

**6.05 OZANIMOD,
Capsule 920 micrograms,
Pack containing 4 capsules 230 micrograms and
3 capsules 460 micrograms,
Zeposia[®],
Celgene Pty Limited.**

1 Purpose of submission

- 1.1 The Category 2 submission requested an Authority Required (in writing) listing of ozanimod (OZA) for the treatment of patients with moderate to severe ulcerative colitis (MSUC) in adults who have had an inadequate response, lost response or were intolerant to prior therapies (5-aminosalicylates, and thiopurines or steroids).
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus intravenous infliximab (IFX IV) as the primary comparator, and vedolizumab (VED), adalimumab (ADA), golimumab (GOL) and tofacitinib (TOF) as secondary comparators. The key components of the clinical issue addressed by the submission are summarised in Table 1.

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

Component	Description
Population	Adult patients with MSUC who have had an inadequate response, lost response, or were intolerant to standard treatment.
Intervention	OZA PO 0.92 mg capsule (1 mg OZA HCl) daily after escalation for 7 days ^a .
Comparator	Primary comparator: <ul style="list-style-type: none"> • IFX IV infusion, 5 mg/kg at 0, 2 and 6 weeks then Q8W thereafter. Secondary comparators: <ul style="list-style-type: none"> • VED IV infusion, 300 mg at Weeks 0, 2 and then Q8W thereafter. • ADA SC injection, 160 mg at Week 0, 80 mg at Week 2 then 40 mg Q2W 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 ^b	Indirect comparison of OZA and comparators for induction and maintenance therapy accounting for differences in trial design: <ul style="list-style-type: none"> • Clinical response • Clinical remission
Clinical claim	Primary comparator: <ul style="list-style-type: none"> • OZA is non-inferior in terms of efficacy and safety to IFX. Secondary comparators: <ul style="list-style-type: none"> • OZA is non-inferior in terms of efficacy to VED, ADA, GOL and TOF. • OZA is non-inferior in terms of comparative safety, with a trend towards more favourable safety compared to VED, ADA, GOL and TOF.

Source: Table 1, p19 of the submission.

ADA = adalimumab; BD = twice daily; GOL = golimumab; HCl = hydrochloride; IFX = infliximab; IV = intravenous; MSUC = moderate to severe ulcerative colitis; OZA = ozanimod; PO = oral; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous; TOF = tofacitinib; VED = vedolizumab

^a 0.23 mg capsule (0.25 mg OZA HCl) daily in Days 1-4, then 0.46 mg capsule (0.50 mg OZA HCl) daily in Days 5-7.

^b No common-reference based indirect comparison of safety outcomes was performed for OZA versus its primary and secondary comparators.

2 Background

Registration status

2.1 TGA status at time of PBAC consideration: not registered. The submission was made under the TGA/PBAC Parallel Process. The TGA application requested an extension of the indication to MSUC. The proposed TGA indication in the draft Product Information (PI) was:

ZEPOSIA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

2.2 At the time of PBAC consideration, the Delegate's Overview was available. The Delegate requested advice from the Advisory Committee on Medicines (ACM) meeting, which took place on 4 February 2022. The Delegate and the ACM were supportive of the indication below.

ZEPOSIA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.

- 2.3 Currently, the approved TGA indication for OZA is for the treatment of adult patients with relapsing forms of multiple sclerosis.

Previous PBAC consideration

- 2.4 This is the first consideration of OZA by the PBAC for this indication. OZA is currently listed on the PBS for the treatment of relapsing remitting multiple sclerosis (RRMS).

3 Requested listing

- 3.1 The listing requested by the Sponsor has not been presented as it is long and complex. The requested listing has been reviewed by the Secretariat according to the usual processes, and the recommended listing is presented in Section 8, incorporating suggested amendments from the Secretariat.
- 3.2 The cost-minimisation analysis for OZA was based on the price for IFX (there is no SPA applied to IFX).
- 3.3 The submission requested the listing of a dose escalation pack for the first 7 days' supply (0.23 mg capsule once daily for 4 days followed by 0.46 mg capsule once daily for 3 days) and a 28-day pack for maintenance treatment listing (0.96 mg capsule once daily). OZA for treatment of MSUC requires an assessment of a patient's response to induction phase of treatment (between 9 and 17 weeks of therapy, as proposed in the submission) to determine whether patients are eligible for OZA maintenance therapy.
- 3.4 The proposed OZA restrictions specified that, to be eligible for OZA, patients must have failed to achieve response to adequate trial of (i) 5-aminosalicylates (≥ 3 months), and (ii) thiopurines (≥ 3 months) or steroids (≥ 6 weeks). The definition of prior treatment failure was stricter in the requested PBS listings compared with that in the OZA trials, but was consistent with current PBS listings for MSUC. The majority of patients in a key OZA trial, True North, had not failed prior corticosteroids, and were naïve to thiopurines. In addition, patients with severe extensive colitis were excluded from True North, but are eligible for OZA according to the proposed PBS listings.
- 3.5 The Pre-Sub-Committee Response (PSCR) acknowledged the requested PBS restriction is narrower than the inclusion criteria for the True North and Touchstone trials, and noted that the requested restriction was consistent with the nominated comparators. The PSCR also stated that there were additional patients in the trials that were intolerant of earlier-line therapies: in True North, the majority of patients had failed or were intolerant to oral 5-ASAs (81-85%) as well as to steroids (57-69%), and 41-48% of patients had failed or were intolerant to immunomodulators. However, the ESC noted that even taking this into account, only about half of the trial population had failed or were intolerant to immunomodulators, and considered the trial population in True North may not be representative of the proposed PBS population. To investigate these issues, the PSCR and Pre-PBAC Response presented additional subgroup analyses, which are discussed further in Section 6.

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

4 Population and disease

- 4.1 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.
- 4.2 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.
- 4.3 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.

5 Comparator

- 5.1 The submission nominated IFX IV as the primary comparator and the other four disease-modifying anti-rheumatic drugs (DMARDs) listed on the PBS for treatment of MSUC, namely VED, ADA, GOL and TOF, as secondary comparators. Of the secondary comparators, only TOF is administered orally, similar to OZA.
- 5.2 The main arguments provided in support of this nomination was that IFX and VED are the most widely prescribed biological DMARDs (bDMARDs) for the treatment of MSUC (Paragraph 5.1, Tofacitinib (MSUC) Public Summary Document [PSD], November 2020 PBAC meeting). IFX is available via PBS as an intravenous (IV) formulation and a subcutaneous (SC) formulation. The submission selected the IV formulation of IFX over the SC formulation as the main comparator, given that IFX SC was listed on a cost-minimisation basis to IFX IV and that IFX IV has been the main comparator in other DMARD submissions, with the exception of VED SC (comparator: VED IV).
- 5.3 In the context of the CMA taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it

must make a statement to this effect. Alternative therapies include IFX, VED, TOF, ADA and GOL.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (5) and organisations (2) via the Consumer Comments facility on the PBS website.

6.3 Consumer comments were provided from Crohn's and Colitis Australia (CCA), and the Gastroenterological Society of Australia (GESA). CCA emphasised the flexibility associated with oral therapy that does not require infusion in a medical facility, thereby avoiding absences from work and reducing travel requirements. Similarly, GESA noted that there are access issues with infusion centres that will be ameliorated with an oral therapy. GESA also noted that efficacy of biological therapies is not universal and persistence is not durable in many cases, leading to a loss of response and an associated decline of the patient, and that it is important to have agents available that will serve all patients in the context of other agents being less well tolerated or contraindicated.

6.4 The comments from health care professionals described the effectiveness of OZA in the treatment of MSUC and highlighted the need for additional therapeutic options for the management of the condition, especially for those with a new mechanism of action for use in patients who have failed existing biological therapies. The comments also described the benefits of having an additional oral therapy option available, given only one other oral alternative is currently PBS listed for MSUC.

Clinical studies

6.5 The primary comparison in the submission was based on anchored indirect treatment comparisons (ITCs) for OZA vs. IFX via two key OZA trials (True North and Touchstone) and five IFX trials (ACT1, ACT2, Kobayashi 2016, Jiang 2015 and REMICADE).

6.6 True North was a Phase 3, randomised, double-blind, placebo-controlled study of OZA as induction and maintenance therapy for subjects with MSUC. The induction period of the study was composed of two cohorts in which subjects were treated for a total of 10 weeks and evaluated for clinical response/remission, followed by a 42-week maintenance phase:

- Cohort 1: subjects were randomised in a 2:1 ratio to receive either OZA 0.92 mg (after 7 days of dose escalation) or placebo once daily in a double-blind fashion,

stratified prior to randomisation by corticosteroid use at screening and prior anti-tumour necrosis factor (TNF) therapy¹.

- Cohort 2: subjects received open-label OZA 0.92 mg (after 7 days of dose escalation) once daily. There was no placebo group for Cohort 2.
- Responders from the OZA arm of Cohort 1 and Cohort 2 were combined for the maintenance period; these responders were re-randomised in a 1:1 ratio and blinded to receive either OZA or placebo during the maintenance phase.

Subjects who were randomised to the Cohort 1 placebo group in the induction period and had at least a clinical response at Week 10 continued to receive placebo in the maintenance period in a double-blind manner; their efficacy data were not used in the evaluation of the maintenance phase, which only compared the re-randomised OZA and placebo groups. Subjects with missing Week 10 efficacy data for the induction period and/or subjects with missing Week 52 efficacy data for maintenance period were considered non-responders using non-responder imputation.

- 6.7 Touchstone was a double-blind, placebo-controlled Phase 2 trial of OZA in 197 adults with MSUC. The trial included blinded induction and maintenance periods and an optional open-label period. Patients were randomly assigned, in a 1:1:1 ratio, to receive oral OZA at a dose of 0.46 mg or 0.92 mg or placebo, once daily. Patients underwent dose escalation during the first week after randomisation; thereafter, the patients received the randomly assigned dose for 8 weeks. Patients who completed the induction period and were responders at Week 8 entered the 24-week maintenance period in which they continued to receive the same trial treatment as during the induction period.
- 6.8 True North was the largest trial (induction phase N = 1,012; maintenance phase N = 526), while Touchstone was comparatively small, with only 132 patients in the OZA 0.92 mg and placebo groups at induction, and 67 patients in the maintenance phase.
- 6.9 All the IFX trials (ACT1, ACT2, Kobayashi 2016, Jiang 2015 and REMICADE) have previously been reviewed by the PBAC. Of the secondary comparators, trials have also been previously reviewed by the PBAC for ADA, GOL and VED.
- 6.10 Details of the studies presented in the submission are provided in Table 2. The TOF study is included in the tables below, as part of the secondary comparison, as it has not been previously reviewed by the PBAC.

¹ Anti-TNF therapy includes IFX, ADA and GOL.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Primary comparison		
OZA vs. placebo		
True North (NCT02435992)	True North Clinical Study Report, Statistical Analysis Plan and related documents	29 October 2020
	Sandborn W, Feagan B, D'Haens G, Wolf D et al. Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis.	<i>New England Journal of Medicine</i> 2021; 385: 1280-1291.
Touchstone (NCT01647516)	Touchstone Clinical Study Report, Statistical Analysis Plan and related documents	04 November 2015
	Sandborn W, Feagan B, Wolf D, D'Haens G, Vermeire S et al. Ozanimod Induction and maintenance Treatment for Ulcerative Colitis.	<i>New England Journal of Medicine</i> 2016; 374 (18): 1754-1762.
IFX vs. placebo		
ACT 1 (Rutgeerts 2005, NCT00036439)	Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A et al. Infliximab for Induction and maintenance therapy for ulcerative colitis.	<i>New England Journal of Medicine</i> 2005; 353 (23): 2462-2476.
Kobayashi 2016	Kobayashi T, Suzuki Y, Motoya S, Hirai F, Ogata H et al. First trough level of infliximab at Week 2 predicts future outcomes of Induction therapy in ulcerative colitis-results from a multicentre prospective randomized controlled trial and its post-hoc analysis.	<i>Journal of gastroenterology</i> 2016; 51(3):241-51.
Jiang 2015	Jiang XL, Cui HF, Gao J, Fan H Low-dose Infliximab for Induction and maintenance Treatment in Chinese Patients With Moderate to Severe Active Ulcerative Colitis.	<i>Journal of Clinical Gastroenterology</i> 2015; 49 (7): 582-588.
REMICADE (NCT01551290)	A Phase 3, Multicentre, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and safety of Infliximab in Chinese Subjects With Active Ulcerative Colitis.	REMICADE Clinical Study Report Synopsis 21 October 2014
Secondary comparison		
TOF vs. placebo		
Study A3921063	Sandborn, W. J., Subrata, G., et. al. Tofacitinib, an Oral Janus Kinase Inhibitor, in Active Ulcerative Colitis.	<i>New England Journal of Medicine</i> 2012; 367:616-624

Source: Data extracted from Table 25, pp 56-57 and Table 26, p 58 and Table 130, p 171 of the submission.

IFX = infliximab; OZA = ozanimod; TOF = tofacitinib.

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcomes
Primary comparison					
OZA v PBO					
True North	IP: 1012 MP: 526	P3, MC, R, DB (cohort 1 IP and MP); OL (cohort 2 IP)	Low	TNFi-n and TNFi-e MP: Week 10 responders	Primary: clinical remission
Touchstone	197	P2, R, DB, PC	Low ^a	TNFi-n and TNFi-e MP: Week 8 responders	Secondary: clinical response
IFX v PBO					
ACT 1 [induction & maintenance]	364	P3 MC, R, PC, DB (52wk), 3-arm	Low ^b	TNFi-n	Primary: clinical response Secondary: clinical remission
ACT 2 [induction & maintenance]	364	P3 MC, R, PC, DB (30wk), 3-arm	Low ^b	TNFi-n	
Jiang 2015 [induction & maintenance]	123	MC, R, PC, DB (30wk), 3-arm	Low ^b	TNFi-n (Chinese)	
REMICADE [induction & maintenance]	99	P3 MC, R, PC, DB (26wk)	Low ^b	Prior TNFi NR (Chinese)	
Kobayashi 2016 [induction & maintenance]	IP: 208 MP:NR	P3 MC, R, PC, DB (30wk), RWD for maintenance (8wk induction, 22wk maintenance)	Low	TNFi-n (Japanese) Maintenance: Wk8 responders	
Secondary comparison					
TOF v PBO					
Study A3921063	194	P2, MC, R, PC, DB (8 wk)	Low	TNF-n and TNF-e	Primary: clinical response Secondary: clinical remission

Source: Compiled during the evaluation based on Sections 2.3-2.4 of the submission.

^a Low risk of bias in the induction phase, but few patients progressed to maintenance (OZA 1 mg N=42; placebo N=25) which made maintenance phase data more vulnerable to confounders.

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

DB = double blind; IFX = infliximab, IP = induction phase; MC = multi-centre; MP = maintenance phase; NR = not reported; OL=open label; PBO = placebo; P2 = Phase 2; P3=phase 3; PC = placebo controlled; R = randomised, RWD = randomised withdrawal design; TNFi-e = tumour necrosis factor inhibitor experience, TNFi-n = tumour necrosis factor inhibitor naïve, TOF = tofacitinib.

6.12 There was a high risk of bias due to attrition bias noted for four of the IFX trials in the maintenance phase. These IFX trials had a higher proportion of patients who were lost to follow-up (2-40%) and discontinued (15–60%) compared to the OZA trials (1-3% and 7-45% respectively). Paucity of available detail for Jiang 2015 meant risk of bias was unclear in some domains.

6.13 One key differentiating factor between these trials is that in the two OZA trials and the Kobayashi 2016 IFX trial, only patients who responded to treatment during the induction phase could continue treatment in the maintenance phase; the other IFX trials did not require response to continue. This means that the OZA and Kobayashi 2016 trials had a selected population of responders in their ‘maintenance’ phases, compared to the other IFX trials. Further, while the Kobayashi 2016 and Touchstone

trials used the ITT-principle, where non-responders from the initiation phase were still counted as non-responders in the maintenance phase, the True North trial measured efficacy in the maintenance period as a proportion of patients who entered the maintenance phase. The PBAC has previously not been presented with indirect comparisons that contain these differences in trial design, due to concerns of bias that would favour TOF over IFX (Paragraph 6.11, tofacitinib (MSUC) PSD, November 2020 PBAC meeting). Therefore, there is a high risk of bias (favouring OZA) in the indirect treatment comparison comparing OZA and IFX.

- 6.14 The PSCR acknowledged the limitations of the indirect comparisons of OZA and IFX due to differences in trial design, however noted the design of the True North trial was consistent with other more recently conducted trials in MSUC including those involving TOF, GOL and VED. The PSCR also presented additional sensitivity analyses for the indirect comparison versus IFX that excluded the True North trial (see paragraph 6.28 below).
- 6.15 The clinically relevant outcomes were clinical remission and clinical response, as assessed using the 4-component Mayo score. The PBAC previously accepted these outcomes when considering biological therapies for MSUC (Infliximab PSD, March 2014 PBAC meeting; Adalimumab PSD, July 2014 PBAC meeting; Vedolizumab PSD, July 2014 PBAC meeting; Tofacitinib (MSUC) PSD, November 2020 PBAC meeting).
- 6.16 The requested OZA listing for MSUC is consistent with current PBS restrictions and required prior failure of 5-aminosalicylate and at least one of either corticosteroids, azathioprine or mercaptopurine therapies. The submission did not state what proportion of patients in True North would have qualified for PBS-funded DMARD therapy; however, 73-80% of patients in True North had failed prior aminosalicylates, 38-47% of patients had failed prior steroids, 13-26% of participants had failed to respond to prior azathioprine, and only 5-7% had failed to respond to prior mercaptopurine. This means the majority of patients in True North had not failed oral corticosteroids, and were naïve to thiopurines, and may have responded to these therapies, which would preclude them from qualifying for DMARD therapy. Further, even fewer patients in True North may have qualified for PBS-funded DMARD therapy, as the definition of prior treatment failure employed by True North required less exposure to lower doses of therapy compared to the PBS restriction, as shown in Table 4. The PSCR noted that there were additional patients in the trials who were intolerant of earlier-line therapies (paragraph 3.5), but the ESC noted that even taking this into account, patients in True North may not be representative of the proposed PBS population. The Pre-PBAC Response acknowledged the requested PBS restriction was narrower than the inclusion criteria of the key OZA clinical trials, however stated the restriction was requested for consistency with other DMARD listings. To further address the issues with differences between the trial design and recruited populations, the Pre-PBAC Response presented additional subgroup analysis (discussed in paragraph 6.29).

Table 4: Comparison of different definitions of 'treatment failure' used by True North and the target PBS population

Prior therapy	True North definition of prior treatment failure	Proposed PBS restriction definition of prior treatment failure
5-Aminosalicylates	Dose of ≥ 2.4 g daily for at least 8 weeks.	Standard dose for 3 or more consecutive months.
Corticosteroids	Dose of oral prednisone ≥ 30 mg for at least 2 weeks.	Tapered course of oral steroids, starting at a dose of at least 40 mg prednisone, over a 6-week period.
Immunomodulators	Azathioprine ≥ 1.5 mg/kg daily OR 6-mercaptopurine ≥ 0.75 mg/kg for at least 8 weeks.	Azathioprine ≥ 2 mg per kg daily OR 6-mercaptopurine ≥ 1 mg per kg daily for ≥ 3 consecutive months.

Source: Compiled during the evaluation, with data extracted from Table 3, pp 44-47 of the True North CSR; Table 18, p 43 of the submission.

- 6.17 The submission noted that the PBAC has not previously defined a non-inferiority margin for outcomes when considering treatments for MSUC, and so nominated a lack of statistically significant differences between OZA and IFX ($p < 0.05$). The ESC noted that a lack of statistically significant difference may not be adequate to support a claim of non-inferiority.
- 6.18 The submission performed ITCs against the nominated secondary comparators TOF, VED, ADA and GOL. The PBAC has previously evaluated the relevant trials used by the submission, apart from the TOF study A3921063² (a double-blind, placebo-controlled trial which examined induction-phase therapy of 192 patients). This trial was determined to have a 'low' risk of bias.
- 6.19 A number of the secondary comparator trials also re-randomised patients who responded to active treatment in the induction phase; these were PURSUIT-M (GOL), PURSUIT-J (GOL), GEMINI 1 (VED), VISIBLE 1 (VED), OCTAVE-SUSTAIN (TOF), and Motoya 2019 (VED). These trial designs are more comparable to True North, however OCTAVE-SUSTAIN included responders to either TOF or placebo during induction treatment, while in True North, 100% of the 'responder' population had demonstrated a response to OZA. The submission noted that the ADA trials did not re-randomise induction phase responders for its maintenance phase, so conducted the ITC of OZA vs. ADA as a sensitivity analysis using only Touchstone OZA data.
- 6.20 Generally, the secondary comparator trials specified patients with moderate to severe disease, previous treatment failures of corticosteroids and/or immunomodulators or anti-TNF agents, and the TOF trials excluded patients with ulcerative colitis limited to the distal 15 cm of the colon. In this regard, the populations of the secondary comparators are more similar to the IFX trial populations than the OZA trial populations.

Comparative effectiveness

- 6.21 The efficacy results for clinical remission and clinical response in the induction and maintenance phases of the OZA trials are shown in Tables 5 and 6, respectively. The

² Sandborn, W. J. et. Al., Tofacitinib, an Oral Janus Kinase Inhibitor, in Active Ulcerative Colitis. The New England Journal of Medicine. 2012; 367:616-624.

True North assessment in the maintenance period only performed statistical comparisons between the re-randomised cohort and excluded the patients who had been in the placebo group from the induction through to maintenance phase.

Table 5: Proportion of patients who had a clinical response or remission during the induction phase, OZA key trials

Clinical Response			
True North – measured at Week 10, ITT population, Non-Responder imputation			
	Cohort 1		Cohort 2
	OZA 0.92 mg N=429	Placebo N=216	OZA 0.92 mg N=367
Subjects in clinical response, n (%) ^a	222 (51.7)	55 (25.5)	209 (56.9)
Odds ratio (95% CI) ^b	3.213 (2.232, 4.626)		-
Difference in proportions (95% CI)	0.263 (0.189, 0.337)		-
p-value	< 0.0001		-
Touchstone– measured at Week 8, ITT population, missing data classified as no response			
	OZA 0.46 mg N=65	OZA 0.92 mg N=67	Placebo N=65
	Subjects in clinical response, n (%)	35 (54)	38 (57)
p-value (vs. placebo)	0.06	0.02	-
Clinical Remission			
True North – measured at Week 10, ITT population, Non-Responder imputation			
	Cohort 1		Cohort 2
	OZA 0.92 mg N=429	Placebo N=216	
Subjects in clinical remission, n (%) ^c	50 (11.7)	10 (4.6)	62 (16.9)
Odds ratio (95% CI) ^b	2.718 (1.351, 5.467)		-
Difference in proportions (95% CI)	0.070 (0.029, 0.111)		-
p-value ^b	0.0037		-
Touchstone– measured at Week 8, ITT population, missing data classified as no response			
	OZA 0.46 mg N=65	OZA 0.92 mg N=67	Placebo N=65
	Subjects in clinical remission, n (%)	9 (14)	11 (16)
p-value (vs. placebo)	0.14	0.048	-

Source: Constructed during the evaluation. Data extracted from Tables 43 & 44, p 103; Tables 57 & 58, pp 107-108 of the submission. CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = Intent-to-Treat; RBS = rectal bleeding subscore; OZA = ozanimod; SFS = stool frequency subscore; TNF = tumour necrosis factor.

^a Clinical response is defined as: A reduction from baseline in the 4-component Mayo score of ≥ 3 points and $\geq 30\%$, and a reduction from baseline in the RBS of ≥ 1 point or an absolute RBS of ≤ 1 point.

^b Odds ratio (active/placebo), treatment difference, 2-sided 95% Wald CI and p-value for comparison between the Cohort 1 ozanimod and placebo group are based on the CMH test, stratified by corticosteroid use at screening and prior anti-TNF use (yes or no).

^c Clinical remission is defined as: 4-component Mayo score of ≤ 2 points and with no individual subscore of > 1 point

Note: In True North, 4-component Mayo score (0-12): Sum of the Rectal Bleeding subscore, Stool Frequency subscore, Physician Global Assessment subscore, and the endoscopy subscore. Subjects with any of the Mayo subscores missing at Week 10 for induction, or Week 52 for maintenance, are classified as non-remitters.

Table 6: Proportion of patients who demonstrated a response or remission during the maintenance period in the OZA trials

Clinical Response			
True North – measured at Week 52, re-randomised responder population, Non-Responder imputation			
	Cohort 1 (re-randomised)^d		Placebo N=69
	OZA 0.92 mg – OZA 0.92 mg N=230	OZA 0.92 mg – placebo N=227	
Subjects in clinical response, n (%) ^a	145 (63.0)	97 (42.7)	28 (40.6)
Odds ratio (95% CI) ^b	2.370 (1.615, 3.477)		
Difference in proportions (95% CI)	0.205 (0.116, 0.293)		
p-value	< 0.0001		
Touchstone – measured at Week 32, ITT population, missing data classified as no response			
	OZA 0.46 mg N=65	OZA 0.92 mg N=67	Placebo N=65
Subjects in clinical response, n (%)	23 (35)	34 (51)	13 (20)
p-value (vs. placebo)	0.06	<0.001	-
Clinical Remission			
True North – measured at Week 52, re-randomised responder population, Non-Responder imputation			
	Cohort 1 (re-randomised)^d		Placebo N=69
	OZA 0.92 mg – OZA 0.92 mg N=230	OZA 0.92 mg – placebo N=227	
Subjects in clinical remission, n (%) ^c	88 (38.3)	42 (18.5)	17 (24.6)
Odds ratio (95% CI) ^b	2.876 (1.854, 4.461)		-
Difference in proportions (95% CI)	0.199 (0.120, 0.278)		-
p-value	< 0.0001		-
Touchstone – measured at Week 32, ITT population, missing data classified as no response			
	OZA 0.46 mg N=65	OZA 0.92 mg N=67	Placebo N=65
Subjects in clinical remission, n (%)	17 (26)	14 (21)	4 (6)
p-value (vs. placebo)	0.002	0.01	-

Source: Constructed during the evaluation. Data extracted from Tables 50 & 51, p 105; Tables 66 & 67, pp 110-111 of the submission.

CI = confidence interval; ITT = Intent-to-Treat; OZA = ozanimod; RBS = rectal bleeding subscore

^a Clinical response is defined as: A reduction from Baseline in the 4-component Mayo score of ≥ 3 points and $\geq 30\%$, and a reduction from Baseline in the RBS of ≥ 1 point or an absolute RBS of ≤ 1 point.

^b Odds ratio (active/placebo), treatment difference, and 2-sided 95% Wald CI and p-value for comparison between the ozanimod 0.92 mg - ozanimod 0.92 mg and ozanimod 0.92 mg — Placebo groups are based on the CMH test, stratified by remission status at Week 10 and corticosteroid use at Week 10 (yes or no).

^c Clinical remission is defined as: 4-component Mayo score of ≤ 2 points and with no individual subscore of > 1 point

^d Cohort 1 and Cohort 2 were re-randomised to form the newly labelled 'Cohort 1'.

Note: In True North, 4-component Mayo score (0-12): Sum of the Rectal Bleeding subscore, Stool Frequency subscore, Physician Global Assessment subscore, and the endoscopy subscore. Subjects with any of the Mayo subscores missing at Week 10 for induction, or Week 52 for maintenance, are classified as non-remitters

6.22 Patients treated with OZA 0.92 mg (the proposed dose in the draft PI) achieved a statistically higher clinical remission and clinical response rates than those in the placebo group in both the induction and maintenance phases across True North and Touchstone trials.

6.23 As stated, the IFX trials have been previously evaluated by the PBAC (paragraph 6.9). They all demonstrated a statistically significant response in IFX 5 mg/kg over placebo in both induction and maintenance phases, except for REMICADE which failed to demonstrate statistically significant remission in the induction phase, and response in

the maintenance phase. The Kobayashi 2016 trial also failed to demonstrate statistical significance in the maintenance phase, but this trial investigated the predictive value of serum trough levels of IFX and short-term induction therapy; this has been recognised in Paragraph 6.6, Tofacitinib PSD, November 2020 PBAC meeting.

- 6.24 There were a number of differences between the patient populations in the OZA and IFX trials. This resulted in substantial differences in baseline disease characteristics, disease severity and concomitant therapy, and led to transitivity and applicability issues when performing an unadjusted, anchored ITC. These included:
- The OZA trials enrolled patients with less pre-treated, and less severe disease compared to the IFX trials (paragraphs 3.5 and 6.16). True North explicitly excluded patients with 'severe extensive colitis'. The OZA trials did not require prior treatment failures, but did require at least one of concomitant oral aminosalicylates or steroids. In contrast, the IFX trials enrolled patients with moderate to severe disease with inadequate response to corticosteroids and/or azathioprine or mercaptopurine.
 - Approximately 38% of patients in the OZA trials had extensive disease (a predictor of aggressive ulcerative colitis³), compared to 45-80% of patients in the IFX trials. There were fewer baseline concomitant corticosteroids required in the OZA cohorts compared to the IFX cohorts (30-40% vs. 50-80%). Despite these differences, the baseline mean Mayo scores were similar between the OZA and IFX trials; this suggests the patients enrolled in the OZA trials may have had poorly controlled disease, while the patients in the IFX trials were more likely to have severe, treatment refractory disease.
- 6.25 The PSCR presented additional sub-group analyses as evidence for the wider applicability of the trial data, including for variables such as prior anti-TNF use, baseline Mayo score and extent of colitis. The ESC noted that several results of the sub-group analyses had lower point estimates for the outcomes analysed of both induction and maintenance phases, including for a range of secondary variables including endoscopic improvement and mucosal healing.
- 6.26 The submission's ITC was based on the results of meta-analyses it conducted for the two OZA trials and the IFX trials, restricted to the arms which used the proposed OZA 0.92 mg/kg and PBS-listed IFX 5 mg/kg doses.
- 6.27 A summary of the ITC results of OZA vs. IFX is presented in Table 7; risk ratios (RR) >1 and risk differences (RD) >0 favoured OZA treatment. No statistically significant differences were identified, apart from the RD of clinical remission at induction which favoured IFX, and is likely due to a low event rate in the OZA studies. The point estimates in the maintenance phase favoured OZA over IFX; this phase compared an

³ Yarur, A. J. et. al. Predictors of aggressive inflammatory bowel disease. *Gastroenterology & hepatology*. 2011; 7(10), 652–659.

enriched (100% responder) population from True North with the ITT populations of the IFX trials, which would likely have biased the results in favour of OZA.

Table 7: Results of the indirect comparison for OZA vs. IFX – ITT populations

Clinical response at induction	
ITC of OZA vs. IFX (RR)	0.968 (0.715, 1.312); p=0.8360
ITC of OZA vs. IFX (RD)	-0.06 (-0.159, 0.039); p=0.2349
Clinical remission at induction	
ITC of OZA vs. IFX (RR)	0.941 (0.482, 1.838); p=0.8591
ITC of OZA vs. IFX (RD)	-0.13 (-0.222, -0.038^a); p=0.0056
Clinical response at maintenance	
ITC of OZA vs. IFX (RR)	1.077 (0.592, 1.958); p=0.8081
ITC of OZA vs. IFX (RD)	0.03 (-0.101, 0.161); p=0.6532
Clinical remission at maintenance	
ITC of OZA vs. IFX (RR)	1.085 (0.725, 1.626); p=0.6910
ITC of OZA vs. IFX (RD)	0.03 (-0.062, 0.122); p=0.5224

Source: Constructed during the evaluation, using data extracted from Tables 110, 111, 112 and 130 of the submission.

CI = confidence interval; IFX = infliximab; OZA = ozanimod; RD = risk difference; RR = relative risk

^a This is a correction of an error made in the submission, which listed this number as '0.038'.

Note: A RR or RD >1 favours OZA, and a RR or RD < 1 favours IFX.

Bold indicates statistically significant difference.

6.28 The PSCR presented additional sensitivity analyses for the indirect comparison versus IFX, excluding the results of the True North trial (i.e. indirect comparisons of OZA and IFX based only on the Touchstone trial), to examine the impact of the differences in trial designs and patient flows, especially in the maintenance phase.

6.29 The Pre-PBAC Response presented additional sensitivity analyses for two subgroups:

- The subgroup of patients who had failed or were intolerant to prior systemic immunomodulator therapies (excluding methotrexate) from the True North trial; and
- The subgroup of patients identified as having 'no moderate disease' from the True North trial. These analyses are presented in the table below.

The subgroup analyses found no statistically significant differences for the outcomes of clinical response or clinical remission in either the induction or maintenance phases, versus IFX, however for some analyses, the width of the 95% confidence intervals was very wide. The PBAC considered the additional subgroup analyses were informative, however noted they had not been evaluated as they were submitted at the Pre-PBAC Response stage.

6.30 The results of the ITC with secondary comparators for response and remission are presented in Tables 8 and 9, respectively. A RR >1 and RD >0 favoured OZA treatment.

Table 8: Overview of results for RR and RD of the indirect comparison for OZA vs. secondary comparators clinical response at induction and maintenance - ITT population

OZA/ Comparator	Pooled RR (95% CI) vs. placebo	Pooled RD (95% CI) vs. placebo	Indirect comparison of pooled RR (95% CI); p- value (OZA vs. comparator)	Indirect comparison of pooled RD (95% CI); p- value (OZA vs. comparator)
Induction				
OZA	1.84 (1.41, 2.40)	0.25 (0.18, 0.32)	N/a	N/a
VED	1.51 (0.99, 2.29)	0.15 (0.00, 0.29)	1.219 (0.742, 2.002); p=0.4353	0.1 (-0.061, 0.261); p=0.2235
TOF	1.79 (1.49, 2.14)	0.26 (0.20, 0.33)	1.028 (0.745, 1.418); p=0.8667	-0.01 (-0.106, 0.086); p=0.8374
GOL	1.68 (1.35, 2.11)	0.21 (0.12, 0.29)	1.095 (0.774, 1.55); p=0.6076	0.04 (-0.07, 0.15); p=0.4765
ADA	1.36 (1.18, 1.58)	0.14 (0.08, 0.20)	1.353 (0.999, 1.832); p=0.0508	0.11 (0.018, 0.202); p=0.0194
Maintenance				
OZA	1.48 (1.23, 1.77)	0.20 (0.11, 0.29)	N/a	N/a
VED	2.22 (1.76, 2.80)	0.34 (0.26, 0.42)	0.667 (0.496, 0.895); p=0.0071	-0.14 (-0.26, -0.02); p=0.0227
TOF 5 mg	2.55 (1.86, 3.51)	0.30 (0.21, 0.39)	0.58 (0.403, 0.837); p=0.0036	-0.1 (-0.227, 0.027); p=0.1236
TOF 10 mg	3.09 (2.27, 4.21)	0.40 (0.31, 0.49)	0.479 (0.335, 0.685); p=0.0001	-0.2 (-0.327, -0.073); p=0.0021
GOL	1.92 (1.11, 3.32)	0.25 (0.08, 0.42)	0.771 (0.433, 1.373); p=0.3768	-0.05 (-0.242, 0.142); p=0.6104
ADA^a	1.68 (1.29, 2.21)	0.12 (0.06, 0.18)	1.512 (0.827, 2.765); p=0.1795	0.19 (0.024, 0.356); p=0.0251

Source: Compiled during the evaluation, data extracted from Table 154, p 233 & Table 156, p 235; Table 150, p 220 of the submission. ADA = adalimumab; CI = confidence interval; GOL = golimumab; ITT = intention-to-treat; N/a = not applicable; OZA = ozanimod; RD = risk difference; RR = relative risk; TOF = tofacitinib; VED = vedolizumab

Bold indicates statistically significant difference.

^a The ITC with ADA was conducted as a sensitivity analysis using only Touchstone OZA data, due to concerns about differences in trial design which favour OZA precluding accurate comparison, as True North re-randomised responders from its induction phase for maintenance phase evaluation and the ADA trials did not. Touchstone had low numbers who progressed to the maintenance phase (OZA 1 mg N=42; placebo N=25).

Table 9: Overview of results for RR and RD of the indirect comparison for OZA vs. secondary comparators clinical remission at induction and maintenance - ITT population

OZA/ Comparator	Pooled RR (95% CI) vs. placebo	Pooled RD (95% CI) vs. placebo	Indirect comparison of pooled RR (95% CI); p- value (OZA vs. comparator)	Indirect comparison of pooled RD (95% CI); p- value (OZA vs. comparator)
Induction				
OZA	2.56 (1.45, 4.50)	0.07 (0.04, 0.11)	N/a	N/a
VED	2.14 (1.03, 4.43)	0.10 (0.05, 0.15)	1.196 (0.475, 3.012); p=0.7037	-0.03 (-0.091, 0.031); p=0.3353
TOF	3.27 (1.95, 5.49)	0.16 (0.07, 0.25)	0.783 (0.364, 1.686); p=0.5317	-0.09 (-0.187, 0.007); p=0.0677
GOL	2.79 (1.62, 4.80)	0.11 (0.06, 0.17)	0.918 (0.419, 2.011); p=0.8298	-0.04 (-0.105, 0.025); p=0.2291
ADA	1.58 (1.05, 2.40)	0.05 (-0.00, 0.11)	1.62 (0.804, 3.266); p=0.1773	0.02 (-0.045, 0.085); p=0.5476
Maintenance				
OZA	1.84 (1.13, 2.99)	0.08 (0.02, 0.14)	N/a	N/a
VED	2.16 (1.34, 3.48)	0.11 (0.05, 0.17)	0.852 (0.431, 1.684); p=0.6447	-0.03 (-0.115, 0.055); p=0.4883
TOF 5 mg	4.40 (2.28, 8.49)	0.17 (0.11, 0.24)	0.418 (0.185, 0.947); p=0.0367	-0.09 (-0.178, -0.002); p=0.0461
TOF 10 mg	5.03 (2.62, 9.62)	0.20 (0.14, 0.27)	0.366 (0.162, 0.824); p=0.0152	-0.12 (-0.208, -0.032); p=0.0078
GOL	3.22 (0.76, 13.63)	0.27 (-0.04, 0.57)	0.571 (0.125, 2.621); p=0.4715	-0.19 (-0.501, 0.121); p=0.2309
ADA^a	2.32 (1.53, 3.50)	0.12 (0.05, 0.19)	1.466 (0.471, 4.562) p=0.5094	0.03 (-0.105, 0.165) p=0.6623

Source: Compiled during the evaluation, data extracted from Table 150, p 220 & Table 155, p 233 & Table 157, p 235 of the submission. CI = confidence interval; GOL = golimumab; ITT = intention-to-treat; N/a = not applicable; OZA = ozanimod; RD = risk difference; RR = relative risk; TOF = tofacitinib; VED = vedolizumab

Bold indicates statistically significant difference.

^a The ITC with ADA was conducted as a sensitivity analysis, due to concerns about differences in trial design which favour OZA precluding accurate comparison, as True North re-randomised responders from its induction phase for maintenance phase evaluation and the ADA trials did not. Touchstone had low numbers who progressed to the maintenance phase (OZA 1 mg N=42; placebo N=25).

6.31 The results of the secondary comparator ITCs showed that for response at induction, OZA appeared similar to all the secondary comparators; the point estimates were close to 1, and the 95% CIs were comparatively narrow, apart from ADA which had a statistically significant RD favouring OZA. Efficacy in the maintenance phase statistically significantly favoured TOF over OZA (both response and remission), and VED over OZA (for response). OZA was statistically significantly favoured over ADA by RD in the maintenance phase; other maintenance phase results had point estimates which favoured VED and GOL over OZA, but wide confidence intervals suggest that the ITC of OZA versus VED and GOL was not sufficiently powered to detect a true difference.

6.32 For the secondary comparators:

- For TOF, efficacy (both response and remission) in the maintenance phase statistically significantly favoured TOF over OZA. The ESC noted the PSCR proposed that a slower onset of action of OZA vs TOF was responsible for this significant difference. The ESC considered that a slower onset of action would have a greater effect on induction outcomes, rather than maintenance where only earlier responders were allowed to continue.
- For VED, efficacy (response) in the maintenance phase statistically favoured VED over OZA. The ESC noted the PSCR argued that adjusting for the higher placebo response in the True North study would remove the statistical significance. The ESC considered however that the higher placebo response rate in the OZA trials would be consistent with the suggestion that the patients included in the OZA trials had less severe/resistant disease.
- For GOL, the ESC noted the point estimates favoured GOL over OZA but considered overall that the wide confidence intervals suggested that the ITC of OZA versus GOL was not sufficiently powered to detect a true difference.

Comparative harms

6.33 The key safety data from True North are summarised in Table 10.

Table 10: Overview of TEAEs, induction and maintenance period, True North safety population

Subjects with at least 1 event, n (%)	Induction ^b		Maintenance ^c		
	Cohort 1 + 2 OZA 0.92 mg N=796	Placebo N=216	OZA 0.92 mg – OZA 0.92 mg N=230	OZA 0.92 mg – placebo N=227	Placebo N=69
TEAE	318 (39.9)	82 (38.0)	113 (49.1)	83 (36.6)	27 (39.1)
Severe TEAE	28 (3.5)	4 (1.9)	9 (3.9)	9 (4.0)	1 (1.4)
Suspected related TEAE ^a	93 (11.7)	17 (7.9)	27 (11.7)	12 (5.3)	2 (2.9)
Serious TEAE	40 (5.0)	7 (3.2)	12 (5.2)	18 (7.9)	4 (5.8)
Suspected related serious TEAE ^a	4 (0.5)	2 (0.9)	0	1 (0.4)	1 (1.4)
TEAE leading to discontinuation	28 (3.5)	7 (3.2)	3 (1.3)	6 (2.6)	0
TEAE leading to interruption	11 (1.4)	3 (1.4)	8 (3.5)	7 (3.1)	0
Death	1 (0.1)	0	0	0	0

Source: Constructed during the evaluation, using data from Table 95, p 121 and Table 96, p 122 of the submission.

AE = adverse event; IP = Induction Period; MP = Maintenance Period; TEAE = treatment-emergent adverse event

^a Assessed as probably, possibly, or related to study drug by the investigator.

^b A TEAE is defined as any AE with date of first onset or date of worsening in severity on or after the date of first IP dose, excluding those with onset after the date of first MP dose.

^c A TEAE is defined as any AE with date of first onset or date of worsening in severity on or after the date of first MP dose, excluding those with onset after the 90-day safety follow up visit.

Note: Subjects with multiple events reported for the same summary level are counted only once.

6.34 A higher proportion of patients experienced severe or serious TEAEs in the OZA cohorts compared to placebo in the induction phase, but not in the maintenance phase. This may be due to patients who experienced serious/severe TEAEs and discontinued OZA during the induction phase, which left a higher proportion of

patients who tolerated OZA in the maintenance phase. Differences in suspected related TEAEs were consistently higher in the OZA arms compared to placebo.

- 6.35 The safety profile of OZA was similar to that of placebo in the Touchstone trial; the low numbers in each cohort detracts from the robustness of this safety profile.
- 6.36 The submission provided a naïve comparison of the safety profiles reported for OZA and IFX to justify its claim of non-inferior safety. A summary of the IFX safety data is provided in Table 11.

Table 11: Safety data for IFX (Safety Population)

	ACT 1		ACT 2		Kobayashi 2016		Jiang 2015		REMICADE	
	IFX 5 mg N=121	PBO N=121	IFX 5 mg N=121	PBO N=123	IFX 5 mg N=104	PBO N=104	IFX 5 mg N=41	PBO N=41	IFX 5 mg N=50	PBO N=49
Any AE	106 (87.6)	103 (85.1)	99 (81.8)	90 (73.2)	100 (96.2)	94 (90.4)	17 (41.5)	16 (39.0)	33 (66.0)	31 (63.3)
Treatment-related AE	NR	NR	NR	NR	NR	NR	NR	NR	8 (16.0)	5 (10.2)
Any serious AE	26 (21.5)	31 (25.6)	13 (10.7)	24 (19.5)	18 (17.3)	19 (18.3)	3 (7.3)	4 (9.8)	7 (14.0)	4 (8.2)
Any AE leading to discontinuation	10 (8.3)	11 (9.1)	2 (1.7)	12 (9.8)	7 (6.7)	8 (7.7)	1 (2.4)	2 (4.9)	4 (8.0)	2 (4.1)

Source: Created during the evaluation; date extracted from Table 115, p 147 of the submission.

AE = adverse event; IFX = infliximab; NR = not reported; PBO = placebo; UC = ulcerative colitis

Note: Safety data for ACT 1 measured through to Week 54; ACT 2 to Week 30; Kobayashi 2016 to Week 38; Jiang 2015 to Week 30; REMICADE to Week 26.

- 6.37 The submission noted that AE incidence of 39-49% in the OZA arm of True North compared favourably with the IFX arms, which reported incidences of 41.5-96.2%. These data are difficult to compare, as the placebo AE profiles differ substantially between the OZA and IFX trials, likely representative of the different populations between these studies. Most IFX treatment groups had similar or numerically lower incidences of AEs compared to their respective placebo groups. The 'Any Serious AE' rates in the IFX trials were approximately 2-5 times greater than in the OZA trials, but incidences were numerically lower in most IFX groups compared to placebo; differences like this make naïve comparisons between OZA and IFX difficult to interpret. The PSCR stated formal indirect comparisons of safety were not presented due to differences in trial methodologies, an approach previously accepted by the PBAC when it considered the TOF submission for MSUC. The ESC considered this was reasonable, however also noted there appeared to be a relatively high amount of tolerability issues associated with OZA treatment.
- 6.38 When comparing OZA with the secondary comparators, the incidence of serious AEs was similar between OZA and TOF, but VED, GOL and ADA trials recorded increased ranges of serious AEs. The TOF, VED, ADA and GOL trials showed lower or similar serious AEs compared to their respective placebo groups, except for the GOL trial PURSUIT-M recorded nearly twice as many serious AEs in the GOL 100 mg arm

compared to placebo (14.3% vs 7.7%). Incidence of serious AEs was reported at between:

- 4.0% and 7.9% for patients treated with OZA
- 3.4% and 5.6% for patients treated with TOF
- 9.4% and 13.0% for patients treated with VED
- 3.0% and 14.3% for patients treated with GOL
- 4.0% and 12.1% for patients treated with ADA.

6.39 The submission stated that the TOF 5 mg and 10 mg groups had higher rates of nasopharyngitis, headaches and arthralgia than OZA treatment groups. The evaluation noted that in the TOF trials, incidences of these AEs are similar or numerically lower in the TOF treatment arms than their respective placebo arms. The submission also highlighted the fact that the US Food and Drug Administration (FDA) are currently revising the Boxed Warning for JAK inhibitors, including TOF, to include information about the risks of serious heart-related events, cancer, blood clots and death. The TGA are yet to provide a position on increased risk warnings.

Clinical claim

6.40 The submission described OZA as non-inferior in terms of effectiveness and safety compared to the primary comparator IFX. The evaluation considered the therapeutic conclusions presented in the submission were uncertain due to differences in trial designs, trial populations and the ensuing bias and transitivity issues of the ITC. Key issues identified were:

- The OZA trials only allowed responders to progress to their maintenance phases; Touchstone still counted non-responders from the initiation phase as non-responders in its maintenance phase, but True North did not. Apart from Kobayashi 2016, the IFX trials had the ITT population progress to maintenance, regardless of response.
- The OZA trials enrolled patients with less pre-treated, and less severe disease compared to the IFX trials. Despite these differences, the baseline mean Mayo scores were similar between the OZA and IFX trials; this suggests the patients enrolled in the OZA trials may have had poorly controlled disease, while the patients in the IFX trials were more likely to have severe, treatment refractory disease.
- The OZA trials did not require prior treatment failure, however the proposed PBS population must have failed prior 5-aminosalicylates, AND corticosteroids OR thiopurine therapies. The majority of patients in True North had not failed prior corticosteroids, and most were naïve to thiopurines. Further, even fewer patients in True North may have qualified for PBS-funded DMARD therapy, as the definition of prior treatment failure employed by True North required less corticosteroid exposure than the proposed treatment population.

- The safety profiles of active therapy in both the OZA and IFX trials were generally similar to placebo, however the IFX trials demonstrated higher rates of AEs compared to the OZA trials. This likely reflects the greater disease severity in the IFX trials and makes a naïve comparison of safety profiles difficult to interpret.
- 6.41 The ESC considered that, due to the noted differences in clinical trial designs and recruited trial populations, and uncertainties with the results of the indirect comparisons, including those presented in the PSCR (paragraphs 6.13, 6.25, 6.28), the claim of non-inferior comparative effectiveness to IFX was not able to be reliably assessed with the data and analyses presented at the time of consideration. Overall, the ESC considered the claim of non-inferior comparative safety to IFX was likely to be reasonable, however noted OZA and IFX have different adverse event profiles.
- 6.42 The submission’s clinical claim regarding the secondary comparators was:
- OZA is non-inferior in terms of efficacy to VED, ADA, GOL and TOF.
 - OZA is non-inferior in terms of comparative safety, with a trend towards more favourable safety, compared to VED, ADA, GOL and TOF.
- 6.43 The ESC agreed with the evaluation that the trial designs and recruited populations of the OZA trials made reliable assessments against the secondary comparators challenging. The trial populations differed substantially, as the comparator trials enrolled patients with more severe, treatment refractory disease than the OZA trials, which created transitivity and applicability issues when interpreting the ITC results. The results of the ITC showed that for response at induction, OZA appeared similar to all the secondary comparators; the RR point estimates were close to 1, and the 95% CIs were comparatively narrow, apart from ADA which had a statistically significant RD favouring OZA. However, efficacy in the maintenance phase statistically significantly favoured TOF over OZA (both response and remission), and VED over OZA (for response). OZA was statistically significantly favoured over ADA using the RD in the maintenance phase, but this was an exploratory sensitivity analysis.
- 6.44 Similar to the safety comparison for IFX, the evaluation noted that the naïve safety analysis for the secondary comparators was made difficult by differences in the safety profiles of placebo groups in the OZA and secondary comparator trials. All treatments had generally similar safety profiles to their respective placebo groups. It was noted that TOF may have additional safety concerns which have been recently identified by the FDA. The ESC noted that serious adverse event (SAE) rates appeared similar across the therapies and considered the claim of a trend towards more favourable safety was poorly supported; however the ESC considered the claim of non-inferior comparative safety was overall likely to be reasonable.
- 6.45 The PBAC considered, 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 was not informative.

- 6.46 The PBAC 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 DMARDs.

Economic analysis

- 6.47 The submission presented a CMA of OZA compared with IFX intravenous injection (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

≡ 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).

- 6.48 The CMA presented in the submission assumed equivalent costs for OZA and IFX IV over the first two years (104 weeks), including only medicine costs and the IV administration cost for IFX. The results of the CMA are presented in Table 12.

Table 12: Results of the cost-minimisation analysis

Component	OZA		IFX IV	
	Initiation pack 230 mcg capsule [4] (& 460 mcg capsule [3]	Maintenance pack 920 mcg capsule	100 mg (public) 10196P, 14559D, 11461F	100 mg (private) 10184B, 11796W, 11797X
A PBS item, max quantity	1 pack (7 capsules)	1 pack (28 capsules)	100 mg vial x1	100 mg vial x1
B DPMQ	\$ ^a	\$ ^a	\$320.71	\$341.32
C AEMP	\$ ^b	\$ ^b	\$320.71	\$320.71
D Dosing regimen	Dosing assumption in draft PI: - Days 1-4: 0.23 mg capsule, once daily - Days 5-7: 0.46 mg capsule, once daily - Days 8 and thereafter: 0.92 mg capsule, once daily		Dosing assumption in PI: - 5mg/kg Week 0, 2, 6, then Q8W - Average weight of 80kg, 400mg per injection (4 vials per administration)	
E Units over 104 weeks Revised	1 pack (7 capsules)	26 packs (728 capsules) 25.75 ^c packs (721 capsules)	15 administrations (60 vials) 14.25 ^d administrations (57 vials)	
F Drug Costs over 104 weeks (AEMP) [CxE] Revised	\$	\$	\$19,242.60	\$18,280.47
	Subtotal Revised	\$		
G Cost per administration (MBS 14245)^e		\$0.00		\$101.90
H Administration costs over 104 weeks [GxE] Revised		\$0.00		\$1,528.50 \$1,452.08
I Total cost per patient over 104 weeks (AEMP) [F+H] Revised		\$		\$20,771.10 \$19,732.55
J Difference Revised	Equal costs OZA cost per patient over two-years is more costly.			

Source: Constructed during evaluation based on Table 160, p245 of the submission. Italicised figures calculated using Excel workbook 'Attachment 2 'Economic evaluation (CMA)'.
AEMP = approved ex-manufacturer price; EMP = ex-manufacturer price; IFX = infliximab; IV = intravenous; MBS = Medicare Benefits Schedule; mcg = microgram; OZA = ozanimod; PI = product information; PBS = Pharmaceutical Benefits Scheme.

^a The proposed effective DPMQ
^b The submission calculated the proposed effective EMP based on cost per day (\$) which is obtained by dividing total cost per patient over two years (\$) by 735 days (105 weeks). The daily cost is then multiplied by 7 capsules and 28 capsules to calculate the proposed prices for OZA initiation pack and maintenance pack, respectively.

^c Revised to 25.75 = (104 weeks – 1 week of escalation) x 7 days per week / 28 capsules per pack, based on 104 weeks treatment duration, instead of submission duration of 105 weeks.
^d Revised to 14.25 = total of 3 administration at induction (at Weeks 0, 2, 6) plus 11.25 administration from Week 14 to Week 104 (= 90 weeks / 8 weeks), based on 104 weeks duration, instead of submission duration of 105 weeks.

^e Fee for 100% benefit, obtained from MBS online December 2021.

6.49 The submission calculated the proposed effective ex-manufacturer price (EMP) based on a constant cost per day (\$), irrespective of the OZA capsule strength or treatment phase. The daily cost was obtained by dividing the total cost per patient over 2 years (\$) by 735 days (105 weeks), rather than 728 days (104 weeks). The daily cost was then multiplied by 7 capsules and 28 capsules to calculate the proposed effective prices for OZA initiation pack and maintenance pack, respectively. During the evaluation, the number of administrations required for IFX IV over 104 weeks was

revised as 14.25 (15 in the submission). This reduced the total treatment cost with IFX IV over 104 weeks to \$19,732.55 (from \$20,771.10) per patient. Consequently, at the price of OZA calculated from the submission’s CMA of OZA vs. IFX IV, the total cost of OZA per patient over 104 weeks would be \$| more costly than the treatment with IFX IV over the same period.

- 6.50 The PBAC could only recommend listing of OZA at a higher cost than an alternative therapy or therapies if it was satisfied that OZA provides, for some patients, a significant improvement in efficacy or reduction of toxicity (National Health Act 1953, Section 101(3B)). Given that no evidence has been provided to support OZA having a better efficacy or safety profile than alternative biological therapies, OZA should be considered on the basis of a CMA against the least costly alternative therapy or therapies.

Ozanimod cost/patient/year

- 6.51 The expected cost per patient of OZA is \$█ over 52 weeks assuming full compliance, based on the effective proposed price. This is based on the daily cost of \$| estimated by the submission.

Estimated PBS usage & financial implications

- 6.52 This submission was not considered by DUSC.
- 6.53 The submission used a market share approach to predict the likely use and financial impact of listing of OZA on the PBS/RPBS. The key inputs for financial estimates are summarised in Table 13.

Table 13: Key inputs for financial estimates

Data	Value					Source / Comment
Treatment utilisation						
Individual annual growth rate of bDMARDs for MSUC		IFX	VED	ADA	GOL	Prospection 10% Data (Jan 2015 – Dec 2020). The exclusion of TOF, IFX SC and VED SC due to limited claims data is not reasonable, and may not reflect total market growth. In addition, the growth rate calculations based on initiating patient numbers could not be validated.
	2021	-7.08%	13.40%	15.76%	19.08%	
	2022	-7.61%	11.81%	13.62%	16.03%	
	2023	-8.24%	10.57%	11.99%	13.81%	
	2024	-8.98%	9.56%	10.70%	12.14%	
	2025	-9.87%	8.72%	9.67%	10.82%	
	2026	-10.95%	8.02%	8.82%	9.77%	
Proportion of substitution of bDMARDs	Treatment naïve uptake rate					The assumptions were based on the sponsor’s Ozanimod UC pre-Advisory Board Survey (Sep 2021). These assumptions are highly uncertain, and did not consider the current market dynamics (such as high VED market share in second line treatment or new products PBS listed for MSUC (i.e.: TOF, ADA biosimilars, IFX SC, VED SC)).
	Proportion of naïve patients treated with OZA				13.75%	
	Treatment experienced uptake rate					
	Switch from IFX patients				33.33%	
	Switch from GOL patients				18.89%	
	Switch from VED patients				25.00%	
Switch from ADA patients				21.11%		
Weighted uptake rate of OZA		IFX	VED	ADA	GOL	The proportion of substitution assumptions were applied to the initiating and switching
	2022	17.96%	16.56%	14.61%	14.70%	

Public Summary Document – March 2022 PBAC Meeting

Data		Value				Source / Comment
	2023	18.94%	16.55%	14.60%	14.69%	patient numbers for individual bDMARDs and the weighted uptake of OZA calculated was used to estimate the annual OZA scripts. The naïve and switch patient ratios were factored in starting from 2015 (IFX and VED), 2016 (ADA) or 2018 (GOL), resulting in higher patient numbers for OZA in year 1 of listing. i.e.: The uptake rate of OZA in year 1 of listing, should have been 13.75% of all treatment naïve patients, and then treatment uptake rates for experienced patients should be factored in for individual bDMARDs.
	2024	20.08%	16.55%	14.60%	14.68%	
	2025	23.03%	16.55%	14.59%	14.68%	
	2026	24.99%	16.53%	14.59%	14.67%	
	2027	27.43%	16.53%	14.58%	14.67%	
Conversion factors	Induction Scripts			Factor		Table 11, TOF (MSUC) PSD, November 2020 PBAC meeting was adjusted for OZA.
OZA=1 0.23 mg capsules [4] & 0.46 mg [3] capsules	ADA 20/40 mg = 3			0.33		
	VED 300 mg = 3			0.33		
	IFX 400 mg = 3			0.33		
	GOL 100 mg = 2			0.50		
	Maintenance Scripts					
OZA=13.04 0.92 mg capsules x 28	ADA 20/40 mg = 13/year			1.00		
	ADA 20/40 mg = 4.35/year			3.00		
	VED 300 mg = 7.1/year			1.83		
	IFX 400 mg = 6.5/year			2.00		
	IFX biosimilar (11796W/11461F) 400 mg = 2.17/year			6.00		
GOL 100 mg = 13/year			1.00			
Compliance	100%			TOF PSD March 2019, PBAC meeting.		
Costs						
Ozanimod	EMP			DPMQ		Requested published price (Requested effective price) The proposed effective EMP was revised as \$█ and \$█ during the evaluation for OZA initiation and continuing packs, respectively, on the basis of CMA compared to IFX IV.
0.23 mg capsules [4] & 0.46 mg [3] capsules	\$514.57 (\$█)			\$588.01 (\$█)		
0.92 mg capsules [28]	\$2,058.29 (\$█)			\$2,219.51 (\$█)		

Source: Tables 162-164, pp250-2 of the submission.

ADA = adalimumab; bDMARD = biologic disease-modifying anti-rheumatic drug; DPMQ = dispensed price maximum quantity; EMP = ex-manufacturer price; GOL = golimumab; IFX = infliximab; IV = intravenous; MSUC = moderate to severe ulcerative colitis; OZA = ozanimod; PSD = public summary document; SC = subcutaneous; TOF = tofacitinib; VED = vedolizumab.

- 6.54 The submission utilised Prospecption 10% Data (Jan 2015 – Dec 2020) to estimate the growth of the DMARDs market. The exclusion of TOF, and SC formulations of IFX and VED in the analysis due to limited claims data may have failed to capture the impact of the recently listed subcutaneous formulations of IFX and VED, biosimilars of ADA, and the first oral therapy, TOF, on the total market growth for DMARDs in the treatment of MSUC.
- 6.55 The submission assumed that the listing of OZA will not affect current market growth and that OZA will substitute for listed bDMARDs of ADA, GOL, IFX, and VED. OZA, if listed, as a second oral treatment option for MSUC and with its different mechanism of action, may increase the market growth, particularly for patients who may have

ceased previous biologic treatment due to an inability to achieve long-term remission or disease control, and/or for whom injectable therapy is inconvenient or undesirable.

- 6.56 The PSCR acknowledged there had been recent changes to the PBS treatment landscape for MSUC, including the listing of an oral agent (TOF) and subcutaneous formulations of IFX and VED; however, it argued that these listings were recent and there was insufficient data available upon which to estimate their impact. The ESC considered this was reasonable and agreed that, where a CMA is accepted, the financial implications are likely to be minimal. However, the ESC also considered it would be informative for the PBAC to see some preliminary utilisation data from these listings, particularly with the listing of TOF as the first oral agent for MSUC. The Pre-PBAC Response presented a summary of PBS data from the Medicare Statistics resource, which included some data on TOF and subcutaneous (SC) VED/IFX prescribing, and argued that while there had been some recent growth, this appeared to be largely driven by SC VED/IFX prescribing, which increased the number of prescriptions for these therapies due to the different dosing regimens for the SC forms (compared to the IV forms).
- 6.57 The estimated net financial implications for the proposed listing of OZA for MSUC over the first 6 years are summarised in Table 14 (revised during the evaluation to correct for annual growth rates and weighted uptake rates of individual bDMARDs, the corrected daily cost of OZA on the basis of the CMA compared to IFX IV, and using MBS item 116).

Table 14: 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	\$4	\$4	\$4	\$4	\$4	\$4
Estimated financial implications for other bDMARDs						
Cost to PBS/RPBS less copayments ^a	-\$4	-\$4	-\$4	-\$4	-\$4	-\$4
Net financial implications						
Net cost to PBS/RPBS ^b	-\$3	-\$3	-\$3	-\$3	-\$3	-\$3
Net cost to MBS ^c	-\$3	-\$3	-\$3	-\$3	-\$3	-\$3
Net cost to PBS/RPBS/MBS^b	-\$3	-\$3	-\$3	-\$3	-\$3	-\$3

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; VED = vedolizumab

^a Script numbers and estimated financial implications for other bDMARDs were revised during the evaluation as a result of the corrections made in annual growth rates and weighted uptake rates of individual bDMARDs 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 VED 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”.

The redacted values correspond to the following ranges:

¹500 to < 5,000

²10,000 to < 20,000

³\$0 to < \$10 million

⁴\$10 million to < \$20 million

6.58 The total cost saving to the PBS/RPBS of listing OZA was estimated to be net cost saving in Year 6, and a total of net cost saving in the first 6 years of listing (revised during the evaluation). However, if OZA is listed on a cost minimisation basis with the least costly alternative using effective prices, it would be cost-neutral to the PBS (assuming no market growth).

6.59 As noted above, the estimated financial impact on the PBS/RPBS is associated with high level of uncertainty, given:

- the estimated current market growth considering the impact of the recently listed subcutaneous formulations of IFX and VED, biosimilars of ADA and the first oral therapy, TOF; and;
- the assumption of no additional market growth from the listing of OZA, a second option of oral therapy with a different mechanism of action.

- 6.60 Although a grandfathering restriction was requested for the Sponsor's Patient Familiarisation Program (PFP), these patients were not included in the financial analysis. There were <500 patients in this program, which the sponsor anticipated to run for approximately 3 months. The financial impact of grandfathered patients is expected to be minimal, given the small number of patients compared to the high uptake rate assumptions for OZA in the first year of listing.

Quality Use of Medicines

- 6.61 The submission stated that the routine risk management activities (providing electronic or hard copies of healthcare professional checklist and patient/caregiver guide to neurologists and multiple sclerosis nurses), which are already conducted for the current listing of OZA in the RRMS treatment, will be extended to gastroenterologists and irritable bowel disease nurses upon launch of OZA for MSUC.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the General Schedule, Authority Required (in writing) listing of ozanimod (OZA) for the treatment of moderate to severe ulcerative colitis (MSUC). The PBAC considered that a claim of non-inferior comparative effectiveness and safety to infliximab (IFX) was, on balance, likely to be reasonable. However, the PBAC considered for purposes of satisfying Section 101(3B) of the *National Health Act 1953*, vedolizumab (VED), golimumab (GOL), tofacitinib (TOF) and adalimumab (ADA), are also alternative relative therapies. The PBAC's recommendation was therefore, among other matters, based on its assessment that the cost of OZA should be no greater than the cost of IFX or the other alternative therapies.
- 7.2 The PBAC considered the equi-effective doses of OZA and alternative disease modifying anti-rheumatic drugs (DMARDs) 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 as outlined below:
- OZA 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
- ≡ 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).
- 7.3 The PBAC noted the input from clinicians, organisations and patients was supportive of the listing of OZA for MSUC and considered that, while the clinical need for an additional therapy that is of similar effectiveness and safety to existing therapies was modest, an additional oral therapy option with a new mechanism of action, as the first sphingosine-1 phosphate (S1P) inhibitor in this indication, may be useful for some patients.

- 7.4 The Committee considered it was reasonable for the listing for OZA to be the same as for other DMARDs for MSUC, with an initial treatment period of 17 weeks, to allow for a one-week dose titration period and 16 weeks' of treatment at the standard dose. The PBAC considered, similar to its previous recommendation for OZA in relapsing-remitting multiple sclerosis (RRMS), it would be reasonable to allow for prescribing of both the titration pack and first full dose pack at the same time and to allow for re-titration after a treatment break for non-efficacy reasons, however noted that the listing of OZA for MSUC will be at the written authority level whereas the listing for RRMS is a streamlined authority. The PBAC considered that, if not otherwise stated in MSUC listings, treatment should be restricted to a single agent being used at any one time and also noted the flow-on changes to other listings to include OZA in the list of eligible therapies as part of a treatment cycle for MSUC.
- 7.5 The PBAC noted the submission requested a restriction to allow patients in a planned product familiarisation program to transition to PBS-subsidised treatment (anticipated to be <500 patients) and considered this was reasonable. The PBAC considered the grandfather restriction should be reviewed after 12 months, as per standard practice.
- 7.6 The PBAC considered the nominated primary comparator of IFX was reasonable, however considered OZA could substitute for all DMARDs listed for MSUC, including VED, GOL, TOF and ADA, and therefore all DMARDs listed for MSUC were relevant alternative therapies.
- 7.7 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.
- 7.8 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.

- 7.9 The PBAC considered that the indirect comparisons versus the secondary comparators (VED, GOL, TOF and ADA) were not informative for considering the comparative effectiveness of OZA to other DMARDs. 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.
- 7.10 The PBAC noted the submission described OZA as being of non-inferior comparative safety, with a trend towards superior safety and highlighted emerging post-market concerns regarding the safety of TOF in practice; however, the PBAC agreed with the ESC and noted that while OZA has a different safety profile to other DMARDs listed for MSUC, also noted that the rates of observed serious adverse events (SAEs) appeared to be similar. The PBAC considered that, based on the evidence presented, that an overall claim of non-inferior comparative safety to alternative DMARDs was likely to be reasonable.
- 7.11 The PBAC considered, given its view that the claim of non-inferior comparative effectiveness and safety to IFX in MSUC had been adequately supported, that a listing on a standard cost minimisation approach with costs over two years, consistent with previous approaches for DMARDs, was the most appropriate approach to determine the cost minimised effective price of OZA. The PBAC considered that on a similar basis over a two year period, the cost of OZA should be no greater than any of the alternative therapies, VED, GOL, TOF or ADA.
- 7.12 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 DMARDs. The PBAC noted the preliminary utilisation information provided in the Pre-PBAC Response indicated the listing of TOF (as the first oral agent) had not substantially grown the MSUC market, however acknowledged this information was limited as TOF had only recently listed.
- 7.13 The PBAC indicated that it would consider a future submission requesting a revision to the number of MSUC-listed drugs that can be attempted within a treatment cycle before a patient must enter a 5-year break.
- 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 alternative DMARDs for MSUC, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.

- 7.15 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 new item(s):

Suggested additions are in italics and deletions are in strikethrough compared to the listing proposed by the sponsor.

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	3	Zeposia
Restriction Summary 11954 / Treatment of Concept: 11940					
)	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)				
<i>(NOTEs applying to all restriction summaries below)</i>					
NOTE: TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS ---- <i>See end of listing for revised concept</i>					
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: 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					

Public Summary Document – March 2022 PBAC Meeting

	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 aged 18 years or older
	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: 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 17 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. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos

Public Summary Document – March 2022 PBAC Meeting

	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 aged 18 years or older
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice), which includes: (i) the completed current Mayo clinic or partial Mayo clinic calculation sheet including the date of assessment of the patient's condition if relevant; and (ii) the details of prior biological medicine treatment including the details of date and duration of treatment.
	Prescribing Instructions: An assessment of a patient's response to this initial course of treatment must be conducted between 8 and 16 weeks of therapy.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within this treatment cycle. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: A patient who fails to demonstrate a response to treatment with this drug under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug in this treatment cycle. A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological medicine was approved in this cycle and the date of the first application under a new cycle under the initial 3 treatment restriction.
	Prescribing Instructions: A maximum of 17 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. EST Monday to Friday).

Public Summary Document – March 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>
Restriction Summary 11881 / Treatment of Concept: 11975	
	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
	Population criteria:
	Patient must be aged 18 years or older
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice), which includes: (i) the completed current Mayo clinic or partial Mayo clinic calculation sheet including the date of assessment of the patient's condition; and (ii) the details of prior biological medicine treatment including the details of date and duration of treatment.
	Prescribing Instructions: The most recent Mayo clinic or partial Mayo clinic score must be no more than 4 weeks old at the time of application.
	Prescribing Instructions: An assessment of a patient's response to this initial course of treatment must be conducted between 8 and 16 weeks of therapy.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within this treatment cycle. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: A maximum of 17 weeks of treatment with this drug will be approved under this criterion.

Public Summary Document – March 2022 PBAC Meeting

	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
Restriction Summary 11976 / Treatment of Concept: 11976	
	<p>Indication: Moderate to severe ulcerative colitis</p>
	<p>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</p>
	<p>Treatment criteria: Must be treated by a gastroenterologist (code 87); or Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)]</p>
	AND
	<p>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 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</p>
	AND
	<p>Clinical criteria: The treatment must provide no more than the balance of up to 17 weeks treatment available under the above restrictions</p>
	<p>Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>

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	5	Zeposia
Restriction Summary 11942 / Treatment of Concept: 11883					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)				
	<i>(NOTES applying to all restriction summaries below)</i>				
	NOTE: TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS				

Public Summary Document – March 2022 PBAC Meeting

	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:
	Patient must be aged 18 years or older Patients must be at least 18 years of age
	Prescribing Instructions: Patients who have failed to maintain a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug.
	Prescribing Instructions: Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain a response.
	Prescribing Instructions: At the time of the authority application, medical practitioners should request sufficient quantity for up to 24 weeks of treatment under this restriction.
	Prescribing Instructions: An application for the continuing treatment must be accompanied with the assessment of response conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from cessation of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within this treatment cycle. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological medicine was approved in this cycle and the date of the first application under a new cycle under the Initial 3 treatment restriction.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Restriction Summary 12279 edited / Treatment of Concept: 12317 edited	
	Indication: Moderate to severe ulcerative colitis

Public Summary Document – March 2022 PBAC Meeting

	Treatment Phase: Initial treatment - Grandfather 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 non-PBS-subsidised treatment with this drug for this condition prior to 1 Month 20XX
	AND
	Clinical criteria:
	Patient must be receiving treatment with this drug for this condition at the time of application
	AND
	Clinical criteria:
	Patient must have had a Mayo clinic score greater than or equal to 6 prior to commencing non-PBS-subsidised treatment with this drug for this condition; or
	Patient must have had a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores were both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo score) prior to commencing non-PBS-subsidised treatment with this drug for this condition; or
	Patient must have a documented history of moderate to severe refractory ulcerative colitis prior to having commenced non-PBS-subsidised treatment with this drug for this condition where a Mayo clinic or partial Mayo clinic baseline assessment is not available
	AND
	Clinical criteria:
	Patient must not receive more than 24 weeks of treatment under this restriction
	AND
	Population criteria:
	Patient must be aged 18 years or older 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 baseline Mayo clinic or partial Mayo clinic calculation sheet prior to initiating treatment (if available) including the date of assessment; (ii) the date of commencement of this drug.
	Prescribing Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only.
	Prescribing Instructions: For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	Prescribing Instructions: The assessment of the patient's response to this PBS-subsidised course of therapy must be conducted no later than 4 weeks from the cessation of the treatment course.
	Prescribing Instructions: Where a response assessment is not conducted within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.
	Prescribing Instructions: Patients who have failed to maintain a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug.
	Prescribing Instructions: Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain a response.
	Prescribing Instructions: At the time of the authority application, medical practitioners should request sufficient quantity for up to 24 weeks of treatment under this restriction.
	Administrative Advice:

Public Summary Document – March 2022 PBAC Meeting

	<p>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <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</p> <p>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</p> <p>Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
Restriction Summary 11882 / Treatment of Concept: 11882	
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Continuing treatment or Grandfathered patients - 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 Continuing treatment restriction to complete 24 weeks treatment; or Patient must have received insufficient therapy with this drug for this condition under the Grandfathered 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. EST Monday to Friday).

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
OZANIMOD					
ozanimod 230 microgram capsule [4] (& ozanimod 460 microgram capsule [3], 7	12278F	1	1	0	Zeposia
Restriction Summary [NEW 1] / Treatment of Concept: [NEW 2]					
	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 2]				
	Indication: Moderate to severe ulcerative colitis				
	Treatment Phase: Dose escalation occurring at initial treatment, or re-initiation of treatment				
	Treatment criteria:				

Public Summary Document – March 2022 PBAC Meeting

	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
	Population criteria:
NEW PC 1	Patient must have an accompanying authority application for the 920 microgram strength that has at least been submitted, but awaiting outcome.
	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.

Revised 27221 concept:

	<p>NOTE: TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS</p> <p>The following information applies to Pharmaceutical Benefits Scheme (PBS) benefits for the indication of moderate to severe ulcerative colitis (MSUC). Patients are eligible for one PBS-subsidised drug treatment indicated for MSUC at any one time.</p> <p>Where the term 'biological medicine' appears in this note and restrictions, it refers to any PBS benefit indicated for MSUC. Some benefits are not biological medicines, but are small molecules. However, for practical purposes, these benefits are included within the term "biological medicine".</p> <p>From 1 July 2021, under the PBS, all adult patients will be able to commence a treatment cycle where they may trial PBS-subsidised biological medicine without having to experience a disease flare when swapping to one of the alternate agents. Under these arrangements, within a single treatment cycle, a patient may continue to receive long-term treatment with a PBS subsidised biological medicine while they continue to show a response to therapy.</p> <p>A patient who received PBS-subsidised biological medicine treatment prior to 1 July 2021 is considered to have started their first cycle as of 1 July 2021. Within the same treatment cycle, the same biological medicine cannot be trialled twice. Where 3 biological medicines have failed to provide the patient with an adequate response a treatment cycle is considered complete. There must be a 5-year break in PBS-subsidised therapy before starting the next cycle. The 5-year break is measured from the date of the last approval for PBS-subsidised biological medicine treatment in the most recent cycle to the date of the first application for initial treatment with a PBS-subsidised biological medicine under the new treatment cycle.</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>Selecting the correct treatment phase listing to seek the authority application:</p> <p>(1) Initial treatment. Apply under an initial 1 treatment listing where the patient has never received a biological medicine.</p> <p>(2) Continuing treatment. 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 an initial 2 treatment listing. The indices of disease severity (i.e. Mayo clinic score or partial Mayo clinic score), or the prior corticosteroid therapy and immunosuppressive therapy will not need to be restated. A patient may trial an alternate biological medicine treatment at any time, regardless of whether they are receiving therapy (initial or continuing) at the time of the application. However, they cannot change to a particular biological medicine if they have failed to respond to prior treatment with that drug once within the same treatment cycle. A response assessment to the preceding supply of biological medicine must accompany this initial 2 treatment authority application.</p> <p>(4) Recommencement of treatment after a 5-year break in PBS-subsidised therapy.</p>
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	<p>Apply under 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>
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This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.