

5.14 OZANIMOD,

**Pack containing 28 capsules 920 micrograms;
Pack containing 4 capsules 230 micrograms and
3 capsules 460 micrograms
Zeposia[®],
Celgene Pty Ltd**

1 Purpose of submission

- 1.1 The submission requested the PBAC re-consider its advice from the March 2022 meeting regarding the comparative effectiveness and safety of ozanimod (OZA) and adalimumab (ADA) for the treatment of moderate to severe ulcerative colitis (MSUC) when it recommended the listing of OZA.
- 1.2 The November 2022 submission requested listing on the basis of a cost minimisation approach to the least costly of infliximab (IFX), tofacitinib (TOF) or vedolizumab (VDZ). The submission requested golimumab (GOL) and ADA not be considered for the purposes of determining the cost minimised price of OZA, following the PBAC recommendation in March 2022 on a cost minimisation with the least costly alternative, including GOL and ADA. The submission claimed OZA was of superior comparative effectiveness to ADA and also argued GOL should be excluded from the cost minimisation on the basis that the PBAC has previously considered it to be of inferior comparative effectiveness to IFX in induction therapy (GOL November 2017 public summary document [PSD]).
- 1.3 The below table presents the key components of the clinical issue addressed by the submission.

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

Component	Description
Population	Adult patients with MSUC who have had an inadequate response, lost response, or were intolerant to standard treatment (unchanged).
Intervention	OZA PO 0.92 mg capsule (1 mg OZA HCl) daily after escalation for 7 days (dose titration) (unchanged).
Comparator	<p>Primary comparator(s):</p> <ul style="list-style-type: none"> IFX IV infusion, 5 mg/kg at 0, 2 and 6 weeks then Q8W thereafter (unchanged). ADA SC injection, 160 mg at Week 0, 80 mg at Week 2 then 40 mg Q2W thereafter (secondary comparator in original submission). <p>Secondary comparators (unchanged):</p> <ul style="list-style-type: none"> VDZ IV infusion, 300 mg at Weeks 0, 2 and then Q8W thereafter. GOL SC injection, 200 mg at Week 0, 100 mg at Week 2, then 100 mg Q4W thereafter. TOF 10 mg BD for at least 8 weeks for induction and then 5 mg BD (for maintenance)
Outcomes	<p>Indirect comparison of OZA and comparators for induction and maintenance therapy accounting for differences in trial design for clinical response and clinical remission (unchanged).</p> <p>Additional analyses versus ADA for clinical response and clinical remission in the induction phase, including a matching-adjusted indirect comparison (MAIC) and a network meta-analysis (NMA). Additional safety comparisons for induction and maintenance therapy were also presented from the MAIC (current submission).</p>
Clinical claim	<p>OZA is of non-inferior comparative effectiveness and safety to IFX (unchanged). In addition, OZA is non-inferior int terms of efficacy to VDZ, ADA, GOL and TOF, with a trend towards more favourable safety (original submission – secondary comparators).</p> <p>Current submission - OZA is of superior comparative effectiveness to ADA and has some safety advantages over ADA in maintenance therapy (analyses presented). Based on previous PBAC advice, OZA should also be considered to be of superior comparative effectiveness to GOL.</p>

Source: Adapted from Table 1 of the ozanimod March 2022 public summary document (PSD) with additional information in the current submission added.

2 Background

Registration status

2.1 Ozanimod was TGA registered on 17 July 2020 for the treatment of relapsing-remitting multiple sclerosis and on 18 March 2022 for MSUC.

Previous PBAC consideration

2.2 At its March 2022 meeting, the PBAC recommended the General Schedule, Authority Required (in writing) listing of OZA for MSUC, on a cost minimisation basis with the least costly alternative therapy. In making its recommendation, the PBAC considered, for the purposes of satisfying Section 101(3B) of the *National Health Act 1953*, that the alternative therapies included IFX, VDZ, GOL, TOF and ADA. The recommendation was based, among other matters, on its assessment that the cost of OZA should be no greater than the cost of IFX or the alternative therapies. When considering the available evidence, the PBAC considered that a claim of non-inferior comparative effectiveness and safety to IFX was, on balance, likely to be reasonable (paragraph 7.1, ozanimod March 2022 PSD).

- 2.3 However, due to uncertainties arising from differences in the design and populations recruited into the clinical trials, the PBAC was not satisfied there was sufficient evidence to conclude OZA was of superior comparative effectiveness to any of the alternative therapies, stating (paragraphs 7.7 – 7.9, OZA March 2022 PSD),

“The PBAC considered there were numerous uncertainties with the clinical evidence presented, which impacted the reliability of the indirect comparisons used to support the non-inferiority claims. The Committee noted the primary OZA trial relied upon in the submission, True North, had a different design to the infliximab trials used to inform the clinical claim, whereby only responders in the initial phase of True North progressed to the maintenance phase, whereas all patients in most IFX trials continued to the maintenance phase. Furthermore, the PBAC also noted that efficacy in the maintenance phase of True North was determined as a proportion of responders who entered the maintenance phase. In addition, the PBAC noted there appeared to be differences in the populations recruited into True North and the included IFX trials, with the True North ITT population appearing to have less severe and less pre-treated disease.

The PBAC acknowledged that the results of the indirect comparisons based on the ITT populations of the OZA and IFX trials should be interpreted with caution due to the differences in trial designs and recruited populations. The PBAC noted that additional subgroup analyses presented in the Pre-PBAC Response, comparing subgroups of patients from the True North trial with ‘no moderate disease’ and ‘prior use/intolerance to immunomodulators’ to the pooled IFX ITT populations, found no statistically significant differences in outcomes for either of these subgroup analyses for either clinical remission or response in the induction or maintenance phases. While the PBAC noted these subgroup analyses had not been evaluated and only partially explored some of the issues with the ITT analyses, it also noted these subgroups were pre-specified in the design of True North and considered these analyses were informative for assessing the claim of non-inferior comparative effectiveness of OZA and IFX. Overall, taking into account the totality of the available evidence, the PBAC considered that the claim of non-inferior comparative effectiveness to the primary comparator, IFX, was adequately supported.

The PBAC considered that the indirect comparisons versus the secondary comparators (VDZ, GOL, TOF and ADA) were not informative for considering the comparative effectiveness of OZA to other bDMARDs/tsDMARDs. The PBAC recalled that it had previously accepted that for some patients, TOF provides a significant improvement in efficacy in the induction phase compared to ADA (Paragraph 7.1, Tofacitinib (MSUC) PSD, November 2020 PBAC meeting). However, the PBAC considered there was insufficient evidence to support that OZA provides, for some patients, a significant improvement in efficacy and/or reduction of toxicity over any of the alternative therapies, including ADA.”

3 Requested listing

3.1 The submission did not request amendment to the listing recommended by the PBAC at its March 2022 meeting (see Recommended listing, ozanimod March 2022 PSD).

3.2 The Secretariat however reviewed the recommended PBS listing contained within the March 2022 PBAC meeting minutes and suggested the following corrections:

3.3 (i). Transitioning from non-PBS to PBS-subsidised supply – ‘grandfather’ arrangements

The March 2022 minutes omitted any requirements regarding mandatory therapies (e.g. 5-aminosalicylate oral preparation, thiopurines, oral corticosteroids). The Secretariat has consequently re-inserted requirements concerning mandatory therapies to be trialled before ozanimod. The intent is that ‘grandfather’ patients meet the same requirements as non-grandfather patients. Although it was noted that the True North and Touchstone clinical trials did not stipulate exactly the same inclusion criteria with respect to these mandatory prior therapies, it is unclear whether these trials included Australian patients, and, if they did, whether such patients would be unable to meet the requirements concerning mandatory prior therapies because of the difference in trial protocols. In the event that this is the case, the PBAC considered that it would be reasonable that ozanimod treatment continue as opposed to stopping ozanimod to trial the mandatory therapy that was missed for these patients coming from the clinical trials.

3.4 (ii). Titration pack arrangements

It was recognised that treatment may sometimes have to pause for unforeseen reasons. In such a case, the patient may already have a supply of the 920 µg strength and would not require a continuing authority prescription approved again. The requirement that there is a concurrent authority application lodged for the 920 µg strength through a written-only authority application only recognises dose titration at initiation – a prescriber may be seeking the titration to re-initiation of treatment where the 920 µg strength has already been obtained through a telephone/online authority approval. Therefore the clinical criterion in question has been re-phrased into an appropriate administrative NOTE.

3.5 (iii). Administrative NOTE concerning 3 treatment attempts per cycle of treatment

As ozanimod has been recommended on a cost-minimisation basis, the treatment failure count has not been reset as this would not be aligned with a cost-minimisation recommendation. The listing remains at 3 treatment attempts (from any number of the different pharmacological classes available). The lengthy administrative NOTE that explains the number of treatment attempts per treatment cycle has been revised to remove the specific date concerning when a patient is considered to have started a new treatment cycle.

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

4 Population and disease

- 4.1 The proposed population has not changed from the original March 2022 submission. The information below is re-presented from the March 2022 PSD.
- 4.2 Ulcerative colitis is a life-long chronic relapsing and remitting inflammatory disease that involves ulceration of the mucosa of the colon. Patients with ulcerative colitis most commonly present with bloody diarrhoea, rectal bleeding, tenesmus (sensation of incomplete defecation), urgency, abdominal pain, and passage of mucus. Disease of moderate to severe activity may be associated with systemic symptoms, including fatigue, fever, anorexia, nausea, weight loss, and dehydration. The most serious complications of ulcerative colitis are bowel perforation and colorectal cancer.
- 4.3 OZA is a sphingosine 1-phosphate (S1P receptor) modulator that binds selectively to S1P1 and S1P5 subtypes. The mechanism through which OZA exerts its effects in MSUC have not been fully elucidated. The draft PI stated that the mechanism by which OZA exerts therapeutic effects in multiple sclerosis and ulcerative colitis is unknown but may involve the reduction of lymphocyte migration into the central nervous system and intestine.
- 4.4 The submission proposed OZA as an alternative to biological therapy in the treatment of adult patients with MSUC (defined by a Mayo score ≥ 6) who have had an inadequate response to, or failure of, standard medical management. The submission indicated that the addition of OZA to the clinical management algorithm will not alter current practice, but will allow for an additional option with a different mechanism of action and oral administration.

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

5 Comparator

- 5.1 The March 2022 submission nominated IFX (intravenous (IV) form) as the primary comparator, and also nominated four other biological or targeted synthetic disease modifying anti-rheumatic drugs (bDMARDs/tsDMARDs) which are PBS listed for the treatment of MSUC including TOF, VDZ, GOL and ADA, as secondary comparators. The PBAC previously considered the nominated comparator of IFX IV was reasonable, however considered OZA could substitute for all bDMARDs/tsDMARDs listed for MSUC. In addition to IV forms of IFX and VDZ, subcutaneous injection (SC) forms have also listed on the PBS. Furthermore, at its July 2022 meeting the PBAC recommended ustekinumab (UST) for the treatment of MSUC. It may be reasonable to also consider UST as an alternative therapy to OZA.
- 5.2 The resubmission argued that ADA and GOL should not be considered relevant for the purposes of a cost minimisation approach to the least costly alternative therapy. To support these arguments, the submission claimed:

- OZA is of superior comparative effectiveness to ADA and provides, for some patients, a significant improvement in efficacy or reduction in toxicity, for the purposes of satisfying Section 101(3B) of the *National Health Act 1953*. To support this claim, additional analyses were presented in the submission, which are discussed further in the ‘Comparative effectiveness’ section below.
- Given the PBAC’s view expressed at its March 2022 meeting that OZA is of non-inferior comparative effectiveness to IFX, OZA should also, by extension, be considered superior to GOL, on the basis the PBAC previously considered GOL to be of inferior effectiveness to IFX in induction therapy. No additional analyses comparing OZA and GOL were presented in the submission; however, the NMA presented as an attachment to the submission included results versus ADA, UST, GOL, VDZ, TOF and IFX. The NMA is discussed further in the ‘Comparative effectiveness’ section below.

5.3 Section 101(3B) of the *National Health Act 1953* states that when the proposed medicine is substantially more costly than an alternative therapy, the Committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. Alternative therapies include IFX, VDZ, TOF, ADA, UST, and GOL. The core proposition of the submission is that as OZA meets this test of a significant improvement in efficacy and/or reduction in toxicity versus ADA (and by extension GOL), a higher price than these two therapies is justified.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician stated adalimumab was the least likely bDMARD/tsDMARD to be selected for the treatment of MSUC in practice due to retrospective analyses and local clinical experience which indicated ADA was less effective than alternative options. The clinician also noted the results of the published matching adjusted indirect comparison (MAIC) (discussed elsewhere in this section) found OZA was associated with statistically significantly higher odds of achieving clinical response and endoscopic improvement in induction therapy versus ADA.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission did not explicitly nominate specific clinical trials to support its clinical claims; however, the additional analyses presented in the submission relied upon

evidence from numerous trials across the alternative therapies noted in Section 5 above, many of which have previously been considered by the PBAC. A complete list of trials for all bDMARDs/tsDMARDs has not been presented; however, a list of key trials for the primary comparison of OZA vs. ADA is presented in the table below, based on trials included in the network meta-analysis (NMA), which includes all trials used in the MAIC. The list of trials included in the original submission is available in the OZA March 2022 PSD.

Table 2: Trials and associated reports relevant to the submission

Trial ID	Protocol title/ Publication title	Publication citation
Ozanimod (vs placebo) trials		
True North (NCT02435992)	True North Clinical Study Report, Statistical Analysis Plan and related documents Sandborn W, Feagan B, D'Haens G, Wolf D et al. Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis.	29 October 2020 <i>New England Journal of Medicine</i> 2021; 385: 1280-1291.
Touchstone (NCT01647516)	Touchstone Clinical Study Report, Statistical Analysis Plan and related documents Sandborn W, Feagan B, Wolf D, D'Haens G, Vermeire S et al. Ozanimod Induction and maintenance Treatment for Ulcerative Colitis.	04 November 2015 <i>New England Journal of Medicine</i> 2016; 374 (18): 1754-1762.
Adalimumab (vs placebo) 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.	<i>Gut.</i> 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.	<i>Gastroenterology.</i> 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.	<i>J Gastroenterol.</i> 2014; 49:283-294.

Source: Compiled during the evaluation from OZA March 2022 PSD, with ADA trials identified in Attachment 2 to the submission (NMA Technical Report April 2021.docx), cross referenced with Table 4 of the TOF November 2020 PSD. Only one key citation included for each trial.

Shaded areas indicate data previously seen by the PBAC.

6.4 The key features of the included evidence and additional analyses are summarised in **Error! Reference source not found..**

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Included in
OZA vs ADA						
True North (OZA)	IP: 1012 MP: 526	P3, MC, R, DB, RMP (cohort 1 IP and MP); OL (cohort 2 IP)	Low	TNFi-n and TNFi-e MP: Week 10 responders	Clinical remission, Clinical response, endoscopic improvement	MAIC NMA
Touchstone (OZA)	197	P2, R, DB	Low	TNFi-n and TNFi-e MP: Week 8 responders		NMA
ULTRA-1 (ADA)	390	P3, MC, R, MD, DB (8wk), IPO	Low	TNFi-n	Clinical remission, clinical response, mucosal healing	MAIC NMA
ULTRA-2 (ADA)	IP: 494 MP: 494	P3, MC, R, DB, (52wk), TMP	Low	TNFi-n & TNFi-e	Clinical remission, clinical response, mucosal healing	MAIC NMA
Suzuki 2014 (ADA)	IP: 273 MP: 273	P2/3, MC, R, PC, DB (52wk), TMP, 3-arm	Low	TNFi-n (Japanese)	Clinical remission, clinical response, mucosal healing	NMA

Summary of additional analyses

MAIC	<p>A propensity score model was used to assign statistical weights to True North patients based on potential prognostic factors or treatment effect modifiers, including age, sex, baseline total Mayo Score, extent of disease and prior anti-TNF therapy. Profile of included data for overall population comparisons below (data from ULTRA-1 was used in the TNFi-naïve comparisons).</p> <p>Before matching + induction phase: True North: OZA n = 429; PBO n = 216. ULTRA-2: ADA n = 248; PBO n = 246</p> <p>After matching + induction phase: True North: OZA ESS n = 395; PBO ESS n = 193. ULTRA-2: ADA n = 248; PBO n = 246</p> <p>Before matching + maintenance phase: True North: OZA n = 230; PBO n = 227. ULTRA-2: ADA n = 125; PBO n = 85</p> <p>After matching + maintenance phase: True North: OZA ESS n = 168; PBO ESS n = 165. ULTRA-2: ADA n = 125; PBO n = 85</p>
NMA	<p>A systematic literature review was undertaken to identify RCTs of targeted therapies for MSUC and assessed using the PRISMA framework, with the search undertaken in October 2020. Bayesian NMAs with random or fixed effects models were performed for all analyses. The NMA identified relevant trials for one S1P inhibitor (OZA), three TNF-α inhibitors (ADA, GOL, IFX), one α4β7 integrin inhibitor (VDZ), one interleukin 12/23 inhibitor (UST) and one Janus kinase inhibitor (TOF).</p> <p>Induction phase included studies: OZA = True North, Touchstone. ADA = ULTRA-1, ULTRA-2, Suzuki 2014</p> <p>Maintenance phase included studies: OZA = True North. ADA = ULTRA-2, Suzuki 2014</p>

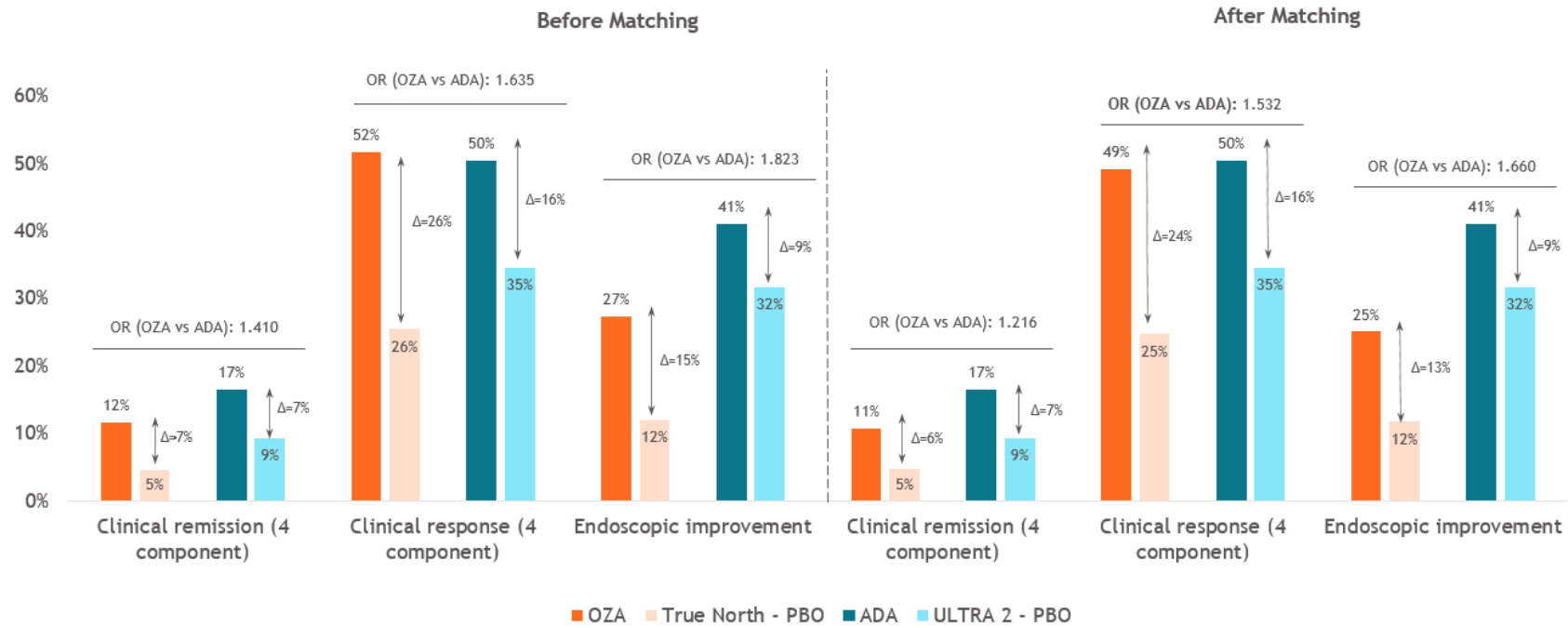
Source: Compiled during the evaluation based on Table 3, OZA March 2022 PSD (OZA trials) and Table 3.3, Attachment 2 of the submission (NMA Technical Report). Risk of bias classifications for trials previously seen by the PBAC extracted from Table 3, OZA March 2022 PSD (OZA trials) and Table 4, TOF November 2020 PSD (ADA trials).

ADA = adalimumab; GOL = golimumab; IFX = infliximab; OZA = ozanimod; PBO = placebo; TOF = tofacitinib; UST = ustekinumab; VDZ = vedolizumab; DB = double blind; ESS = estimated sample size; IP = induction phase; IPO = induction phase only study; MAIC = matching-adjusted indirect comparison; MC = multi-centre; MD = multi-dose; MP = maintenance phase; MSUC = moderate to severe ulcerative colitis; NMA = network meta-analysis; OL = open label; OS = overall survival; P2 = Phase 2; P3 = Phase 3; PFS = progression-free survival; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; R = randomised; RCT = randomised controlled trial; RMP = re-randomised/randomised withdrawal maintenance phase; S1P = sphingosine-1 phosphate; TMP = treat-through maintenance phase; TNF-α = tumor necrosis factor alpha; TNFi-n = tumor necrosis factor alpha-naïve; TNFi-e = tumor necrosis factor alpha-experienced;. Shaded areas indicate data previously seen by the PBAC.

- 6.5 Of the relevant ADA trials, only ULTRA 2 included both anti-tumour necrosis factor alfa (TNF- α) therapy naïve and experienced patients and therefore was considered a key trial for the comparisons of OZA and ADA.
- 6.6 There are noteworthy differences between baseline characteristics of populations recruited into the True North (OZA) and ULTRA 2 (ADA) studies. In particular, the population in the True North (OZA) trial had a lower proportion of patients with extensive colitis or pancolitis and a lower proportion of patients with prior anti TNF- α therapy use than ULTRA 2 study¹.
- 6.7 There may also be other differences in the design, conduct and/or recruited populations in the OZA and ADA trials which were not or cannot be adjusted for in the MAIC. The MAIC matched patients on characteristics of age, sex (male), baseline total Mayo score, extensive colitis/pancolitis status and prior anti-TNF therapy use. However, after matching, the point estimates for most OZA outcomes did not substantially change and there remained noteworthy differences in the absolute clinical remission, clinical response and endoscopic improvement outcomes for the intervention and placebo arms between the OZA and ADA studies (see Figure 1 below) for the overall population analyses. This may indicate differences in additional (known or unknown) variables or differences in assessment of the outcomes which either have not or cannot be adjusted for in the MAIC. Overall, the evaluation considered these transitivity issues may impact the reliability of all comparisons in the submission. The ESC considered the design of the MAIC adjusted for variables which could reasonably be expected to be treatment effect modifiers and considered the methodology of the MAIC was likely to be reliable.

¹ Source: Tables 1 and 2 Dubinsky, M.C., Betts, K.A., Yin, L., Eren, D., Tang, W., Gupte-Singh, K. (10/2021). Comparative Efficacy and Safety of Ozanimod and Adalimumab in Patients with Moderately to Severely Active Ulcerative Colitis. [Poster]. United European Gastroenterology (UEG) Week Virtual 2021.

Figure 1: Induction phase efficacy comparison among the overall population



Source: Figure 7, pg. 44 of Attachment 1 to the submission MAIC OZA vs ADA Study Report March 2021.docx
 Patients were matched on Age, Male, Baseline total Mayo score, Extensive colitis (or pancolitis), Prior anti-TNF use.

6.8 The following design aspects of the MAIC are also noteworthy:

- A propensity score model was used to assign statistical weights to True North patients based on potential prognostic factors or treatment effect modifiers, including age, sex, baseline total Mayo Score, extent of disease and prior anti-TNF therapy.
- For maintenance phase comparisons, further adjustments were made to the results of the ULTRA-2 study to estimate the outcomes if the study had a re-randomised design. This was done by including only data from patients in ULTRA 2 who achieved a primary endpoint of clinical response at week 8 in the maintenance population (prior to matching).

6.9 The following design aspects of the NMA are noteworthy:

- Adjustments were made to the maintenance results in studies with a treat-through trial design to better align with what would be expected to be observed in a re-randomised trial of similar design.
- For the ULTRA-2 study, the NMA authors noted sustained clinical response and clinical remission among induction responders for all treatment arms in all populations were reported in a recent ICER UC evidence report from manufacturer-provided data and could be directly inputted into the TT [treat-through] to RR [re-randomised] NMAs².
- For Suzuki 2014, data were unavailable for sustained clinical responders and those in clinical remission among induction responders for the placebo arm. To impute the sustained clinical responder data, data from the biologic-naïve placebo arm of ULTRA 2 maintenance phase was used to inform the adjustments.

Comparative effectiveness

Unadjusted indirect comparison

6.10 The submission re-presented the results of the unadjusted indirect comparisons (using the Bucher method) from the March 2022 submission. The results for the outcome of clinical response and clinical remission in induction therapy provided in the original submission are presented in the table below.

² ICER. Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value; Final Evidence Report and Meeting Summary. 2020.

Table 4: Results of the indirect comparison for OZA vs. ADA from the March 2022 submission (re-presented)

Trial	OZA events n/N (%)	Placebo events n/N (%)	ADA events n/N (%)	RR/RD (95% CI); p-value
Clinical response at Induction - ITT population				
Pooled OZA	260/496 (52.4)	79/281 (28.1)	N/a	RR: 1.84 (1.41, 2.40); p<0.00001 RD: 0.25 (0.18, 0.32); p<0.00001
Pooled ADA	N/a	177/472 (37.5)	241/468 (51.5)	RR: 1.36 (1.18, 1.58); p<0.0001 RD: 0.14 (0.08, 0.20); p<0.0001
ITC of OZA vs. ADA (RR)				1.353 (0.999, 1.832); p=0.0508
ITC of OZA vs. ADA (RD)				0.11 (0.018, 0.202); p=0.0194
Clinical remission at Induction - ITT population				
Pooled OZA	61/496 (12.3)	14/281 (5.0)	N/a	RR: 2.56 (1.45, 4.50); p<0.001 RD: 0.07 (0.04, 0.11); p<0.0001
Pooled ADA	N/a	46/472 (9.7)	74/468 (15.8)	RR: 1.58 (1.05, 2.40); p=0.03 RD: 0.05 (-0.00, 0.11); p=0.06
ITC of OZA vs. ADA (RR)				1.62 (0.804, 3.266); p=0.1773
ITC of OZA vs. ADA (RD)				0.02 (-0.045, 0.085); p=0.5476

Source: OZA March 2022 PBAC Submission Table 146 p. 212 & Table 147 p. 213.

Abbreviations: ADA = adalimumab; CI = confidence interval; ITT = intention-to-treat; OZA = ozanimod; RD = risk difference; RR = relative risk; N/a = not applicable

Statistically significant results are highlighted by **bold** text. Shaded cells indicate results previously seen by the PBAC.

- 6.11 The submission noted the indirect comparisons of OZA and ADA for maintenance therapy were based on sensitivity analyses comparing data from the Phase II Touchstone trial (OZA) and pooled data from ULTRA-2 and Suzuki 2014 (ADA) trials, as the True North (OZA) study used a re-randomised design and the ADA trials used a treat-through design. The submission noted the Touchstone (OZA) study had low numbers who progressed to the maintenance phase (OZA n = 42, PBO n = 25).
- 6.12 The results of the unadjusted indirect comparisons for the outcome of clinical response resulted in differing results depending on statistical methodology. The results on the risk difference (RD) statistic statistically significantly favoured OZA (over ADA) for both induction and maintenance therapy; however, for the relative risk (RR) statistic, there was no statistically significant difference between OZA and ADA for either induction or maintenance therapy. Furthermore, there appeared to be a substantial difference in placebo response rates between the pooled OZA and pooled ADA trials.
- 6.13 As noted in the original commentary (March 2022), differences in the trial designs and recruited populations led to transitivity and applicability issues when interpreting a lack of statistically significant difference as non-inferiority. Furthermore, for the maintenance comparison, the use of only a small subset of the Phase II Touchstone study who progressed to the maintenance phase as the sole source of data for OZA makes the reliability of the unadjusted indirect comparison in maintenance therapy highly uncertain.

Matching adjusted indirect comparison (MAIC)

- 6.14 To provide relevant context to the MAIC, selected baseline characteristics before and after matching for the MAIC (full population, i.e. anti-TNF- α naïve and experienced) are presented in the tables below.

Table 5: MAIC before and after matching populations – induction comparison of ozanimod vs adalimumab (True North vs ULTRA 2)

Baseline Matching Variables Mean (SD); n (%)	Before matching						After matching			
	True North		ULTRA 2		P-values		True North		ULTRA 2	
	Ozanimod	Placebo	Adalimumab	Placebo			Ozanimod	Placebo	Adalimumab	Placebo
	N = 429	N = 216	N = 248	N = 246	p-value	p-value	N = 429 ESS = 395	N = 216 ESS = 193	N = 130	N = 429
[A]	[B]	[C]	[D]	[A] vs. [C]	[B] vs. [D]	[A]	[B]	[C]	[D]	
Age	41.4 ± 13.5	41.9 ± 13.6	39.6 ± 12.5	41.3 ± 13.2	0.1	0.6	39.6 ± 13.4	41.3 ± 13.6	39.6 ± 12.5	41.3 ± 13.2
Male	245 (57.1%)	143 (66.2%)	142 (57.3%)	152 (61.8%)	1.0	0.4	57.3%	61.8%	57.3%	61.8%
Baseline total Mayo score	8.9 ± 1.5	8.9 ± 1.3	8.9 ± 1.5	8.9 ± 1.8	0.8	0.8	8.9 ± 1.5	8.9 ± 1.3	8.9 ± 1.5	8.9 ± 1.8
Extensive colitis or pancolitis	161 (37.5%)	82 (38.0%)	120 (48.4%)	120 (48.8%)	< 0.01 *	< 0.05 *	48.4%	48.8%	48.4%	48.8%
Prior anti-TNF therapy use	130 (30.3%)	65 (30.1%)	97 (39.1%)	101 (41.1%)	< 0.05 *	< 0.05 *	39.1%	41.1%	39.1%	41.1%

Source: Table 11 of Attachment 1 (MAIC OZA vs ADA Study Report March 2021.docx, also presented in Dubinsky 2021)
Abbreviations: SD = standard deviation; N = number in sample; ESS = effective sample size (after matching)

Table 6: MAIC before and after matching populations –maintenance comparison of ozanimod vs adalimumab (True North vs ULTRA-2)

Baseline Matching Variables Mean (SD); n (%)	Before matching						After matching			
	True North		ULTRA 2		P-values		True North		ULTRA 2	
	Ozanimod	Placebo	Adalimumab	Placebo			Ozanimod	Placebo	Adalimumab	Placebo
	N = 230	N = 227	N = 125	N = 85	p-value	p-value	N = 230 ESS = 168	N = 227 ESS = 165	N = 125	N = 85
[A]	[B]	[C]	[D]	[A] vs. [C]	[B] vs. [D]	[A]	[B]	[C]	[D]	
Age	42.4 ± 13.5	43.0 ± 13.7	38.8 ± 11.9	38.8 ± 11.9	< 0.01 *	< 0.01 *	38.8 ± 13.0	38.8 ± 12.4	38.8 ± 11.9	38.8 ± 11.9
Male	117 (50.9%)	122 (53.7%)	73 (58.5%)	50 (58.5%)	0.2	0.5	58.5%	58.5%	58.5%	58.5%
Baseline total Mayo score	8.9 ± 1.6	8.6 ± 1.4	8.7 ± 1.5	8.7 ± 1.5	0.2	0.8	8.7 ± 1.6	8.7 ± 1.4	8.7 ± 1.5	8.7 ± 1.5
Extensive colitis or pancolitis	78 (33.9%)	70 (30.8%)	67 (53.7%)	46 (53.7%)	< 0.001 *	< 0.001 *	53.7%	53.7%	53.7%	53.7%
Prior anti-TNF therapy use	76 (33.0%)	69 (30.4%)	36 (28.5%)	24 (28.5%)	0.4	0.9	28.5%	28.5%	28.5%	28.5%

Source: Table 14 of Attachment 1 (MAIC OZA vs ADA Study Report March 2021.docx)
Abbreviations: SD = standard deviation; N = number in sample; ESS = effective sample size (after matching)

- 6.15 The submission presented selected results for the outcomes of clinical response and endoscopic improvement in induction therapy for the overall population, as well as TNF- α inhibitor naïve and experienced subgroups. For completeness, results for the outcome of clinical remission were also included from Attachment 1 to the submission and the included poster presentation of the MAIC (Dubinsky et al 2021).
- 6.16 The results of the MAIC vs ADA (before and after matching) for induction therapy are presented in the table below.

Table 7: Results of the matching adjusted indirect comparison (MAIC) - induction therapy (anchor-based)

	Before matching	After matching
Overall population		
Clinical response		
MAIC of OZA vs. ADA - OR (95% CI)	1.635 (1.117, 2.392, p<0.05)	1.532 (1.036, 2.265, p<0.05)
Clinical remission		
MAIC of OZA vs. ADA - OR (95% CI)	1.410 (0.621, 3.200, p=0.41)	1.216 (0.523, 2.831, p=0.65)
Endoscopic improvement		
MAIC of OZA vs. ADA - OR (95% CI)	1.823 (1.124, 2.955, p<0.05)	1.660 (1.008, 2.734, p<0.05)
Anti-TNF-α naïve population		
Clinical response		
MAIC of OZA vs. ADA - OR (95% CI)	1.942 (1.218, 3.096, p<0.01)	1.679 (1.028, 2.743, p<0.05)
Clinical remission		
MAIC of OZA vs. ADA - OR (95% CI)	1.501 (0.542, 4.154, p=0.43)	1.468 (0.499, 4.320, p=0.49)
Endoscopic improvement		
MAIC of OZA vs. ADA - OR (95% CI)	2.680 (1.501, 4.782, p<0.001)	2.728 (1.439, 5.170, p<0.01)
Anti-TNF-α experienced population		
Clinical response		
MAIC of OZA vs. ADA - OR (95% CI)	2.979 (1.376, 6.450, p<0.01)	2.527 (1.126, 5.669, p<0.05)
Clinical remission		
MAIC of OZA vs. ADA - OR (95% CI)	0.998 (0.200, 4.977, p=1.00)	0.706 (0.134, 3.730, p=0.68)
Endoscopic improvement		
MAIC of OZA vs. ADA - OR (95% CI)	1.374 (0.533, 3.542, p=0.51)	1.014 (0.388, 2.654, p=0.98)

Source: Tables 4, 9 and 13, Attachment 1 (MAIC OZA vs ADA Study Report March 2021.docx)

Abbreviations: MAIC = matching-adjusted indirect comparison; OZA = ozanimod; ADA = adalimumab; OR = odds ratio; CI = confidence interval. Statistically significant results are highlighted by bold text.

- 6.17 In the induction phase MAIC (after matching), the analysis found statistically significant results favouring OZA for the outcomes of clinical response (odds ratio (OR) 1.532, 95% CI 1.036, 2.265) and endoscopic improvement (OR 1.660, 95% CI 1.008, 2.734), but not for clinical remission (OR 1.216, 95% CI 0.523, 2.831). The results of the before and after matching comparisons did not appear to be substantially different. However, as discussed in paragraph 6.7 above, after matching there remained differences in the absolute estimates of effect (particularly in the placebo arms) of the OZA and ADA trials which may indicate the presence of other variables or differences in assessment of response which have not or cannot be adjusted for in the MAIC. The presentation of odds ratios (ORs) as the primary statistical comparison may mask absolute differences in outcomes that are related to issues not adjusted for by the MAIC. This is particularly evident for the outcome of endoscopic improvement, where after matching, the absolute response rates for OZA (25%) and placebo (12%) in True North were both substantially lower than response rates for ADA (41%) and

placebo (32%) in ULTRA-2 (see Figure 1). Interpretation is complicated by the lack of a MCID or non-inferiority margin (NIM) previously accepted by the PBAC in MSUC against which a formal test could be undertaken. Furthermore, due to the transitivity issues which may not have been entirely addressed in the MAIC, overall it is uncertain whether the claimed differences between OZA and ADA are likely to be a true reflection of the comparative effectiveness of these agents, and it is uncertain if any such differences are likely to be clinically significant.

- 6.18 The results of the MAIC in maintenance therapy did not find any statistically significant differences between OZA and ADA for clinical response or clinical remission, either before or after matching. The impact of the approach used to estimate the effectiveness of ADA as if it had a similar trial design to True North (paragraph 6.5) is unclear. Issues with the comparability of OZA and ADA in maintenance therapy due to differences in the clinical trials notwithstanding, it is noted the PBAC has previously been satisfied to advise, based on established superiority in induction therapy, that TOF, for some patients, provides a significant improvement in efficacy over ADA (paragraph 7.1 TOF PSD, November 2020 PBAC).
- 6.19 With regards to the comparisons based on prior anti TNF- α status, the PBAC has previously considered these analyses to be problematic for several reasons, including (paragraph 7.9, TOF PSD, November 2020 PBAC):
- The comparisons may not be a fair representation of comparative efficacy in patients who are TNF naïve or experienced as a priori patients who have failed a TNFi would be more likely to respond to TOF, and conversely, patients who have failed TOF (or another JAK inhibitor) would be more likely to respond to a TNFi; and
 - The subpopulation analyses would have reduced statistical power as there were potential differences between study populations that may be diluted by reduced sample size and would likely have a higher risk of bias due to increased risks of confounding effects.
- 6.20 These issues notwithstanding, the evaluation considered the MAIC (overall population) may be a more robust basis upon which to consider the comparative effectiveness of OZA and ADA than the unadjusted indirect comparison, as it specifically adjusted for patient baseline characteristics the PBAC previously considered impacted the reliability of the indirect comparisons in the March 2022 submission.
- 6.21 The Pre-Sub-Committee Response (PSCR) noted the True North and Touchstone studies represent the best available evidence for OZA in patients with MSUC and stated that given the PBAC's previous view that treatment effect modifiers could impact the reliability of the unadjusted indirect comparisons presented in the March 2022 submission, a MAIC was presented in this submission. The PSCR acknowledged the view of the evaluation that the MAIC may be a more robust basis upon which to consider the comparative effectiveness of OZA and ADA than the unadjusted

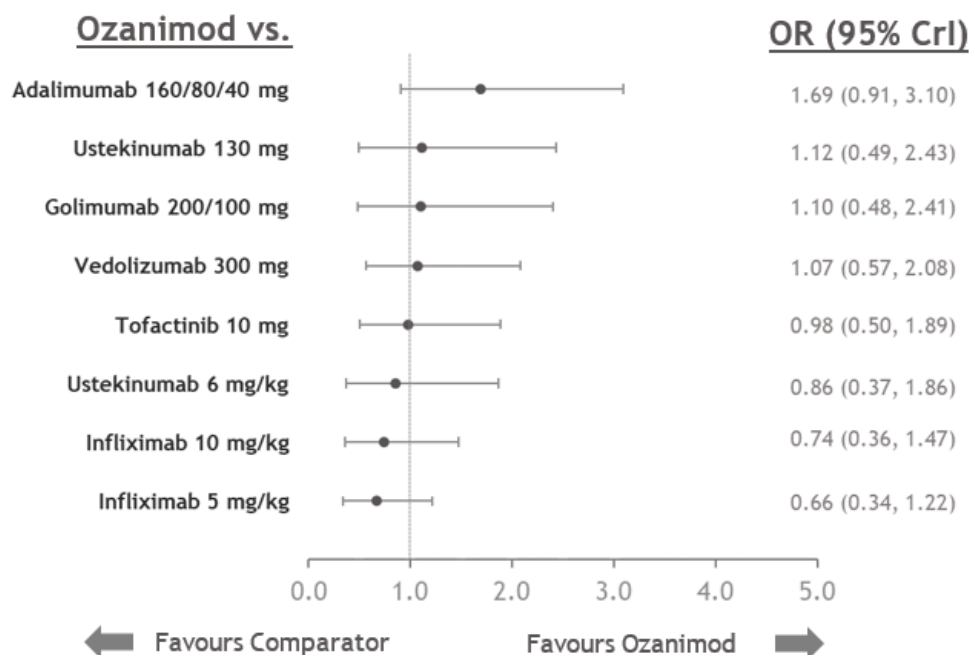
comparison, and argued, given the PBAC have not previously established a NIM for outcomes in MSUC, non-inferiority (and superiority) can be inferred by a statistically significant difference, and noted OZA achieved statistically superior results over ADA for the outcomes of clinical response and endoscopic improvement in the MAIC.

- 6.22 The ESC noted the MAIC was anchored and adjusted for relevant baseline characteristics such as extensive colitis or pancolitis status and prior anti-TNF therapy use but there were some differences between the trials, such as timing of endpoints and differences in the reporting of baseline characteristics that could not be adjusted for. Overall, the ESC considered the MAIC was likely to be a reliable basis upon which to consider the comparative effectiveness of OZA and ADA and considered the results of the MAIC may support a conclusion that OZA provides, for some patients, an improvement in effectiveness over ADA (in terms of achieving clinical response and/or endoscopic improvement).

Network meta-analysis (NMA)

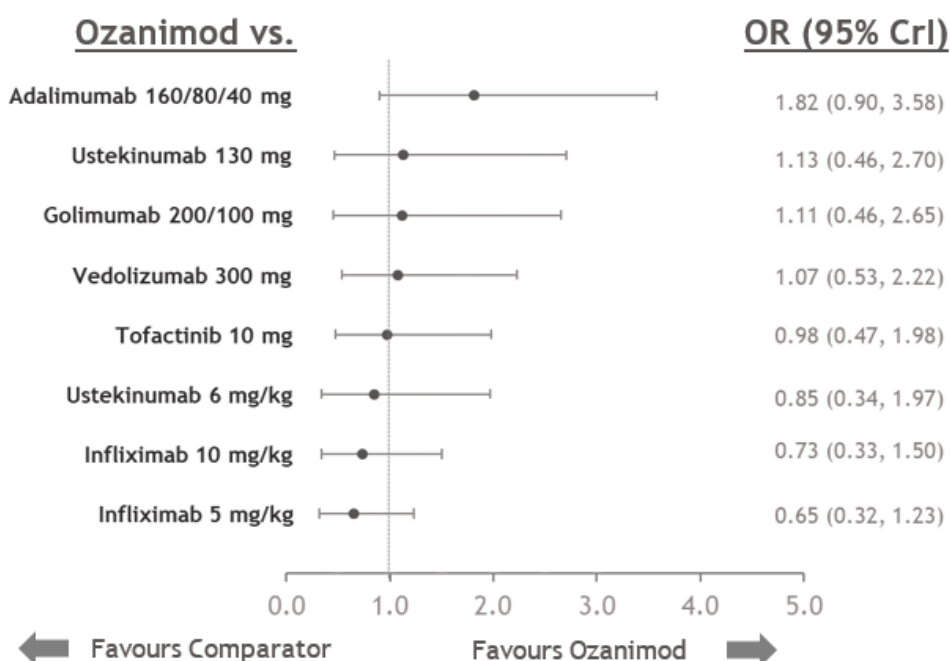
- 6.23 The NMA included results for the outcomes of clinical response, clinical remission and endoscopic improvement for both induction and maintenance therapy, with results for both random and fixed effects models presented. The results of the NMA may require further consideration, as it is unclear whether the methodology adjusted for the differences in trial design and baseline characteristics in the OZA trials which the PBAC previously considered impacted the reliability of the indirect comparisons.
- 6.24 The forest plots for the ORs for the overall population, using a random effects model (the preferred modelling approach adopted in the induction phase NMA), are presented in the figures below. Given the transitivity issues with the comparisons of OZA to the alternative therapies, it is reasonable to conclude a random effects model would be the preferred approach for the NMA.

Figure 2: NMA response (clinical response) for OZA vs other included therapies (overall population, induction, random effects model)



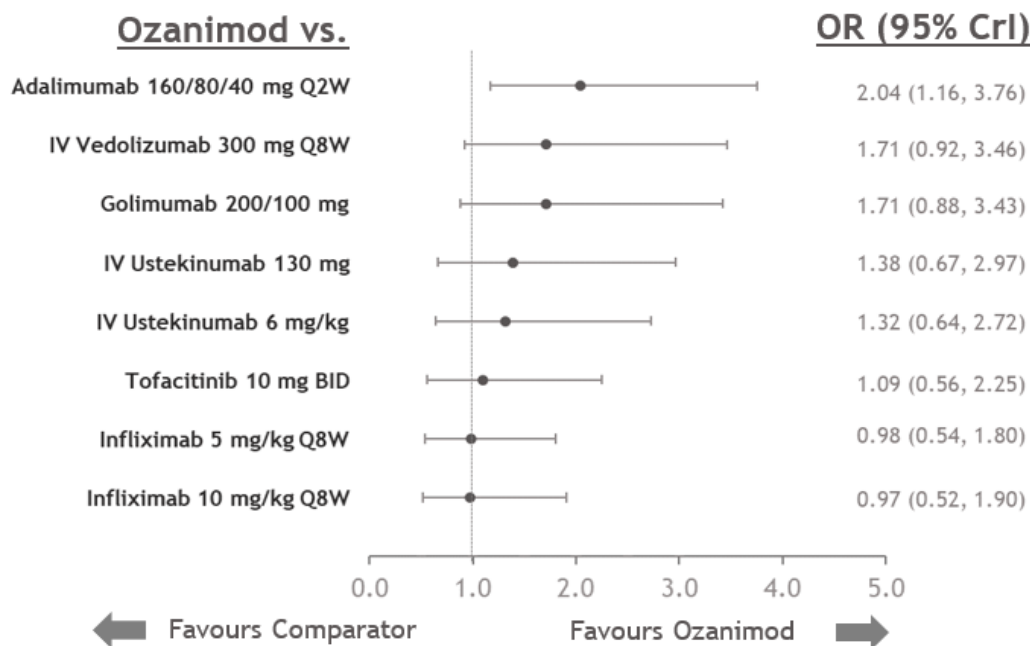
Source: Figure 6.2(b), Attachment 2 to the submission (NMA Technical Report April 2021)
Abbreviations: OR = odds ratio CrI = credible interval

Figure 3: NMA results (clinical remission) for OZA vs other included therapies (overall population, induction, random effects model)



Source: Figure 6.3(b), Attachment 2 to the submission (NMA Technical Report April 2021)
Abbreviations: OR = odds ratio; CrI = credible interval

Figure 4: NMA results (endoscopic improvement) for OZA vs other included therapies (overall population, induction, random effects model)



Source: Figure 6.11(b), Attachment 2 to the submission (NMA Technical Report April 2021)

Abbreviations: Q2W = once every two weeks; Q8W = once every 8 weeks; BID = twice daily; OR = odds ratio; CrI = credible interval

6.25 The results in the figures above found no statistically significant differences between OZA and any of the other therapies included in the NMA, except for the outcome of endoscopic improvement, which favoured OZA over ADA. The results of the random effects model NMA do not appear to strongly support the claim that OZA is of superior comparative effectiveness to ADA in induction therapy. While the point estimates of the OR numerically favoured OZA over ADA for the outcomes of clinical response (OR 1.69, 95% CI 0.91, 3.10), clinical remission (OR 1.82, 95% CI 1.90, 3.58), and endoscopic improvement (OR 2.04, 95% CI 1.16, 3.76, statistically significant in favour of OZA) the lower bounds of the 95% credible interval (CrI)³ crossed 1.0 for response and remission outcomes.

6.26 Forest plot results for the fixed effects model for induction therapy were not presented in the NMA. Tabularised results from the NMA using a fixed effects model, are presented in the table below.

³ The credible interval/CrI in Bayesian statistics refers to the interval within which an unobserved parameter value falls within a particular probability and differs from the frequentist 95% confidence interval.

Table 8: Results of the NMA (fixed effects model) - OZA vs intervention

Ozanimod vs intervention			
Ozanimod vs. [treatment]	Clinical response OR (95% CrI)	Clinical remission OR (95% CrI)	Endoscopic improvement OR (95% CrI)
Adalimumab 160/80/40 mg	1.72 (1.19, 2.45)	1.85 (1.22, 2.75)	1.99 (1.22, 3.28)
Ustekinumab 130 mg	1.13 (0.75, 1.70)	1.15 (0.72, 1.80)	1.34 (0.75, 2.39)
Golimumab 200/100 mg	1.12 (0.73, 1.72)	1.14 (0.71, 1.82)	1.65 (0.97, 2.84)
Vedolizumab 300 mg	1.02 (0.69, 1.49)	1.03 (0.67, 1.54)	1.68 (0.97, 2.92)
Tofacitinib 10 mg	0.97 (0.65, 1.44)	0.97 (0.63, 1.49)	1.09 (0.62, 1.95)
Ustekinumab 6 mg/kg	0.87 (0.57, 1.32)	0.86 (0.55, 1.35)	1.29 (0.72, 2.32)
Infliximab 10 mg/kg	0.77 (0.50, 1.19)	0.75 (0.48, 1.20)	0.96 (0.56, 1.66)
Infliximab 5 mg/kg	0.68 (0.46, 1.02)	0.67 (0.43, 1.02)	0.96 (0.58, 1.61)

Source: Tables O.1 and O.4 of Attachment 2 (NMA Technical Report April 2021)

Abbreviations: OR = odds ratio; CrI = credible interval

Bold values indicate statistical significance

- 6.27 The results of the fixed effects model found OZA was associated with statistically significantly higher odds of achieving clinical response, clinical remission and endoscopic improvement versus ADA. Given the previously expressed view of the PBAC that the OZA trials recruited a population with a different disease profile to most other comparator trials, relying on the fixed effects model should be done with caution, and the underlying assumption the studies are similar enough to support a fixed effects model may not be reasonable.
- 6.28 When considering the overall reliability of the NMA, the evaluation considered the heterogeneity and transitivity issues discussed in paragraph 6.7 may impact the reliability of the comparisons. The PSCR noted the view of the evaluation regarding the MAIC and argued the NMA should be considered a supportive analysis. The PSCR also argued that, while a random effects model may be the preferred model given the identified heterogeneity between the various included trials in MSUC, the networks of evidence behind the NMAs largely consisted of single-study pairwise comparisons, inhibiting the ability to estimate between-study heterogeneity parameters, resulting in failure of convergence or imprecise estimates. The PSCR further argued that a consequence of the model is that the random effects model was likely to exacerbate biases introduced by the results of smaller studies (such as Touchstone (OZA) and Suzuki 2014 (ADA)). On that basis, the PSCR argued the fixed effects model is important to the totality of the evidence.
- 6.29 The ESC considered the NMA was overall of high quality and the supporting documentation included a rigorous exploration of heterogeneity and sensitivity and was undertaken consistent with the NICE DSU TSD 3⁴ guidance. The ESC noted the

⁴ Dias, S., Sutton, A., Welton, N., Ades, AE. (2012). NICE DSU Technical Support Document 3: Heterogeneity: Subgroups, meta-regression, bias and bias-adjustment. Decision Support Unit, SchARR, University of Sheffield (UK).

structure of the network made separating inconsistency and heterogeneity⁵ difficult, however also noted no evidence of inconsistency was found. The ESC considered the density of the network was variable and was limited for some analyses, including the endoscopic improvement outcome, in maintenance therapy and for the biologic-experienced subgroup. Overall, the ESC considered the NMA was also likely to be reliable supportive evidence for the overall clinical claim, at least for the analyses most relevant to the current submission (i.e. clinical response/remission and endoscopic improvement in induction therapy in the overall population).

- 6.30 With regards to the supplementary claim of superior comparative effectiveness versus GOL, the NMA results (random effects model) for the comparison of OZA vs. GOL overall did not meaningfully favour OZA for the outcomes of clinical response (OR 1.10, 95% CI 0.48, 2.41) or clinical remission (OR 1.11, 95% CI 0.46, 2.65). When a fixed effects model was used, the overall conclusions are the same. The PSCR noted the NMA results for the fixed effects model, for the biologic-naïve population results statistically favoured OZA over GOL for in induction therapy (OR 1.88, 95% CI 1.02, 3.55). The ESC considered it was highly uncertain that a claim that OZA was of superior comparative effectiveness to GOL was adequately supported by one statistically significant result, in one subgroup (biologic-naïve patients) under one modelling approach (fixed effects model) and given the totality of the available evidence in the NMA, did not consider a conclusion that OZA is of superior comparative effectiveness to GOL was adequately supported.
- 6.31 The Pre-PBAC Response noted the ESC considered the NMA to be overall of high quality and argued the NMA represents the best available evidence to compare OZA and GOL in lieu of head to head data and further argued the GOL induction study (PURSUIT-SC⁶) was in biologic-naïve patients only, therefore comparing with the biologic-naïve subgroup from True North (OZA) had lower inherent heterogeneity and therefore the comparison presented in the PSCR was valid. The PBAC agreed with the ESC and considered the totality of the evidence presented did not adequately support a claim of superior comparative effectiveness versus GOL.
- 6.32 The results of the maintenance therapy NMAs (using a fixed effects model) found no statistically significant difference between OZA and ADA in the maintenance phase for the outcomes of clinical response, clinical remission or endoscopic improvement. However, interpretation of the maintenance therapy comparisons are complicated as adjustments were made to the ADA trial data (which used a treat-through design) to

⁵ Inconsistency refers to where the direct and indirect evidence in an NMA do not concur; heterogeneity refers to variation in study outcomes between studies.

⁶ Sandborn WJ, Feagan BG, Marano C, et al; PURSUIT-SC Study Group. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014; 146:85-95.

estimate the maintenance treatment effect as if the trial used a re-randomised/randomised withdrawal design.

- 6.33 The PBAC has previously advised that it was satisfied that tofacitinib (TOF, November 2020) was of superior comparative effectiveness to ADA based on comparisons in induction therapy only, where there were alternative therapies with comparable trial designs upon which to consider their comparative effectiveness in maintenance therapy. In its March 2022 consideration of OZA, the PBAC considered a claim of non-inferior comparative effectiveness to infliximab (IFX) was reasonable for both induction and maintenance therapy. The PSCR noted the submission did not make a claim of superiority in maintenance therapy and acknowledged the prior PBAC recommendation for tofacitinib in November 2020 (discussed earlier in this paragraph).

Comparative harms

- 6.34 The MAIC (of OZA vs ADA) was undertaken for the outcomes of any serious treatment-emergent adverse event (TEAE), any TEAE leading to discontinuation and any infectious adverse event (AE) in the maintenance phase. The results, before and after matching, are presented in the table below.

Table 9: Summary of key safety outcome comparisons in the submission for ozanimod vs. adalimumab (maintenance phase)

Safety outcome	Before Matching			After Matching		
	Risk Diff	95% CI	P-value	Risk Diff	95% CI	P-value
Any serious TEAE	-7.943%	(-15.517, -0.369)	<0.05	-5.612%	(-14.199, 2.975)	0.20
Any TEAE leading to discontinuation	-6.013%	(-10.808, -1.218)	<0.05	-5.459%	(-10.606, -0.312)	<0.05
Any infectious AE	-9.517%	(-15.321, -3.714)	<0.01	-8.931%	(-14.874, -2.987)	<0.01

Source: Table 17, Attachment 1 to the submission and Table 4 of the submission

Abbreviations: Risk diff = risk difference; CI = confidence interval

Bold values indicate statistical significance; negative results favour OZA over ADA

- 6.35 The NMA undertook statistical analyses of comparative safety, however noted the analyses were limited by data availability and overall low event rates across several safety outcomes, and the use of low event rates to inform binomial models led to high levels of uncertainty in the NMA results. Overall, the NMA found ozanimod consistently demonstrated comparable safety outcomes across to the alternative therapies.
- 6.36 With regards to comparative safety, the PBAC has previously considered, while OZA has a different safety profile to other bDMARDs/tsDMARDs currently PBS listed for the treatment of MSUC, that the rates of observed serious adverse events (SAEs) appeared to be similar between therapies and considered a claim of non-inferior comparative safety between OZA and the alternative therapies was likely to be reasonable (paragraph 7.10, OZA March 2022 PSD). Furthermore, the evaluation

considered focusing on a comparison of differing rates of adverse events between therapies may not be sufficient to justify a claim of an overall superior safety profile, as the toxicity profiles of OZA and ADA are different and the individual safety profiles of these therapies also merits consideration.

- 6.37 The PSCR noted OZA was not associated with a statistically significant difference in adverse events to placebo in the True North study and noted ADA was associated with higher rates of injection site reactions (ADA 12.1% vs. PBO 3.8%) and haematologic-related adverse events (ADA 1.9% vs. PBO 0%) than placebo in the ULTRA 2 study. A summary of safety profiles provided in the PSCR is presented in the table below.

Table 10: PSCR summary of safety profiles (OZA vs ADA)

	True North (OZA) - Wk 10 to 52 (Sandborn et al 2021)		ULTRA 2 (ADA) - to Wk 52 (Sandborn et al 2012)	
	Placebo (N=227)	OZA (N=230)	Placebo (N=260)	ADA (N=257)
Adverse event	83 (36.6)	113 (49.1)	218 (83.8)	213 (82.9)
Serious adverse event	18 (7.9)	12 (5.2)	32 (12.3)	31 (12.1)
AE leading to discontinuation	6 (2.6)	3 (1.3)	34 (13.1)	23 (8.9)
Most frequent adverse events, reported in ≥5% of patients or with a statistically significant difference vs placebo				
Infection	27 (11.9)	53 (23.0)	103 (39.6)	116 (45.1)
Alanine aminotransferase ≥2xULN	12 (5.3)	32 (13.9)	NR	NR
Absolute lymphocyte count <500 cells per mm ³	4 (1.8)	100 (43.5)	NR	NR
Any injection site reaction-related AE	NR	NR	10 (3.8) ^a	31 (12.1) ^a
Any hematologic-related AE	NR	NR	0 ^b	5 (1.9) ^b

Abbreviations: ADA = adalimumab; AE = adverse event; NR = not reported; OZA = ozanimod; ULN = upper limit normal
a. p<0.001; b=0.030

- 6.38 In addition to the outcomes noted in the PSCR, the ESC also noted OZA appeared to be associated with numerically higher infection events (OZA 23% vs. PBO 11.9%) and liver function test derangement (ALT >2x ULN, OZA 13.9% vs PBO 5.3%). Overall, the ESC considered the safety profiles of OZA and ADA was most reasonably characterised as different, with neither being superior to the other.

Clinical claim

- 6.39 The March 2022 submission described OZA as non-inferior in terms of effectiveness and safety compared to IFX. The PBAC considered, at that time, whilst there were numerous uncertainties with the indirect comparisons due to differences in the trial designs and recruited populations, taking into account the totality of the available evidence, that the claim of non-inferior comparative effectiveness to the primary comparator, IFX, was adequately supported. The Committee considered that the analysis of OZA against the secondary comparators (non-inferior comparative effectiveness and safety) was not informative. The PBAC also considered that the claim of non-inferior comparative safety to alternative therapies was adequately supported, however noted OZA appeared to have a different safety profile to other bDMARDs/tsDMARDs.

- 6.40 The current submission described OZA as superior in terms of effectiveness compared to ADA (as well as maintaining the previous non-inferiority claim versus IFX). The submission also made a supplementary claim of superiority over GOL (on the basis the PBAC previously considered GOL to be inferior to IFX in induction therapy). While the results of the MAIC (after matching) found statistically significant results favouring OZA for the outcomes of clinical response and endoscopic improvement in induction therapy, interpretation of the results is complicated by the lack of an established MCID or NIM in MSUC. Overall, the ESC considered the claim that OZA is superior in terms of effectiveness compared to ADA was, on balance, likely to be reasonable, at least for some patients. For the reasons outlined in paragraph 6.30 above, the ESC did not consider the claim of superior comparative effectiveness over GOL was adequately supported.
- 6.41 The submission described OZA as having a reduced risk of some adverse events (specifically the risk of infection) compared to ADA. While this specific claim may be supported (based on the MAIC), the ESC considered the individual safety profiles of OZA and ADA also required consideration and considered, on balance, that a claim of different but not worse safety was reasonable.
- 6.42 The ESC also considered there was a modest overall clinical need for additional therapies for severe MSUC, however considered OZA, as an oral therapy with a new mechanism of action and comparable effectiveness to existing PBS listed therapies, may address a clinical need for some patients.
- 6.43 The PBAC reaffirmed its view previously expressed view (in March 2022) that a claim of non-inferior comparative effectiveness to IFX was adequately supported. The PBAC also considered that the claim of superior comparative effectiveness to ADA was reasonable, however considered the claim of superior comparative effectiveness over GOL was not adequately supported.
- 6.44 The PBAC considered that a claim of different but not worse safety to ADA and overall non-inferior comparative safety to the alternative bDMARDs/tsDMARDs was reasonable.

Economic analysis

- 6.45 The submission did not present a revised economic analysis or request a change to the methodology of the cost minimisation approach (CMA) from the previous submission; however, the main request in the submission relates to which therapies should (or should not) be considered alternatives for the purposes of the cost minimisation approach. Relevant detail from the March 2022 economic analysis section are presented below.
- 6.46 The March 2022 submission presented a CMA of OZA compared with IFX IV, consistent with the claim of non-inferiority. The proposed equi-effective doses were based on the recommended doses:

- OZA 0.23 mg on Days 1 to 4, 0.46 mg on Days 5 to 7, then 0.92 mg orally once daily \equiv IFX 5 mg/kg IV at Weeks 0, 2, 6 and then every 8 weeks from Week 14 on the assumption of four vials per infusion (average patient weight of 80 kg).
- 6.47 At its March 2022 meeting, the PBAC considered the equi-effective doses of OZA and the alternative bDMARDs/tsDMARDs could be derived with reference to the relevant Product Information documents, noting the equi-effective doses should account for the one-week titration period (noted above).
- 6.48 At its March 2022 meeting, the PBAC considered that a listing of OZA on a cost minimisation basis with costs over two years, consistent with previous approaches for bDMARDs/tsDMARDs was the most appropriate approach to determine the cost minimised effective price of OZA for MSUC. The PBAC considered in March 2022 that on a similar basis over a two-year period, the cost of OZA should be no greater than any of the alternative therapies, including VDZ, GOL, TOF or ADA.
- 6.49 As no changes to the overall methodology of the CMA were proposed in the submission, a full summary is not presented. The results of the CMA and the cost-minimised effective price of OZA can be determined based on the overall methodology previously recommended by the PBAC at its March 2022 meeting (i.e., cost minimised over two years), based on the Committee's advice regarding which therapies should be considered alternative therapies for the purposes of the CMA, noting equi-effective doses can be determined from the relevant Product Information documents. Given the evaluation and ESC considered the claim of superior comparative effectiveness to GOL was not adequately supported (paragraph 6.30), it may not be reasonable to for OZA to be more costly than GOL.
- 6.50 The ESC also noted IFX was subject to price disclosure-related reductions on 1 October 2022.

Drug cost/patient/year

- 6.51 The expected cost per patient of OZA, at the effective price proposed in the March 2022 submission, is \$| over 52 weeks (a new effective price was not explicitly proposed in the submission); however, the ESC noted the cost per patient per year will require re-calculation following a recommendation, based on the advice of the PBAC.

Estimated PBS usage & financial implications

- 6.52 This submission was not considered by DUSC. The submission did not request any changes to the utilisation and financial estimates previously considered by the PBAC. Relevant extracts from the March 2022 PSD are reproduced here.
- 6.53 The estimated net financial implications for the proposed listing of OZA for MSUC over the first 6 years are summarised in the table below (revised during the March 2022 evaluation to correct for annual growth rates and weighted uptake rates of individual bDMARDs/tsDMARDs, the corrected daily cost of OZA on the basis of the CMA compared to IFX IV, and using MBS item 116). The below is based on the original

submission requested published DPMQs of \$588.01 for the titration pack, and \$2,219.51 for the standard pack of OZA.

Table 11: Estimated use and financial implications (based on effective price of OZA, using published price of comparators)

	2022	2023	2024	2025	2026	2027
Estimated extent of use						
Number of scripts dispensed (OZA initiation) ^a	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed (OZA continuing) ^a	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Estimated financial implications of OZA						
Cost to PBS/RPBS less copayments ^b (\$)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Estimated financial implications for other bDMARDs/tsDMARDs						
Cost to PBS/RPBS less copayments ^a (\$)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Net financial implications						
Net cost to PBS/RPBS ^b (\$)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Net cost to MBS ^c (\$)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Net cost to PBS/RPBS/MBS^b (\$)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴

Source: Table 165-170, p253-7 of the submission and the Excel Workbook “Attachment 3_Ozanimod MSUC Utilisation and Cost Model”
 bDMARD = biologic disease-modifying anti-rheumatic drug; CMA = cost-minimisation analysis; EMP = ex-manufacturer price; IFX = infliximab; IV = intravenous; MBS = Medicare Benefits Schedule; MSUC = moderate to severe ulcerative colitis; OZA = ozanimod; PBS = Pharmaceutical Benefits Scheme; PSD = public summary document; RPBS = Repatriation Pharmaceutical Benefits Scheme; SC = subcutaneous;

^a Script numbers and estimated financial implications for other bDMARDs/tsDMARDs were revised during the evaluation as a result of the corrections made in annual growth rates and weighted uptake rates of individual bDMARDs/tsDMARDs in the “Attachment 3_Ozanimod MSUC Utilisation and Cost Model, 2e. Scripts – market and 4a. Scripts – affected”.

^b These figures are calculated using the corrected daily cost of \$█ for OZA (\$█ in the submission). The cells D302 and D303 in worksheet “3c. Impact – proposed (eff)” were revised using the effective EMP \$█ and \$█ for OZA initiation and continuing packs, respectively, on the basis of CMA compared to IFX IV.

^c These figures obtained during the evaluation using MBS item 116 for VDZ IV (para 5.19, Vedolizumab PSD, July 2014 PBAC Meeting & para 6.46, Vedolizumab PSD, November 2020 PBAC Meeting). The cell O461 was revised as \$79.75 in the “Attachment 3_Ozanimod MSUC Utilisation and Cost Model, 7. Net changes – MBS”.

Shaded cells indicate data previous seen by the PBAC.

The redacted values correspond to the following ranges:

¹ 500 to < 5000

² 10,000 to < 20,000

³ \$10 million to < \$20 million

⁴ Net cost save

6.54 At its March 2022 meeting, the PBAC noted that the listing of OZA was likely to be cost neutral or modestly cost saving to the PBS, as it may also substitute for more costly bDMARDs/tsDMARDs.

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

7 PBAC Outcome

7.1 The PBAC amended its March 2022 recommendation for the General Schedule, Authority Required (in writing) listing of ozanimod (OZA) for the treatment of moderate to severe ulcerative colitis (MSUC). In considering the additional evidence presented in the current submission, the PBAC’s revised recommendation for listing

was based on, among other matters, its assessment that the cost-effectiveness of OZA would be acceptable if it were cost minimised to the least costly alternative therapy out of infliximab (IFX), tofacitinib (TOF), vedolizumab (VDZ), golimumab (GOL), upadacitinib (UPA) and ustekinumab (UST), noting the last two had been considered since March 2022.

- 7.2 The PBAC reaffirmed its view (from March 2022) the equi-effective doses of OZA and alternative therapies could be derived with reference to the Therapeutic Relativity Sheets and relevant Product Information documents, noting the OZA equi-effective dose component should account for the titration period in be based on an OZA dose of 0.23 mg on Days 1 to 4, 0.46 mg on Days 5 to 7, then 0.92 mg orally once daily in both induction and maintenance therapy.
- 7.3 The PBAC considered that while the clinical need for additional therapies for the treatment of MSUC was low, also considered OZA, as an additional oral therapy with a new mechanism of action, was likely to be of value for some patients.
- 7.4 The PBAC considered the nominated primary comparators of IFX and adalimumab (ADA) were reasonable, and considered the nominated secondary comparators of TOF, VDZ and GOL were also appropriate. The Committee agreed ustekinumab (UST) and upadacitinib (UPA), which were considered in July 2022, could also be considered alternate therapies (however not yet PBS listed at the time of consideration).
- 7.5 The PBAC noted no new clinical trials were presented in the matching-adjusted indirect comparison (MAIC) and further noted the vast majority of trials included in the network meta-analysis (NMA), had previously been considered across the breadth of bDMARD/tsDMARD submissions for MSUC.
- 7.6 The PBAC noted additional analyses were presented in the submission, including a MAIC and NMA, and considered these provided additional confidence regarding the comparative effectiveness of OZA with ADA and the alternative therapies. The PBAC considered there is likely sufficient evidence that OZA, for some patients, provides a significant improvement in effectiveness in the induction phase compared to adalimumab (ADA) and considered OZA is likely to be of non-inferior comparative effectiveness and safety to IFX, TOF, VDZ, GOL, UPA and UST in MSUC for both induction and maintenance therapy.
- 7.7 The PBAC agreed with the ESC and considered the MAIC and NMA presented in the submission were methodologically sound and informative for assessing the comparative effectiveness of OZA and ADA (and to a lesser extent GOL). The Committee noted the MAIC adjusted for differences in the trial populations, such as extent of colitis or pancolitis and extent of prior treatment compared to other bDMARD/tsDMARD trials it previously considered were likely to be impactful for assessing the clinical claim. The PBAC noted the results of the MAIC found statistically significant results in favour of OZA over ADA for the outcomes of clinical response (odds ratio (OR) 1.532, 95% CI 1.036, 2.265) and endoscopic improvement (OR 1.660, 95% CI 1.008, 2.734), but not for clinical remission (OR 1.216, 95% CI 0.523, 2.831) in

induction therapy. The PBAC considered, on balance, the results of the MAIC likely support a conclusion that OZA, for some patients, provides a significant improvement in effectiveness over ADA. The PBAC also considered the results of the NMA were overall likely supportive of this conclusion and noted there were uncertainties with the results of the NMA due to differences arising between the fixed effects and random effects model approaches. However, the Committee agreed with the ESC and PSCR/Pre-PBAC Response that there were strengths and weaknesses with both these statistical model approaches in the context of the MSUC comparison and considered it was reasonable to consider the totality of evidence presented in the NMA.

- 7.8 The PBAC agreed with the ESC that it was highly uncertain that a claim that OZA was of superior comparative effectiveness to GOL was adequately supported by one statistically significant result, in one outcome, for one subgroup, under one modelling approach. Therefore, the PBAC did not consider a conclusion that OZA is of superior comparative effectiveness to GOL was adequately supported (discussed further in paragraph 6.30).
- 7.9 With regards to comparative safety, the PBAC agreed with the ESC and considered OZA and ADA had different but generally well-characterised safety profiles and considered a claim of different but not worse safety was reasonable. Overall, the Committee reaffirmed its view expressed in March 2022 that OZA is likely to be of overall non-inferior comparative safety to the alternative bDMARDs/tsDMARDs in MSUC but noted OZA has a different safety profile to these therapies.
- 7.10 The PBAC considered its view that the claim of non-inferior comparative effectiveness and safety to IFX in MSUC had been adequately supported (March 2022), that a listing on a cost minimisation approach was reasonable. Furthermore, given superior comparative effectiveness to ADA had been adequately supported (current submission), it was reasonable for OZA to be more costly than ADA. The PBAC considered the cost should be no greater than any of the alternative therapies, IFX, VDZ, GOL, TOF, UPA or UST, based on a cost minimisation approach over two years, consistent with prior PBAC recommendations for MSUC.
- 7.11 The PBAC affirmed its previously expressed view in March 2022 that, if listed on a cost minimisation basis with the least costly of IFX, VDZ, GOL, TOF, UPA or UST bDMARD/tsDMARD, the listing of OZA for MSUC was likely to be cost neutral or modestly cost saving to the PBS (as it may also substitute for more costly alternatives). The PBAC noted the submission did not provide updated utilisation or financial estimates and therefore considered the estimates of utilisation remained reasonable, however noted prices of some items had changed since its March 2022 recommendation.
- 7.12 The PBAC noted in its March 2022 recommendation for OZA that it would consider a future submission to request revision to the number of drugs listed for MSUC that can be attempted within a treatment cycle before a patient must enter a 5-year break. Further to its earlier-expressed view, the PBAC considered 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 noted such a review was broader than the scope of the OZA recommendation and considered listing could progress under current arrangements (i.e. 3 treatment failures).

- 7.13 The PBAC noted the submission did not request a change to the restriction recommended at the March 2022 meeting but advised the restriction corrections suggested by the Secretariat at this November 2022 consideration are appropriate (noting a corrigendum was issued after the March 2022 recommendation to account for the titration period in the timing of assessment of response). The PBAC noted the flow-on restriction changes previously noted in its March 2022 recommendation for MSUC remained applicable.
- 7.14 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because OZA is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over the alternative bDMARDs/tsDMARDs, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add indication as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
OZANIMOD					
ozanimod 920 microgram capsule, 28	NEW	1	28	3	Zeposia
Restriction Summary [NEW] / Treatment of Concept: [NEW]					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)				
(NOTEs applying to all restriction summaries below)					
NOTE: TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS --- --- See end of listing for revised concept					
NOTE: No increase in the maximum quantity or number of units may be authorised.					
NOTE: No increase in the maximum number of repeats may be authorised.					

Public Summary Document – November 2022 PBAC Meeting

NOTE: Special Pricing Arrangements apply.
Indication: Moderate to severe ulcerative colitis
Treatment Phase: Initial treatment - Initial 1 (new patient)
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)]
AND
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
Population criteria:
Patient must be at least 18 years of age.
Prescribing Instructions:
The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice), which includes: (i) the completed current Mayo clinic or partial Mayo clinic calculation sheet including the date of assessment of the patient's condition; and (ii) 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 9 and 17 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:

Public Summary Document – November 2022 PBAC Meeting

	If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition 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
Restriction Summary 11830 / Treatment of Concept: 11915	
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Initial treatment - Initial 2 (change or re-commencement of treatment after a break in biological medicine of less than 5 years)
	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)]
	AND
	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
	Population criteria:
	Patient must be at least 18 years of age
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice), which includes: (i) the completed current Mayo clinic or partial Mayo clinic calculation sheet including the date of assessment of the patient's condition if relevant; and

Public Summary Document – November 2022 PBAC Meeting

	(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 9 and 17 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
Restriction Summary TMP / Treatment of Concept: TMP Authority Required	
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Initial treatment - Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)
	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)]
	AND
	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

Public Summary Document – November 2022 PBAC Meeting

	Population criteria:
	Patients must be at least 18 years of age
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice), which includes: (i) the completed current Mayo clinic or partial Mayo clinic calculation sheet including the date of assessment of the patient's condition; and (ii) the details of prior biological medicine treatment including the details of date and duration of treatment.
	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 9 and 17 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 TMP24858 / Treatment of Concept: TMP24858 Authority Required	
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Initial 1 (new patient) or Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) or Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) - balance of supply
	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)]
	AND
	Clinical criteria:
	Patient must have received insufficient therapy with this drug for this condition under the Initial 1 (new patient) restriction to complete 17 weeks treatment; or

Public Summary Document – November 2022 PBAC Meeting

	Patient must have received insufficient therapy with this drug for this condition under the Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) restriction to complete 17 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 17 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
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OZANIMOD					
ozanimod 920 microgram capsule, 28	NEW	1	28	5	Zeposia
Restriction Summary TMP24860 / Treatment of Concept: TMP24859 Authority Required					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required				
<i>(NOTEs applying to all restriction summaries below)</i>					
NOTE: TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS -----					
NOTE: No increase in the maximum quantity or number of units may be authorised.					
NOTE: No increase in the maximum number of repeats may be authorised.					
NOTE: Special Pricing Arrangements apply.					
Indication: Moderate to severe ulcerative colitis					
Treatment Phase: Continuing treatment					
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)]					
AND					
Clinical criteria:					
Patient must have previously received PBS-subsidised treatment with this drug for this condition					
AND					
Clinical criteria:					
Patient must have demonstrated or sustained an adequate response to treatment by having a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 while receiving treatment with this drug					
AND					
Population criteria:					
Patients must be at least 18 years of age					
Prescribing Instructions:					

Public Summary Document – November 2022 PBAC Meeting

	Patients who have failed to maintain a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug.
	Prescribing Instructions: Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain a response.
	Prescribing Instructions: At the time of the authority application, medical practitioners should request sufficient quantity for up to 24 weeks of treatment under this restriction.
	Prescribing Instructions: An application for the continuing treatment must be accompanied with the assessment of response conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from cessation of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within this treatment cycle. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological medicine was approved in this cycle and the date of the first application under a new cycle under the Initial 3 treatment restriction.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Restriction Summary 11882 edited / Treatment of Concept: 11882: Authority Required	
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Balance of supply for the continuing treatment phase
	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)]
	AND
	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 restriction
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Restriction Summary TMP24862 / Treatment of Concept: TMP24861 Authority Required	
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment – ‘grandfather’ arrangements

Public Summary Document – November 2022 PBAC Meeting

	Clinical criteria:
	Patient must be receiving non-PBS-subsidised treatment with this drug for this indication which commenced prior to [1 Month 20XX]
	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 the 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
	Population criteria:
	Patients must be at least 18 years of age
	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 baseline Mayo clinic or partial Mayo clinic score at the time of initiating non-PBS subsidised treatment (if available), including the date of assessment; (ii) the date of commencement of this drug.
	Administrative advice:
	Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Administrative advice:
	This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative Advice:
	Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Public Summary Document – November 2022 PBAC Meeting

<p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OZANIMOD					
ozanimod 230 microgram capsule [4] (&) ozanimod 460 microgram capsule [3], 7	12278F	1	1	0	Zeposia
Restriction Summary TMP24885 / Treatment of Concept: TMP24884					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED – NEW CODE)				
Indication: Moderate to severe ulcerative colitis					
Treatment Phase: Dose escalation occurring at initial treatment, or re-initiation of treatment					
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)]					
NOTE: No increase in the maximum quantity or number of units may be authorised.					
NOTE: No increase in the maximum number of repeats may be authorised.					
NOTE: Special Pricing Arrangements apply.					
NOTE: Ensure that PBS-subsidy is approved for the 920 mcg strength prior to supply of this titration pack. It is advisable to only have the titration pack prescription dispensed at the same time as a prescription for the 920 mcg capsules, or where a supply of the 920 mcg capsules is already in existence (in the case of mid treatment dose interruption).					

Revised explanatory NOTE concept to replace the corresponding NOTE in all drugs listed for moderate to severe ulcerative colitis:

<p>NOTE: TREATMENT CYCLES AND TREATMENT PHASES IN MODERATE TO SEVERE ULCERATIVE COLITIS LISTINGS</p> <p>The following information applies to Pharmaceutical Benefits Scheme (PBS) benefits listed 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.</p> <p>Where the term 'biological medicine' appears in this note and restrictions, it refers to any PBS benefit where the PBS indication specifies: Moderate to severe ulcerative colitis. Some benefits are not biological medicines, but are small molecules. However, for administrative purposes, these benefits are included within the term "biological medicine".</p> <p>Treatment cycles: The same biological medicine cannot be prescribed twice within the same treatment cycle where it has resulted in an inadequate response in terms of Mayo clinic score improvement in the same treatment cycle.</p>
--

<p>Where treatment has resulted in an inadequate response on 3 occasions in total, a treatment cycle is considered to have been completed and there must be a 5-year break in PBS-subsidy from all medicines with the PBS indication: 'Moderate to severe ulcerative colitis' before starting a new treatment 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.</p> <p>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.</p> <p>Prescribing under the correct 'Treatment phase' listing for the authority application:</p> <p>(1) Initial treatment. Apply under the 'Initial 1' treatment listing where the patient has never received a biological medicine for moderate to severe ulcerative colitis.</p> <p>(2) Continuing treatment. Apply under the 'Continuing treatment' listing where the patient is experiencing an adequate response as defined in the restriction where there has been no change in prescribed biological medicine. Under no circumstance is continuing treatment to proceed initial treatment. An authority application for continuing treatment is not to be made on the same day as initial treatment.</p> <p>(3) Changing therapy. Apply under the '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 it has failed to provide the patient with an adequate response within the same treatment cycle. A response assessment to the preceding supply of biological medicine must accompany this initial 2 treatment authority application.</p> <p>(4) Recommencement of treatment after a 5-year break in PBS-subsidised therapy. Apply under the 'Initial 3' treatment listing. Prior corticosteroid and immunosuppressive therapies need not be re-trialled.</p> <p>(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".</p>
--

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

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

10 Sponsor's Comment

The Sponsor looks forward to continuing to work with the PBAC and the Department of Health to provide access to ozanimod for the treatment of moderate to severe ulcerative colitis (MSUC).