosal inflammation of the colon. The clinical course of the disease consists of periods of exacerbation (flares) and remission. Common symptoms of flares include rectal bleeding, diarrhoea, abdominal pain, bowel urgency and tenesmus. More severe disease typically leads to an increase in bloody diarrhoea and the presence of systemic symptoms such as weight loss, fever, nausea and vomiting. Disease severity (mild to severe) is generally assessed using criteria such as stool frequency, a combination of endoscopic and histological assessment and presence of systemic symptoms.
- 4.2 The Mayo Score is used to assess disease severity. The FMS, also known as Total Mayo Score, is a composite of four subscores comprising endoscopy, stool frequency, rectal bleeding and Physician's Global Assessment (PGA) of disease activity; each subscore is scored from 0 to 3 to give a maximum composite score of 12. An FMS score of 0-2 indicates remission, 3-5 mild disease activity, 6-10 moderate disease activity and 11-12 severe disease activity. Partial Mayo uses three of the four subscores of FMS (i.e. does not include the endoscopy score).
- 4.3 The main trials of MIRI supporting the submission (LUCENT 1 and LUCENT 2) were based on the MMS, which differs to the FMS as follows: the definition of an endoscopy score of 1 no longer includes mucosal friability and the PGA was removed from the MMS. The maximum total score for MMS is 9. A recently published cross-sectional real-world observational study by Naegeli et al 2021¹ showed that FMS, MMS and partial Mayo were highly correlated and indicated that MMS may be used as a proxy for FMS in clinical trials and in practice. MMS was recommended by the FDA² in 2016. The submission also presented post-hoc analyses from LUCENT 1 that showed similar results for clinical response and remission based on MMS and FMS.
- 4.4 Under current PBS criteria, patients with MSUC (FMS ≥ 6 or partial Mayo score >6 provided both rectal bleeding and stool frequency subscores ≥ 2), who have failed (or are unable to tolerate) a 5-aminosalicylate (5-ASA) oral agent and at least one of azathioprine, mercaptopurine or oral steroids, are eligible for treatment with a bDMARDs/tsDMARDs (e.g. TOF, UPA, IFX, VDZ, GOL, UST, OZA and ADA). The addition

¹ Naegeli AN, Hunter T, Dong Y et al. 2021. Full, partial and modified permutations of the Mayo score: Characterizing clinical and patient-reported outcomes in ulcerative colitis patients. *Crohn's & Colitis* 360. 3(1):1-8. doi: 10.1093/crocol/otab007.

² FDA Guidance Document, 2016. Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry. Available from: www.fda.gov/regulatory-information/search-fda-guidance-documents/ulcerative-colitis-clinical-trial-endpoints-guidance-industry

of MIRI to the clinical management algorithm will not alter current practice but will allow for an additional treatment option.

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

5 Comparator

- 5.1 The submission nominated VDZ as the main comparator, given VDZ has the largest market share (41%) for MSUC and has the same route of administration (IV induction and SC maintenance). The submission nominated ADA as a secondary comparator and identified UST as a near market comparator, given it is in the same interleukin proinflammatory cytokines class and that the PBAC recommended the listing of UST for MSUC at the July 2022 PBAC meeting.
- 5.2 In the context of the cost-minimisation approach taken by the submission, a further consideration for the PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. Alternative therapies include VDZ, ADA, OZA, UPA, UST, IFX, GOL and TOF.
- 5.3 The submission claimed that MIRI is of non-inferior comparative effectiveness versus VDZ and of superior effectiveness versus ADA; however, the evaluation and Economics Sub Committee (ESC) considered a claim of non-inferior effectiveness versus ADA may be more reasonable (see Comparative effectiveness and Clinical claim sections).
- 5.4 The ESC noted that there are currently eight different bDMARD/tsDMARD therapies currently listed on the PBS for the treatment of MSUC and considered there is a low clinical need for the addition of a new therapy on the PBS. The pre-PBAC response acknowledged that other bDMARD/tsDMARD therapies are available on the PBS but argued there remains a significant unmet need as a number of patients with UC fail to have an adequate response to currently available biological therapies and do not achieve sustained clinical benefit. The pre-PBAC response claimed that the availability of drugs with distinct mechanisms of action is therefore critical, and MIRI is the first treatment for UC that works to reduce mucosal inflammation by selectively targeting the p19 subunit of IL-23, a key mediator of immune dysfunction in patients with UC. The pre-PBAC response also stated that while the overall safety profile is comparable there are differences in safety aspects, meaning MIRI may be preferred over other treatments.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed input from health care professionals (1) via the Consumer Comments facility on the PBS website. The comment noted that a range of therapies were available for MSUC, however stated that despite this, a significant proportion of patients do not respond to therapies available and require surgery. The comment stated there is a strong need for more classes of effective medical therapies to be available through the PBS, and stated benefits of MIRI included its high safety profile and the convenience of SC maintenance dosing.

Clinical trials

6.3 There were no head-to-head trials of MIRI versus VDZ, ADA or UST for the treatment of MSUC. In the absence of direct head-to-head evidence, the submission conducted a review of all available PBAC PSDs for the treatment of MSUC as well as a search of the published literature (January 2020 to December 2022) to identify more recent randomised controlled trials (RCTs) to identify all placebo (PBO) controlled trials that would permit an indirect comparison between MIRI and the nominated comparators (VDZ, ADA and UST). Although this was a departure from standard practice for literature searches for PBAC submissions, an independent search conducted during the evaluation located no other relevant trials.

6.4 The submission presented indirect comparisons using PBO as common reference, consisting of data from 11 PBO-controlled RCTs:

- nine RCTs for induction therapy:
 - MIRI vs. PBO (one RCT): LUCENT 1
 - VDZ vs. PBO (two RCTs): GEMINI 1 (induction phase), Motoya et al 2019 (induction phase)
 - ADA vs. PBO (five RCTs): ULTRA I, ULTRA II (induction phase); Suzuki et al 2014 (induction phase); HIBISCUS I, HIBISCUS II (induction phase)
 - UST vs. PBO (one RCT): UNIFI (induction phase).
- seven RCTs for maintenance therapy:
 - MIRI vs. PBO (one RCT): LUCENT 2
 - VDZ vs. PBO (three RCTs): GEMINI 1 (maintenance phase), Motoya et al 2019 (maintenance phase); VISIBLE 1
 - ADA vs. PBO (two RCTs): ULTRA II (maintenance phase); Suzuki et al 2014 (maintenance phase)

- UST vs. PBO (one RCT): UNIFI (maintenance phase).

The PBAC has considered evidence from all of the comparator trials in past decisions for MSUC, with the exception of HIBISCUS I and HIBISCUS II for ADA. The HIBISCUS trials were placebo-controlled and active-controlled trials evaluating the efficacy and safety of etrolizumab versus ADA and PBO for induction treatment in MSUC.

- 6.5 The results of the indirect treatment comparison were sourced from an unpublished report by Moura et al 2023. The submission also presented the results of a Bayesian network meta-analysis (NMA) in an unpublished report by Kroep et al 2023 as supportive evidence. The NMA included data from 37 trials and compared 10 interventions (MIRI, VDZ, ADA, UST, UPA, TOF, GOL, IFX, OZA and filgotinib), but the submission did not provide any detail of the additional trials included in the NMA.
- 6.6 Details of the trials presented in the submission are provided in Table 2. The submission excluded an ongoing Phase 3, open-label long-term extension study of MIRI SC in patients with MSUC (LUCENT 3; NCT03519945; no results available; estimated completion April 2029), which is potentially relevant as it evaluates the long-term efficacy and safety of MIRI, with the primary outcome of clinical remission (measured by MMS).

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Mirikizumab trials		
LUCENT 1 (6T-MC-AMAN) NCT03518086	A phase 3, multicenter, randomized, double-blind, parallel, placebo-controlled study of mirikizumab in conventional-failed and biologic-failed patients with moderately to severely active ulcerative colitis. D'Haens G, Kobayashi T, Morris N, et al. Efficacy and safety of mirikizumab as induction therapy in patients with moderately to severely active ulcerative colitis: Results from the Phase 3 LUCENT-1 study	June 2021 Abstracts of the 17 th Congress of ECCO – European Crohn's and Colitis Organisation: OP26
LUCENT 2 (16T-MC-AMBG) NCT03524092	A phase 3, multicenter, randomized, double-blind, parallel-arm, placebo-controlled maintenance study of mirikizumab in patients with moderately to severely active ulcerative colitis Begun J, Dubinsky MC, Irving PM, et al. Efficacy and safety of mirikizumab as maintenance therapy in patients with moderately to severely active ulcerative colitis: Results from the phase 3 LUCENT-2 study.	December 2021. Gastroenterol & Hepatol 2022; 18(7) Suple. 2: 3.
Vedolizumab trials		
GEMINI 1 NCT00783718	Feagan B, Rutgeerts P, Sands B, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis.	N Engl J Med. 2013; 369(8):699-710.
Motoya 2019 NCT02039505	Motoya S, Watanabe K, Ogata H, et al. Vedolizumab in Japanese patients with ulcerative colitis: A phase 3, randomized, double-blind, placebo-controlled study.	PLOS ONE February 2019; 14(2): e0212989.
VISIBLE 1 NCT02611830	Sandborn W, Baert F, Danese S, et al. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis.	Gastroenterology 2020; 158: 562-572.
Adalimumab trials		
ULTRA 1 NCT00385736	Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active UC: results of a randomised controlled trial.	Gut. 2011;60(6):780-787
ULTRA 2 NCT00408629	Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate to severe UC.	Gastroenterology. 2012;142(2):257-65[e1-3]
Suzuki 2014 NCT00853099	Suzuki Y, Motoya S, Hanai H, et al. Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis.	J Gastroenterol. 2014; 49:283-294.
HIBISCUS I NCT02163759	Rubin D, Dotan I, DuVall A, et al. Etrolizumab versus adalimumab or placebo as induction therapy for moderately to severely active ulcerative colitis (HIBISCUS): two phase 3 randomised, controlled trials.	Lancet Gastroenterol Hepatol 2022; 7:17-27.
HIBISCUS II NCT02171429		
Ustekinumab trial		
UNIFI NCT02407236	Janssen. A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis. UNIFI. Sands BE, Sandborn R, Panaccione CD, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis.	Clinical study report – report date: 3 December 2018. N Engl J Med. 2019; 381 (13): 1201-1214.

Source: Table 18, pp.78-79 of the submission. Shaded areas indicate data previously seen by the PBAC.

6.7 The key features of the included evidence are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)
MIRI vs PBO					
LUCENT 1 [induction] 2018-2021	IP: 1162	P3, MC, R, PC, DB (12 wk induction)	Low	TNFi-e ; TNFi-n	1 ^{ary} : clinical remission (MMS) 2 ^{ary} : clinical response (MMS), endoscopic remission, symptomatic remission
LUCENT 2 [maintenance] 2018-2021	MP:544 ^a	P3, MC, R, PC, DB (maintenance to Wk 52)	Some concerns	LUCENT 1- Wk 12 active responders	1 ^{ary} : clinical remission (MMS) 2 ^{ary} : clinical response (MMS), endoscopic healing, corticosteroid-free remission
VDZ v PBO					
GEMINI 1 [induction & maintenance]	IP Ct1:374 IP Ct2:521 MP:373	P3, MC, R, DB (58 wk), RWD for maintenance (6 wk induction, maintenance to Wk 52), 3-arm. Cohort 1 - randomised induction. Cohort 2 - OL induction	IP: Low MP: High	TNFi-n & TNFi-e. Maintenance: Wk 6 active responders in cohort 1 and 2.	1 ^{ary} : clinical response (FMS) 2 ^{ary} : clinical remission (FMS), mucosal healing, sustained clinical response, sustained clinical remission, corticosteroid-free remission
Motoya 2019 [induction & maintenance]	IP Ct1: 246 IP Ct2: 46 ^e MP: 83	P3, MC, R, DB, RWD for maintenance (10 wk induction, maintenance to Wk 60). Randomised induction	IP: Low MP: High	TNFi-n & TNFi-e	1 ^{ary} : clinical response (FMS) 2 ^{ary} : clinical remission (FMS), mucosal healing
VISIBLE-1 [maintenance]	IP ^f : 383 MP: 216	P3, MC, R, DB, RWD for maintenance (6 wk OL induction, maintenance to Wk 52, R, DB maintenance).	MP: High	TNFi-n & TNFi-e	1 ^{ary} : clinical remission (FMS) 2 ^{ary} : mucosal healing, sustained clinical response, sustained clinical remission, corticosteroid-free remission
ADA v PBO					
ULTRA 1 [induction]	390	P3, MC, R, PC, DB (8 wk), 3-arm	Low	TNFi-n	1 ^{ary} : clinical remission (FMS) 2 ^{ary} : clinical response (FMS), mucosal healing
ULTRA 2 [induction & maintenance]	494	P3, MC, R, PC, DB (52 wk)	IP: Low MP: High	TNFi-n & TNFi-e	1 ^{ary} : clinical remission (FMS) 2 ^{ary} : clinical response (FMS), mucosal healing, IBDQ response, sustained clinical remission, sustained clinical response, sustained mucosal healing
Suzuki 2014 [induction & maintenance]	274	P2/3, MC, R, PC, DB (52 wk), 3-arm	IP: Low MP: High	TNFi-n (Japanese)	1 ^{ary} : clinical remission (FMS) 2 ^{ary} : clinical response (FMS), mucosal healing
HIBISCUS I [induction]	358	P3, MC, R, PC, DB (10 wk); 3-arm	IP: Low	TNFi-n	1 ^{ary} : clinical remission (FMS) 2 ^{ary} : clinical response (FMS), endoscopic remission
HIBISCUS II [induction]	358		IP: Low		
UST v PBO					
UNIFI [induction & maintenance]	IP: 961. MP: 783 ^c	P3, MC, R, PC, DB (8/16 ^b wk induction; maintenance to Wk 52); 3-arm.	IP: Low MP: Some concerns	TNFi-n & TNFi-e. Maintenance: Wk 8/16 active responders ^d	1 ^{ary} : clinical remission (FMS) 2 ^{ary} : clinical response (FMS), mucosal healing, sustained clinical response, sustained clinical remission, corticosteroid-free remission

Source: Table 19-20, pp83-94 of the submission. Shaded areas indicate data previously seen by the PBAC.

^{1ary}=primary, ^{2ary}=secondary, ADA=adalimumab, Ct=cohort, DB=double blind, FMS=Full Mayo Score, IBDQ= Inflammatory Bowel Disease Questionnaire, IP=induction phase, MC=multi-centre, MIRI = mirikizumab, MP=maintenance phase, mITT=modified intention-to-treat, MMS=Modified Mayo Score, OL=open label, P2/3=Phase 2/3, P3=Phase 3, PBO=placebo, PC=placebo-controlled, R=randomised, RWD=randomised withdrawal design, TNFi-e=tumour necrosis factor inhibitor experience, TNFi-n= tumour necrosis factor inhibitor naïve, UST=ustekinumab, VDZ=vedolizumab, Wk=week.

- ^a LUCENT 2: 544 responders to MIRI induction dosing. Subjects who were in clinical response to MIRI IV 300 mg, were assigned treatment to MIRI SC or PBO at Week 12 (179 PBO; 365 MIRI). An additional 405 induction non-responders (subjects who were not in clinical response to induction therapy at Week 12; 133 PBO induction non-responders and 272 MIRI induction non-responders) received three additional MIRI IV Q4W doses (open-label extended induction).
- ^b UNIFI: At Week 8, subjects who were not in clinical response were assigned treatment as follows: those randomised to PBO at Week 0 received UST IV ~ 6 mg/kg plus PBO SC (to maintain the blind); those randomised to UST at Week 0 received UST 90 mg SC plus PBO IV (to maintain the blind). A total of 417 subjects who were not in clinical response at Week 8 received an additional dose of study agent at Week 8.
- ^c UNIFI: Total subjects enrolled in maintenance. Of these, 523 were in the primary population for the maintenance study (clinical response to UST IV induction) and were randomised. 260 subjects were not part of the primary population (PBO induction responders and UST induction delayed responders) and were not randomised.
- ^d UNIFI: Additional subjects entering the maintenance study not part of the primary population included the following: subjects in clinical response to PBO IV induction received placebo SC; subjects who were delayed responders to UST induction (i.e. not in clinical response to UST at Week 8 but were in clinical response at Week 16) received UST 90 mg SC Q8W.
- ^e Motoya: Cohort 2 patients received open-label VDZ (induction phase).
- ^f VISIBLE 1: All patients received open-label VDZ IV induction treatment.

- 6.8 The induction trials / induction phases were similar in terms of trial design. The maintenance trials / maintenance phases differed in terms of the trial design; the MIRI, UST and VDZ trials used randomised withdrawal designs (active induction clinical responders – based on the MMS for MIRI and FMS for VDZ and UST - were re-randomised to active versus PBO) whereas the ADA (ULTRA 2 and SUZUKI et al 2014) trials used treat-through designs (patients were randomised once and continued the same treatment for induction and maintenance therapy).
- 6.9 The LUCENT trials for MIRI were multicentre (including Australia), randomised, double-blind, parallel-arm, PBO-controlled trials comprising LUCENT 1 (randomised induction trial) and LUCENT 2 (re-randomised responder maintenance trial). Patients who did not achieve clinical response with either MIRI or PBO during LUCENT 1 (at 12 weeks) received open-label extended induction therapy with MIRI IV 300 mg Q4W (additional 3 doses over 12 weeks) in LUCENT 2.
- 6.10 Overall, the risk of bias in the induction trials was considered low whereas there were some concerns of high risk of bias in the maintenance trials. Although there were higher rates of discontinuation in the PBO group compared to active treatment, in most induction trials the absolute discontinuation rates were relatively low (13% or less), with the exception of high rates in HIBISCUS I and II (76%-94%) attributed mostly to lack of efficacy. The maintenance trials generally had high risk of attrition bias due to higher discontinuations, most commonly for adverse events and loss of effect.
- 6.11 Patient characteristics at baseline were generally balanced across the treatment arms within the trials. Based on available data, there were some differences in patient characteristics across the induction trials / phases, mainly due to differences in the eligibility criteria, including:

- Disease location: MIRI trials (LUCENT 1) and ADA trials (HIBISCUS I and HIBISCUS II) included a higher proportion (59-67%) of patients with disease located in the left side of the colon compared to the other included trials (30%-58%). Whilst not reported in MIRI trials, a varying proportion of patients (9-70%) had extensive disease in the comparator trials.
 - Duration of disease: ADA trials (HIBISCUS I and HIBISCUS II) had slightly shorter median duration of disease (4.0-4.7 years) compared to the other included trials (5.4-6.1 years).
 - Prior use of TNF inhibitors: Of the trials that enrolled patients with prior biologic treatment, the MIRI trial (LUCENT 1) had a slightly lower proportion of patients with prior use of TNF inhibitor (34-39%) compared to the VDZ trials (48-52% in GEMINI 1 and Motoya et al 2019) and ADA trial (39-41% in ULTRA 2).
 - Race: Of the trials that reported race, the proportion of Asian patients enrolled in MIRI trials (23-29% in LUCENT 1 and LUCENT 2) were similar to the comparator trials (14-19%) with the exception of Motoya et al 2019 and Suzuki et al 2014 which enrolled all Japanese patients.
 - Mean C-reactive protein (CRP) at baseline: Patients in ULTRA 2 (mean 13.1-14.5 mg/L) and UNIFI trials (mean 9.6-12.1 mg/L) had higher baseline mean CRP compared to the other included induction trials (mean 2.2-4.2 mg/L).
- 6.12 A comparison of baseline characteristics across the maintenance trials / phases was limited because most trials did not report separate characteristics for patients treated with maintenance treatment. Based on available data, patients (i.e. induction responders) enrolled in LUCENT 2 appeared to be fairly similar to patients enrolled in the other maintenance trials (VISIBLE 1 and UNIFI).
- 6.13 The submission noted a number of factors that may affect the transitivity of the trials in the indirect comparison including:
- Differences in the trial design for maintenance treatment phase, in particular the MIRI trials were re-randomised responder design whereas the ADA maintenance trials had a treat-through design. Patients entering the maintenance phase in the re-randomised trials and treat-through trials are different in terms of their study drug exposure and those participating in re-randomised trials who have received active treatment during induction followed by re-randomisation to PBO in maintenance may have a 'carry over' effect and a heightened level of response at maintenance. To account for this potential bias, both the ITC and NMA 'adjusted' the results of the treat-through trials to align with the results of the randomised withdrawal trials. The method of adjustment was similar to the approach used in

several NICE appraisals^{3,4,5,6}. There appeared to be a few errors with the submission's calculations used to adjust the ADA treat-through trials, although corrected estimates did not change the overall interpretation of the ITC conclusions. The PSCR acknowledged the discrepancies in the ITC results identified by the evaluators, however agreed with the evaluation that the interpretation of the results does not change regardless and reiterated that the superiority of MIRI over ADA was supported by the results of the analyses.

- Differences in trial eligibility and baseline characteristics of patients across the trials for induction and maintenance. To reduce heterogeneity observed across the population characteristics, the submission conducted separate analyses for the induction and the maintenance phase, and for populations based on prior exposure to bDMARDs/tsDMARDs therapy. However, the categorisation of patients as 'bDMARDs/tsDMARDs naïve' and 'bDMARDs/tsDMARDs experienced' varied in their definitions across the trials. For example, for the bDMARDs/tsDMARDs subgroup, some trials reported data on a subset of patients who had failed (i.e. intolerant or inadequate responders) on previous biologic therapies, while others reported on data for patients who were exposed to previous biologic therapies (i.e. failed or exposed without failure). Similarly, the naïve populations could have been defined as a lack of failure or a lack of exposure to a previous biologic. It was noted for LUCENT, the submission labelled the subgroups that were bDMARDs/tsDMARDs naïve and experienced as patients who had not failed previous biologic and failed (inadequate responder) on a previous biologic, respectively. Despite the heterogeneity, there were often only minor differences in the number of patients in the 'exposed' and 'failure' subgroups, as patients who were previously treated with a biologic often stop therapy due to reasons associated with failure.
- Differences in the PBO response rates in the maintenance trials. A number of population characteristics have been shown to impact PBO response (or baseline risk) within trials of ulcerative colitis, such as study location, disease status, disease duration, and prior exposure to biologics. The NMA adjusted baseline risk (i.e. PBO response adjustment) using a meta-regression model with baseline risk as a covariate. The methodology followed the NICE DSU technical supplement document 3.⁷

³ NICE (National Institute for Health and Care Excellence), Vedolizumab for treating moderately to severely active ulcerative colitis (TA342). 2015.

⁴ NICE, Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (TA329). 2015.

⁵ NICE, Tofacitinib for moderately to severely active ulcerative colitis (TA547). 2018.

⁶ NICE, Filgotinib for treating moderately to severely active ulcerative colitis (TA792). 2022.

⁷ Dias S, Sutton AJ, Welton NJ, Ades AE. 2013. Evidence Synthesis for Decision Making 3: Heterogeneity - Subgroups, Meta-Regression, Bias, and Bias-Adjustment. *Medical Decision Making*. 33(5):618-640.

- Differences in the definitions of clinical remission and response in the MIRI trials (MMS) and the comparator trials (FMS). The submission presented post-hoc analyses from LUCENT 1 for MMS vs FMS in clinical remission and clinical response, indicating similar results across the two definitions.

Comparative effectiveness

6.14 The clinically relevant outcomes for MSUC are clinical remission (absence of symptoms outcome) and clinical response (relative improvement in symptoms outcome), as assessed using the Mayo score. The clinical response and clinical remission outcomes following induction therapy were reported at different time points across the trials; Week 12 in the MIRI trial, Week 6-10 in the VDZ trials, Week 8 in the UST trial and Week 8-10 in the ADA trials.

Trial results

6.15 Table 4 presents the results of clinical remission and clinical response at induction and maintenance from the LUCENT I and II trials. For brevity, results of the comparator trials are not presented below.

Table 4: Clinical remission and clinical response for MIRI vs PBO in LUCENT I and II

Trial	MIRI n/N (%)	PBO n/N (%)	RR (95% CI)	RD (95% CI)	OR (95%CI)
Clinical remission MMS (induction therapy)					
LUCENT I Wk12, ITT	210/868 (24.2)	39/294 (13.3)	1.82 (1.33, 2.50)	0.11 (0.06, 0.16)	2.09 (1.44, 3.02)
LUCENT I Wk12, bDMARD-NF ^a	155/507 (30.6)	29/176 (16.5)	1.86 (1.30, 2.65)	0.14 (0.07, 0.21)	2.23 (1.44, 3.47)
LUCENT I Wk12, bDMARD-fail ^b #	55/361 (15.2)	10/118 (8.5)	1.80 (0.95, 3.41)	0.07 (0.01, 0.13)	1.94 (0.96, 3.94)
LUCENT I Wk12, bDMARD-naïve	152/492 (30.9)	27/171 (15.8)	1.96 (1.35, 2.83)	0.15 (0.08, 0.22)	2.38 (1.52, 3.75)
LUCENT I Wk12, bDMARD-exp ^c	58/376 (15.4)	12/123 (9.8)	1.58 (0.88, 2.84)	0.06 (-0.01, 0.12)	1.69 (0.87, 3.26)
Clinical remission FMS^d (induction therapy)					
LUCENT I Wk12, ITT	165/868 (19.0)	28/294 (9.5)	2.00 (1.37, 2.91)	0.09 (0.05, 0.14)	2.23 (1.46, 3.41)
LUCENT I Wk12, bDMARD-naïve	NR	NR	NR	NR	NR
LUCENT I Wk12, bDMARD-fail ^e	45/361 (12.5)	5/118 (4.2)	2.94 (1.20, 7.24)	0.08 (0.03, 0.13)	3.22 (1.25, 8.31)
Clinical response MMS (induction therapy)					
LUCENT I Wk12, ITT	551/868 (63.5)	124/294 (42.2)	1.51 (1.30, 1.74)	0.21 (0.15, 0.28)	2.38 (1.82, 3.12)
LUCENT I Wk12, bDMARD-NF ^a	354/507 (69.8)	89/176 (50.6)	1.38 (1.18, 1.62)	0.19 (0.11, 0.28)	2.26 (1.59, 3.21)
LUCENT I Wk12, bDMARD-fail ^b	197/361 (54.6)	35/118 (29.7)	1.84 (1.37, 2.47)	0.25 (0.15, 0.35)	2.85 (1.82, 4.45)
LUCENT I Wk12, bDMARD-naïve	345/492 (70.1)	86/171 (50.3)	1.39 (1.19, 1.64)	0.20 (0.11, 0.28)	2.32 (1.62, 3.31)
LUCENT I Wk12, bDMARD-exp ^c	206/376 (54.8)	38/123 (30.9)	1.77 (1.34, 2.35)	0.24 (0.14, 0.33)	2.71 (1.76, 4.18)
Clinical response FMS^d (induction therapy)					
LUCENT I Wk12, ITT	521/868 (60.0)	117/294 (39.8)	1.51 (1.30, 1.75)	0.20 (0.14, 0.27)	2.27 (1.73, 2.98)
LUCENT I Wk12, bDMARD-naïve	NR	NR	NR	NR	NR
LUCENT I Wk12, bDMARD-fail ^e	177/361 (49.0)	34/118 (28.8)	1.70 (1.26, 2.30)	0.20 (0.11, 0.30)	2.38 (1.52, 3.72)
Clinical remission clinical response following induction treatment (maintenance therapy) MMS					
LUCENT 2 Wk52, ITT	182/365 (49.9)	45/179 (25.1)	1.98 (1.51, 2.61)	0.25 (0.17, 0.33)	2.96 (1.99, 4.40)
LUCENT 2 Wk52, bDMARD-NF ^f	123/237 (51.9)	35/115 (30.4)	1.71 (1.26, 2.31)	0.21 (0.11, 0.32)	2.47 (1.54, 3.95)
LUCENT 2 Wk52, bDMARD-fail ^g	59/128 (46.1)	10/64 (15.6)	2.95 (1.62, 5.37)	0.30 (0.18, 0.43)	4.62 (2.16, 9.86)
LUCENT 2 Wk52, bDMARD-naïve	118/229 (51.5)	35/114 (30.7)	1.68 (1.24, 2.27)	0.21 (0.10, 0.31)	2.40 (1.49, 3.86)
LUCENT 2 Wk52, bDMARD-exp ^h	64/136 (47.1)	10/65 (15.4)	3.06 (1.68, 5.56)	0.32 (0.20, 0.44)	4.89 (2.30, 10.38)
Clinical response clinical response following induction treatment (maintenance therapy) MMS					
LUCENT 2 Wk52, ITT	293/365 (80.3)	88/179 (49.2)	1.63 (1.40, 1.91)	0.31 (0.23, 0.39)	4.21 (2.85, 6.22)
LUCENT 2 Wk52, bDMARD NF ^f	202/237 (85.2)	62/115 (53.9)	1.58 (1.32, 1.89)	0.31 (0.21, 0.41)	4.93 (2.95, 8.24)
LUCENT 2 Wk52, bDMARD fail ^g	91/128 (71.1)	26/64 (40.6)	1.75 (1.28, 2.40)	0.30 (0.16, 0.45)	3.59 (1.92, 6.74)
LUCENT 2 Wk52, bDMARD-naïve	NR	NR	-	-	-
LUCENT 2 Wk52, bDMARD-exp ^h	NR	NR	-	-	-

Source: Tables 45-46, pp142-143, Table 47, p145, Table 52-70, pp163-180 of the submission.

ADA=adalimumab, CI=confidence interval, bDMARD=biologic disease-modifying antirheumatic drugs, FMS=full Mayo score, ITT=intention to treat, IV=intravenous, JAKi=janus kinase inhibitor, MA=meta-analysis, MIRI=mirikizumab, MMS=modified Mayo score, NF=not failed, NR=not reported, OR=odds ratio, PBO=placebo, RD=risk difference, RE=random effects, RR=relative risk, TNF=tumour necrosis factor, tsDMARD=targeted synthetic disease modifying anti-rheumatic drugs, UC=ulcerative colitis, UST=ustekinumab, VDZ=vedolizumab, wk=week.

Fail defined as those who have an inadequate response to, loss of response to, or are intolerant to biologic therapy for UC.

a Results for the subgroup in LUCENT 1 who have not failed prior biologic or tofacitinib therapy (i.e. patients not exposed to prior biologic and patients exposed but not failed prior biologic). The submission incorrectly labelled this subgroup as 'bDMARDs/tsDMARDs naïve population'.

b The submission labelled this subgroup as 'bDMARDs/tsDMARDs experienced population'. In LUCENT 1, results presented only for the subgroup with prior biologic exposure and failed at least one therapy (excluding patients exposed to prior biologic but have not failed therapy).

c Subgroup with any prior biologic exposure in LUCENT 1 (i.e. patients exposed but not failed and exposed and failed at least one therapy).

d The submission conducted post hoc sensitivity analysis on the LUCENT 1 induction data where the definitions of the key endpoints of clinical remission and clinical response based on MMS were reconstructed for FMS (Attachment 4.1 of the submission).

e The submission labelled this subgroup as 'bDMARDs/tsDMARDs experienced population'. Based on the denominator, the results were only for the subgroup in LUCENT 1 who had prior biologic exposure and failed at least one therapy. It excluded the subgroup exposed to prior biologic but have not failed therapy.

f The submission labelled this subgroup as 'bDMARDs/tsDMARDs naïve population'. However, based on the denominator, the results were for the subgroup in LUCENT 2 who have not failed prior biologic or tofacitinib therapy (i.e. patients not exposed to prior biologic and patients exposed but not failed prior biologic).

g The submission labelled this subgroup as 'bDMARDs/tsDMARDs experienced population'. However, based on the denominator, the results were only for the subgroup in LUCENT 2 with prior biologic exposure and failed at least one therapy (excluding patients exposed to prior biologic but have not failed therapy).

h Subgroup with any prior biologic exposure in LUCENT 2 (i.e. patients exposed but not failed and exposed and failed at least one therapy).

- 6.16 For induction treatment, the trial results demonstrated that more patients achieved clinical remission and/or clinical response following induction treatment with MIRI, VDZ, ADA and UST compared to PBO, irrespective of the population (ITT, bDMARDs/tsDMARDs experienced or bDMARDs/tsDMARDs naïve subgroup), and irrespective of the Mayo scoring method.
- 6.17 For maintenance treatment, the trial results demonstrated that patients with clinical response to induction treatment were more likely to maintain clinical response and achieve clinical remission at Week 52 to 60 with MIRI, VDZ and UST compared to PBO, irrespective of the population. In contrast, the results for the ADA (adjusted) trial results were mixed, with no difference in the proportion of patients maintaining clinical response at Week 52 but a higher proportion of patients achieving clinical remission at Week 52 in the ITT population with ADA compared to PBO.

Indirect treatment comparisons (ITCs)

- 6.18 Table 5 and Table 6 summarise the results of the ITC for clinical remission and clinical response outcomes for induction treatment (at Week 6, 8, 10 or 12) and maintenance treatment (at Week 52/60), respectively. The ITC report by Moura et al 2023 stated that the calculations were performed in R using the netmeta package, but the estimates differed to those calculated independently during the evaluation using the standard Bucher formulas. Given these discrepancies, the table below presents the results calculated independently during the evaluation.

Table 5: Summary of ITCs* comparing MIRI versus VDZ, ADA and UST (INDUCTION)

ITC Commentary	Remission (Wk 6/8/10/12)		Response (Wk 6/8/10/12)	
	RR (95% CI)	RD (95% CI)	RR (95% CI)	RD (95% CI)
ITT				
MIRI (LUCENT I, MMS) v VDZ (MA RE, FMS)	0.85 (0.38,1.88)	0.01 (-0.06,0.08)	1.00 (0.64,1.56)	0.06 (-0.10,0.22)
MIRI (LUCENT I, FMS) v VDZ (MA RE, FMS)	0.93 (0.41,2.12)	-0.01 (-0.08,0.06)	1.00 (0.64,1.56)	0.05 (-0.11,0.21)
MIRI (LUCENT I, MMS) v ADA (MA RE, FMS)	0.97 (0.60,1.56)	0.02 (-0.06,0.10)	1.15 (0.95,1.39)	0.08 (-0.01,0.17)
MIRI (LUCENT I, MMS) v ADA (MA RE, FMS, exclude HIBISCUS I/II)	1.15 (0.68,1.94)	0.06 (-0.01,0.13)	1.11 (0.90,1.36)	0.07 (-0.02,0.16)
MIRI (LUCENT I, FMS) v ADA (MA RE, FMS)	1.06 (0.63,1.79)	0.00 (-0.08,0.08)	1.15 (0.95,1.40)	0.07 (-0.02,0.16)
MIRI (LUCENT I, FMS) v ADA (MA RE, FMS, exclude HIBISCUS I/II)	-	-	1.11 (0.90,1.37)	0.06 (-0.03,0.15)
MIRI (LUCENT I, MMS) v UST (UNIFI, FMS)	0.63 (0.34,1.16)	0.01 (-0.06,0.08)	0.77 (0.61,0.97)	-0.09 (-0.19,0.01)
MIRI (LUCENT I, FMS) v UST (UNIFI, FMS)	0.69 (0.36,1.31)	-0.01 (-0.07,0.05)	0.77 (0.60,0.97)	-0.10 (-0.20,0.00)
bDMARDs/tsDMARDs-naive				
MIRI (LUCENT I, MMS) v VDZ (MA RE, FMS)	0.78 (0.38,1.59)	-0.01 (-0.11,0.09)	0.80 (0.56,1.14)	-0.03 (-0.17,0.11)
MIRI (LUCENT I, FMS) v VDZ (MA RE, FMS)	-	-	-	-
MIRI (LUCENT I, MMS) v ADA (MA RE, FMS)	1.01 (0.60,1.70)	0.05 (-0.04,0.14)	1.05 (0.86,1.29)	0.07 (-0.03,0.17)
MIRI (LUCENT I, MMS) v ADA (MA RE, FMS, exclude HIBISCUS I/II)	-	-	1.01 (0.81,1.26)	0.05 (-0.06,0.16)
MIRI (LUCENT I, MMS) v UST (UNIFI, FMS)	1.06 (0.53,2.12)	0.07 (-0.03,0.17)	0.75 (0.56,1.00)	-0.11 (-0.25,0.03)
bDMARDs/tsDMARDs-experienced				
MIRI (LUCENT I, MMS) v VDZ (MA RE, FMS)	1.03 (0.29,3.65)	0.02 (-0.07,0.11)	1.33 (0.62,2.84)	0.15 (-0.08,0.38)
MIRI (LUCENT I, FMS) v VDZ (MA RE, FMS)	1.91 (0.45,8.07)	0.04 (-0.04,0.12)	1.28 (0.60,2.74)	0.11 (-0.12,0.34)
MIRI (LUCENT I, MMS) v ADA (ULTRA 2, FMS)	1.19 (0.39,3.63)	0.04 (-0.06,0.14)	1.38 (0.85,2.25)	0.16 (0.00,0.32)
MIRI (LUCENT I, FMS) v ADA (ULTRA 2, FMS)	2.21 (0.60,8.18)	0.06 (-0.03,0.15)	1.33 (0.81,2.19)	0.12 (-0.04,0.28)
MIRI (LUCENT I, MMS) v UST (UNIFI, FMS)	0.16 (0.03,0.73)	-0.05 (-0.14,0.04)	0.85 (0.57,1.26)	-0.06 (-0.20,0.08)
MIRI (LUCENT I, FMS) v UST (UNIFI, FMS)	0.29 (0.05,1.57)	-0.03 (-0.10,0.04)	0.81 (0.54,1.23)	-0.10 (-0.24,0.04)

*Source: Tables 45-46, pp142-143, Tables 52-61, pp163-170, Tables 71-80, pp182-191, Tables 87-92, pp199-203, Table 99, pp212-213 of the submission; Tables 8-19, pp28-32, Tables 32-39, pp45-48, Tables 48-59, pp59-66 of Attachment A4.1 Lilly 2019-8488 OH20061_UC_Australia ICTs_final report_8Feb2023_clean.docx.

ADA=adalimumab, bDMARD=biologic disease-modifying antirheumatic drugs, CI=confidence interval, FMS=full Mayo score, IR=inadequate response, ITC=indirect treatment comparison, ITT=intention to treat, IV=intravenous, JAKi=janus kinase inhibitor, MA=meta-analysis, MIRI=mirikizumab, MMS=modified Mayo score, NF=not failed, PBO=placebo, RD=risk difference, RE=random effects, RR=relative risk, TNF=tumour necrosis factor, tsDMARD=targeted synthetic disease modifying anti-rheumatic drugs, UC=ulcerative colitis, UST=ustekinumab, VDZ=vedolizumab, Wk=week.

* Note that the results presented in Table 5 are derived from post-hoc analyses conducted during the evaluation-specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the included studies Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 6: Summary of ITCs* comparing MIRI versus VDZ, ADA and UST (MAINTENANCE)

ITC Commentary	Remission (Wk 52/60) Ind. response		Response (Wk 52/60) Ind. response	
	RR (95% CI)	RD (95% CI)	RR (95% CI)	RD (95% CI)
ITT				
MIRI (LUCENT 2, MMS) v VDZ IV (MA RE, FMS)	0.84 (0.55,1.26)	-0.01 (-0.13,0.11)	0.72 (0.54,0.96)	-0.04 (-0.16,0.08)
MIRI (LUCENT 2, MMS) v VDZ IV/SC (MA RE, FMS)	0.82 (0.55,1.24)	-0.03 (-0.14,0.08)	0.73 (0.56,0.97)	-0.03 (-0.14,0.08)
MIRI (LUCENT 2, MMS) v ADA (MA RE, FMS)	1.23 (0.57,2.66)	0.09 (-0.16,0.34)	1.16 (0.84,1.61)	0.17 (0.03,0.31)
MIRI (LUCENT 2, MMS) v ADA corrected (MA RE, FMS)	-	-	1.20 (0.87,1.65)	0.18 (0.03,0.32)
MIRI (LUCENT 2, MMS) v UST (UNIFI, FMS)	1.16 (0.78,1.73)	0.08 (-0.03,0.19)	1.04 (0.82,1.33)	0.06 (-0.06,0.18)
bDMARDs/tsDMARDs-naive				
MIRI (LUCENT 2, MMS) v VDZ IV (MA RE, FMS)	0.78 (0.49,1.24)	-0.06 (-0.21,0.09)	0.71 (0.49,1.09)	-0.06 (-0.22,0.10)
MIRI (LUCENT 2, MMS) v VDZ IV/SC (MA RE, FMS)	0.77 (0.49,1.24)	-0.08 (-0.23,0.07)	-	-
MIRI (LUCENT 2, MMS) v ADA (MA RE, FMS)	1.13 (0.43,2.93)	0.07 (-0.24,0.38)	1.23 (0.87,1.75)	0.19 (0.03,0.35)
MIRI (LUCENT 2, MMS) v ADA corrected (MA RE, FMS)	-	-	1.27 (0.90,1.80)	0.16 (-0.05,0.37)
MIRI (LUCENT 2, MMS) v UST (UNIFI, FMS)	1.11 (0.70,1.75)	0.04 (-0.12,0.20)	1.07 (0.81,1.43)	0.06 (-0.10,0.22)
bDMARDs/tsDMARDs-experienced				
MIRI (LUCENT 2, MMS) v VDZ IV (MA RE, FMS)	0.75 (0.28,2.02)	0.02 (-0.15,0.19)	0.76 (0.40,1.45)	0.00 (-0.22,0.22)
MIRI (LUCENT 2, MMS) v VDZ IV/SC (MA RE, FMS)	0.73 (0.27,1.96)	0.02 (-0.14,0.18)	-	-
MIRI (LUCENT 2, MMS) v ADA (ULTRA 2, FMS)	1.42 (0.36,5.59)	0.20 (-0.01,0.41)	0.87 (0.37,2.07)	0.09 (-0.17,0.35)
MIRI (LUCENT 2, MMS) v UST (UNIFI, FMS)	1.62 (0.74,3.55)	0.17 (0.01,0.33)	1.11 (0.72,1.70)	0.08 (-0.11,0.27)

*Source: Table 47, p145, Tables 62-63, pp172-173, Tables 65-70, pp176-180, Tables 81-86, pp193-197, Tables 93-99, pp205-213 of the submission; Tables 20-31, pp36-41, Tables 40-47, pp52-55, Tables 60-71, pp70-75, Tables 80 and 85, pp83-84, Table 93, p87 of Attachment A4.1 Lilly 2019-8488 OH20061_UC_Australia ICTs_final report_8Feb2023_clean.docx.

ADA=adalimumab, bDMARD=biologic disease-modifying antirheumatic drugs, CI=confidence interval, FMS=full Mayo score, Ind=induction, ITC=indirect treatment comparisons, ITT=intention to treat, IV=intravenous, JAKi=janus kinase inhibitor, MA=meta-analysis, MIRI=mirikizumab, MMS=modified Mayo score, NF=not failed, PBO=placebo, RD=risk difference, RE=random effects, RR=relative risk, SC=subcutaneous, TNF=tumour necrosis factor; tsDMARD=targeted synthetic disease modifying anti-rheumatic drugs, UC=ulcerative colitis, UST=ustekinumab, VDZ=vedolizumab, wk=week.

* Note that the results presented in Table 6 are derived from post-hoc analyses conducted during the evaluation-specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the included studies. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.19 The results of the ITC showed that:

- MIRI vs VDZ: There were generally no statistically significant differences between the two treatments for induction or maintenance treatment, with the exception of one comparison favouring VDZ over MIRI using the relative risk (RR) statistic for maintenance of response. The results using the RD statistic showed no difference between the two treatments for induction or maintenance treatment.
- MIRI vs ADA: There were generally no statistically significant differences between the two treatments for induction or maintenance treatment, with the exception of a few comparisons that favoured MIRI over ADA using the risk difference (RD) statistic. The results using the RR statistic showed no difference between the two treatments for induction or maintenance treatment.
- MIRI vs UST: There were generally no statistically significant differences between the two treatments for induction or maintenance treatment, with the exception of a few comparisons favouring UST over MIRI in the bDMARDs/tsDMARDs experienced subgroup using the RR statistic. Results using the RD statistic showed no difference between the two treatments for induction or maintenance treatment.

- 6.20 The PSCR argued OR is the more appropriate relative effect measure in the context of ITCs compared to RR, as the use of RR can lead to inferential fallacies, whilst the OR consistently informs inference with respect to the direction of effect⁸. The PSCR further argued the results based on OR and RD support a claim that that MIRI provides improved outcomes compared to ADA, based on the 'near statistically significant and statistically significant' results for induction and maintenance in the ITT population, and the results within the biologic-naïve and experienced subgroup analyses. The ESC considered the argument that OR should be considered more appropriate than RR was not particularly compelling and was of the view the totality of the evidence should be considered. The ESC considered that while some of the analyses produced statistically significant results favouring MIRI over ADA, it considered the transitivity issues and differences in maintenance trial designs (discussed in the 'Clinical trials' section) made interpretation of the ITCs challenging. The ESC also noted the authors of the ITC report (referred to elsewhere in this advice) also concluded that MIRI had similar efficacy compared to ADA.
- 6.21 The PBAC noted arguments in the PSCR and Pre-PBAC Responses about reliance on different statistics, such as the odds ratio over the relative risk (paragraph 6.20 refers), and further noted results based on the odds ratio were not presented in the submission (only after the evaluation was completed). Overall, the PBAC considered the differences in whether the results based on odds ratio were statistically significant appeared primarily driven by a smaller standard error with the odds ratio rather than being driven by any inherent interpretation issue with the relative risk.

Network meta-analyses (NMAs)

- 6.22 The NMA estimated all comparisons under a Bayesian framework using a Monte Carlo Markov Chain. The outcomes of clinical response and remission were analysed using a multimodal model with probit link. As discussed, the NMA also estimated models with and without an adjustment for baseline risk (PBO response rates) using both fixed effects and random effects models. The submission stated that the unadjusted (random effect) results for induction and the adjusted (fixed effect) results for maintenance were the preferred models based on goodness of fit for both subgroup populations. Despite this statement, the submission only presented results using a random effects model for the bDMARDs/tsDMARDs naïve population and results using a fixed effects model for the bDMARDs/tsDMARDs experienced. In addition, the source document only presented results of the random effects model for the bDMARDs/tsDMARDs naïve population for induction and results of the fixed effects model for all other comparisons. There were also a number of discrepancies between results presented in the main body of the submission and the source document using the same model.

⁸ Eckermann S, Coory M, Willian A. Indirect Comparison: relative risk fallacies and odds solution. *Journal of clinical Epidemiology*. 2009; 62: p1031-1036, accessed on 23 May 2023.

6.23 Table 7 presents the results of NMA comparing MIRI versus VDZ, UST and ADA by prior biologic treatment (bDMARDs/tsDMARDs naïve and bDMARDs/tsDMARDs experienced populations) presented in the submission. For completeness, the table also includes corresponding results from the ITC (using the OR statistic).

Table 7: Summary of ITC and NMA comparing MIRI versus VDZ, ADA and UST

	OR (95% CI)					
	ITC, Submission	ITC, Commentary	NMA Unadjusted BL, Submission	NMA Adjusted BL, Submission	NMA Unadjusted BL, Attachment	NMA Adjusted BL, Attachment
INDUCTION: Remission, bDMARDs/tsDMARDs- naïve						
			RE#	RE^	RE	RE
MIRI v VDZ IV	0.72 (0.31, 1.65)	0.77 (0.33, 1.77) ^a	0.71 (0.36, 1.46)	0.95 (0.37, 2.37)	0.66 (0.33, 1.34)	0.91 (0.46, 1.82)
MIRI v ADA	1.02 (0.44, 2.36)	1.00 (0.40, 2.46) ^a	1.28 (0.66, 2.52)	1.58 (0.67, 3.55)	1.15 (0.59, 2.15)	1.57 (0.83, 3.05)
MIRI v UST	1.09 (0.49, 2.45)	1.17 (0.52, 2.63) ^a	0.77 (0.34, 1.80)	0.99 (0.35, 2.64)	0.77 (0.33, 1.80)	0.95 (0.42, 2.04)
INDUCTION: Remission, bDMARDs/tsDMARDs-experienced						
			FE‡	FE°	FE	FE
MIRI v VDZ IV	1.20 (0.23, 6.39)	1.04 (0.27, 4.09) ^b	1.34 (0.64, 2.82)	1.39 (0.29, 3.31)	1.35 (0.64, 2.92)	1.37 (0.39, 3.00)
MIRI v ADA	1.43 (0.41, 4.99)	1.24 (0.37, 4.20) ^b	3.16 (1.41, 7.42)	3.13 (0.91, 9.99)	3.19 (1.41, 7.74)	3.15 (1.13, 8.90)
MIRI v UST	0.17 (0.03, 0.86)	0.15 (0.03, 0.73) ^b	0.69 (0.34, 1.41)	0.70 (0.14, 1.73)	0.69 (0.34, 1.41)	0.70 (0.21, 1.43)
INDUCTION: Response, bDMARDs/tsDMARDs- naïve						
			RE#	RE^	RE	RE
MIRI v VDZ IV	0.86 (0.47, 1.56)	0.88 (0.48, 1.61) ^a	0.73 (0.38, 1.44)	0.95 (0.40, 2.33)	0.68 (0.36, 1.32)	0.91 (0.49, 1.76)
MIRI v ADA	1.34 (0.87, 2.04)	1.36 (0.89, 2.10) ^{a,c}	1.25 (0.69, 2.35)	1.53 (0.70, 3.36)	1.14 (0.62, 2.01)	1.51 (0.84, 2.79)
MIRI v UST	0.63 (0.35, 1.14)	0.65 (0.36, 1.17) ^a	0.78 (0.36, 1.73)	0.99 (0.37, 2.54)	0.78 (0.36, 1.70)	0.95 (0.46, 1.94)
INDUCTION: Response, bDMARDs/tsDMARDs-experienced						
			FE‡	FE°	FE	FE
MIRI v VDZ IV	1.89 (0.39, 9.22)	1.79 (0.61, 5.28) ^b	1.27 (0.69, 2.30)	1.30 (0.39, 2.69)	1.27 (0.70, 2.33)	1.29 (0.49, 2.40)
MIRI v ADA	1.98 (0.94, 4.16)	1.88(0.90,3.94) ^{b,d}	2.45 (1.31, 4.65)	2.45 (0.93, 5.88)	2.46 (1.31, 4.77)	2.44 (1.10, 5.16)
MIRI v UST	0.80 (0.42, 1.52)	0.76 (0.35, 1.27) ^b	0.73 (0.40, 1.34)	0.74 (0.21, 1.60)	0.74 (0.40, 1.34)	0.74 (0.28, 1.34)
MAINTENANCE: Remission Ind. Response, bDMARDs/tsDMARDs- naïve						
			RE#	RE^	FE	FE
MIRI v VDZ IV	0.72 (0.35, 1.46)	0.70 (0.34, 1.42) ^a	0.96 (0.53, 1.71)	2.61 (1.37, 6.24)	0.96 (0.55, 1.69)	2.61 (1.37, 6.12)
MIRI v VDZ IV/SC	0.69 (0.35, 1.38)	0.67 (0.34, 1.35) ^a	0.76 (0.32, 1.79) ^j	4.10 (1.42, 12.2) ^j	0.76 (0.32, 1.79) ^j	4.13 (1.44, 12.0) ^j
MIRI v ADA	1.32 (0.14, 12.41)	1.28 (0.30, 5.41) ^a	1.23 (0.68, 2.22)	2.79 (1.68, 5.90)	1.23 (0.70, 2.19)	2.80 (1.66, 5.80)
MIRI v UST Q8/Q12W	1.22 (0.59, 2.52)	1.19 (0.58, 2.45) ^a	1.20 (0.58, 2.50) / 1.31 (0.65, 2.65)	1.20 (0.68, 2.10) / 1.30 (0.77, 2.24)	1.20 (0.59, 2.47) / 1.31 (0.66, 2.66)	1.20 (0.68, 2.12) / 1.31 (0.77, 2.22)
MAINTENANCE: Remission Ind. Response, bDMARDs/tsDMARDs-experienced						
			FE°	FE‡	FE	FE
MIRI v VDZ IV	0.63 (0.18, 2.19)	0.66 (0.19, 2.31) ^b	1.78 (0.72, 4.71)	3.42 (1.68, 7.81)	0.90 (0.37, 2.20)	1.02 (0.07, 3.10)
MIRI v VDZ IV/SC	0.60 (0.17, 2.08)	0.64 (0.18, 2.20) ^b	0.98 (0.25, 3.87) ^j	4.67(1.19,19.40) ^j	0.63 (0.17, 2.26) ^j	0.74 (0.04, 5.26)
MIRI v ADA	1.86 (0.37, 9.41)	1.97(0.39,9.95) ^{b,d}	1.18 (0.42, 3.50)	2.81 (1.26, 6.81)	0.83 (0.30, 2.34)	0.97 (0.04, 3.65)
MIRI v UST Q8/Q12W ^f	1.99 (0.73, 5.39)	2.11 (0.78, 5.68) ^b	1.30 (0.54, 3.15) / 2.35 (0.95, 6.39)	1.33 (0.77, 2.32) / 2.34 (1.30, 4.48)	1.30 (0.56, 3.03) / 2.33 (0.96, 5.97)	1.30 (0.42, 4.20) / 2.35 (0.76, 9.28)
MAINTENANCE: Response Ind. Response, bDMARDs/tsDMARDs-naïve						
			RE#	RE^	FE	FE
MIRI v VDZ IV	1.05(0.48, 2.30)	1.05 (0.48, 2.30) ^e	0.96 (0.53, 1.71)	2.72 (1.38, 7.12)	0.96 (0.54, 1.70)	2.73 (1.39, 6.97)
MIRI v VDZ IV/SC	NR	-	0.76 (0.31, 1.78) ^j	4.25(1.43,13.40) ^j	0.76 (0.31, 1.79) ^j	4.29 (1.45, 13.2) ^j
MIR v ADA	3.06(1.47, 6.35)	3.06 (1.47, 6.36) ^e	0.99 (0.35, 2.64)	2.91 (1.69, 6.84)	1.23 (0.70, 2.18)	2.93 (1.69, 6.65)
MIRI v ADA corrected ^h	3.06 (1.47, 6.35)	3.31(1.59,6.87) ^{eh}				
MIRI v UST Q8/Q12W ^f	1.62 (0.76, 3.45)	1.62 (0.76, 3.44) ^e	1.19 (0.58, 2.45) / 1.30 (0.65, 2.60)	1.21 (0.66, 2.23) / 1.33 (0.75, 2.40)	1.20 (0.59, 2.45) / 1.31 (0.65, 2.63)	1.22 (0.66, 2.26) / 1.33 (0.75, 2.37)
MAINTENANCE: Response Ind. Response, bDMARDs/tsDMARDs-experienced						
			FE°	FE‡	FE	FE

	OR (95% CI)					
	ITC, Submission	ITC, Commentary	NMA Unadjusted BL, Submission	NMA Adjusted BL, Submission	NMA Unadjusted BL, Attachment	NMA Adjusted BL, Attachment
MIRI v VDZ IV	0.87 (0.30, 2.52)	0.87 (0.30, 2.52) ^g	1.74 (0.73, 4.25)	3.35 (1.67, 7.41)	0.90 (0.38, 2.14)	1.02 (0.09, 3.03)
MIRI v VDZ IV/SC	NR	-	0.98 (0.25, 3.56) ^j	4.52(1.19,15.90)^j	0.63 (0.17, 2.17) ^j	0.75 (0.05, 5.00)
MIRI v ADA	1.31 (0.36, 4.73)	1.31 (0.36, 4.71) ^g	1.18 (0.43, 3.28)	2.80 (1.26, 6.50)	0.84 (0.30, 2.26)	0.97 (0.05, 3.46)
MIRI v UST Q8/Q12W ^f	1.45 (0.64, 3.32)	1.45 (0.64, 3.31) ^g	1.29 (0.55,3.01) / 2.25 (0.95, 5.58)	1.34 (0.77,2.36) / 2.33 (1.30, 4.45)	1.28 (0.58,2.87) / 2.21 (0.97, 5.15)	1.29 (0.45,3.76) / 2.25 (0.78, 7.46)

Source: Tables 56-61, pp168-170, Tables 65-70, pp176-180, Tables 75-80, pp187-191, Tables 83-86, pp195-197, Tables 89-92, pp201-203, Tables 95-99, pp207-213, Tables 102-103, pp222 and 226 of the submission; Table 8, p28 Tables 12-14, pp29-30, Tables 18-20, pp32-36, Tables 24-26, pp37-39, Tables 30-47, pp40-55, Table 102, p222, Table 103, pp-226 of Attachment A4.1 Lilly 2019-8488 OH20061_UC_Australia ICTs_final report_8Feb2023_clean.docx; Figures 12-13, pp61-62, Figures 20-21, pp77-78, Figure 28, p91, Figures 35-36, pp103-104, Figures 200-201, pp324-325, Figure 210, p333, Figures 219-220, pp341-342, Figures 231-232, pp353-354 of Attachment A4.2 Lilly 2019-8488 OH20061_UC_NMA_final report_16Feb2023.docx.

ADA=adalimumab, bDMARD=biologic disease-modifying antirheumatic drugs, BL=baseline, CI=confidence interval, FE=fixed effects, Ind=induction, ITC=indirect treatment comparison, IV=intravenous, JAKi=janus kinase inhibitor, MA=meta-analysis, MIRI=mirikizumab, NA=not applicable, NMA=network meta-analysis, NR=not reported, OR=odds ratio, PBO=placebo, RE=random effects, QxW=every x week, SC=subcutaneous, TNF=tumour necrosis factor, tsDMARD=targeted synthetic disease modifying anti-rheumatic drugs, UC=ulcerative colitis, UST=ustekinumab, VDZ=vedolizumab.

#I Unadjusted primary analysis in bDMARDs/tsDMARDs naïve population across induction and maintenance: RE model using a half normal prior without baseline risk meta-regression.

^ Adjusted primary analysis in bDMARDs/tsDMARDs naïve population across induction and maintenance: RE model using a half normal prior with baseline risk meta-regression.

‡ Unadjusted and adjusted primary analysis in bDMARDs/tsDMARDs experienced population across induction and maintenance: FE model

◇ Adjusted and unadjusted complementary analysis in bDMARDs/tsDMARDs experienced population across induction and maintenance: FE model.

a Results corrected for the subgroup in LUCENT 1 who were biologic or tofacitinib naïve. The submission used the results for the subgroup in LUCENT 1 who have not failed prior biologic or tofacitinib therapy (i.e. patients not exposed to prior biologic and patients exposed but not failed prior biologic) and labelled this subgroup as 'bDMARDs/tsDMARDs naïve population'.

b Results corrected for the subgroup in LUCENT 1 with any prior biologic exposure (i.e. patients exposed but not failed and exposed and failed at least one therapy). The submission used the results for the subgroup exposed to prior biologic and failed at least one therapy (excluding patients exposed to prior biologic but have not failed therapy) and labelled this group as 'bDMARDs/tsDMARDs experienced population'.

c Corrected during the evaluation for the proportion in ADA arm achieving clinical response (i.e. 152/285 (53%)). The submission made a typographical error using 151/285 (53%). HIBISCUS I and II publication (Rubin 2022) reported only pooled data for ADA treatment arms.

d The submission labelled the subgroup for ADA as the 'bDMARDs/tsDMARDs experienced population'. In ULTRA 2, all biologic-exposed patients were biologic failures (loss of response or intolerance). Patients were excluded if they had previous treatment with ADA.

e The submission used the results for the subgroup in LUCENT 2 who have not failed prior biologic or tofacitinib therapy (included patients not exposed to prior biologic and patients exposed but not failed prior biologic) and labelled this subgroup as 'bDMARDs/tsDMARDs naïve population'. Response data was not reported for the subgroup in LUCENT 2 who were biologic or tofacitinib naïve.

f The submission presented ITC using pooled data from UNIFI of UST 90 mg Q8W and UST 90 mg Q12W treatment arms at maintenance.

g The submission used the results for the subgroup in LUCENT 2 with prior biologic exposure and failed at least one therapy (excluding patients exposed to prior biologic but have not failed therapy). The submission labelled this subgroup as the 'bDMARDs/tsDMARDs experienced population'. Response data was not reported for the subgroup in LUCENT 2 with any prior biologic exposure (i.e. patients exposed but not failed and exposed and failed at least one therapy).

h Corrected during the evaluation. Based on trial design adjustments (maintenance phase) in Attachment 4.2 of the submission, the number of sustained responders from the ratio of sustained clinical responders to maintenance clinical responders in the same active arms that report both outcomes in ULTRA 2 was 41 (i.e. (44/89)x82). The submission reported 45/82 (54.9%) achieved sustained clinical response, which could not be verified.

j Results for VDZ SC at maintenance. The submission presented ITC using VDZ IV/SC pooled at maintenance, whereas the NMA included VDZ IV and VDZ SC arms separately.

6.24 The results of the NMA showed that:

- MIRI vs VDZ: For induction treatment, there were no statistically significant differences between the two treatments. For maintenance treatment, there were no statistically significant differences between the two treatments without

adjusting for baseline risk but results generally favoured MIRI after adjusting for baseline risk.

- MIRI vs ADA: For induction treatment, there were no statistically significant differences between the two treatments in the bDMARDs/tsDMARDs naïve population but results generally favoured MIRI in the bDMARDs/tsDMARDs experienced population. For maintenance treatment, there were no statistically significant differences between the two treatments without adjusting for baseline risk but results generally favoured MIRI after adjusting for baseline risk (but results did vary depending on the model assumed and source of the estimates).
- MIRI vs UST: There were generally no statistically significant differences between the two treatments for induction or maintenance treatment.

6.25 The submission-reported results of the NMA did not include analyses based on ITT populations for studies that recruited both bDMARD/tsDMARD naïve and experienced patients. In its consideration of TOF in November 2020, the PBAC considered the ITT analyses were the most appropriate basis upon which to consider the comparative effectiveness of TOF, given both the requested listing and current bDMARD/tsDMARD listings for MSUC are line-agnostic and allow for any sequence of therapies within a treatment cycle (paragraph 7.8, tofacitinib PSD, November 2020 PBAC meeting). The inclusion of NMA results based on ITT data (where available) may also be informative for assessing the clinical claim.

6.26 The ESC noted that the PSCR stated that NMA results based on ITT data could not be provided as these analyses were not feasible and claimed that this evaluation would cause further uncertainty to the conclusions of the analysis. However, the ESC also noted that a previous PBAC submission for OZA conducted a NMA for the ITT population. The ESC therefore considered that, in the absence of analyses based on the ITT population, the NMA presented was of limited value for considering the comparative effectiveness of MIRI to the alternative therapies.

Comparative harms

6.27 Table 8 and Table 9 summarise the naïve comparison of the adverse event (AE) outcomes to inform the relative safety profile of MIRI vs VDZ, UST and ADA. It was noted that the safety data was not reported consistently across the trials, with some trials only reporting safety for induction only, maintenance only or both combined. Time of assessment also varied for induction treatment (at Week 6, 8, 10 or 12).

Table 8: Summary of adverse events at Weeks 6/8/10/12 in induction trials for MIRI, VDZ, ADA and UST

Trial ID	Drug n/N (%)	PBO n/N (%)	RR (95% CI)	RD (95% CI)
Any adverse event				
MIRI IV 300 mg v PBO (LUCENT 1)	426/958 (44.5)	148/321 (46.1)	0.96 (0.84, 1.11)	-0.02 (-0.08, 0.05)
VDZ IV 300mg v PBO (MA: GEMINI-1, Motoya)	172/389 (44.2)	112/231 (48.5)	0.90 (0.76, 1.07)	-0.05 (-0.13, 0.03)
ADA 160->80mg v PBO (MA: ULTRA 1, Suzuki)	152/313 (48.6)	153/319 (48.0)	1.01 (0.86, 1.19)	0.01 (-0.07, 0.08)
UST IV ~ 6mg/kg v PBO (UNIFI)	160/320 (50.0)	153/319 (48.0)	1.04 (0.89, 1.22)	0.02 (-0.06, 0.10)
Serious adverse event				
MIRI IV 300 mg v PBO (LUCENT 1)	27/958 (2.8)	17/321 (5.3)	0.53 (0.29, 0.96)	-0.02 (-0.05, 0.00)
VDZ IV 300mg v PBO (MA: GEMINI-1, Motoya)	15/389 (3.9)	14/231 (6.1)	0.63 (0.17, 2.33)	-0.02 (-0.08, 0.04)
ADA 160->80mg v PBO (MA: ULTRA 1, Suzuki)	13/313 (4.2)	24/319 (7.5)	0.55 (0.29, 1.07)	-0.03 (-0.07, 0.00)
UST IV ~ 6mg/kg v PBO (UNIFI)	10/320 (3.1)	21/319 (6.6)	0.47 (0.23, 0.99)	-0.03 (-0.07, -0.00)
Discontinuation due to adverse event				
MIRI IV 300 mg v PBO (LUCENT 1)	15/958 (1.6)	23/321 (7.2)	0.22 (0.12, 0.41)	-0.06 (-0.09, -0.03)
VDZ IV 300mg v PBO (Motoya)	8/164 (4.9)	2/82 (2.4)	2.00 (0.43, 9.21)	0.02 (-0.02, 0.07)
ADA 160->80mg v PBO (MA: ULTRA-1, Suzuki)	18/313 (5.8)	16/319 (5.0)	1.14 (0.59, 2.21)	0.01 (-0.03, 0.04)
UST IV ~ 6mg/kg v PBO (UNIFI)	1/320 (0.3)	3/319 (0.9)	0.33 (0.03, 3.18)	-0.01 (-0.02, 0.01)
Serious Infections				
MIRI IV 300 mg v PBO (LUCENT 1)	7/958 (0.7)	2/321 (0.6)	1.17 (0.24, 5.62)	0.00 (-0.01, 0.01)
VDZ IV 300mg v PBO (MA: GEMINI-1, Motoya)	2/389 (0.5)	5/231 (2.2)	0.23 (0.05, 1.20)	-0.02 (-0.04, 0.00)
ADA 160->80mg v PBO (MA: ULTRA-1, Suzuki)	3/313 (1.0)	3/319 (0.9)	1.03 (0.02, 49.90)	0.01 (-0.42, 0.06)
UST IV ~ 6mg/kg v PBO (UNIFI)	1/320 (0.3)	4/319 (1.3)	0.25 (0.03, 2.22)	-0.01 (-0.02, 0.00)

Source: Table 100, p214 of the submission, with risk statistics conducted during the evaluation. Shaded areas indicate data previously seen by the PBAC.

ADA=adalimumab, CI=confidence interval, IV=intravenous, MA=meta-analysis, MIRI=mirikizumab, n=number of participants with event, N=total participants in group, PBO=placebo, RD=risk difference, RR=risk ratio, UST=ustekinumab, VDZ=vedolizumab.

Table 9: Summary of adverse events in MIRI, VDZ, ADA and UST maintenance trials

Trial ID	Drug n/N (%)	PBO n/N (%)	RR (95% CI)	RD (95% CI)
Any adverse event				
MIRI SC 200mg v PBO (LUCENT 2)	251/389 (64.5)	132/192 (68.8)	0.94 (0.83, 1.06)	-0.04 (-0.12, 0.04)
VDZ IV 300mg or SC 108mg pooled v PBO (MA: GEMINI-1, VISIBLE 1, Motoya)	643/821 (78.3)	296/373 (79.4)	1.00 (0.91, 1.09)	-0.00 (-0.07, 0.07)
ADA 80mg v PBO (ULTRA 2)	213/257 (82.9)	218/260 (83.8)	0.99 (0.92, 1.07)	-0.01 (-0.07, 0.05)
UST SC 90 mg Q8W or Q12 QW pooled v PBO (UNIFI)	255/348 (73.3)	138/175 (78.9)	0.93 (0.84, 1.03)	-0.06 (-0.13, 0.02)
Serious adverse event				
MIRI SC 200mg v PBO (LUCENT 2)	13/389 (3.3)	15/192 (7.8)	0.43 (0.21, 0.88)	-0.04 (-0.09, -0.00)
VDZ IV 300mg or SC 108mg pooled v PBO (MA: GEMINI-1, VISIBLE 1, Motoya)	98/821 (11.9)	46/373 (12.3)	0.95 (0.69, 1.32)	0.00 (-0.04, 0.04)
ADA 80mg v PBO (ULTRA 2)	31/257 (12.1)	32/260 (12.3)	0.98 (0.62, 1.56)	0.00 (-0.06, 0.05)
UST SC 90 mg Q8W or Q12 QW pooled v PBO (UNIFI)	28/348 (8.0)	17/175 (9.7)	0.83 (0.47, 1.47)	-0.02 (-0.07, 0.04)
Discontinuation due to adverse events				
MIRI SC 200mg v PBO (LUCENT 2)	6/389 (1.5)	16/192 (8.3)	0.19 (0.07, 0.47)	-0.07 (-0.11, -0.03)
VDZ 300mg v PBO (MA: Motoya, VISIBLE 1)	9/201 (4.5)	11/98 (11.2)	0.43 (0.18, 1.06)	-0.06 (-0.13, 0.01)
ADA 80mg v PBO (ULTRA 2)	23/257 (8.9)	34/260 (13.1)	0.68 (0.41, 1.13)	-0.04 (-0.10, 0.01)
UST SC 90 mg Q8W or Q12 QW pooled v PBO (UNIFI)	14/348 (4.0)	20/175 (11.4)	0.35 (0.18, 0.68)	-0.07 (-0.13, -0.02)
Serious Infections				
MIRI SC 200mg v PBO (LUCENT 2)	3/389 (0.8)	3/192 (1.6)	0.49 (0.10, 2.42)	-0.01 (-0.03, 0.01)
VDZ 300mg v PBO (MA: GEMINI 1, Motoya, VISIBLE 1)	15/821 (1.9)	9/373 (2.4)	0.74 (0.33, 1.67)	-0.00 (-0.02, 0.02)
ADA 80mg v PBO (ULTRA 2)	4/257 (1.6)	5/260 (1.9)	0.81 (0.22, 2.98)	0.00 (-0.03, 0.02)
UST SC 90 mg Q8W or Q12 QW pooled v PBO (UNIFI)	9/348 (2.6)	4/175 (2.3)	1.13 (0.35, 3.62)	0.00 (-0.02, 0.02)
Malignancy				
MIRI SC 200mg v PBO (LUCENT 2)	1/389 (0.5)	1/192 (0.5)	0.49 (0.03, 7.85)	-0.00 (-0.01, 0.01)
VDZ 300mg v PBO (GEMINI 1)	1/620 (0.2)	3/275 (1.1)	0.15 (0.02, 1.42)	-0.01 (-0.02, 0.00)
ADA 80mg v PBO (ULTRA 2)	2/257 (0.8)	0/260 (0)	5.06 (0.24, 104.84)	0.01 (-0.01, 0.02)
UST SC 90 mg Q8W or Q12 QW pooled v PBO (UNIFI)	2/348 (0.6)	0/175 (0)	2.52 (0.12, 52.24)	0.01 (-0.01, 0.02)

Source: Table 101, p215 of the submission, with risk statistics conducted during the evaluation. Shaded areas indicate data previously seen by the PBAC.

ADA=adalimumab, CI=confidence interval, IV=intravenous, MA=meta-analysis, MIRI=mirikizumab, n=number of participants with event, N=total participants in group, PBO=placebo, QxW=once every x weeks, RD=risk difference, RR=risk ratio, SC=subcutaneous, UST=ustekinumab, VDZ=vedolizumab.

6.28 Overall, the incidence of any AEs was similar between MIRI and PBO for induction and maintenance therapy, with fewer patients experiencing serious or severe AEs. Significantly fewer patients treated with MIRI experienced an AE leading to study discontinuation compared to PBO during induction and maintenance therapy (mostly attributed to ulcerative colitis). More patients treated with MIRI experienced non-

immediate hypersensitivity reactions (mainly rash) and injection-site reactions during maintenance therapy, compared to PBO.

- 6.29 A side-by-side comparison across the active arms of the trials indicated that the proportion of AEs, including serious AEs and infections, were comparable between MIRI, VDZ, ADA and UST at induction and maintenance. There were fewer discontinuations due to AEs in MIRI compared to VDZ and ADA. However, the number of events were small. As discussed, interpretation of the naïve comparison of safety data is problematic due to inadequate power to detect differences in safety outcomes, differences in the durations of exposure (i.e. unadjusted for exposure time) and differences in the maintenance trial designs (i.e. control patients in the treat-through trials only received PBO throughout, whereas in the randomised withdrawal trials controls received active induction treatment, except for the LUCENT trials where PBO induction responders received PBO at maintenance).

Benefits/harms

- 6.30 A benefits and harms table is not presented as the submission made a claim of non-inferiority for MIRI versus VDZ and UST, and the clinical claim of superiority for MIRI versus ADA was not adequately supported (see Clinical claim).

Clinical claim

- 6.31 Based on the results from the ITC and NMA, the submission described MIRI for the treatment of MSUC as non-inferior in terms of effectiveness compared with VDZ and UST and superior in terms of effectiveness compared to ADA, for both induction and maintenance therapy. In terms of safety, the submission described MIRI as comparable (non-inferior) to VDZ, UST and ADA.
- 6.32 Overall, the evaluation considered the clinical evidence presented in the submission reasonably supported the claim of non-inferior comparative effectiveness for MIRI versus VDZ and UST. In contrast, the clinical evidence did not adequately support the claim of superior comparative effectiveness for MIRI versus ADA and a claim of non-inferior effectiveness may be more reasonable:
- The results of the ITC showed there were generally no statistically significant differences between MIRI versus ADA for induction or maintenance treatment across the different populations considered, with the exception of a few comparisons favouring MIRI using the RD statistic. Corresponding results using the RR statistic showed no statistically significant differences between the two treatments. The authors of the ITC report (Moura et al 2023) also concluded that MIRI had similar efficacy compared to ADA.
 - The results of the NMA for induction treatment only favoured MIRI versus ADA for the bDMARDs/tsDMARDs experienced subgroup. But given the majority of patients in the bDMARDs/tsDMARDs experienced subgroup likely received prior treatment with a TNF-inhibitor, the statistically significant result favouring MIRI

over ADA in this subgroup may simply be due to patients benefiting from using a treatment with a different mechanism of action (i.e. MIRI) compared to re-treatment with another TNF-inhibitor (i.e. ADA). The PSCR acknowledged the observed results may, in part, be due to patients benefitting from treatment with a therapy with a different mechanism of action, however also noted statistically significant results in the maintenance phase favoured MIRI over ADA in the bDMARDs/tsDMARDs naïve subgroup, and concluded that these combined results demonstrated the superiority of MIRI over ADA for patients in both the treatment naïve and experienced populations in both the short and longer term. The ESC disagreed with the PSCR and considered the differential results between treatment phases and bDMARD/tsDMARD subgroups, with statistically significant results for induction therapy + bDMARD/tsDMARD naïve and maintenance therapy + bDMARD/tsDMARD experienced, did not strongly support an overall claim of superiority over ADA in the context of the clinical claim as a whole.

- The results of the NMA for maintenance treatment showed no difference between MIRI versus ADA in the models that did not adjust for baseline risk, and results presented in the submission only favoured MIRI after adjusting for baseline risk. The results presented in the submission, however, could not be verified from the source document (Kroep et al 2023). For the bDMARDs/tsDMARDs experienced subgroup, corresponding results using the fixed effects model adjusted for baseline risk in the source document showed no statistically significant difference between the two treatments. For the bDMARDs/tsDMARDs naïve subgroup, the source document did not report the corresponding results using the random effects model adjusted for baseline risk. On balance, the selective reporting of results and discrepancies between results presented in the main body of the submission and source document increases the uncertainty around any conclusions from the NMA. In addition, all comparisons between MIRI and ADA for maintenance treatment were based on predicted rather than observed trials results for ADA (to convert treat-through trial results to randomised withdrawal trial results), which adds further uncertainty to the conclusions of the analysis. The pre-PBAC response claimed that to base therapeutic conclusions on the induction period alone is likely to be biased against MIRI with respect to the comparison against ADA and does not take into account the importance of longer-term outcomes of the disease. The sponsor maintained that MIRI provides a significant improvement in efficacy for some patients.

6.33 The PSCR also presented additional results of the NMA for the alternative model fit (Table 2 and UC NMA_Supplementary Report of the PSCR) and reiterated the analyses presented in the submission were the best-fitting models, which were the fixed effects models in most cases, except for the biologic/targeted synthetic disease modifying anti-rheumatic drugs (bDMARDs/tsDMARDs) naïve population at induction. The ESC noted the PBAC has previously considered analyses based on separate bDMARD/tsDMARD naïve and experienced subgroups to not be key analyses in MSUC,

given the line-agnostic nature of PBS listings for this indication. The ESC therefore considered the NMA provided limited value for considering the comparative effectiveness of MIRI to the alternative therapies, given the lack of analyses on the ITT populations, which would be most aligned with the PBS population. The pre-PBAC response acknowledged the NMA in this submission was not conducted on an ITT basis and noted the PSCR stated that on a technical and methodological level, the evaluation of the ITT population was not feasible due to heterogeneity observed within the UC trials.

- 6.34 The pre-PBAC response stated that the difficulties in interpreting the NMA results in maintenance therapy has been a recurring issue for bDMARDs seeking a superiority claim over ADA, and the PBAC have previously used available evidence to make positive recommendations, citing recommendations made by the PBAC for ozanimod at its November 2022 meeting and for tofacitinib at its November 2020 meeting.
- 6.35 The pre-PBAC response claimed that MIRI demonstrated statistically better efficacy compared to VDZ in the maintenance phase for both clinical response and remission in the naïve population. It claimed that MIRI should be considered to be of the same efficacy for reimbursement as that of VDZ, which does not include ADA, at least for some patients.
- 6.36 The PBAC considered that the claim of non-inferior comparative effectiveness for MIRI was reasonable for all nominated comparators. The PBAC considered that the claim of superior comparative effectiveness compared to ADA was not adequately supported by the data.
- 6.37 The PBAC considered that the claim of non-inferior comparative safety for MIRI versus all nominated comparators was reasonable.

Economic analysis

- 6.38 The submission presented a cost-minimisation approach comparing MIRI with VDZ (IV formulation only), assuming equivalent total costs over the first two years (104 weeks), and accounting for IV infusion administration costs. Given VDZ is subject to a Special Pricing Arrangement and the effective AEMP was unknown to the sponsor, the results presented in the submission used the published AEMP. The submission stated that the 'hypothetical' analysis can be updated during the post-PBAC processes using the effective AEMP for VDZ.
- 6.39 The proposed equi-effective doses were based on the recommended doses:
- MIRI standard dosing:
 - MIRI IV 300 mg at week 0, 4, 8 and then MIRI SC 200 mg Q4W thereafter
 - VDZ IV 300 mg at weeks 0, 2, 6, then Q8W thereafter.
 - MIRI extended dosing:
 - MIRI IV 300 mg at week 0, 4, 8, 12, 16, 20 and then MIRI SC 200 mg Q4W thereafter
 - VDZ IV 300 mg at weeks 0, 2, 6, then Q8W thereafter.

6.40 Table 10 shows the results of the cost-minimisation approach presented in the submission, based on the following assumptions:

- Equivalent total costs for MIRI and VDZ over the first two years (i.e. 104 weeks) of treatment at the nominated equi-effective doses, corresponding to 15 doses of VDZ and 26 doses of MIRI.
- An administration cost for each IV infusion of MIRI and VDZ, based on Medicare Benefits Schedule (MBS) item 116 (\$81.05 100% benefit level).
- The published AEMP for VDZ 300 mg vial (\$2,949.93).
- A flat pricing structure between MIRI IV and SC formulations.
- A weighted AEMP for MIRI, assuming 76.4% of ‘responders’ (i.e. 63.5% / 83.1% from LUCENT 1 and 2) would receive standard induction (3 x MIRI IV doses + 23 x MIRI SC injections) and 23.6% of responders would receive extended induction (6 x MIRI IV doses + 20 x MIRI SC injections).

Table 10: Results of the cost-minimisation approach presented in the submission

Component	VDZ IV	MIRI (standard dosing; 3 IV induction doses)	MIRI (extended dosing; 6 IV induction doses)
PBS item (max qty)	300 mg vial (1)	300 mg vial (1) 200 mg pre-filled pen (2)	300 mg vial (1) 200 mg pre-filled pen (2)
AEMP	\$2,949.93	\$1,739.29	\$1,729.94
Units (infusions / injections)	15 ^a	IV infusions: 3 SC injections: 23	IV infusions: 6 SC injections: 20
PBS costs	\$44,248.95	\$45,221.55	\$44,978.40
Administration (IV infusion)	\$1,215.75	\$243.15	\$486.30
Total / 104 weeks	\$45,464.70	\$45,464.70	\$45,464.70
Weighted average AEMP			
Dosing regimen	Proportional use		Proposed MIRI AEMP per dose
MIRI standard	76.41%		\$1,739.29
MIRI extended	23.59%		\$1,729.94
Requested weighted average AEMP per dose			\$1,737.08

Source: Tables 121-122, p254 of the submission.

AEMP=approved ex-manufacturer price, IV=intravenous, max=maximum, MIRI=mirikizumab, PBS=Pharmaceutical Benefits Scheme, qty=quantity, SC=subcutaneous, VDZ=vedolizumab.

^a The last dose is administered at Week 102 so it may be more accurate to cost 14.25.

6.41 The PBAC considered clinical claim of superior effectiveness versus ADA was not adequately supported and a claim of non-inferior effectiveness may be more reasonable. Therefore, there was no clear basis for MIRI to have a price advantage compared to the least costly alternative therapy. Over the first two years, the average cost of treatment with ADA is \$17,329.20 (calculated during the evaluation, based on the published AEMP of \$618.90 per 2 pre-filled syringes).

6.42 The ESC considered the methodology of the cost minimisation approach was reasonable.

Drug cost/patient: \$45,222 (first two years)

6.43 Based on the proposed published AEMPs and standard induction dosing (3 IV doses) and maintenance dosing once every four weeks, the average drug cost for MIRI per patient over the first two years of treatment is \$45,222 (excluding IV administration costs) based on the assumptions in Table 10.

Estimated PBS usage & financial implications

6.44 This submission was not considered by the Drug Utilisation Sub-Committee (DUSC).

6.45 The submission used a market share approach to the financial estimates based on the published prices. Table 11 summarises the inputs used for the financial estimates.

Table 11: Key inputs for financial estimates

Parameter	Value applied and source				
Current market and market growth	To estimate the size of the current market over the first six years of the proposed listing, the submission fitted a linear trend to monthly script data (Jan 2015 to Nov 2022) using Medicare Australia claims data. The linear function was generally reasonable despite underestimating utilisation in 2022. However, the estimated number of scripts modelled / presented in the submission differed to the linear function. The table below compares the predictions from the linear function to the predictions used in the financial model, and shows that the submission likely overestimated the size of the market (e.g. 144k scripts modelled vs 119k scripts predicted in Year 6). These differences were due to the 2022 script numbers used (the submission used Jan to Nov in the model instead of a full year) and the growth rate assumed for 2022 (the submission used the observed 29.3% growth rate for 2021 to 2022 instead of the predicted 4.3% growth rate for 2022 to 2023). In addition, the submission did not distinguish between ADA and IFX scripts dispensed for adult and paediatric populations. Given the proposed listing of MIRI is for adults only, the eligible population should exclude paediatric patients.				
		Linear trend predictions		Scripts modelled (without MIRI)	
		Scripts	% change	Scripts	% change
	2022	70,262 (Jan-Dec)*	29.3%	68,555 (Jan-Nov)	-
	2023	73,255	4.3%	88,634	29.3%
	2024	82,420	12.5%	99,722	12.5%
	2025	91,585	11.1%	110,811	11.1%
	2026	100,750	10.0%	121,904	10.0%
	2027	109,915	9.1%	132,997	9.1%
	2028	119,080	8.3%	144,089	8.3%
	Source: Extracted from A7.1 Section 4_workbook_Miri.xls * Observed scripts Jan to Nov 2022, plus predicted scripts Dec 2022.				
Market shares, and split between 'Initiating' and 'Continuing' treatment	To estimate the utilisation of the comparators in the absence of MIRI, the submission split the market by 43 PBS item numbers and applied the estimated market growth rates (see above) to the scripts observed for each PBS item number in 2022 (Jan to Nov). The submission expanded the Section 4 workbook to accommodate the forty-three 'comparators' rather than aggregate similar item numbers and as such, further review be required following a recommendation to affirm the estimates. The following issues are noted. The PBS item numbers for VDZ do not distinguish between 'Initiating' and 'Continuing'; for this analysis, the submission assumed items 10384M, 10398G, 12644L were for 'Initiating' treatment and items 12639F and 12647P were for 'Continuing' treatment. By applying the same aggregate growth rates to all PBS items, the submission assumed no change in the proportional use of scripts for Initiating and Continuing treatment over time, which was not reasonable for recently listed treatments (e.g. TOF, listed from July 2021).				
Uptake rate, Substitution rate, Distribution	The submission assumed that MIRI would account for 1% of the total market scripts in Year 1, increasing to 25% market share in Year 6, with proportional substitution across all comparator scripts. To account for the fact that utilisation of 'Initiating' MIRI scripts will be higher than 'Continuing' MIRI scripts in the early				

Public Summary Document – July 2023 PBAC Meeting

Parameter	Value applied and source
of MIRI Initial and Continuing scripts	years, the submission 'reconfigured' the uptake rates to reflect based on the proportional use of IFX Initial and Continuing scripts over time, summarised in the table below. The assumed uptake rates appeared generally reasonable (albeit slightly optimistic given there are now eight alternative therapies compared to five at the time of the submission), but the submission's estimates only corresponded to approx. half the uptake rates assumed. For example, the submission estimated MIRI would substitute for 19,716 comparator scripts in Year 6, corresponding to an uptake rate of 13.7% (19,716 / 144,089) rather than the assumed 25%. This difference was largely due to the submission applying the reconfigured uptake rates for initial and continuing scripts directly to the PBS items by initial and continuing treatment, rather than first applying the overall uptake rates and then applying the distribution of MIRI scripts by initial and continuing treatment. There were also a number of programming errors identified in applying the reconfigured uptake rates: The submission applied 'Continuing' rates to 'Initial' item 12333D, and 'Initiating' rates to 'Continuing' items 12557X, 12351C and 12391E. The submission also applied an uptake rate of 1% in Year 1 to items 12347W, 12412G and 12351C rather than the reconfigured rates.
Script equivalence	<p>The submission estimated dose equivalence between MIRI and the comparators based on the number of scripts required to provide 12 weeks of treatment for initial treatment and 12 months of continuing treatment.</p> <p>The submission did not adequately explain or justify the approach for calculating script equivalence, based on 12 weeks on induction treatment rather than the maximum duration of induction treatment or average duration per script. The submission also did not make any distinction between IV and SC forms of IFX or VDZ, despite differences in dosing frequencies and script durations by dose form. It was also unclear how the submission derived the estimates, for example, the first 12 weeks of treatment with MIRI, GOL IV and VDZ IV requires only 3 scripts rather than 4 scripts, and 52 weeks of maintenance treatment with IFX requires 6.5 scripts rather than 7 scripts. The submission also appeared to apply the wrong script equivalence to item 12370C in the spreadsheet (ADA initial treatment, 1.0 applied instead of 0.8). Alternative script equivalence estimates calculated during the evaluation showed the submission likely overestimated the number of MIRI scripts required to substitute for initial treatment with TOF, GOL and IFX; and underestimated the number of MIRI scripts required to substitute for initial treatment with VDZ IV and continuing treatment with IFX. The alternative estimates based on average duration of treatment provided by each script and the recommended doses for initial and continuing treatment, assumed 12 weeks of initial treatment with MIRI and the maximum duration of treatment on the PBS with the comparators. The assumed 12 weeks of initial treatment with MIRI was consistent with the submission's assumptions for the base case analysis. The submission considered the impact of allowing up to 24 weeks of initial treatment with MIRI in a sensitivity analysis, assuming all patients would receive 6 scripts with MIRI and no change in the number of initial scripts with comparator treatments.</p>
Drug cost of proposed medicine and comparators	<p>To estimate the net cost to the PBS/RPBS, the submission applied the published prices (DPMQ), from January 2023 (see 'Market share' above), to the estimated number of MIRI scripts and change in the estimated number of comparator scripts. The submission stated that effective prices of the comparators are unknown to the sponsor. The following issues were identified:</p> <ul style="list-style-type: none"> the stated prices for ADA in the financial estimates were correct at the time of the submission, but are higher than the current prices (ADA underwent a statutory price reduction in April 2023) the submission did not adjust the cost for IFX IV (e.g. DPMQ for most items based on pricing quantity 1 vial) to account for the average number of vials provided per script (dose requires approx. 4 vials) the submission applied a DPMQ of \$0 to item 12351C the submission applied the DPMQ of item 11381B to item 11382C and vice versa.
MBS costs	The submission assigned an administration cost to MIRI IV scripts and VDZ IV scripts based on MBS item 116 (80% fee, \$65.84), and an administration cost to IFX IV scripts based on MBS item 14245 (80% fee, \$82.84). The assumed unit costs for administration of IV infusions was appropriate. However, the submission only costs IV administration for IFX IV script for initial treatment, and therefore likely overestimated the cost to the MBS, given the substitution of MIRI SC for IFX IV for continuing treatment would reduce the number IV administrations required.

Source: Table 123, pp. 257-259 of the submission.

approx.=approximately, ADA=adalimumab, DPMQ=Dispensed Price for Maximum Quantity, GOL=golimumab, IFX=infliximab, IV=intravenous, MBS=Medicare Benefits Schedule, MIRI=mirikizumab, PBS=Pharmaceutical Benefits Scheme, RPBS=Repatriation Pharmaceutical Benefits Scheme, SC=subcutaneous, TOF=tofacitinib, UST=ustekinumab, VDZ=vedolizumab.

6.46 The estimated script numbers and costs for the PBS listing of MIRI (using published prices) for the treatment of MSUC are provided in Table 12.

Table 12: Estimated use and financial implications using published prices*

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
MIRI scripts ^a	1	3	4	4	5	5
Initial	1	2	2	2	2	2
Continuing	1	3	4	4	5	5
Estimated financial implications of MIRI						
Cost to PBS/RPBS less copayments	6	7	8	9	10	11
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments	12	12	12	12	12	12
Net financial implications						
Net cost to PBS/RPBS	12	6	7	7	8	8
Net cost to MBS	6	6	6	6	6	6
Net cost to PBS/RPBS/MBS	12	6	7	7	8	8

Source: Tables 131-135, pp. 266-270 of the submission.

* The estimates presented in the table correspond to the estimates presented in the submission, without correcting any errors identified during the evaluation

^a Dispensed scripts were based on the assumed substitution rates and calculated script equivalence between each drug and MIRI. MIRI=mirikizumab, MBS=Medicare Benefits Schedule, PBS=Pharmaceutical Benefits Scheme, RPBS=Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

¹ <500

² 500 to < 5,000

³ 5,000 to < 10,000

⁴ 10,000 to < 20,000

⁵ 20,000 to < 30,000

⁶ \$0 to < \$10 million

⁷ \$10 million to < \$20 million

⁸ \$20 million to < \$30 million

⁹ \$30 million to < \$40 million

¹⁰ \$40 million to < \$50 million

¹¹ \$50 million to < \$60 million

¹² net cost saving

6.47 For the base case analysis, assuming a 12-week induction course with MIRI, the submission estimated that the proposed listing of MIRI would result in a net cost to the PBS/RPBS of \$80 million to < \$90 million and a net cost to the MBS of \$0 to < \$10 million, over the first 6 years. For a sensitivity analysis, assuming a 24-week induction course with MIRI, the net cost to the PBS/RPBS increased to \$90 million to < \$100 million and the net cost to the MBS increased to \$0 to < \$10 million, over the first 6 years. The submission stated that the high estimated net cost of the proposed listing was an artefact owing to the use of published rather than effective prices.

6.48 In addition to the use of published prices, the evaluation also identified the following key issues/errors with the financial estimates model:

- The submission likely overestimated the size of the market due to differences between the growth rates estimated from the linear function and the growth rates

actually applied in the model. In addition, the submission did not distinguish between comparator scripts (ADA and IFX) dispensed for adult and paediatric populations. Given the proposed listing of MIRI is for adults only, the eligible population should exclude paediatric patients.

- The submission applied the uptake rates incorrectly, which resulted in MIRI substituting at approximately half of the assumed rates. There were also several programming errors with uptake rates applied to the comparators.
- The submission did not adequately explain or justify the approach for calculating script equivalence, based on scripts required for 12 weeks of initial treatment rather than the average duration of treatment provided per script. Some of the script numbers used in the calculations did not appear to match the assumed 12 weeks of initial treatment and the submission did not distinguish between the IV and SC form of VDZ and IFX, which require different numbers of scripts. There was also a programming error identified with the script equivalence applied to one comparator.
- There were several issues identified with the prices applied, beyond the use of published prices. The submission did not adjust the cost of IFX IV (pricing quantity of 1 vial) to account for the average number of vials likely provided per script (i.e. required per dose). There were also several programming errors with the published prices applied to specific items. In addition, while correct at the time the submission was lodged, the price of ADA reduced on 1 April 2023.

6.49 The PSCR acknowledged the errors in the financial estimates model identified in the commentary and presented updated results. Table 13 below summarises the estimated use and financial implications based on the issues identified during the evaluation.

Table 13: Estimated use and financial implications using published prices (PSCR updated)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
MIRI scripts - submission	1	2	3	3	4	4
MIRI scripts - PSCR	7	3	3	4	5	6
Estimated financial implications of MIRI						
Cost to PBS/RPBS less co-pay - submission	8	9	10	11	12	13
Cost to PBS/RPBS less co-pay - PSCR	8	9	11	13	14	14
Estimated financial implications for other medicines						
Cost to PBS/RPBS less co-pay - submission	15	15	15	15	15	15
Cost to PBS/RPBS less co-pay - PSCR	15	15	15	15	15	15
Net financial implications						
Net cost to PBS/RPBS - submission	15	8	9	9	10	10
Net cost to PBS/RPBS - PSCR	15	8	9	10	10	11
Net cost to health budget - submission	15	8	9	9	10	10
Net cost to health budget - PSCR	15	8	9	10	10	11

Source: A7.1. Section 4_workbook_Miri_updated230523_FINAL.xlsx

MIRI=mirikizumab, MBS=Medicare Benefits Schedule, PBS=Pharmaceutical Benefits Scheme, RPBS=Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

¹ < 500

² 5,000 to < 10,000

³ 10,000 to < 20,000

⁴ 20,000 to < 30,000

⁵ 30,000 to < 40,000

⁶ 40,000 to < 50,000

⁷ 500 to < 5,000

⁸ \$0 to < \$10 million

⁹ \$10 million to < \$20 million

¹⁰ \$20 million to < \$30 million

¹¹ \$30 million to < \$40 million

¹² \$40 million to < \$50 million

¹³ \$50 million to < \$60 million

¹⁴ \$70 million to < \$80 million

¹⁵ net cost saving

6.50 Assuming the published prices of the comparators, the relevant changes increased the net cost to the PBS/RPBS from \$80 million to < \$90 million in the submission to \$90 million to < \$100 million in the PSCR over a period of 6 years. The PBAC noted these costs were based on the published price of the comparator, and the net cost to the PBS will reduce once the effective price of the comparator is applied.

6.51 These issues notwithstanding, assuming MIRI is listed on a cost-minimisation basis to the least costly alternative therapy current market growth was unchanged, the evaluation and ESC considered the requested listing would be expected to be approximately cost neutral or modestly cost-saving to the PBS/RPBS, as it would primarily replace therapies that are of equivalent cost or are more costly.

Quality Use of Medicines

- 6.52 The sponsor intends to engage in a range of activities supporting the quality use of MIRI for use in patients with MSUC. These include training clinicians in the appropriate use of the medicine.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program) and General Schedule listings of mirikizumab (MIRI) for the treatment of moderate to severe ulcerative colitis (MSUC). The Section 100 recommendation was for listing the vial for intravenous (IV) infusion for initial treatment, and the General Schedule listing was for the pre-filled pen for subcutaneous (SC) injection for maintenance therapy. The PBAC's recommendation for listing was based on, among other matters, its assessment the cost effectiveness of MIRI would be acceptable if it were cost minimised to the least costly alternative therapy of adalimumab (ADA), golimumab (GOL), infliximab (IFX), ozanimod (OZA), tofacitinib (TOF), ustekinumab (UST), upadacitinib (UPA) and vedolizumab (VDZ).
- 7.2 The PBAC considered the nominated comparator of VDZ was reasonable, however considered all biologic or targeted synthetic disease modifying anti-rheumatic drugs (bDMARDs/tsDMARDs) to be relevant comparators. The PBAC considered the equi-effective doses of MIRI and the alternatives could be derived with reference to the therapeutic relativity sheets and relevant Product Information documents, however noted there were two initial dose regimens for MIRI and considered the equi-effective doses to be:
- MIRI standard dosing (with standard 12 week initial period):
 - MIRI IV 300 mg at week 0, 4, 8 and then MIRI SC 200 mg every 4 weeks (Q4W) thereafter
 - MIRI extended dosing (with extended 24 week initial period):
 - MIRI IV 300 mg at week 0, 4, 8, 12, 16, 20 and then MIRI SC 200 mg Q4W thereafter
 - The PBAC advised the split of regimens of 76.4% receiving standard induction and 23.6% of responders receiving extended induction, as proposed in the cost minimisation approach (see Table 10), was reasonable.
- 7.3 The PBAC considered it was reasonable for the PBS listing of MIRI to be consistent with other disease modifying anti-rheumatic drugs (DMARDs) for MSUC, with prescribing restricted to eligible medical practitioners. The PBAC noted that extending the induction period with MIRI from 12 to 24 weeks may also delay induction non-responders from receiving an effective alternative treatment, however considered this option would be reasonable if included in the Product Information. To facilitate

both schedules, the PBAC considered a maximum of 2 repeats for the Initial treatment listings (MIRI 300 mg/15 mL injection) was appropriate to allow for an initial assessment of response at Week 12, and that an additional three doses could be requested through a Balance of Supply listing if patients required extended induction doses. The PBAC considered a grandfather listing was appropriate to allow patients currently enrolled in the LUCENT-3 trial who meet the requirements for the PBS listing to transition to accessing MIRI through the PBS and recommended the grandfather listing should be in operation for a 12 months.

- 7.4 The PBAC noted that there are currently eight different bDMARD/tsDMARD therapies listed on the PBS for the treatment of MSUC and considered that as MIRI does not appear to provide a significant benefit over other existing treatments, there is a low clinical need for the addition of a new therapy on the PBS. The PBAC noted the comment from a health care professional that stated a significant proportion of patients do not respond to therapies available and require surgery, and there is therefore a strong need for more classes of effective medical therapies to be available through the PBS. The PBAC also noted the comment stated the benefits of MIRI include its favourable safety profile and the convenience of SC maintenance dosing.
- 7.5 The submission nominated vedolizumab (VDZ) as the main comparator, adalimumab (ADA) as the secondary comparator and ustekinumab (UST) as a near market comparator. The PBAC considered the comparators were reasonable but noted MIRI may substitute for any of the DMARDs listed for MSUC, including IFX, GOL, OZA, TOF and UPA.
- 7.6 The PBAC noted the trial results demonstrated that more patients achieved clinical remission and/or clinical response following induction treatment with MIRI compared to placebo, and that response was generally well maintained out to 52 weeks. The PBAC also noted the results of indirect treatment comparisons generally found no statistically significant differences between MIRI and VDZ for induction or maintenance treatment, with the exception of one comparison favouring VDZ over MIRI using the relative risk statistic for maintenance of response. For the indirect comparisons versus UST, the Committee noted there were a few comparisons that favoured MIRI over UST using the risk difference statistic, and there were a few comparisons favouring UST over MIRI in the bDMARDs/tsDMARDs experienced subgroup using the relative risk statistic.
- 7.7 The PBAC noted the submission made a claim of superior comparative effectiveness versus ADA, however also noted the evaluation found there were generally no statistically significant differences between the two treatments for induction or maintenance treatment, with the exception of a few comparisons that favoured MIRI over ADA using the risk difference (RD) statistic and the results using the RR statistic showed no difference between the two treatments for induction or maintenance treatment. Overall, the PBAC considered the totality of the available evidence did not strongly support a contention that MIRI is likely to be of superior comparative effectiveness to ADA.

- 7.8 The PBAC noted the results of the network meta-analysis (NMA) found no statistically significant differences between MIRI and either VDZ or UST for induction or maintenance treatment, and further noted that for the comparisons versus ADA, the results only favoured MIRI when the models adjusted for baseline risk. Overall, the PBAC agreed with the ESC and considered the NMA was of limited informative value for assessing the clinical claim, as the NMA results were only presented based on bDMARD/tsDMARD naïve/experienced subgroups and no intention to treat (ITT) population results were reported. The PBAC noted the arguments in the Pre-PBAC Response that evaluation of the ITT population was not feasible due to heterogeneity (paragraph 6.32 refers), however noted that previous submissions such as OZA for MSUC in November 2022 had presented an NMA which included analyses based on ITT populations and therefore considered the argument to not undertake such analyses was not well justified. Overall, the PBAC agreed with the ESC and considered the NMA was not particularly informative for assessing the clinical claims, as the ITT population most closely aligns with the PBS restrictions for bDMARDs/tsDMARDs for MSUC. The PBAC noted that the proportion of adverse events, serious adverse events and infections were comparable between MIRI and VDZ, UST and ADA during induction and maintenance treatment, and there were fewer discontinuations due to adverse events in patients treated with MIRI versus VDZ or ADA. Overall, the PBAC considered the evidence presented supported a claim that MIRI is of non-inferior comparative safety to the nominated comparators.
- 7.9 Overall, the PBAC accepted MIRI is likely of non-inferior comparative effectiveness to the nominated comparators UST and VDZ and considered the totality of the available evidence did not strongly support a contention that MIRI is likely to be superior or inferior in terms of comparative effectiveness or safety to any of the alternative therapies. The PBAC noted the submission's claim that MIRI demonstrated superior effectiveness compared to ADA, however, considered that the evidence did not support this claim and considered MIRI was more likely to be of non-inferior comparative effectiveness to ADA.
- 7.10 The PBAC recalled that OZA, UST and UPA were recommended for PBS listing on the basis that cost-effectiveness would be acceptable if they were cost minimised to the least costly alternative PBS listed therapy, excluding ADA. The PBAC considered there was sufficient evidence that OZA, UST and UPA, for some patients, provided a significant improvement in effectiveness in the induction phase compared to adalimumab. The PBAC considered the clinical evidence for MIRI presented in the submission did not support a significant improvement in effectiveness in the induction phase compared to ADA.
- 7.11 The PBAC considered that a listing based on a cost minimisation approach with costs over two years, consistent with the approach previously used for bDMARDs/tsDMARDs, was appropriate to determine the cost minimised price of MIRI. The PBAC considered the cost of MIRI should be no greater than the alternative

therapies, including the proposed weighted AEMP for MIRI, assuming 76.4% receiving standard induction and 23.6% receiving extended induction (see Table 10).

- 7.12 The PBAC noted an estimated net cost to the PBS/RPBS of \$90 million to < \$100 million over 6 years with the listing of MIRI and noted that this cost was based on the published price of the comparator. The PBAC considered that, under the parameters of its recommended listing on a cost minimisation basis with the least costly alternative, the listing of MIRI would be expected to be cost neutral or modestly cost saving to the PBS/RPBS, as it would primarily replace therapies that are of equivalent cost or more expensive.
- 7.13 The PBAC advised that MIRI should be treated as interchangeable on an individual patient basis with vedolizumab, adalimumab, ozanimod, upadacitinib, ustekinumab, infliximab, golimumab and tofacitinib.
- 7.14 The PBAC advised that MIRI is not suitable for prescribing by nurse practitioners, similar to other PBS listings for MSUC.
- 7.15 The PBAC advised that the Early Supply Rule should not apply to the IV form of MIRI but should apply to the SC form for maintenance therapy.
- 7.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because MIRI is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over VDZ, 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 2022* for Pricing Pathway A were not met.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
MIRIKIZUMAB					
mirikizumab 300 mg/15 mL injection, 15 mL vial	NEW	1	1	2	OmvoH
Restriction Summary based on 12180 / Treatment of Concept: based on 12080					
Category / Program: Section 100 – Highly Specialised Drugs Program					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice:					

Public Summary Document – July 2023 PBAC Meeting

	No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Initial treatment – Initial 1 (new patient)
	Clinical criteria:
	Patient must have failed to achieve an adequate response to a 5-aminosalicylate oral preparation in a standard dose for induction of remission for 3 or more consecutive months or have intolerance necessitating permanent treatment withdrawal,
	AND
	Clinical criteria:
	Patient must have failed to achieve an adequate response to azathioprine at a dose of at least 2 mg per kg daily for 3 or more consecutive months or have intolerance necessitating permanent treatment withdrawal; OR
	Patient must have failed to achieve an adequate response to 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more consecutive months or have intolerance necessitating permanent treatment withdrawal; OR
	Patient must have failed to achieve an adequate response to a tapered course of oral steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period or have intolerance necessitating permanent treatment withdrawal, and followed by a failure to achieve an adequate response to 3 or more consecutive months of treatment of an appropriately dosed thiopurine agent,
	AND
	Clinical criteria:
	Patient must have a Mayo clinic score greater than or equal to 6; OR
	Patient must have a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo clinic score).
	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)].
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing Instructions: The authority application must be in writing and must include: (1) a completed authority prescription form; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice), which includes: (i) the completed current Mayo clinic or partial Mayo clinic calculation sheet including the date of assessment of the patient's condition; and (ii) details of prior systemic drug therapy [dosage, date of commencement and duration of therapy].
	Prescribing Instructions: All tests and assessments should be performed preferably whilst still on treatment, but no longer than 4 weeks following cessation of the most recent prior conventional treatment
	Prescribing Instructions: The most recent Mayo clinic or partial Mayo clinic score must be no more than 4 weeks old at the time of application.
	Prescribing Instructions: An assessment of a patient's response to this initial course of treatment must be conducted 12 weeks after initial dose.

Public Summary Document – July 2023 PBAC Meeting

	<p>Prescribing Instructions: If patients do not have adequate therapeutic response at Week 12 after induction dosing, additional doses to extend induction treatment to 20 weeks can be accessed through the balance of supply (IV infusion to occur at week 12,16 and 20.) An assessment of a patient's response to extended induction treatment must be made no later than 4 weeks from the last induction dose.</p>
	<p>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.</p>
	<p>Prescribing Instructions: If treatment with any of the above-mentioned drugs is contraindicated according to the relevant TGA-approved Product Information, details must be provided at the time of application.</p>
	<p>Prescribing Instructions: If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, details of this toxicity must be provided at the time of application.</p>
	<p>Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug after 24 weeks of treatment 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.</p>
	<p>Prescribing Instructions: The Services Australia website (www.servicesaustralia.gov.au) has details of the toxicities, including severity, which will be accepted where one is claimed.</p>
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
Restriction Summary based on 12136 / Treatment of Concept: based on 12179	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Initial treatment - Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years)
	Clinical criteria:
	Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle,
	AND
	Clinical criteria:
	Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with this drug for this condition during the current treatment cycle.

Public Summary Document – July 2023 PBAC Meeting

	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)].
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice), which includes: (i) the completed current Mayo clinic or partial Mayo clinic calculation sheet including the date of assessment of the patient's condition if relevant; and (ii) the details of prior biological medicine treatment including the details of date and duration of treatment.
	Prescribing Instructions: An assessment of a patient's response to this initial course of treatment must be conducted 12 weeks after initial dose.
	Prescribing Instructions: If patients do not have adequate therapeutic response at Week 12 after induction dosing, additional doses to extend induction treatment to 20 weeks can be accessed through the balance of supply (IV infusion to occur at week 12,16 and 20.) An assessment of a patient's response to extended induction treatment must be made no later than 4 weeks from the last induction dose.
	Prescribing Instructions: An application for a patient who has received PBS-subsidised biological medicine treatment for this condition who wishes to change or recommence therapy with this drug, must be accompanied by evidence of a response to the patient's most recent course of PBS-subsidised biological medicine treatment, within the timeframes specified below.
	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 after 24 weeks of treatment they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within this treatment cycle. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: A patient who fails to demonstrate a response to treatment with this drug under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug in this treatment cycle. 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: The Services Australia website (www.servicesaustralia.gov.au) has details of the toxicities, including severity, which will be accepted where one is claimed.

Public Summary Document – July 2023 PBAC Meeting

	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
Restriction Summary based on 12079 / Treatment of Concept: based on 12219	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Initial treatment - Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with a biological medicine for this condition,
	AND
	Clinical criteria:
	Patient must have had a break in treatment of 5 years or more from the most recently approved PBS-subsidised biological medicine for this condition,
	AND
	Clinical criteria:
	Patient must have a Mayo clinic score greater than or equal to 6; OR
	Patient must have a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo clinic score).
	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)].
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice), which includes: (i) the completed current Mayo clinic or partial Mayo clinic calculation sheet including the date of assessment of the patient's condition; and (ii) the details of prior biological medicine treatment including the details of date and duration of treatment.

Public Summary Document – July 2023 PBAC Meeting

	<p>Prescribing Instructions: The most recent Mayo clinic or partial Mayo clinic score must be no more than 4 weeks old at the time of application.</p>
	<p>Prescribing Instructions: An assessment of a patient's response to this initial course of treatment must be conducted 12 weeks after initial dose.</p>
	<p>Prescribing Instructions: If patients do not have adequate therapeutic response at Week 12 after induction dosing, additional doses to extend induction treatment to 20 weeks can be accessed through the balance of supply (IV infusion to occur at week 12,16 and 20.) An assessment of a patient's response to extended induction treatment must be made no later than 4 weeks from the last induction dose</p>
	<p>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.</p>
	<p>Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug after 24 weeks of treatment 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.</p>
	<p>Prescribing Instructions: The Services Australia website (www.servicesaustralia.gov.au) has details of the toxicities, including severity, which will be accepted where one is claimed.</p>
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
Restriction Summary: modification of / Treatment of Concept: modification of	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required immediate/real time assessment by Services Australia (telephone/online application avenues)
	Indication: Moderate to Severe Ulcerative Colitis
	Treatment Phase: Initial 1 (new patient) or Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) or Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) – Balance of Supply
	Clinical criteria:
	Patient must have received insufficient therapy with this drug for this condition under the Initial 1 (new patient) restriction to complete 20 weeks of treatment (administered at weeks 0, 4, 8, 12,16 and 20); OR

Public Summary Document – July 2023 PBAC Meeting

	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 20 weeks of treatment (administered at weeks 0, 4, 8, 12, 16 and 20); OR
	Patient must have received insufficient therapy with this drug for this condition under the Initial 3 (change or recommencement of treatment after a break in biological medicine of more than 5 years) restriction to complete 20 weeks of treatment (administered at weeks 0, 4, 8, 12, 16 and 20); OR
	Patient must have received insufficient therapy with this drug for this condition under the Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements restriction to complete 20 weeks of non-PBS and PBS treatment (administered at weeks 0, 4, 8, 12, 16, 20)
	AND
	Clinical criteria:
	The treatment must provide no more than the balance of up to 20 weeks treatment available under the above restrictions.
	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)]
	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. Monday to Friday).

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
MIRIKIZUMAB					
mirikizumab 100 mg/mL injection 2 x 1 mL pen devices	NEW	1	2	5	OmvoH

Restriction Summary 12181 / Treatment of Concept: 12135

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment 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.

Public Summary Document – July 2023 PBAC Meeting

	AND
	Clinical criteria:
	Patient must not receive more than 24 weeks of treatment under this restriction
	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)].
	Population criteria:
	Patient must be at least 18 years of age
	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 a 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: 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.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within this treatment cycle. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: 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: 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. Monday to Friday).
Restriction Summary based on 12181 / Treatment of Concept: based on 12135	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Continuing treatment – balance of supply
	Clinical criteria:

Public Summary Document – July 2023 PBAC Meeting

	Patient must have received insufficient therapy with this drug for this condition under the continuing treatment restriction to complete 24 weeks treatment
	AND
	Clinical criteria:
	The treatment must provide no more than the balance of up to 24 weeks treatment available under the above restriction
	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)].
	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. Monday to Friday).

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
MIRIKIZUMAB					
mirikizumab 300 mg/15 mL injection, 15 mL vial	NEW	1	1	2	OmvoH
mirikizumab 100 mg/mL injection 2 x 1 mL pen devices	NEW	1	2	5	OmvoH

Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: Intravenous form: Section 100 – Highly Specialised Drugs Program Subcutaneous form: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements Apply.
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements
	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [PBS listing date].
	AND
	Clinical criteria:
	Patient must be receiving treatment with this drug for this condition at the time of application
	AND
	Clinical criteria:
	The condition must have responded inadequately to a 5-aminosalicylate oral preparation in a standard dose for induction of remission for at least 3 consecutive months prior to treatment initiation with this drug; or

Public Summary Document – July 2023 PBAC Meeting

	Patient must have experienced a severe intolerance to the above therapy leading to a permanent treatment discontinuation
	AND
	Clinical criteria:
	The condition must have responded inadequately to azathioprine at a dose of at least 2 mg per kg daily for at least 3 consecutive months prior to treatment initiation with this drug; or
	The condition must have responded inadequately to 6-mercaptopurine at a dose of at least 1 mg per kg daily for at least 3 consecutive months prior to treatment initiation with this drug; or
	The condition must have responded inadequately to a tapered course of oral steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period, followed by an inadequate response to at least 3 consecutive months of treatment with an appropriately dosed thiopurine agent, prior to treatment initiation with this drug; or
	Patient must have experienced a severe intolerance to each of the above 3 therapies leading to permanent treatment discontinuation
	AND
	Clinical criteria:
	Patient must have had a Mayo clinic score greater than or equal to 6 prior to commencing non-PBS-subsidised treatment with this drug for this condition; or
	Patient must have had a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo clinic score) prior to commencing non-PBS-subsidised treatment with this drug for this condition; or
	Patient must have a documented history of moderate to severe refractory ulcerative colitis prior to having commenced non-PBS-subsidised treatment with this drug for this condition where a Mayo clinic or partial Mayo clinic baseline assessment is not available.
	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)].
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice), which includes: (i) the completed baseline Mayo clinic or partial Mayo clinic calculation sheet prior to initiating treatment (if available) including the date of assessment; (ii) the date of commencement of this drug.
	Prescribing Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only.
	Prescribing Instructions: For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	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.

	<p>Prescribing Instructions: Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain a response.</p>
	<p>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.</p>
	<p>Prescribing Instructions: The assessment of the patient’s response to this PBS-subsidised course of therapy must be conducted no later than 4 weeks from the cessation of the treatment course.</p>
	<p>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.</p>
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
	<p>Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</p>

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

The sponsor had no comment.