5.10 ETRASIMOD, Tablet 2 mg, Velsipity®, Pfizer Australia Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule, Authority Required (Written) listing for etrasimod (ETR) for the treatment of patients 16 years and older with moderate to severe ulcerative colitis (MSUC).

1.2 If listed, ETR would become the second sphingosine-1 phosphate (S1P) receptor modulator available on the PBS for MSUC and the ninth biologic or targeted synthetic disease-modifying anti-rheumatic drug (b/tsDMARD) treatment option including infliximab (IFX), adalimumab (ADA), golimumab (GOL), tofacitinib (TOF), upadacitinib (UPA), ustekinumab (UST), vedolizumab (VDZ) and ozanimod (OZA).

1.3 Listing was requested on the basis of a cost-minimisation approach versus OZA.

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

Component	Description
Population	Patients 16 years and over with MSUC
Intervention	ETR (oral tablet), 2 mg daily
Comparator	Primary: OZA (oral tablet), 0.23 mg for 4 days, then 0.46 mg for 3 days, then 0.92 mg thereafter Secondary: • IFX IV^ infusion, 5 mg/kg at Week 0, 2 and 6, then once every 8 weeks thereafter • ADA SC injection, 160 mg at Week 0, 80 mg at Week 2 then 40 mg once every 2 weeks thereafter
Outcomes	Clinical remission and clinical response
Clinical claim	In patients aged 16 years and over with MSUC, ETR is no worse than OZA or IFX and more effective than ADA at improving clinical remission and clinical response, with non-inferior safety compared to OZA, IFX or ADA.

Source: Table 1.1.1, pp13-14 of the submission.

ADA = adalimumab; ETR = etrasimod; IFX = infliximab; IV = intravenous; MSUC = moderate to severe ulcerative colitis; OZA = ozanimod; SC = subcutaneous

^ IFX is also available as a subcutaneous (SC) injection for use after at least two induction doses with the IFX IV. The IFX SC preparation was PBS-listed based on cost-minimisation to the IFX IV preparation.

2 Background

Registration status

2.1 The submission was made under TGA/PBAC parallel process. TGA status at time of PBAC consideration: Not registered. The Round 1 and 2 Clinical Evaluation Reports (CERs) and Delegate's Overview were available. ETR was under evaluation by the TGA for the indication 'treatment of patients 16 years of age and older with moderate to severely active ulcerative colitis.'

3 Requested listing

3.1 An abbreviated version of the requested restriction for initial and continuing treatment is presented below.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Initial treatment					
Etrasimod, 2 mg, tablet	$[redacted] published price $TBC effective price^	1	28	3	Velsipity
Continuing treatment					
Etrasimod, 2 mg, tablet	$[redacted] published price $TBC effective price^	1	28	5	Velsipity

Source: Table 1.4.1, p24 of the submission.
TBC = to be confirmed
^ effective price to be confirmed, based on cost-minimisation approach using the effective price of OZA.

Category / Program:	General Schedule
Restriction type:	☒Authority Required (in writing only via post/HPOS upload)
PBS Indication:	Moderate to severe ulcerative colitis
Treatment Phase:	Initial treatment
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** 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** 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 or a consultant physician [internal medicine specialising in gastroenterology] or a consultant physician [general medicine specialising in gastroenterology].
Population criteria:	Patient must be aged 16 years or older.
Prescriber Instructions:	The most recent Mayo clinic or partial Mayo clinic score must be no more than 4 weeks old at the time of application. An assessment of a patient's response to this initial course of treatment must be conducted between 9 and 17 weeks of therapy. A maximum of 16 weeks of treatment with this drug will be approved under this criterion.
Category / Program:	General Schedule
Restriction type:	☒Authority Required (in writing only via post/HPOS upload)
PBS Indication:	Moderate to severe ulcerative colitis

Treatment Phase:	Continuing treatment
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition, **AND** 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 or a consultant physician [internal medicine specialising in gastroenterology] or a consultant physician [general medicine specialising in gastroenterology].
Population criteria:	Patient must be aged 16 years or older.
Prescriber 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. Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain a response.

Source: Section 1.4.2, pp 24-27 of the submission.

3.2 The submission requested General Schedule, Authority Required (Written) PBS listing of ETR 2 mg tablets for initial and continuing treatment of MSUC. The submission also requested a grandfather restriction to allow patients enrolled in a patient familiarisation program to transition to PBS-subsidised treatment. The requested maximum quantity (including repeats) allows for up to 16 weeks of initial treatment and 24 weeks of continuing treatment.

3.3 The Sponsor requested a Special Pricing Arrangement (SPA) for ETR, with a published DPMQ of $ and an effective price derived from a cost-minimisation approach that maintains cost equivalence between ETR and OZA at the effective price. As the effective price of OZA was currently unknown to the sponsor, the submission stated that the sponsor would work with the Department to finalise the cost-minimisation approach during the post-PBAC process.

3.4 The submission requested wording of the restriction that would align with currently listed b/tsDMARDs for MSUC. Across the available treatments, the main difference in the restrictions would be the population criteria, with ETR available for patients ≥ 16 years compared to ≥ 6 years for IFX and ADA, and ≥ 18 years for the other treatments. The submission noted that key eligibility and response criteria in the restrictions would continue to be based on the full Mayo score (FMS) or partial Mayo score (pMayo), despite the clinical evidence for ETR based on the modified Mayo score (MMS). Given the similarity between the different Mayo scores, the submission stated it was appropriate to maintain the same criteria for simplicity and to avoid confusion. This was consistent with the listing of UPA, in which the clinical evidence was based on the MMS but the PBS restriction is based on the FMS or pMayo (paragraph 6.10, UPA Public Summary Document [PSD], November 2022 PBAC meeting).

3.5 The submission also requested that the PBAC review the 'three strikes' policy of the current restrictions, which requires patients who have failed to respond to three PBS-subsidised b/tsDMARDs. At the November 2022 PBAC meeting, the PBAC considered that 'it may be reasonable to review the design of treatment cycle requirements for

bDMARDs/tsDMARDs broadly given the range of available treatments with different mechanisms of action since these requirements were originally devised.' The PBAC also noted that such a review was broader than the scope of its consideration of an individual treatment for a specific indication (paragraph 7.3, UPA PSD, November 2022 PBAC meeting).

3.6 The Pre-Sub-Committee Response (PSCR) acknowledged there was limited data for the 16 and 17 year old patients, however noted that in response to the TGA clinical evaluation report, additional post-hoc analyses by age (≤ 25 years and > 25 years old) were provided (Table 3 of the PSCR) were provided. The Response stated these analyses were used to support the EMA evaluation, which included approval for patients aged 16 years and over, and argued evidence of efficacy in the younger population may provide additional confidence in the effectiveness of ETR in younger patients. The Response noted the results of these analyses were generally similar between aged-based subgroups. The ESC noted this issue remained unresolved in the TGA documentation available to it at time of consideration.

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

4 Population and disease

4.1 Ulcerative colitis is a type of chronic inflammatory bowel disease (IBD) characterised by relapsing and remitting mucosal inflammation of the colon. Inflammation is continuous, extending from the rectum varying distances. Symptoms include rectal bleeding, diarrhoea, abdominal pain and tenesmus. Extra-intestinal manifestations include arthropathy, skin and ocular manifestations and hepatobiliary disease. Patients with moderate to severe disease (i.e. MSUC) are typically either dependent on or refractory to corticosteroids, have severe endoscopic disease activity, such as the presence of ulcers, or are at high risk of colectomy.

4.2 The Mayo clinic score is the most widely used index for defining severity of disease and assessing response to treatment. Over time, different versions of the Mayo score have been developed: the original FMS incorporates four subscores related to endoscopy, stool frequency, rectal bleeding and Physician's Global Assessment; the pMayo excludes the endoscopic subscore; and the more recent MMS excludes the physician rating sub-score (as well as excluding friability from endoscopic score of 1). The pMAYO and MMS are highly correlated with the FMS (Naegeli 2021[1]).

4.3 The addition of ETR to the clinical management algorithm will not alter current practice, but will allow for an additional treatment option.

[1] April N Naegeli, Theresa Hunter, Yan Dong, et al., Full, Partial, and Modified Permutations of the Mayo Score: Characterizing Clinical and Patient-Reported Outcomes in Ulcerative Colitis Patients, Crohn's & Colitis 360, Volume 3, Issue 1, January 2021, otab007.

4.4 ETR is a synthetic, oral sphingosine-1 phosphate (S1P) receptor modulator. ETR is selective for S1P receptors 1, 4 and 5. The mechanism of action for the therapeutic effect of ETR is unknown, but is thought to involve fewer peripheral immune cells moving to sites of inflammation, such as the gastrointestinal tract in patients with UC.

5 Comparator

5.1 The submission nominated OZA as the main comparator and ADA and IFX (IV form) as secondary comparators, but acknowledged that ETR could replace any of the currently listed b/tsDMARDs (OZA, ADA, IFX, GOL, TOF, UPA, and VDZ). The submission also identified that mirikizumab may be considered as a near market comparator given it was recently recommended by the PBAC but it was not yet listed for MSUC.

5.2 The submission noted that OZA was the only currently listed treatment with the same mechanism of action as ETR (both S1P receptor modulators), but differences in trial designs for maintenance treatment only permitted a clinical comparison between ETR and OZA for induction treatment. As the trials for ETR, ADA and IFX used a similar trial design for both induction and maintenance treatment, the available evidence permitted clinical comparisons between ETR versus ADA and IFX for both induction and maintenance treatment. The submission made a clinical claim of non-inferior effectiveness and safety between versus OZA and IFX, and a claim of superior effectiveness and non-inferior safety versus ADA (see Clinical claim).

5.3 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. The alternative therapies in MSUC include ADA, GOL, IFX, OZA, TOF, UPA, UST and VDZ.

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

6 Consideration of the evidence

Sponsor hearing

6.1 A hearing was requested for this item. The clinician discussed the high clinical need for additional therapies with new mechanisms of action for adolescent patients and discussed the devastating impact of MSUC and inflammatory bowel conditions to this group, including effects on school attendance and career development, as well as mental and physical health. The clinician outlined that where MSUC occurs in paediatric patients, onset is often at an early age, and while there is low mortality, there is significant morbidity and the condition is often not curable with current pharmacological interventions. The clinician also stated that early treatment with highly efficacious options (such as the b/tsDMARDs) can help patients reach clinical,

endoscopic and histologic goals that will improve outcomes for patients, both in terms of reduced surgeries and colorectal cancers, but also improve quality of life through better symptom control. The clinician also discussed the lifelong impacts that surgical options, such as colectomy, can have on patients. The clinician also described that patients in the older adolescent age range are physiologically on a spectrum to adulthood and their characteristics such as weight, metabolic function and disease behaviour are more similar to adults than to younger children.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments from the health professional described the efficacy of ETR in MSUC, the difference with OZA as it does not require a dose titration period, and that unlike some b/tsDMARDs ETR does not appear to lead to an increased risk of infections during treatment. The PBAC also welcomed the input from consumer organisation Crohn's and Colitis Australia, which supported the listing and highlighted the benefits of additional treatment options for patients, particularly oral therapies, and noted that ETR appears to have a simpler dose titration than other S1P modulators.

Clinical trials

6.3 The submission conducted a literature search to identify any head to head randomised controlled trials (RCTs) comparing ETR and OZA or placebo-controlled RCTs of ETR and OZA which would be suitable for an indirect treatment comparison. The evaluation conducted an additional literature search to identify recent IFX and ADA trials. The submission inappropriately excluded two potentially relevant 3-arm RCTs comparing etrolizumab versus ADA or placebo (PBO) for induction therapy in MSUC, HIBISCUS I and HIBISCUS II (reported together in Rubin 2022[2]). The PBAC has previously considered evidence from the ADA and placebo arms of the HIBISCUS trials, which was incorporated into an indirect comparison between mirikizumab and ADA (Mirikizumab, PSD, July 2023 PBAC meeting).

6.4 There were no head-to-head trials comparing ETR with OZA or the secondary comparators for treatment of MSUC. To inform the comparative effectiveness between the treatments, the submission presented a series of indirect comparisons using placebo (PBO) as a common reference based on data from 12 placebo-controlled RCTs:

- all 12 RCTs provided evidence for induction therapy:
  - ETR v PBO: ELEVATE UC 12, ELEVATE UC 52;

[2] 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 Jan;7(1):17-27.

- OZA v PBO: True North, Touchstone;
- IFX v PBO: ACT 1, ACT 2, Jiang 2015, Kobayashi 2016, Remicade;
- ADA v PBO: ULTRA 1, ULTRA 2, Suzuki 2014;

- three RCTs provided evidence for maintenance therapy:
  - ETR v PBO: ELEVATE UC 52;
  - IFX v PBO: ACT 1;
  - ADA v PBO: ULTRA 2.

6.5 Details of the trials presented in the submission are provided in Table 2. The PBAC had considered evidence from all of the comparator trials in past decisions for MSUC.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Etrasimod trials		
ELEVATE UC 12 (NCT03996369)	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 12-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis.	Clinical study report – report date: 9 September 2021.
	Sandborn W, Vermiere S, Peyrin-Biroulet L, Dubinsky M et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies.	Lancet 2023; 401:1159-71
ELEVATE UC 52 (NCT03945188)	Phase 3, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis.	Clinical study report – report date: September 2021.
	Sandborn W, Vermiere S, Peyrin-Biroulet L, Dubinsky M et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies.	Lancet 2023; 401:1159-71
Ozanimod trials		
True North (NCT02435992)	Sandborn W, Feagan B, D'Haens G, Wolf D et al. Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis.	N Engl J Med. 2021; 385: 1280-1291
Touchstone (NCT01647516)	Sandborn W, Feagan B, Wolf D, D'Haens G, Vermeire S et al. Ozanimod Induction and maintenance Treatment for Ulcerative Colitis.	N Engl J Med 2016; 374 (18): 1754-1762.
Infliximab trials		
ACT 1 (NCT00036439) ACT 2 (NCT00096655)	Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis.	N Engl J Med. 2005; 353:2462-2476.
Jiang 2015	Jiang XL, Cui HF, Gao J, Fan H. Low-dose Infliximab for Induction and Maintenance Treatment in Chinese Patients With Moderate to Severe Active Ulcerative Colitis.	J Clin Gastroenterol. 2015, 49(7):582-588.
REMICADE (NCT01551290)	Jansen Research and Development. Clinical Study Report Synopsis. CNTO312 (infliximab). A Phase 3, multicentre, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of infliximab in Chinese subjects with active ulcerative colitis. REMICADEUCO3001.	Clinical study report – report date: 21 October 2014
Kobayashi 2016 (Japic CTI-06029)	Kobayashi T, Suzuki Y, Motoya S, et al. First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis-results from a multicenter prospective randomized controlled trial and its post hoc analysis. Serum trough level as predictor of response.	J Gastroenterol 2016; 51(3):241-5.
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.

Source: Tables 2.2.1, pp34-35 and 2.5.1, p56 of the submission, Table 3, p7, Tofacitinib PSD, November 2020 PBAC Meeting.

6.6 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)
ETR vs PBO					
Elevate UC 12 [induction]	352	P3, MC, R, PC, DB/ 12 weeks	Low	TNFi-e & TNFi-n	1°: clinical remission 2°: clinical response, safety
Elevate UC 52 [induction & maintenance]	433	P3, MC, R, PC, DB/ 52 weeks (12-week induction[a])	Low	TNFi-e & TNFi-n	1°: clinical remission at 12 and 52 weeks 2°: clinical response, endoscopic improvement with histologic remission, symptomatic remission; CS-free remission; sustained remission; safety up to 52 weeks
OZA vs PBO					
True North [induction & maintenance]	1012	*P3, MC, R, PC, DB, 3-arm (Cohort 1; n=645) & OL (Cohort 2; n=367)/ 52 weeks (10-week induction[b])*	*Low*	*TNFi-e & TNFi-n*	*1°: clinical remission at 10 and 52 weeks* *2°: clinical response, endoscopic improvement, mucosal healing at weeks 10 and 52; CS-free remission; histologic remission; durable clinical remission at week 52*
Touchstone [induction & maintenance]	133[c]	*P2, PC, DB/ 32 weeks (8-week induction[a])*	*Low*	*TNFi-e & TNFi-n*	*1°: clinical remission at week 8* *2°: clinical response, mucosal healing at week 8*
IFX v PBO					
ACT 1 [induction & maintenance]	364	P3, MC, R, PC, DB, 3-arm/ 52 weeks (8-week induction)	Low*	TNFi-n	1°: clinical response 2°: clinical remission, mucosal healing, sustained clinical response, sustained clinical remission
ACT 2 [induction & maintenance]	364	P3, MC, R, PC, DB, 3-arm/ 30 weeks (8-week induction)	Low*	TNFi-n	1°: clinical response 2°: clinical remission, mucosal healing
Jiang 2015 [induction & maintenance]	123	MC, R, PC, DB, 3-arm/ 30 weeks (8-week induction)	Low*	TNFi-n (Chinese)	1°: clinical response 2°: clinical remission, mucosal healing
REMICADE [induction & maintenance]	99	P3, MC, R, PC, DB/ 26 weeks (8-week induction)	Low*	Prior TNFi NR[d] (Chinese)	1°: clinical response 2°: clinical remission, mucosal healing, sustained clinical response, sustained clinical remission
Kobayashi 2016 [induction & maintenance]	IP: 208 MP:NR	P3, MC, R, PC, DB/ 30 weeks, RWD for maintenance (8-week induction, 22-week maintenance)	Low	TNFi-n (Japanese) Maintenance: Wk8 responders	1°: clinical response 2°: clinical remission, mucosal healing
ADA v PBO					
ULTRA 1 [induction]	390	P3, MC, R, PC, DB/ 8 weeks	Low	TNFi-n	1°: clinical remission 2°: clinical response, mucosal healing
ULTRA 2 [induction & maintenance]	494	P3, MC, R, PC, DB/ 52 weeks (8-week induction)	Low*	TNFi-n & TNFi-e	1°: clinical remission 2°: clinical response, mucosal healing, IBDQ response, sustained clinical remission, sustained clinical response, sustained mucosal healing

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)
Suzuki 2014 [induction & maintenance]	273	P2/3, MC, R, PC, DB, 3-arm/ 52 weeks (8-week induction)	Low*	TNFi-n (Japanese)	1°: clinical remission 2°: clinical response, mucosal healing

Italics indicate results extracted during the evaluation.

Source: Table 2.3.4, p44 of the submission, Clinical study reports for Elevate UC 12 and Elevate UC 52, Table 1.1, Attachment 1 of the submission, Sandborn 2023, Sandborn 2021, Sandborn 2016, Table 4, p9, Tofacitinib PSD, November 2020 PBAC meeting.

1° = primary; 2° = secondary; 5-ASA = 5-aminosalicylates; ADA=adalimumab; DB=double blind; ETR = etrasimod; IBDQ = inflammatory bowel disease questionnaire; IFX=infliximab, IP=induction phase; MC=multi-centre; MP=maintenance phase; OL=open label; OZA = ozanimod; Px = phase x; PC= placebo-controlled R=randomised, RWD=randomised withdrawal design; TNFi-e=tumour necrosis factor inhibitor experience; TNFi-n= tumour necrosis factor inhibitor naïve.

* Low risk of bias in the induction phase, but high risk of bias during maintenance due to high attrition bias.

[a] treat-through design

[b] OZA responders re-randomised to OZA or PBO after induction period.

[c] Total study n=197, of which n=133 were randomised to either PBO or OZA 0.92 mg.

[d] Remicade inclusion criteria doesn't mention prior biologic treatment and no baseline characteristics were reported, but likely naïve patients given date of trial enrolment 2012-2014 prior to approval of other treatments in China.

6.7 The ELEVATE UC trials were similar to the comparator trials in terms of trial design with a few exceptions. For induction treatment, patients with MSUC were randomly assigned to active treatment or placebo with key outcomes measured at Week 12, and for maintenance treatment, the key ETR trial used a 'treat through' design where patients continued the same treatment for both the induction and maintenance phases, with outcomes measured week 52. The durations of treatment in both induction and maintenance treatment varied between trials (see above table for details), and two maintenance trials used a re-randomisation approach (in which patients who achieved a clinical response following active induction treatment were re-randomised to active or placebo for maintenance treatment). Overall, the risk of bias in the included RCTs was low for induction treatment, but the risk of bias for maintenance treatment was higher due to attrition rates of up to 50%.

6.8 The submission did not present an indirect comparison between ETR and OZA for maintenance treatment due to differences in trial design between ELEVATE UC 52 (treat through) and True North (responder re-randomisation), and differences in timing of outcomes between ELEVATE UC 52 (Week 52) and Touchstone (Week 32). The submission also excluded Suzuki 2014 from the indirect treatment comparison versus ADA for maintenance treatment without providing any rationale. Suzuki 2014 had been included in indirect treatment comparisons considered by the PBAC in past decisions for other b/tsDMARDs, but the trial only reported results for ADA maintenance treatment pooled across two ADA induction arms, in patients who received ADA 180 mg Week 0 then 80 mg Week 2 (approved dose) and ADA 80 mg Week 0 then 40 mg Week 2 (not approved dose).

6.9 The eligibility criteria across the trials were generally similar, as each trial recruited older adolescent or adult patients with MSUC but there were some notable differences across the trials that may reduce the exchangeability of the trials for the indirect treatment comparison:

- Patient age. The mean age was generally comparable across the ETR and OZA trials (range of means: 39 to 41 years), but varied more with younger patients across the IFX and ADA trials (range of means: 34 to 42 years).
- MSUC criteria. The mean full Mayo score was generally comparable across the ETR and OZA trials (range of means: 8.7 to 9.1), but varied more with slightly lower scores across the IFX and ADA trials (range of means: 8.0 to 8.9).
- Extent of disease and disease duration. The proportions of patients with left-sided colitis and pancolitis were generally similar across the ETR and OZA trials (approx. 60:40), but a higher proportion of patients had pancolitis in the ADA (approx. 40-70%) and IFX trials (approx. 40-80%). The ETR trials also enrolled some patients with proctitis (approx. 7%). The average duration of disease also similar between the ETR and OZA trials (range of means: 6-7 years), but varied more with slightly shorter durations across the IFX and ADA trials (range of means: 4 to 7 years).
- Prior treatment. Patients in the ETR trials must have had an inadequate response to or failed to tolerate at least one prior therapy (cDMARD, bDMARD or JAK inhibitor) but could have had prior treatment with up to three bDMARDs/JAK inhibitors, whereas the OZA trials did not recruit on the basis of failed response to any therapy and excluded patients with ≥ two prior bDMARDs/S1P receptor modulators (True North) or prior lymphocyte trafficking blockers (e.g. natalizumab, fingolimod) (Touchstone). Patients enrolled in the IFX and ADA trials must have had an inadequate response to or failed to tolerate prior cDMARDs but all patients were bDMARD naïve, with the exception of patients enrolled in the ULTRA 2 and possibly REMICADE (not reported, although the trial was conducted prior to the development / approval of other b/tsDMARDs).
- Concomitant therapies allowed during the study period. Use of 5-ASAs was similar across the ETR, OZA and IFX trials (67%-88%), however the ADA trials had the lowest and highest use (59% in Ultra 2 vs 92% in Suzuki 2014). The use of corticosteroids was lower in the ETR (32%-33%) and OZA (28%-49%) trials compared to the IFX (49%-80%) and ADA (55%-69%) trials. Stable doses of immunomodulators were allowed in the IFX and ADA trials and were used by 29% to 54% of participants, however, these drugs were not allowed in the ETR and OZA trials.

6.10 At the March 2022 PBAC meeting, the PBAC considered that patients enrolled in True North appeared to have less severe and less pre-treated disease, and only about half had failed or were intolerant to immunomodulators as required under the PBS eligibility criteria. The PBAC acknowledged the results of the indirect treatment comparisons between OZA and IFX should be interpreted with caution due to differences in recruited patients, but ultimately relied on the available evidence to assess the comparative effectiveness between OZA and IFX. The PBAC had considered that subgroup analyses showing similar results for patients in True North with 'no

moderate disease' and 'prior use/intolerance to immunomodulators' was informative (paragraphs 3.5, 7.7, 7.8, OZA PSD, March 2022 PBAC meeting).

Comparative effectiveness

6.11 The clinically relevant outcomes for MSUC are clinical remission (absence of symptoms) and clinical response (relative improvement in symptoms), as assessed using the Mayo score. The submission stated that clinical remission following induction treatment and sustained clinical remission (i.e. continued remission) following maintenance treatment were most aligned with the PBS continuation criteria.

6.12 Table 4 presents the key outcomes reported in the ELEVATE UC 12 and ELEVATE UC 52 for induction (Week 12) and maintenance treatment (Week 52), in the ITT population and subgroups by prior b/tsDMARD exposure. The results for the ITT population are based on the 'FAS+MMS 5-9' dataset whereas results by TNF exposure show outcomes based on the 'FAS' dataset (i.e. MMS 4-9).

Table 4: Key outcomes reported in ELEVATE UC 12 and ELEVATE UC 52 comparing ETR versus placebo, relevant arms only

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI)^	RD (95% CI)^	OR (95% CI)^
Clinical remission, Week 12					
ELEVATE UC 12, ITT	55/222 (24.8)	17/112 (15.2)	**1.63 (1.00,2.68)**	**0.10 (0.01,0.18)**	**1.84 (1.01,3.35)**
-ELEVATE UC 12, AT-n	46/159 (28.9)	12/77 (15.6)	**1.86 (1.05, 3.30)**	**0.13 (0.03, 0.24)**	**2.21 (1.09, 4.46)**
-ELEVATE UC 12, AT-e	16/79 (20.3)	5/39 (12.8)	1.58 (0.62, 4.00)	0.07 (-0.06, 0.21)	1.73 (0.58, 5.12)
ELEVATE UC 52, ITT	74/274 (27.0)	10/135 (7.4)	**3.65 (1.95,6.83)**	**0.20 (0.13,0.26)**	**4.63 (2.30,9.29)**
-ELEVATE UC 52, AT-n	66/205 (32.2)	9/99 (9.1)	**3.54 (1.84, 6.81)**	**0.23 (0.15, 0.32)**	**4.75 (2.25, 10.00)**
-ELEVATE UC 52, AT-e	15/84 (17.9)	3/45 (75.0)	2.68 (0.82, 8.77)	0.11 (0.00, 0.22)	3.04 (0.83, 11.14)
Meta, ITT	129/496 (26.0)	27/247 (10.9)	**2.38 (1.07,5.30)**	**0.15 (0.05,0.25)**	**2.87 (1.16,7.10)**
Meta, AT-n	112/364 (30.8)	21/176 (11.9)	**2.52 (1.33, 4.76)**	**0.19 (0.09, 0.28)**	**3.20 (1.51, 6.81)**
Meta, AT-e	31/163 (19.0)	8/84 (9.5)	1.93 (0.93, 4.01)	**0.10 (0.01, 0.18)**	2.18 (0.95, 5.02)
Clinical response, Week 12					
ELEVATE UC 12, ITT	138/222 (62.2)	46/112 (41.1)	**1.51 (1.19,1.93)**	**0.21 (0.10,0.32)**	**2.36 (1.48,3.75)**
-ELEVATE UC 12, AT-n	105/159 (66.0)	33/77 (42.9)	**1.54 (1.16, 2.04)**	**0.23 (0.10, 0.36)**	**2.59 (1.48, 4.53)**
-ELEVATE UC 12, AT-e	46/79 (58.2)	15/39 (38.5)	1.51 (0.98, 2.35)	**0.20 (0.01, 0.39)**	**2.23 (1.02, 4.89)**
ELEVATE UC 52, ITT	171/274 (62.4)	46/135 (34.1)	**1.83 (1.42,2.36)**	**0.28 (0.18,0.38)**	**3.21 (2.09,4.95)**
-ELEVATE UC 52, AT-n	141/205 (68.8)	39/99 (39.4)	**1.75 (1.34,2.27)**	**0.29 (0.18, 0.41)**	**3.39 (2.05, 5.59)**
-ELEVATE UC 52, AT-e	41/84 (48.8)	13/45 (28.9)	**1.69 (1.02, 2.81)**	**0.20 (0.03, 0.37)**	**2.35 (1.08, 5.09)**
Meta, ITT	309/496 (62.3)	92/247 (37.2)	**1.66 (1.38,2.00)**	**0.25 (0.18,0.33)**	**2.78 (2.03,3.82)**
Meta, AT-n	246/364 (67.6)	72/176 (40.9)	**1.65 (1.36, 2.00)**	**0.27 (0.18, 0.35)**	**3.01 (2.07, 4.37)**
Meta, AT-e	87/163 (53.4)	28/84 (33.3)	**1.59 (1.14, 2.21)**	**0.20 (0.07, 0.32)**	**2.29 (1.32, 3.97)**
Clinical remission, Week 52					
ELEVATE UC 52, ITT	88/274 (32.1)	9/135 (6.7)	**4.82 (2.50,9.27)**	**0.25 (0.19,0.32)**	**6.62 (3.22,13.64)**
-ELEVATE UC 52, AT-n	75/205 (36.6)	8/99 (8.1)	**4.53 (2.27,9.01)**	**0.29 (0.20,0.37)**	**6.56 (3.02,14.27)**
-ELEVATE UC 52, AT-e	19/84 (22.6)	3/45 (6.7)	**3.39 (1.06,10.85)**	**0.16 (0.04,0.27)**	**4.09 (1.14,14.69)**
Clinical response, Week 52					
ELEVATE UC 52, ITT	132/274 (48.4)	31/135 (23.0)	**2.10 (1.50,2.93)**	**0.25 (0.16,0.34)**	**3.12 (1.96,4.97)**
-ELEVATE UC 52, AT-n	111/205 (54.1)	28/99 (28.3)	**1.91 (1.37,2.68)**	**0.26 (0.15,0.37)**	**2.99 (1.79,5.02)**
-ELEVATE UC 52, AT-e	32/84 (38.1)	7/45 (15.6)	**2.45 (1.18,5.10)**	**0.23 (0.08,0.37)**	**3.34 (1.33,8.37)**
Sustained clinical remission, Week 52 | Week 12					
ELEVATE UC 52, ITT	49/274 (17.9)	3/135 (2.2)	**8.05 (2.55,25.35)**	**0.16 (0.10,0.21)**	**9.58 (2.93,31.35)**
-ELEVATE UC 52, AT-n	45/205 (22.0)	2/99 (2.0)	**10.87 (2.69,43.88)**	**0.20 (0.14,0.26)**	**13.64 (3.24,57.50)**
-ELEVATE UC 52, TNFi-e	9/84 (10.7)	2/45 (4.4)	2.41 (0.54,10.68)	0.06 (-0.03,0.15)	2.58 (0.53,12.49)
Sustained clinical response, Week 52 | Week 12					
ELEVATE UC 52, ITT	123/274 (44.9)	25/135 (18.5)	**2.42 (1.66,3.54)**	**0.26 (0.18,0.35)**	**3.58 (2.18,5.88)**
-ELEVATE UC 52, AT-n	106/205 (51.7)	22/99 (22.2)	**2.33 (1.57,3.44)**	**0.29 (0.19,0.40)**	**3.75 (2.17,6.48)**
-ELEVATE UC 52, TNFi-e	26/84 (31.0)	7/45 (15.6)	1.99 (0.94,4.22)	**0.15 (0.01,0.30)**	2.43 (0.96,6.16)

Source: Tables 2.5.2, 2.5.3, 2.5.5, 2.5.6, 2.6.1, 2.6.2, 2.6.3, 2.6.4, pp57-61 and pp70-74 of the submission.

AT-n = advanced therapy naïve (biologic or targeted synthetic disease modifying anti-rheumatic drugs); AT-e = advanced therapy experienced (biologic or targeted synthetic disease modifying anti-rheumatic drugs); ITT = intention to treat TNFi = tumour necrosis factor inhibitor; TNFi-e = TFNi experienced.

6.13 The results show ETR was more effective than placebo for clinical response and clinical remission at Weeks 12 and 52, as well as sustained clinical response and sustained clinical remission at Week 52. The subgroup analyses by prior b/tsDMARD exposure were not powered to detect differences between ETR and placebo, but the submission argued that evidence suggests that ETR was efficacious in both b/tsDMARD naïve and experienced patients.

6.14 To compare the effectiveness of ETR versus the nominated comparators, the submission conducted a series of anchored indirect treatment comparisons using

placebo as the common comparator. For induction treatment, the submission compared ETR versus OZA, IFX and ADA in terms of clinical remission and clinical response. For maintenance treatment, the submission compared ETR versus IFX and ADA in terms of clinical remission, clinical response, sustained clinical remission and sustained clinical response. The outcomes were measured at slightly different time points across the trials for induction treatment (Week 8 to 12) and maintenance treatment (Week 52 to 54), and used slightly different outcome definitions based on either the FMS (OZA, IFX and ADA trials) or MMS (ETR trials). The submission did not nominate a non-inferiority margin for any outcome. The PBAC has not previously accepted a non-inferiority margin for MSUC (paragraph 6.17, OZA PSD, November 2022 PBAC meeting).

6.15 The submission conducted the indirect comparisons using the ITT population for all outcomes, as well as by prior b/tsDMARD exposure in the sustained clinical remission and sustained clinical response outcomes. The submission noted that the IFX and ADA trials were conducted in mostly TNF naïve patients as these were the first treatments developed. It was unclear why the submission conducted the indirect treatment comparisons by b/tsDMARD exposure for only two of the six outcomes. Furthermore, the PBAC has previously considered subgroup analyses by prior b/tsDMARD exposure were problematic due to reduced statistical power and because the comparisons in TNF experienced patients may not be a fair representation of comparative efficacy when comparing TNF inhibitor versus a drug of another class (paragraph 6.17, UPA PSD, July 2022 PBAC meeting).

6.16 Table 5 presents results of the indirect treatment comparisons for clinical response and clinical remission outcomes following induction treatment (Week 8-12) and maintenance treatment (Week 52-54). For completeness, the following sensitivity analyses were conducted during the evaluation:

- indirect treatment comparisons by prior b/tsDMARD exposure for clinical response and clinical remission outcomes following induction and maintenance treatment, where there was available data.
- Indirect treatment comparison versus ADA for induction treatment incorporating data from the HIBISCUS trials, where there was available data.
- Indirect treatment comparisons versus ADA for maintenance treatment incorporating data from the Suzuki 2014, where there was available data.

Table 5: Results of the indirect treatment comparisons comparing ETR versus OZA, IFX and ADA across the key outcomes clinical remission and clinical response

	RR (95% CI)^	RD (95% CI)^	OR (95% CI)^
ETR versus OZA			
Clinical remission at Weeks 8-12			
ETR (Meta, ITT) vs OZA (Meta, ITT)	0.93 (0.35,2.48)	0.08 (-0.03,0.19)	1.03 (0.35,3.06)
Clinical response at Weeks 8-12			
ETR (Meta, ITT) vs OZA (Meta, ITT)	0.90 (0.65,1.25)	0.00 (-0.10,0.10)	0.95 (0.61,1.49)
ETR versus IFX			
Clinical remission at Weeks 8-12			
ETR (Meta, ITT) vs IFX (Meta, ITT/TNFi-n)	0.88 (0.36,2.10)	-0.05 (-0.18,0.08)	0.77 (0.28,2.13)
ETR (Meta, AT-n) vs IFX (Meta, ITT/TNFi-n)	0.93 (0.45, 1.92)	-0.01 (-0.14, 0.12)	0.86 (0.36, 2.08)
Clinical response at Weeks 8-12			
ETR (Meta, ITT) vs IFX (Meta, ITT/TNFi-n)	0.89 (0.71,1.13)	-0.05 (-0.15,0.05)	0.80 (0.51,1.25)
ETR (Meta, AT-n) vs IFX (Meta, ITT/TNFi-n)	0.89 (0.67, 1.18)	-0.03 (-0.14, 0.08)	0.86 (0.53, 1.42)
Clinical remission at Weeks 52-54			
ETR (ELEVATE UC 52, ITT) v IFX (ACT 1, ITT)	**2.30 (1.02,5.14)**	0.07 (-0.06,0.20)	2.47 (0.96,6.35)
ETR (ELEVATE UC 52, AT-n) vs IFX (ACT 1, ITT/TNFi-n)	2.16 (0.94, 4.97)	0.11 (-0.03, 0.25)	2.45 (0.91, 6.56)
Clinical response at Weeks 52-54			
ETR (ELEVATE UC 52, ITT) v IFX (ACT 1, ITT/TNFi-n)	0.92 (0.54,1.56)	-0.01 (-0.16,0.14)	0.93 (0.44,1.94)
ETR (ELEVATE UC 52, AT-n) vs IFX (ACT 1, ITT/TNFi-n)	0.83 (0.49, 1.42)	0.00 (-0.16, 0.16)	0.89 (0.41, 1.92)
Sustained clinical remission at Weeks 52-54			
ETR (ELEVATE UC 52, ITT) v IFX (ACT 1, ITT/TNFi-n)	2.68 (0.68,10.64)	0.03 (-0.07,0.13)	2.74 (0.64,11.77)
ETR (ELEVATE UC 52, AT-n) v IFX (ACT 1, ITT/TNFi-n)	3.62 (0.74,17.76)	0.07 (-0.03,0.17)	3.91 (0.74,20.73)
Sustained clinical response at Weeks 52-54			
ETR (ELEVATE UC 52, ITT) v IFX (ACT 1, ITT)	0.88 (0.47,1.63)	0.01 (-0.13, 0.15)	0.92 (0.41, 2.05)
ETR (ELEVATE UC 52, AT-n) v IFX (ACT 1, ITT/AT-n)	0.84 (0.45,1.59)	0.04 (-0.11, 0.19)	0.96 (0.42, 2.22)
ETR versus ADA			
Clinical remission at Weeks 8-12			
ETR (Meta, ITT) vs ADA (Meta, ITT)	1.51 (0.61,3.71)	0.1 (-0.01,0.21)	1.70 (0.61,4.74)
ETR (Meta, ITT) vs ADA (Meta incl HIBISCUS, ITT)	1.27 (0.30, 5.35)	0.07 (-0.05, 0.19)	1.45 (0.53, 3.99)
ETR (Meta, AT-n) vs ADA (Meta, TNFi-n)	1.56 (0.71, 3.42)	**0.13 (0.02, 0.24)**	1.84 (0.73, 4.66)
ETR (Meta, AT-n) vs ADA (Meta incl HIBISCUS, TNFi-n)	1.35 (0.64, 2.87)	0.11 (-0.01, 0.23)	1.56 (0.64, 3.79)
ETR (Meta, AT-e) vs ADA (ULTRA 2, TNFi-e)	1.45 (0.44, 4.82)	0.08 (-0.03, 0.19)	1.60 (0.43, 6.00)
Clinical response at Weeks 8-12			
ETR (Meta, ITT) vs ADA (Meta, ITT)	1.22 (0.96,1.55)	**0.11 (0.01,0.21)**	**1.57 (1.04,2.36)**
ETR (Meta, ITT) vs ADA (Meta incl HIBISCUS, ITT)	**1.27 (1.01, 1.58)**	**0.12 (0.03, 0.21)**	**1.67 (1.14, 2.46)**
ETR (Meta, AT-n) vs ADA (Meta, TNFi-n)	1.20 (0.93, 1.53)	**0.12 (0.01, 0.23)**	1.61 (1.00, 2.59)
ETR (Meta, AT-n) vs ADA (Meta incl HIBISCUS, TNFi-n)	1.25 (0.99, 1.57)	**0.14 (0.04, 0.24)**	**1.77 (1.14, 2.76)**
ETR (Meta, AT-e) vs ADA (ULTRA 2, TNFi-e)	1.24 (0.74, 2.09)	0.12 (-0.06, 0.30)	1.59 (0.71, 3.58)
Clinical remission at Weeks 52			
ETR (ELEVATE UC 52, ITT) v ADA (ULTRA 2)	**2.43 (1.07,5.53)**	**0.17 (0.08,0.26)**	**3.04 (1.22,7.56)**
ETR (ELEVATE UC 52, ITT) v ADA (Meta incl Suzuki, ITT)	2.10 (0.96,4.60)	**0.13 (0.03,0.23)**	**2.51 (1.03,6.12)**
ETR (ELEVATE UC 52, AT-n) v ADA (Meta incl Suzuki, TNFi-n)	2.04 (0.84,4.98)	**0.16 (0.06, 0.26)**	2.53 (0.93, 6.90)
ETR (ELEVATE UC 52, AT-e) vs ADA (ULTRA 2, TNFi-e)	0.99 (0.18, 5.48)	0.09 (-0.04, 0.22)	1.10 (0.18, 6.93)
Clinical response at Weeks 52			
ETR (ELEVATE UC 52, ITT) v ADA (ULTRA 2, ITT)	1.27 (0.80,2.03)	**0.13 (0.01,0.25)**	1.61 (0.86,3.01)
ETR (ELEVATE UC 52, ITT) v ADA (Meta incl Suzuki, ITT)	1.25 (0.81,1.92)	**0.13 (0.02,0.24)**	1.57 (0.88,2.80)
ETR (ELEVATE UC 52, AT-n) v ADA (Meta incl Suzuki, TNFi-n)	1.19 (0.77, 1.86)	0.13 (0.00, 0.26)	1.62 (0.88, 2.97)
ETR (ELEVATE UC 52, AT-e) vs ADA (ULTRA 2, TNFi-e)	1.19 (0.43, 3.29)	0.12 (-0.05, 0.29)	1.43 (0.42, 4.91)
Sustained clinical remission at Weeks 52			
ETR (ELEVATE UC 52, ITT) v ADA (ULTRA 2, ITT)	3.87 (0.99,15.11)	**0.12 (0.05,0.19)**	**4.39 (1.07,18.09)**
ETR (ELEVATE UC 52, AT-n) v ADA (ULTRA 2, TNFi-n)	**6.32 (1.27,31.37)**	**0.16 (0.07,0.25)**	**7.58 (1.43,40.29)**
ETR (ELEVATE UC 52, AT-e) v ADA (ULTRA 2, TNFi-e)	0.47 (0.03,6.31)	0.02 (-0.13,0.17)	0.48 (0.03,6.98)

	RR (95% CI)^	RD (95% CI)^	OR (95% CI)^
Sustained clinical response at Weeks 52			
ETR (ELEVATE UC 52, ITT) v ADA (ULTRA 2, ITT)	1.24 (0.71,2.16)	**0.14 (0.03, 0.25)**	1.59 (0.80, 3.18)
ETR (ELEVATE UC 52, AT-n) v ADA (UTLRA 2, TNFi-n)	1.32 (0.73,2.38)	**0.16 (0.02, 0.30)**	1.79 (0.82, 3.93)
ETR (ELEVATE UC 52, AT-e) v ADA (ULTRA 2, TNFi-e)	0.77 (0.24,2.50)	0.06 (-0.11, 0.23)	0.85 (0.22, 3.31)

Source: Tables 2.6.19, 2.6.20, 2.6.21, 2.6.22, 2.6.23, 2.6.24, 2.6.25, 2.6.26, pp90-99 of the submission

ADA = adalimumab; AT-n = advanced therapy naïve (biologic or targeted synthetic disease modifying anti-rheumatic drugs); AT-e = advanced therapy experienced (biologic or targeted synthetic disease modifying anti-rheumatic drugs); ETR = etrasimod; IFX = infliximab; ITT = intention to treat; Meta = meta-analysis; OZA = ozanimod; TNFi = tumour necrosis factor inhibitor; TNFi-e = TNFi-experienced; TNFi-n = TNFi-naïve.

Note that the results presented in Table 5 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for any of the studies presented in the submission. 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.

6.17 For comparisons between ETR versus OZA, there were no statistically significant differences between the two treatments for clinical remission or clinical response following induction treatment.

6.18 For comparisons between ETR versus IFX, there were no statistically significant differences between the two treatments for clinical remission or clinical response following induction treatment or maintenance treatment, with the exception of the relative risk statistic for clinical remission at Week 52-54 favouring IFX.

6.19 For comparisons between ETR versus ADA, the results were mixed and either favoured ETR or showed no statistically significant difference between the two treatments depending on the outcome. For induction therapy, the results in the ITT population generally favoured ETR in terms of clinical response but showed no difference in terms of clinical remission. For maintenance therapy, the results in the ITT population generally favoured ETR in terms of clinical remission or sustained clinical remission but showed no difference in terms of clinical response or sustained clinical response with the exception of the risk difference statistic. The submission also noted that most of the point estimates numerically favoured ETR over ADA even if they did not reach statistical significance.

6.20 The ESC considered the indirect treatment comparisons versus ADA were associated with inherent uncertainty, however considered there was a general trend towards results favouring ETR over ADA, but with statistical significance only demonstrated in some comparisons.

Comparative harms

6.21 The submission presented a side by side comparison of adverse events reported in the ETR and OZA trials, summarised in Table 6 for induction therapy and Table 7 for maintenance treatment. Given S1P receptor modulators inhibit lymphocyte trafficking from lymph nodes and have an important regulatory function in the cardiovascular system, adverse events of special interest focus on infection and cardiovascular effects.

Table 6: Adverse events reported in the induction phase

	ELEVATE UC 12 (Wk 12)		True North (Wk 10)		
	ETR 2 mg N=238	PBO N=116	OZA 0.92 mg (cohort 1), N=429	PBO N=216	OZA 0.92 mg (cohort 2), N=367
Summary outcomes, n (%)					
Any TEAE	112 (47.1)	54 (46.6)	172 (40.1)	82 (38.0)	146 (39.8)
Related TEAEs	30 (12.6)	8 (6.9)	93 (11.7)^	17 (7.9)	-
Any serious TEAE	6 (2.5)	2 (1.7)	17 (4.0)	7 (3.2)	23 (6.3)
Related Serious TEAEs	0	0	1 (0.2)	2 (0.9)	3 (0.8)
TEAEs leading to death	0	0	1 (0.1)^	0	-
Any TEAE resulting in disc.	13 (5.5)	1 (0.9)	14 (3.3)	7 (3.2)	14 (3.8)
Most common TEAEs (>3% in ETR arm), n (%)					
Anaemia	14 (5.9)	8 (6.9)	18 (4.2)	12 (5.6)	16 (4.4)
Headache	11 (4.6)	2 (1.7)	14 (3.3)	4 (1.9)	10 (2.7)
Nausea	10 (4.2)	2 (1.7)	NR	NR	NR
Colitis ulcerative	9 (3.8)	1 (0.9)	NR	NR	NR
Pyrexia	8 (3.4)	3 (2.6)	NR	NR	NR
TEAEs of special interest, n (%)					
Serious Infection	0	0	4 (0.9)	1 (0.5)	6 (1.6)
Herpes Zoster	0	2 (1.7)	2 (0.5)	0	1 (0.3)
Opportunistic infections	1 (0.4)	0	NR	NR	NR
Hypertension	4 (1.7)	2 (1.7)	6 (1.4)	0	7 (1.9)
Bradycardia	3 (1.3)	0	2 (0.5)	0	3 (0.8)
AV conduction delay	0	1 (0.4)	NR	NR	NR

Source: Table 2.5.7, pp64-65 of the submission

Disc = discontinuation; ETR = etrasimod; OZA = ozanimod; PBO = placebo; TEAE = treatment emergent adverse event.

^ result pooled across cohort 1 and cohort 2

Table 7: Adverse events reported in the maintenance phase

	ELEVATE UC 52 (Wk 52)		Touchstone (Wk 32)		True North (Wk 52)		
	ETR 2 mg N=289	PBO N=144	OZA 0.92 mg N=67	PBO N=65	OZA 0.92 mg-OZA 0.92 mg N=230	OZA 0.92 mg-PBO N=227	PBO^ N=69
Summary outcomes, n (%)							
Any TEAE	206 (71.3)	81 (56.3)	26 (38.8)	26 (40.0)	113 (49.1)	83 (36.6)	27 (39.1)
Related TEAEs	46 (15.9)	12 (8.3)	NR	NR	27 (11.7)	12 (5.3)	2 (2.9)
Any serious TEAE	20 (6.9)	9 (6.3)	3 (4.5)	6 (9.2)	12 (5.2)	18 (7.9)	4 (5.8)
Related Serious TEAEs	1 (0.3)	1 (0.7)	NR	NR	0	1 (0.4)	1 (1.4)
TEAEs leading to Death	0	0	NR	NR	0	0	0
Any TEAE resulting in disc.	12 (4.2)	7 (4.9)	1 (1.5)	4 (6.2)	3 (1.3)	6 (2.6)	0
Most frequent AE (>3% in ETR arm), n (%)							
Anaemia	24 (8.3)	14 (9.7)	0	4 (6.2)	3 (1.3)	4 (1.8)	NR
Headache	24 (8.3)	7 (4.9)	2 (3.0)	3 (4.6)	8 (3.5)	1 (0.4)	NR
Colitis ulcerative	22 (7.6)	13 (9.0)	3 (4.5)	5 (7.7)	NR	NR	NR
COVID-19	20 (6.9)	9 (6.3)	NR	NR	NR	NR	NR
Dizziness	15 (5.2)	1 (0.7)	NR	NR	NR	NR	NR
Pyrexia	14 (4.8)	6 (4.2)	3 (4.5)	0	NR	NR	NR
Arthralgia	13 (4.5)	3 (2.1)	2 (3.0)	1 (1.5)	NR	NR	NR
Abdominal pain	11 (3.8)	5 (3.5)	1 (1.5)	1 (1.5)	NR	NR	NR
Nausea	9 (3.1)	2 (1.4)	2 (3.0)	2 (3.1)	NR	NR	NR
TEAE of special interest, n (%)							
Serious Infection	3 (1.0)	5 (3.5)	NR	NR	2 (0.9)	4 (1.8)	NR
Herpes Zoster	2 (0.7)	0	NR	NR	5 (2.2)	1 (0.4)	NR
Opportunistic infections	0	1 (0.7)	NR	NR	NR	NR	NR
Hypertension	9 (3.1)	0	NR	NR	4 (1.7)	3 (1.3)	NR
Bradycardia	1 (0.3)	0	NR	NR	0	0	NR
AV conduction delay	2 (0.7)	0	NR	NR	NR	NR	NR

Source: Table 2.5.8, pp67-68 of the submission

Disc = discontinuation; ETR = etrasimod; OZA = ozanimod; PBO = placebo; TEAE = treatment emergent adverse event.

^ Patients who were responders to PBO during induction who continued blinded PBO during maintenance.

6.22 For induction treatment, the incidence of any TEAEs was similar with ETR (47.1%) compared to placebo (46.6%) and the proportion of patients with any serious TEAE was low. The most common adverse events reported for ETR included anaemia, headache and nausea. The submission stated that adverse events with ETR reported in ELEVATE UC 12 were generally similar to OZA reported in True North, despite some differences.

6.23 For maintenance treatment, the incidence of any TEAEs was higher with ETR (71.3%) compared to placebo (56.3%) but the proportion of patients with any serious TEAE remained relatively low. There were two grade 4 (i.e. life threatening) adverse events reported in ELEVATE UC 52 including one case of lymphopenia with ETR and one case of increased Alanine aminotransferase with placebo. The submission cautioned against comparing results between ELEVATE UC 52 (treat through) and True North (randomised withdrawal) due to differences in trial design.

Benefits/harms

6.24 There were no expected clinically meaningful differences between ETR versus OZA, IFX and ADA in terms of safety and no expected clinically meaningful differences between ETR versus OZA and IFX in terms of effectiveness. Compared to ADA, the indirect evidence suggested that for every 100 adults treated:

- approximately 11 additional patients would achieve clinical response following induction treatment with ETR. There was no difference in the number of patients who would achieve clinical remission following induction treatment, which more closely aligns with the PBS continuation criteria.
- approximately 12 additional patients with clinical remission following induction treatment would maintain clinical remission to one year with ETR.

Clinical claim

6.25 Based on the results from the indirect treatment comparisons, the submission described ETR as having non-inferior effectiveness and non-inferior safety versus OZA and IFX, and superior effectiveness and non-inferior safety versus ADA.

6.26 Notwithstanding that potential transitivity issues may impact the reliability of the indirect treatment comparisons, the evaluation and ESC considered the results of the indirect treatment comparisons presented in the submission reasonably supported the clinical claim of non-inferior effectiveness versus OZA and IFX and non-inferior safety versus OZA, IFX and ADA. On balance, the evaluation considered the claim of superior effectiveness versus ADA was also likely to be reasonable. Although the results showed no statistically significant differences between ETR and ADA for some outcomes, the evaluation considered ETR was generally superior to ADA in terms of clinical response following induction treatment and in terms of clinical remission / sustained clinical remission following maintenance treatment.

6.27 The PSCR reiterated the evidence supported the claim of superiority over adalimumab and noted NICE in the UK had reached a similar conclusion[3].

6.28 The ESC considered that, overall, the evidence was mixed and a claim of superior comparative effectiveness over ADA was uncertain. The Pre-PBAC Response argued that while not all measures presented in the submission were statistically significant for all outcomes, the results clearly favoured ETR over ADA for all outcomes and no statistics favoured ADA for any comparison.

6.29 The PBAC considered that the claim of non-inferior comparative effectiveness to OZA and IFX was reasonable and superior comparative effectiveness to ADA was, on balance, likely to be reasonable.

6.30 The PBAC considered that the claim of non-inferior comparative safety to OZA, IFX and

[3] https://www.nice.org.uk/guidance/indevelopment/gid-ta10991

ADA was reasonable.

Economic analysis

6.31 The submission presented a cost-minimisation approach between ETR versus OZA, based on published AEMP of OZA because the effective AEMP was unknown to the sponsor. The submission stated that the calculations would need to be updated during the post-PBAC process using the effective AEMP of OZA following a positive recommendation for listing. The submission nominated the following equi-effective doses were based on the recommended doses:

- ETR 2 mg orally daily;
- OZA 0.23 mg orally daily for four days, then OZA 0.46 mg orally daily for three days, then OZA 0.92 mg orally daily thereafter.

6.32 Table 8 presents the results of the cost-minimisation approach presented in the submission, based on the following assumptions:

- Equivalent total costs for ETR and OZA over the first two years (104 weeks) of treatment at the nominated equi-effective doses, corresponding to 26 packs of ETR and 26.75 packs of OZA (1 titration pack plus 25.75 post-titration packs).
- No additional costs or cost offsets associated with administration, monitoring or adverse events, as both ETR and OZA are orally administered treatments with similar safety profiles. An electrocardiogram is recommended prior to initiation with both ETR and OZA, therefore the cost was omitted.
- The published AEMP for OZA (titration pack: $514.57; post-titration pack: $2,058.29).

Table 8: Results of the cost-minimisation approach based on the published AEMP of OZA

Component	ETR	OZA	
		Titration pack	Post-titration pack
PBS item (max qty)	2 mg tablet (28)	0.23 mg capsule (4) & 0.46 mg capsule (3)	0.92 mg capsule (28)
AEMP	$[redacted]	$514.57	$2,058.29
Units over 104 weeks (packs)	26	1	25.75
PBS costs	$[redacted]	$514.57	$53,000.97
Total / 104 weeks	$[redacted]	$53,515.54	

Source: Section 3.4.1, p107 of the submission and the Cost-Min workbook.xlsx file supplied by the submission.
AEMP = approved ex-manufacturer price; ETR = etrasimod; max = maximum; OZA = ozanimod; PBS = Pharmaceutical Benefits Scheme; qty = quantity.

ETR cost/patient/year: $[redacted]

6.33 Assuming a DPMQ of $[redacted] (the requested published price) and 13 scripts required for the first year of treatment, inclusive of initial and continuing treatment with ETR 2 mg once daily, the cost per patient is $[redacted].

Estimated PBS usage & financial implications

6.34 This submission was not considered by DUSC. The submission used a market share approach to estimate the financial implications to the health budget for the proposed listing of ETR, including an incremental cost associated with the treatment of < 500 grandfather patients to be enrolled in a patient familiarisation program. The analysis used published DPMQs because the sponsor was not aware of the confidential effective prices of substituted treatments.

6.35 The submission estimated the size of the market over the first six years of listing based on scripts dispensed for all PBS-listed b/tsDMARDs (ADA, GOL, IFX, OZA, TOF, UPA, UST, VDZ) between Jan 2018 to Dec 2022, but assumed that ETR would only substitute for OZA, VDZ, IFX, ADA, UST and GOL (no substitution with oral treatments TOF or UPA). The submission also assumed that the proposed listing of ETR would not influence the current market growth rate, with the exception of< 500 patients enrolled in a patient familiarisation scheme (whom the submission assumed would not be captured in the current market estimates at the anticipated listing date). The evaluation considered this may not be reasonable as an unclear proportion of patients in the scheme would likely otherwise been treated with an alternative PBS subsidised b/tsDMARD.

6.36 Table 9 summarises the key inputs in the financial estimates.

Table 9: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value, source and comments
Current market, market growth	To estimate the size of the current market over the first six years of the proposed listing (2024 to 2029), the submission fitted a linear trend to scripts dispensed for current treatments (ADA, GOL, IFX, OZA, TOF, UPA, UST, VDZ) from Jan 2018 to Dec 2022. For treatments listed before 2018 (ADA, GOL, IFX and VDZ), the submission used an individual linear trend for each treatment; for other more recent treatments (OZA, TOF, UPA and UST), the submission used the total market trend. The approach was reasonable; however, there was an error in estimating scripts for OZA, TOF, UPA and UST. For these recently listed treatments, the submission applied the assumed growth rate to scripts dispensed in a partial year (Jan-Aug 2023) rather than a full year of data. Instead, the submission could have inflated the estimates for the partial year to account for the number of months with data and then applied the market growth rates thereafter.
% current treatment for patients ≥16 years	ADA and IFX IV are indicated for patients ≥6 years, and other treatments (GOL, IFX SC, OZA, TOF, UPA, UST, VDZ) are indicated for patients ≥18 years. Given the proposed ETR indication is for patients ≥16 years, ETR would not substitute for ADA and IFX IV scripts dispensed to patients <16 years. Based on the 1:10 PBS data, the submission estimated that 95% of ADA and 96% of IFX IV is used by patients ≥16 years. This was reasonable, although listing a third treatment for patients aged 16-17 years may potentially increase the number of adolescent patients on any treatment (i.e. size of the market) due to ETR being an oral treatment option.

<table>
<tr><th>Data</th><th>Value, source and comments</th></tr>
<tr><td>Substitution rate / Uptake rate</td><td>The submission argued that ETR would be more likely to substitute for OZA (the same mechanism of action), followed by VDZ (the most widely used treatment) and then in decreasing order IFX, ADA, UST and GOL. The submission assumed ETR would not substitute for TOF or UPA (i.e. JAK inhibitors). The assumed substitution rates are presented below, corresponding to ETR achieving an overall market share of [redacted]% in Year 1 increasing to [redacted]% in Year 6. The submission did not adequately justify why ETR would not substitute for TOF or UPA. There was also a programming error identified in the spreadsheet, whereby the substitution rate assumed for UST was applied to item number for UPA (13265E), see cells E643:J643 in 'scrips-market' tab.
<table>
<tr><th></th><th>2024</th><th>2025</th><th>2026</th><th>2027</th><th>2028</th><th>2029</th></tr>
<tr><td>ADA</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td></tr>
<tr><td>GOL</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td></tr>
<tr><td>IFX</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td></tr>
<tr><td>OZA</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td></tr>
<tr><td>TOF</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td></tr>
<tr><td>UPA</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td></tr>
<tr><td>UST</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td></tr>
<tr><td>VDZ</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td><td>[redacted]%</td></tr>
</table>
Source: Table 4.2.4, p116 of the submission</td></tr>
<tr><td>Grandfathered patients</td><td>The submission estimated there would be approximately < 500 grandfather patients on the anticipated date of PBS listing in 2024, who would be receiving ETR through a patient familiarisation programme. The submission assumed these patients would not be captured in the estimates for the current market and calculated incremental costs for these patients. The submission applied a 10% discontinuation rate and 85% compliance rate to estimate the number of grandfather patients remaining on treatment in the first six years of the proposed listing. The evaluation considered this may not be reasonable as an unclear proportion of patients in the scheme would likely otherwise been treated with an alternative b/tsDMARD.</td></tr>
<tr><td>Script equivalence</td><td>The submission stated that script equivalence between ETR and the comparators were based on the dosages for induction and maintenance, summarised in the table below. The submission did not provide any further explanation of how the script equivalences were calculated and there were several errors identified with the submission's approach. For ADA 40 mg, the script equivalence for 40 mg x 2 injection initial treatment scripts should be 1 rather than 0.33. For ADA 20 mg, the script equivalence should be the same as the 40 mg formulation. For GOL, the script equivalence for 100 mg x 1 injection initial treatment scripts should be 1 rather than 0.33. For IFX initial treatment, patients require 3 x IV infusions for 14 weeks of treatment, and hence it was unclear why each IV script was assumed to only provide 2 weeks (i.e. script equivalence of 0.5). For IFX continuing treatment, patients require 1 infusion every 8 weeks at 5mg/kg. For VDZ initial treatment, patients require 3x IV infusions for 14 weeks of treatment. For VDZ continuing treatment, the submission assumed none of the IV scripts would be used for continuing treatment despite being listed for both initial and continuing treatment.
<table>
<tr><th></th><th>Initiating</th><th>Continuing</th></tr>
<tr><td>ETR</td><td>2 mg x 28 tablets (4 weeks)</td><td>2 mg x 28 tablets (4 weeks^)</td></tr>
<tr><td>ADA</td><td>20 mg x 2 injection (0.66 weeks^): 0.17
40 mg x 2 injection (1.33 weeks^): 0.33
40 mg x 6 injection (4 weeks^): 1.0
80 mg x 3 injection (4 weeks^): 1.0</td><td>20 mg x 2 injection (2 weeks^): 0.5
40 mg x 2 injection (4 weeks^): 1.0</td></tr>
<tr><td>GOL</td><td>100 mg/mL x 3 injection (4 weeks^): 1
100 mg/mL x 1 injection (1.33 weeks^): 0.33</td><td>100 mg/mL x 1 injection (4 weeks^): 1</td></tr>
<tr><td>IFX</td><td>100 mg/mL x 1 infusion (2 weeks^): 0.50
120 mg/mL x 2 injection (4 weeks^): 1</td><td>100 mg/mL x 1 infusion (8 weeks^): 2
100 mg/mL x 5 infusion (40 weeks^): 10
120 mg/mL x 2 injection (4 weeks^): 1</td></tr>
<tr><td>OZA</td><td>230 mcg x 4, 460 mcg x 3 capsules (1 week^): 0.25
920 mcg x 28 capsules (4 weeks^): 1</td><td>920 mcg x 28 capsules (4 weeks^): 1</td></tr>
</table></td></tr>
</table>

Data	Value, source and comments		
	TOF	5mg x 56 tablets (4 weeks^): 1 10 mg x 56 tablets (4 weeks^): 1	5mg x 56 tablets (4 weeks^): 1 10 mg x 56 tablets (4 weeks^): 1
	UPA	45 mg x 28 tablets (4 weeks^): 1	15 mg x 28 tablets (4 weeks^): 1 30 mg x 28 tablets (4 weeks^): 1
	UST	130 mg x 4 infusion (4 weeks^): 1 90 mg x 1 injection (8 weeks^): 2	90 mg x 1 injection (8 weeks^): 2
	VDZ	300 mg x 1 infusion (2 weeks^): 0.5 108 mg/0.68 mL x 2 injection (4 weeks^): 1	108 mg/0.68 mL x 2 injections (4 weeks^): 1
	^Implied number of weeks provided by each script based on the script equivalence Source: 'Section 4_estraimod_UC_utilisation-and-cost-model.xlsm'		
Drug costs	Based on the requested published DPMQ for ETR and published DPMQs for comparator treatments.		
Cost of IV infusion	The submission estimated a reduction in the cost of IV administration costs associated with the substitution of ETR for IV formulations of IFX (10184B, 11797X, 11796W, 10196P, 11459D, 11461F), UST (13255P, 13272M), and VDZ (10384M, 10398G). The submission assumed a unit cost per IV infusion of $85.84 based on the 80% schedule fee of MBS item 14245 ($107.30). This was appropriate; however, there were several programming errors identified in the spreadsheet. There were errors in cells Z494:Z503, which did not return the appropriate reference numbers corresponding to all of the IV formulations, and excluded approximately half of the corresponding scripts. Also, the submission applied incorrect unit costs to VDZ infusions (80%*$108.30 and 80%*$109.30).		

Source: pp112-131 of the submission

ADA = adalimumab, ETR = etrasimod; DPMQ = dispensed price maximum quantity; GOL = golimumab; IFX = infliximab; IV = intravenous; JAK = Janus kinase; OZA = ozanimod; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; QxW = every x weeks; RPBS = Repatriation Pharmaceutical Benefits Scheme; TOF = tofacitinib; UPA = upadacitinib; UST = ustekinumab; VDZ = vedolizumab.

6.37 Table 10 presents the estimated net financial implications to the PBS/RPBS and health budget for the proposed listing of ETR for the treatment of MSUC over the first six years. Several programming errors were identified and corrected during the evaluation, but these had minimal impact on the estimated net cost to the health budget:

- The workbook incorrectly excluded the reduction in the number of scripts and costs associated with the substitution for VDZ item 12647P (cells E66:J66, L66:Q66 on '4a scripts-affected'; cells D15:I17, D20:I22 on 'Impact – affected (pub)')
- The workbook applied the incorrect substitution rate to UPA item 13265E, with the substitution rate of UST applied instead of the assuming 0% substitution for UPA (cells E643:J643 on 'scrips-market').
- The workbook incorrectly excluded RPBS costs associated with UPA item 13256Q and 13265E, UST all items and VDZ all items (cells D22:I22 on 'Impact – affected (pub)').
- The workbook incorrectly counted the number of scripts associated with IV infusions, and applied the incorrect unit costs to two item numbers (cells Z483:AA492 on 'Net changes – MBS').

6.38 The PSCR noted updated utilisation and financial estimates were included with the Response using complete year 2023 data, as well as updated 2024 patient co-payments and integrating programming corrections outlined in the evaluation. These have not been evaluated.

Table 10: Estimated net cost of ETR to the PBS/RPBS and health budget using published prices, accounting for programming errors identified during the evaluation^

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of the use and financial impact of ETR						
ETR scripts – total	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]
Initial	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Continuing	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
ETR scripts – comparator substitution	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]
ETR scripts - grandfather patients	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
ETR, net cost to PBS/RPBS	[redacted][5]	[redacted][6]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][8]
Estimation of changes in use and financial impact of other medicines						
Comparator scripts	[redacted][4]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]
ADA	[redacted][10]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
GOL	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
IFX	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
OZA	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
TOF	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
UPA	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
UST	[redacted][10]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
VDZ	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Comparators, net cost to PBS/RPBS	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
ADA	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
GOL	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
IFX	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
OZA	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
TOF	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
UPA	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
UST	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
VDZ	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
Estimated financial implications for the PBS/RPBS and the health budget						
Change in IV infusions	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
IFX IV	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
UST IV	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
VDZ IV	[redacted][10]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net cost to MBS	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
Net cost to PBS/RPBS	[redacted][5]	[redacted][6]	[redacted][6]	[redacted][5]	[redacted][5]	[redacted][6]
Net cost to health budget	[redacted][5]	[redacted][6]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]

Source: Tables 4.2.1, 4.2.2, 4.2.3, 4.2.5, 4.2.10, 4.3.1, 4.3.2, 4.4.1, 4.5.1, 4.5.2, pp115-131 of the submission

ADA = adalimumab, ETR = etrasimod; GOL = golimumab; IFX = infliximab; IV = intravenous; OZA = ozanimod; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; TOF = tofacitinib; UPA = upadacitinib; UST = ustekinumab; VDZ = vedolizumab.

^ estimates presented in the submission: incorrectly excluded scripts associated with change in the utilisation of VDZ item number 12647P; incorrectly applied the substitution rate for UST to one item number for UPA; incorrectly excluded RPBS costs associated with UPA (13256Q, 13265E), UST and VDZ; incorrectly counted the decrease in IFX, UST and VDZ scripts associated with IV infusions

The redacted values correspond to the following ranges

[1] *5,000 to < 10,000*

[2] *10,000 to < 20,000*

[3] *20,000 to < 30,000*

[4] *500 to < 5,000*

[5] *$0 to < $10 million*

[6] *$10 million to < $20 million*

[7] *$20 million to < $30 million*

[8] *$30 million to < $40 million*

[9] *net cost saving*

[10] *< 500*

6.39 Over the first six years of the proposed listing of ETR for MSUC, the submission estimated a net cost of approximately $50 million to < $60 million to the PBS/RPBS and net cost savings to the MBS. This was likely an overestimate, driven by the use of published prices (as the published price of ETR is relatively high compared to the published prices of some comparators) and use in grandfathered patients.

6.40 Assuming ETR is listed on a cost-minimisation basis to the least costly alternative therapy (excluding ADA) and current market growth remained unchanged, the evaluation and ESC considered ETR would primarily replace therapies that are of equivalent cost or are less costly and the requested listing would be expected to be approximately cost neutral to the PBS/RPBS. There would also likely only be an incremental cost associated with grandfather patients enrolled in the patient familiarisation scheme if those patients would not otherwise have been treated with an alternative PBS-listing therapy (i.e. not captured in the current market estimates).

Quality Use of Medicines

6.41 The submission stated that the sponsor is committed risk minimisation activities described in the Australian Specific Annex of the EU-RMP, which is currently undergoing evaluation as part of the regulatory dossier with the TGA. No further detail was provided.

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

7 PBAC Outcome

7.1 The PBAC recommended the General Schedule, Authority Required (in writing) listing of etrasimod (ETR) for the treatment of moderate to severe ulcerative colitis (MSUC). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost effectiveness of ETR would be acceptable if it were cost minimised to the least costly alternative biologic or targeted synthetic biologic disease modifying anti-rheumatic drug (b/tsDMARD) therapy out of infliximab (IFX), tofacitinib (TOF), ozanimod (OZA), vedolizumab (VDZ), ustekinumab (UST) and golimumab (GOL). The PBAC considered, based on the evidence presented, that ETR is likely to be of non-inferior comparative effectiveness and safety to these agents in MSUC and considered the available evidence on balance supports that ETR, for some patients, likely provides a significant improvement in effectiveness compared to adalimumab (ADA).

7.2 The PBAC considered the equi-effective doses of ETR and the alternative therapies could be derived with reference to the relevant Product Information documents, noting the ETR equi-effective dose component is 2 mg given once daily for both induction and maintenance therapy.

7.3 The PBAC considered it was reasonable for the listing of ETR to be consistent with other b/tsDMARDs for MSUC, with prescribing restricted to specific specialists and an initial treatment period of 16 weeks, followed by maintenance therapy with re-assessment at 24-week intervals. The PBAC noted that the assessment of response

should be conducted between week 8 and 16 weeks of therapy as ETR has no dose titration unlike OZA.

7.4 The PBAC noted a grandfather restriction was requested for ETR and considered this was reasonable, and the grandfather listing should remain in place for 12 months from the date of listing, per standard policy. The grandfather restriction will have similar eligibility criteria to the initial restriction. A grandfather patient would be required to have met these criteria prior to the non-PBS supply of ETR.

7.5 The PBAC considered it was reasonable for the listing to not include a specific age restriction, noting that there was some limited clinical evidence in older adolescents. Further to this point, the PBAC considered it may be reasonable and timely to review current age restrictions on b/tsDMARD listings with a view to identifying opportunities to allow greater flexibility in individual clinical decision-making where appropriate.

7.6 The PBAC noted that seven b/tsDMARDs are currently listed for MSUC and that another sphingosine-1 phosphate (S1P) inhibitor (OZA) is already listed for this indication, and the clinical need for additional therapies that are of similar effectiveness and safety to existing options was low in patients aged 18 years and over. However, the Committee also considered there was a clinical need for additional therapies in younger patients, as current PBS listed options were limited to ADA and IFX, with both being tumour necrosis factor inhibitors.

7.7 The PBAC considered the nominated main comparator of OZA was reasonable as the only other S1P inhibitor currently listed for MSUC, and that the nominated secondary comparators of ADA and IFX (IV form) were also reasonable. However, the Committee considered that ETR could substitute for any of the PBS listed b/tsDMARDs for MSUC in practice. The PBAC also noted there is a current recommendation for mirikizumab for MSUC from July 2023, however at time of consideration it had not listed on the PBS.

7.8 The PBAC noted the submission presented indirect treatment comparisons (ITCs) versus OZA, IFX and ADA and that no direct trials comparing ETR to any of these (or any other b/tsDMARDs) were available. The PBAC noted the clinical claim was that ETR is of non-inferior comparative effectiveness to IFX and OZA, is of superior comparative effectiveness to ADA and is of non-inferior comparative safety to all three of these agents. These claims are discussed further below.

7.9 The Committee noted the submission presented ITCs versus OZA for induction therapy and versus ADA and IFX for the outcomes of clinical response and remission in the induction phase (at weeks 8-12), as well as clinical remission, clinical response (at week 52), sustained clinical remission and sustained clinical response (between weeks 12 and 52) in the maintenance phase. The Committee recalled in its consideration of UPA (July/November 2022), OZA (March/November 2022) and TOF (November 2020) that comparisons of these agents with ADA and IFX were not possible due to differences in the design of the maintenance trials (i.e. whether a treat-through or re-randomised/randomised withdrawal design was used) and considered the approach

taken by the ETR submission to present comparisons in the maintenance phase to other trials with similar designs was appropriate. The discussion on comparative effectiveness below is based on the results presented in Table 5.

7.10 For induction therapy, the PBAC noted the results of the ITCs did not show statistically significant differences with either OZA or IFX for the outcomes of clinical remission or response at 12 weeks, for any of the statistical measures (RR, RD or OR). The Committee noted that for the comparison versus ADA, the available evidence overall did not suggest a statistically or clinically meaningful difference for the outcome of clinical remission but did show an overall trend towards a statistically significant difference favouring ETR for clinical response for the RD and OR statistics (but not for RR), but that the clinical importance of this difference was uncertain.

7.11 For maintenance therapy, the PBAC considered the results of the ITCs did not suggest a statistically or clinically meaningful difference between ETR and IFX, and noted only one comparison (clinical remission at weeks 52-54) statistically favoured ETR, but that the lower bound of the 95% CI approached the null. For the comparison versus ADA, the Committee noted the ITCs produced mixed statistical results (none favouring ADA), with some analyses statistically favouring ETR (particularly for the RD statistic). On balance, the PBAC considered the results of the ITCs for the outcomes of clinical remission and sustained clinical remission at week 52 suggested that ETR may be superior to ADA for these outcomes.

7.12 Taking the results of the ITCs for induction and maintenance therapy together, the PBAC considered the results suggested that ETR is likely to be of superior comparative effectiveness to ADA and it likely provides, for some patients, an improvement in effectiveness over 52 weeks of treatment. The PBAC also considered the available evidence suggested ETR was likely to be of non-inferior comparative effectiveness to IFX and OZA, but noted there were no comparisons to OZA in the maintenance phase (for reasons outlined above).

7.13 With respect to comparative safety, the PBAC noted the submission presented a summary of adverse events across the ETR and OZA trials and considered that on balance, the safety profiles of these agents appeared to be similar. Overall, the Committee considered the claim of non-inferior comparative safety to OZA, and likely to IFX and ADA was reasonable.

7.14 Given its view of the clinical claims, the PBAC considered that listing based on a cost minimisation approach with costs over two years, consistent with the approach previously used for b/tsDMARDs was appropriate to determine the cost minimised price of ETR and that the cost of ETR should be no greater than the alternative therapies (excluding ADA).

7.15 The PBAC noted the utilisation and financial estimates as presented in the submission resulted in an incremental cost for the listing of ETR, however also noted the estimates were based on a price of ETR calculated from a cost minimisation approach using the published price of OZA (rather than the least costly alternative). The PBAC considered

the uptake and rate of replacement of specific b/tsDMARDs to be uncertain, however considered that if listed on a cost minimisation basis with the least costly alternative (excluding ADA), the listing would, on balance, likely be cost neutral to the PBS. The Committee considered there may be a small incremental cost associated with a cohort of patients who may be aged under 18 and could be considered clinically appropriate for treatment however are not currently receiving therapy, but considered this was likely to be a very small number of patients.

7.16 The PBAC recommended that etrasimod should be treated as interchangeable on an individual patient basis with IFX, TOF, OZA, VDZ, UST and GOL.

7.17 The PBAC advised that ETR is not suitable for prescribing by nurse practitioners, as the recommended listing is restricted to specialist medical practitioners.

7.18 The PBAC recommended that the Early Supply Rule should apply.

7.19 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because ETR is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over OZA or IFX (or the alternative b/tsDMARDs, except ADA), 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.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

The large overarching administrative note is presented once at the end of this section.

Initial treatment

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands	Manufacturer
ETRASIMOD						
Etrasimod 2 mg tablet, 28	NEW	1	28	3	Velsipity	Pfizer Australia Pty Ltd

Concept ID	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required – In Writing
	Administrative Advice: Overarching note
	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.
Variant of Restriction Summary 13995 / Treatment of Concept: 13995 Authority Required	
	Severity: Moderate to severe
	Condition: Ulcerative to colitis
	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)
	AND
	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)]
	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) 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 between 8 and 16 weeks of therapy.

	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: 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.
	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.
	Prescribing Instructions: A maximum of 16 weeks of treatment with this drug will be approved under this criterion.
	Administrative Advice: The Services Australia website (www.servicesaustralia.gov.au) has details of the toxicities, including severity, which will be accepted where one is claimed.
	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
Variant of Restriction Summary 14003 / Treatment of Concept: 14003	
	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
	AND
	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)]
	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.
	Prescribing Instructions: An assessment of a patient's response to this initial course of treatment must be conducted between 8 and 16 weeks of therapy.
	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 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: A maximum of 16 weeks of treatment with this drug will be approved under this criterion.
	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
Variant of Restriction Summary 14004 / Treatment of Concept: 14004	
	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)
	AND
	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)]
	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.

	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 between 8 and 16 weeks of therapy.
	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 maximum of 16 weeks of treatment with this drug will be approved under this criterion.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday)., Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au, Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos, Or mailed to:, Services Australia, Complex Drugs, Reply Paid 9826, HOBART TAS 7001
Restriction Summary 14005 / Treatment of Concept: 14005	
	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 16 weeks treatment; or
	Patient must have received insufficient therapy with this drug for this condition under the Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) restriction to complete 16 weeks treatment; or
	Patient must have received insufficient therapy with this drug for this condition under the Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) restriction to complete 16 weeks treatment
	AND
	Clinical criteria:
	The treatment must provide no more than the balance of up to 16 weeks treatment available under the above restrictions
	AND
	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).

Continuing & grandfather treatment

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands	Manufacturer
ETRASIMOD						
Etrasimod 2 mg tablet, 28	NEW	1	28	5	Velsipity	Pfizer Australia Pty Ltd

Concept ID	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction Type: ☒Authority Required
	Administrative Advice: Overarching note
	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.
Variant of Restriction Summary 13982 / ToC: 14002: Authority Required	
	Severity: Moderate to severe
	Condition: Ulcerative to colitis
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have demonstrated or sustained an adequate response to treatment by having a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 while receiving treatment with this drug
	AND
	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)]
	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).
variant of Restriction Summary: 14016 / Treatment of Concept: 13993	
	Treatment Phase: Transitioning from non-PBS to PBS-subsided treatment - Grandfather arrangements
	Clinical criteria:
	Patient must have previously 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
	Patient must have experienced a severe intolerance to the above therapy leading to 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 were both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo 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
	AND
	Clinical criteria:
	Patient must not receive more than 24 weeks of treatment under this restriction
	AND
	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)]
	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: 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.
	Prescribing Instructions: Where a response assessment is not conducted within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.
	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.
	Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday)., Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au, Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos, Or mailed to:, Services Australia, Complex Drugs, Reply Paid 9826, HOBART TAS 7001

Variant of Restriction Summary 13983 / Treatment of Concept: 13946	
	Treatment Phase: Continuing treatment - balance of supply
	Clinical criteria:
	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 restrictions
	AND
	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).

Administrative Advice	TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS, The following information applies to Pharmaceutical Benefits Scheme (PBS) benefits for the indication of moderate to severe ulcerative colitis (MSUC). Patients are eligible for one PBS-subsidised drug treatment indicated for MSUC at any one time., Where the term 'biological medicine' appears in this note and restrictions, it refers to any PBS benefit indicated for MSUC., Some benefits are not biological medicines, but are small molecules. However, for practical purposes, these benefits are included within the term 'biological medicine'., From 1 July 2021, under the PBS, all adult patients will be able to commence a treatment cycle where they may trial PBS-subsidised biological medicine without having to experience a disease flare when swapping to one of the alternate agents. Under these arrangements, within a single treatment cycle, a patient may continue to receive long-term treatment with a PBS-subsidised biological medicine while they continue to show a response to therapy., A patient who received PBS-subsidised biological medicine treatment prior to 1 July 2021 is considered to have started their first cycle as of 1 July 2021. Within the same treatment cycle, the same biological medicine cannot be trialled twice. Where 3 biological medicines have failed to provide the patient with an adequate response a treatment cycle is considered complete. There must be a 5-year break in PBS-subsidised therapy before starting the next cycle. The 5-year break is measured from the date of the last approval for PBS-subsidised biological medicine treatment in the most recent cycle to the date of the first application for Initial treatment with a PBS-subsidised biological medicine under the new treatment cycle., A serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment, including serious infusion or injection related reactions, Steven's Johnson Syndrome, development of a demyelinating lesion, progressive multifocal leukoencephalopathy and malignancy related to treatment with the biological medicine, is not considered as a treatment failure., Selecting the correct treatment phase listing when applying for authority approval:, (1) Initial treatment., Apply under an Initial 1 treatment listing where the patient has never received a biological medicine., (2) Continuing treatment., Under no circumstance is Continuing treatment to precede Initial treatment. An authority application for Continuing treatment is not to be made on the same day as Initial treatment., (3) Changing therapy., Apply under an Initial 2 treatment listing. The indices of disease severity (i.e. Mayo clinic score or partial Mayo clinic score), or the prior corticosteroid therapy and immunosuppressive therapy will not need to be restated. A patient may trial an alternate biological medicine treatment at any time, regardless of whether they are receiving therapy (initial or continuing) at the time of the application. However, they cannot change to a particular biological medicine if they

	have failed to respond to prior treatment with that drug once within the same treatment cycle. A response assessment to the preceding supply of biological medicine must accompany this Initial 2 treatment authority application., (4) Recommencement of treatment after a 5-year break in PBS-subsidised therapy., Apply under an Initial 3 treatment listing. Prior corticosteroid and immunosuppressive therapies need not be re-trialled., (5) Balance of supply., Where the full number of repeat prescriptions have not been requested under any initial or continuing listing, apply for the balance of the supply of the repeats under any treatment phase listing containing the words "balance of supply".

***The 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.