

6.10 UPADACITINIB, Tablet 15 mg, Tablet 30 mg, Tablet 45 mg, Rinvoq[®], AbbVie Pty Ltd.

1 Purpose of submission

- 1.1 The Category 2 submission requested Authority Required listing of upadacitinib (UPA) for the treatment of moderate to severe ulcerative colitis (MSUC). If listed, UPA would become the second Janus kinase (JAK) inhibitor available on the PBS for MSUC and the sixth treatment option including tofacitinib (TOF), vedolizumab (VDZ), golimumab (GOL), infliximab (IFX) and adalimumab (ADA).
- 1.2 For induction treatment (Week 0 to 16), listing was sought on the basis of a cost per incremental responder analysis, where the requested price of UPA corresponded to the same incremental cost per responder versus no treatment as the nominated comparator (comprising of a weighted average of TOF, VDZ, GOL and IFX) (Table 1). For maintenance treatment (after Week 16), listing was sought on the basis of a cost-minimisation analysis versus TOF.

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

Component	Description
Population	Adult patients with MSUC who have failed to achieve an adequate response, or are contraindicated, to conventional therapies
Intervention	Induction: UPA 45 mg once daily for 8 weeks (up to a maximum of 16 weeks); Maintenance: UPA 15 mg or 30 mg once daily based on patient presentation (the recommended dose is 15 mg once daily for patients ≥65 years and the lower dose may be appropriate for patients with low burden of disease).
Comparator	Main comparator: TOF 10 mg twice daily for 8 weeks; then 5mg twice daily (10 mg twice daily in patients who fail to maintain a response with 5mg) Supplementary comparators: IFX, VDZ, ADA, GOL. Near-market comparator: OZA
Outcomes	Indirect comparison of UPA and the nominated comparators was conducted for the following outcomes, following induction and maintenance therapy: Clinical remission, clinical response, mucosal healing / endoscopic improvement (TOF only)
Clinical claim	Effectiveness, induction treatment: <ul style="list-style-type: none"> ○ UPA is more effective than TOF, IFX, VDZ, ADA, GOL, and OZA. Effectiveness, maintenance treatment: <ul style="list-style-type: none"> ○ UPA is as effective as TOF, VDZ and GOL. ○ UPA is more effective than OZA. ○ The therapeutic conclusions versus ADA and IFX are uncertain given comparisons for maintenance versus these agents were not possible due to differences in trial design. Safety: <ul style="list-style-type: none"> ○ UPA is non-inferior in terms of safety compared to TOF IFX, VDZ, ADA, GOL, and OZA.

Source: Table 1-1, p6 of submission.

ADA = adalimumab; GOL = golimumab; IFX = infliximab; MSUC = moderate to severe ulcerative colitis; OZA = ozanimod; TOF = tofacitinib; UPA = upadacitinib; VDZ = vedolizumab.

2 Background

Registration status

- 2.1 The submission was made under PBAC/TGA parallel process. At time of PBAC consideration, the clinical evaluation report (CER) was available.
- 2.2 The TGA CER recommended approval of UPA for the treatment of adult patients with moderate to severe active ulcerative colitis who have had an inadequate response, loss of response or intolerance to conventional or biologic therapies (to better reflect the target population), subject to acceptable responses to some clinical questions identified.

Previous PBAC consideration

- 2.3 The PBAC has not previously considered UPA for MSUC. UPA is PBS listed for rheumatoid arthritis (May 2020), psoriatic arthritis (October 2021), ankylosing spondylitis (October 2021) and atopic dermatitis (February 2022).

3 Requested listing

- 3.1 The Sponsor requested PBS listing of the UPA 45 mg formulation for initial treatment, and the UPA 30 mg and UPA 15 mg formulations for initial and continuing treatment. For brevity reasons, an abbreviated version of the requested restrictions for initial and continuing treatment is presented below.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
UPADACITINIB					
Initial treatment					
45 mg tablet, 28	1	28	3	\$ ■ (published*)	
Initial treatment – dose change					
30 mg tablet, 28	1	28	1	\$2076.38 (published*)	RINVOQ®
15 mg tablet, 28	1	28	1	\$1271.40 (published*)	AbbVie Pty Ltd
Continuing treatment					
30 mg tablet, 28	1	28	5	\$2076.38 (published*)	
15 mg tablet, 28	1	28	5	\$1271.40 (published*)	
Category/Program:	General Schedule				
PBS indication:	Moderate to severe ulcerative colitis				
Treatment phase:	Initial treatment 1 (new patient)				
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing				
Treatment criteria:	Must be treated by a gastroenterologist or consultant physician [internal medicine specialising in gastroenterology] or consultant physician [general medicine specialising in gastroenterology]				

Clinical criteria:	<p>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,</p> <p>AND</p> <p>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;</p> <p>OR</p> <p>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;</p> <p>OR</p> <p>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,</p> <p>AND</p> <p>Patient must have a Mayo clinic score greater than or equal to 6;</p> <p>OR</p> <p>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).</p>
Population criteria:	Patient must be aged 18 years or older.
Prescriber criteria:	<p>An assessment of a patient's response to this initial course of treatment must be conducted up to 12 weeks after the first dose.</p> <p>A maximum of 16 weeks of treatment with this drug will be approved under this criterion.</p>
Category/Program:	General Schedule
PBS indication:	Moderate to severe ulcerative colitis
Treatment phase:	Continuing treatment
Restriction:	<input checked="" type="checkbox"/> Authority Required – Telephone, Electronic
Treatment criteria:	Must be treated by a gastroenterologist or consultant physician [internal medicine specialising in gastroenterology] or consultant physician [general medicine specialising in gastroenterology]
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition</p> <p>AND</p> <p>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.</p>
Population criteria:	Patient must be aged 18 years or older.
Prescriber criteria:	<p>Patients who have failed to maintain a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1 with continuing treatment with this drug, will not be eligible to receive further PBS-subsidised treatment with this drug.</p> <p>Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain a response.</p>

Source: Table 1-7, pp19-20 of the submission; Key documents 0.3.4 Restriction criteria upadacitinib moderate to severe UC.

* The submission requested a special pricing arrangement. The effective price of UPA cannot be calculated as the effective prices for the treatment of UC are not publicly available.

3.2 The restriction criteria were equivalent to those applying to the comparator. For induction treatment (which the Treatment phase terms as 'Initial treatment'), the requested number of repeats allows patients to start and remain on UPA 45 mg for 16 weeks or start on UPA 45 mg for 8 weeks and switch to UPA 30 mg or 15 mg doses for a further 8 weeks, in-line with the recommended dose. For maintenance treatment (which the Treatment phase terms as 'continuing treatment'), the requested number

of repeats provides for up to 24 weeks of treatment with UPA 30 mg and/or 15 mg. This is because the draft Product Information does not recommend maintenance treatment with 45 mg.

- 3.3 There is the potential for wastage with the UPA 45 mg dose if patients have their 45 mg prescription dispensed, but is then given instruction to lower the dose (UPA 30 mg or 15 mg) after 8 weeks as a 45 mg tablet would not be able to be accurately divided into smaller doses. In addition, separate listings to allow for dose changes during initial treatment (i.e. decreasing from UPA 45 mg to 30 mg or 15 mg) and maintenance treatment (i.e. increasing from UPA 15 mg to 30 mg or decreasing from UPA 30 mg to 15 mg) may be unnecessary given dose changes with other treatments (e.g. TOF) are permitted under Balance of supply restrictions.
- 3.4 The submission requested a Special Pricing Arrangement (SPA). The proposed published price for UPA for MSUC is equivalent to the published price of UPA 15 mg and 30 mg in other indications. As UPA 45 mg is not currently available on the PBS for any other indication, the sponsor proposed a new published price approximately one and one-thirds of the 30 mg price at an AEMP level. The submission requested a flat effective pricing structure across all dose formulations.
- 3.5 Based on the published prices of the nominated comparators, the submission originally estimated an indicative effective price of UPA for initial treatment using a cost-per-responder analysis (AEMP = \$5,032.48, flat price for 45 mg, 30 mg and 15 mg formulations) and an indicative effective price of UPA for continuing treatment using a cost-minimisation analysis (AEMP = \$1,092.47, flat price for 30 mg and 15 mg formulations). In its Pre-PBAC Response, the sponsor indicated a willingness to list UPA for MSUC on a cost minimisation basis with alternative therapies.

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), abdominal pain, and passage of mucus. Patients with MSUC may also have 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 The Mayo score is an indicator of disease activity based on assessment/grading of disease across up to four categories (endoscopy, stool frequency, rectal bleeding and physician's global assessment). Over time, different permutations of the Mayo score have been developed to define severity of disease and assess response to treatment. The original full Mayo score incorporates the subscores of all four categories; the

partial Mayo score excludes the endoscopic subscore; and the more recent modified/adapted Mayo score (recommended by the FDA in 2016¹) excludes the physician rating sub-score (as well as excluding friability from endoscopic score of 1). Although some studies^{2,3} have demonstrated that the full Mayo score, partial Mayo score and adapted Mayo score are correlated with each other, the evolving nature of the Mayo score (and related definitions of severity and response to treatment) means clinical evidence developed over time is likely to become less comparable in terms of selection criteria and measurement of key outcomes. In this submission, the more recent UPA trials defined key eligibility criteria and trial outcomes using the adapted Mayo score whereas older comparator trials generally used the full Mayo score.

- 4.3 Under current PBS criteria, patients with MSUC (full Mayo score ≥ 6 or partial Mayo score > 6 provided both rectal bleeding and stool frequency subscores ≥ 2), who have failed (or are unable to tolerate) a 5-aminosalicylate (5-ASA) oral agent and at least one of azathioprine, mercaptopurine or oral steroids, are eligible for treatment with TOF (JAK inhibitor), IFX (TNF inhibitor), VDZ (integrin inhibitor), GOL (TNF inhibitor), and ADA (TNF inhibitor). The addition of UPA (JAK1 selective inhibitor) to the clinical management algorithm will not alter current practice, but will allow for an additional option.

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

5 Comparator

- 5.1 The submission nominated TOF as the main comparator, given TOF is the closest pharmacological analogue, has the same oral route of administration (other alternatives are intravenous (IV) and/or subcutaneous (SC) injections) and clinicians would likely consider UPA and TOF for similar patients. The submission also nominated other PBS-listed treatments (IFX, ADA, VDZ and GOL) as supplementary comparators, as well as ozanimod (OZA; a SP1 modulator) as a near-market comparator given the PBAC recommended OZA for MSUC at the March 2022 PBAC meeting. Ustekinumab (UST; an interleukin inhibitor) may also be considered a near-market comparator, given the PBAC considered PBS-listing of UST for MSUC at the July 2022 PBAC meeting.

¹ FDA Guidance Document, 2016. *Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry*. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ulcerative-colitis-clinical-trial-endpoints-guidance-industry>

² Lewis JD, Chhuai S, Nessel L et al. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflammatory bowel diseases* 2008; 14: 1660-1666.

³ Naegeli AN, Hunter T, Dong Y et al. Full, partial and modified permutations of the Mayo score: Characterizing clinical and patient-reported outcomes in ulcerative colitis patients. *Crohn's & Colitis* 360 2021; 13 (1) doi: 10.1093/crocol/otab007.

- 5.2 The nomination of TOF and all other PBS-listed treatments for MSUC as relevant comparators was appropriate, and all are alternative therapies as UPA may replace any of these treatments in practice. TOF was recommended for PBS listing on the basis of cost minimisation against the least costly biologic therapy of IFX, GOL or VDZ. The PBAC accepted that TOF is likely of non-inferior safety and efficacy to these agents in MSUC, and that there is sufficient basis to conclude that TOF, for some patients, provides a significant improvement in efficacy in the induction phase compared to ADA, based on the ITT analyses (paragraph 7.1, TOF Public Summary Document (PSD), November 2020).
- 5.3 Under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

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 one organisation via the Consumer Comments facility on the PBS website. The comments from consumer organisation Crohn's and Colitis Australia described the additional flexibility for patients an oral treatment for MSUC offers for patients, particularly those in rural and remote areas who may otherwise need to travel substantial distances for infusible therapies.

Clinical trials

- 6.3 The submission conducted a literature search to identify all randomised controlled trials (RCTs) that would permit a comparison between UPA and the nominated main comparator TOF. For comparisons between UPA and other supplementary comparators (IFX, VDZ, GOL and ADA), the submission included results from all comparator trials identified in the TOF PSD November 2020. The methodology of relying on a list of trials from a previous PBAC PSD is a departure from standard practice for literature searches for PBAC submissions. Ideally, the submission would have conducted an updated literature search versus the supplementary comparators, but an independent search located no other relevant trials.
- 6.4 The submission focused on the clinical trial evidence for UPA and TOF , based on assumption that TOF was sufficiently comparable to the supplementary comparator

trials. The submission argued that the comparator trials were comparable enough to inform decision making given that the PBAC had made a positive recommendation for TOF in November 2020 despite noting several ‘exchangeability’ concerns with the trials.

- 6.5 This argument was poorly justified, given a range of factors are taken into consideration when drawing conclusions about the expected outcomes of different treatments from indirect treatment comparisons, namely the risk of bias and exchangeability of trials included. Given the submission’s approach, the evaluation focused on the comparison between the UPA and TOF trials but also summarises key differences between the UPA and supplementary comparator trials.
- 6.6 There were no head-to-head trials of UPA vs. TOF or any of the supplementary comparators for the treatment of MSUC. The submission presented a series of indirect comparisons from 21 placebo (PBO) controlled RCTs, consisting of:
- 16 RCTs providing evidence for induction therapy:
- UPA vs PBO (three RCTs): U-ACHIEVE 1, U-ACHIEVE 2 and U-ACCOMPLISH; each U-ACHIEVE sub-study was counted separately in the evaluation.
 - TOF vs PBO (two RCTs): OCTAVE 1 and OCTAVE 2;
 - IFX vs PBO (five RCTs): ACT 1, ACT 2, Jiang 2015, REMICADE, Kobayashi 2016;
 - ADA vs PBO (three RCTs): ULTRA 1, ULTRA 2, Suzuki;
 - GOL vs PBO (one RCT): PURSUIT SC;
 - VDZ vs PBO (two RCTs): GEMINI 1 (induction phase), Motoya 2019 (induction phase)
- Six RCTs providing evidence for maintenance therapy:
- UPA vs PBO (one RCT): U-ACHIEVE 3
 - TOF vs PBO (one RCT): OCTAVE SUSTAIN
 - GOL vs PBO (one RCT): PURSUIT-M, PURSUIT-J
 - VDZ vs PBO (three RCTs): GEMINI 1 (maintenance phase), Motoya 2019 (maintenance phase), VISIBLE
- 6.7 Details of the UPA and TOF trials presented in the submission are provided in Table 2; details of the other comparator trials are provided in Table 3 of TOF PSD, November 2020. The PBAC has considered evidence from all of the comparator trials in past decisions for MSUC.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Upadacitinib trials		
U-ACHIEVE 1	AbbVie Inc. A multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of upadacitinib (ABT-494) for induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis. Sandborn WJ, Ghosh S, Panes J, et al. Efficacy of upadacitinib in a randomized trial of patients with active ulcerative colitis.	Clinical study report: Phase 2b and 3 Induction – report date: 10 August 2021 <i>Gastroenterology</i> 2020; 158 (8): 2139-2149.
U-ACHIEVE 2	AbbVie Inc. A multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of upadacitinib (ABT-494) for induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis.	Clinical study report: Phase 2b and 3 Induction – report date: 10 August 2021
U-ACHIEVE 3	AbbVie Inc. A multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of upadacitinib (ABT-494) for induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis.	Clinical study report: Phase 3 maintenance – report date: 3 August 2021.
U-ACCOMPLISH	AbbVie Inc. A multicenter, randomized, double-blind, placebo-controlled induction study to evaluate the efficacy and safety of upadacitinib (ABT-494) in subjects with moderately to severely active ulcerative colitis.	Clinical study report – report date: 29 June 2021.
Tofacitinib trials		
OCTAVE trials (OCTAVE 1, OCTAVE 2, OCTAVE sustain)	Sandborn WJ, Chinyu S, Sands BE, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis	<i>N Engl J Med.</i> 2017; 376 (18): 1723-1736

Source: Table 2-5, p83 of the submission. Shaded areas indicate data previously seen by the PBAC.

6.8 The key features of the UPA and TOF trials are summarised in Table 3. The UPA trials (2016 to 2021) were conducted approximately 4 years after the TOF trials (2012 to 2016), just after the development of the adapted Mayo score in 2016 and three (of the four) UPA trials included the start of the COVID-19 pandemic. The trials impacted by COVID-19 used non-responder-imputation with multiple imputation for missing data due to COVID-19 for their primary analysis but results were very similar using standard non-responder imputation. It was unknown, however, whether trials conducted during the COVID-19 pandemic would systematically differ to trials conducted prior to COVID-19 (i.e. potential differences in access to background care, rates of UC symptom flare-ups, etc.).

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
UPA vs. PBO						
U-ACHIEVE 1 [induction]	250	P2b/3 MC, R, PC, DB (8wk), 5-arm (dose ranging).	Low	VDZ/TNFi-n & VDZ/TNFi-e	1 ^{ary} : clinical remission (AMS) 2 ^{ary} : clinical remission (FMS), clinical response (AMS), endoscopic improvement ^b	clinical remission (FMS)
U-ACHIEVE 2 [induction]	474	P3 MC, R, PC, DB (8wk ^a).	Low	VDZ/TNFi-n & VDZ/TNFi-e	1 ^{ary} : clinical remission (AMS) 2 ^{ary} : clinical remission (FMS), clinical response (AMS), endoscopic improvement ^b	clinical remission (FMS)
U-ACCOMPLISH [induction]	522	P3 MC, R, PC, DB (8wk ^a).	Low	VDZ/TNFi-n & VDZ/TNFi-e	1 ^{ary} : clinical remission (AMS) 2 ^{ary} : clinical remission (FMS), clinical response (AMS), endoscopic improvement ^b	clinical remission (FMS)
U-ACHIEVE 3 [maintenance]	451 ^c (1046)	P3 MC, R, PC, DB (52wk), RWD, 3-arm.	High	Wk8 clinical responders (AMS) in U-ACHIEVE 1,2, U-ACCOMPLISH	1 ^{ary} : clinical remission (AMS) 2 ^{ary} : clinical remission (FMS), clinical response (AMS), endoscopic improvement ^b	Not used
TOF vs. PBO						
OCTAVE 1 [Induction]	598	P3 MC, R, PC, DB (8wk).	Low	TNFi-n & TNFi-e	1 ^{ary} : remission (FMS) 2 ^{ary} : clinical remission (FMS), clinical response (FMS), mucosal healing	clinical remission (FMS)
OCTAVE 2 [Induction]	541		Low	TNFi-n & TNFi-e	1 ^{ary} : remission (FMS) 2 ^{ary} : clinical remission (FMS), clinical response (FMS), mucosal healing	Not used
OCTAVE SUSTAIN [maintenance]	593	P3, MC, R, PC, DB (52wk), RWD, 3-arm.	High	Wk8 clinical responders (FMS) in OCTAVE 1,2	1 ^{ary} : remission (FMS) 2 ^{ary} : clinical remission (FMS), clinical response (FMS), mucosal healing	Not used

Source: Compiled during the evaluation based on source reports and publications. Shaded areas indicate data previously seen by the PBAC.

AMS = adapted Mayo score; DB=double blind; FMS = full Mayo score; IFX=infliximab, MC=multi-centre; R=randomised, RWD=randomised withdrawal design; TOF=tofacitinib, TNFi-e=tumour necrosis factor inhibitor experience, TNFi-n= tumour necrosis factor inhibitor naïve, UPA=upadacitinib, VDZ=vedolizumab.

^a There was an 8-week, open-label, Extended Treatment Period for clinical non-responders after the initial 8-week induction period.

^b The definition of the endoscopic improvement outcome (endoscopic sub-score of 0 or 1) in the UPA trials matched the definition of the 'mucosal healing' outcome in the TOF trials and was used for the indirect comparison. The 'mucosal healing' outcome reported in the UPA trials referred to a different outcome.

^c The ITT_A population consisted of the first 451 patients with clinical response at Week 8 following UPA 45 mg induction treatment and who were enrolled under the protocol amendment for 52-week maintenance treatment period. A total of 1046 patients received a blinded treatment in U-ACHIEVE 3 but this depended on prior treatment received for induction therapy.

6.9 The UPA induction trials (U-ACHIEVE 1, U-ACHIEVE 2 and U-ACCOMPLISH) were similar to the TOF induction trials (OCTAVE 1 and OCTAVE 2) in terms of trial design. All trials

were relatively large Phase 3 (with the exception of the U-ACHIEVE 1 dose ranging trial) multi-centre trials, in which patients with MSUC were randomised to active treatment or PBO with response to treatment assessed at Week 8. The UPA maintenance trial (U-ACHIEVE 3) was also generally similar to the TOF maintenance trial (OCTAVE SUSTAIN) in terms of trial design. Both trials enrolled patients with clinical response at Week 8 following active induction treatment (at the end of the induction trials), randomised patients to continue active treatment or PBO (i.e. randomised withdrawal design), and measured outcomes at Week 52 (from the start of induction).

- 6.10 The main difference between the trials was that the UPA trials used the adapted Mayo score whereas the TOF trials used the full Mayo score, to define eligibility criteria and key clinical outcomes; however, the importance of this difference was unclear. Overall, the UPA and TOF induction trials were considered to have low risk of bias, while the UPA and TOF maintenance trials were considered to have a high risk of bias due to high attrition bias (20.8% to 66% discontinued treatment in U-ACHIEVE 3 and 35.7% to 73.2% discontinued treatment in OCTAVE SUSTAIN).
- 6.11 Unlike the UPA trials, all of the supplementary comparator trials used the full Mayo score to define eligibility criteria and key clinical outcomes; and there were also other differences in some eligibility criteria. The PBAC had previously noted that these trials used heterogeneous trial designs, including induction only designs, induction/maintenance ‘treat-through’ designs, and induction/maintenance ‘randomised withdrawal’ designs (paragraph 6.7, TOF PSD, March 2019). Despite this, all induction trials/phases were fairly similar as patients with MSUC were randomised to active treatment or PBO with response assessed after 6 to 10 weeks. The main difference across the maintenance trials/phases was that the ADA and IFX trials used treat-through designs (patients remain on active or PBO for both induction and maintenance treatment), whereas the VDZ and GOL trials used randomised withdrawal designs (responders to active induction treatment are randomised to active treatment or PBO for maintenance treatment). The submission appropriately excluded evidence for ADA and IFX maintenance treatment from the indirect treatment comparisons due to the differences in trial design.
- 6.12 There were key differences in terms of baseline characteristics and concomitant medications across the UPA and comparator trials, that may potentially influence results, but any overall impact was uncertain.

Compared to the TOF trials:

- Patients in the UPA induction trials had a slightly higher average (full) Mayo score compared to the TOF induction trials;
- Patients in the UPA induction trials were slightly older than the TOF induction trials;
- A smaller proportion of patients in the UPA trials were using concomitant corticosteroids at baseline compared to the TOF trials;

Compared to the supplementary comparator trials:

- Patients in the UPA induction trials had a slightly higher average (full) Mayo score compared to the supplementary trials;
- Patients in the UPA trials were slightly older and had longer duration of disease than most of the supplementary trials;
- A higher proportion of patients in the UPA trials had used a prior biologic at baseline compared to most supplementary trials (and a similar proportion to the VDZ trials);
- There was a wide variation in the proportion of patients using concomitant corticosteroids at baseline across the supplementary trials (some trials with more patients and some less compared to the UPA trials).

6.13 There was insufficient data reported across the trials to assess the extent of prior exposure to previous biologic treatments beyond a simple binary (yes, no) statistic. For example, the proportion with any prior exposure to a biologic treatment was similar across the UPA and TOF trials, but it was unclear how many biologic treatments had been used.

Comparative effectiveness

6.14 The clinically relevant outcomes for MSUC are clinical remission (absence of symptoms outcome) and clinical response (relative improvement in symptoms outcome), as assessed using the Mayo score. The PBS continuation criteria requires that patients demonstrate clinical remission (defined as a partial Mayo score ≤ 2 with no sub-scores >1 , see Requested listing), but the PBAC had previously accepted both clinical remission and clinical response (defined using the full Mayo score) as the clinically relevant trial outcomes to assess the relative effectiveness and non-inferiority of treatments (page 3, IFX PSD, March 2014; paragraph 7.2, ADA PSD July 2014; paragraph 6.12, VDZ PSD, July 2014; paragraph 6.12, TOF PSD, March 2019).

6.15 All of the comparator trials reported clinical remission and clinical response using the full Mayo score whereas the UPA trials reported outcomes using both the adapted Mayo score and full Mayo score. The submission noted that the results of the UPA trials were similar irrespective of which scoring method was used.

6.16 To compare the effectiveness of UPA versus the PBS-listed comparators for induction and maintenance treatment, the submission conducted a series of standard (unadjusted) anchored indirect comparisons for clinical remission and clinical response using the full Mayo score in the ITT populations. The submission excluded comparisons between UPA, ADA and IFX for maintenance treatment due to differences in trial design, and comparisons between UPA, VDZ and GOL in terms of clinical response following maintenance treatment due to lack of comparable data. It was noted that the VDZ trials did report a comparable clinical response outcome for maintenance treatment, referred to as 'durable' clinical response at Week 52 or 60 in the trial publications.

- 6.17 The submission only presented indirect comparisons for the ITT population of the included trials because the PBAC had considered that the ITT population was the most relevant population because treatment can be used in biologic-naïve and biologic-experienced patients (paragraph 6.13, TOF PSD, November 2020). The PBAC considered that subgroup analysis by prior TNF exposure were problematic due to reduced statistical power and because the comparisons in patients with prior exposure may not be a fair representation of comparative efficacy when comparing a TNF inhibitor versus a drug of another class (paragraph 7.2, TOF PSD, November 2020).
- 6.18 Although the ITT results may be more relevant to practice than individual subgroups by prior biologic exposure in this setting (i.e. a line-agnostic listing), and acknowledging the issues with subgroup data, it is still important to consider the potential impact of differences across the trials (i.e. prognostic factors and treatment effect modifiers) on absolute and relative treatment effects estimated using standard (unadjusted) anchored indirect comparison methods.
- 6.19 Table 4 and Table 5 present the results of the indirect comparisons for clinical remission and clinical response outcomes in induction trials (at Week 6, 8 or 10) and maintenance trials (at Week 52, 54 or 60), respectively. For maintenance treatment, the submission appeared to compare the results of ‘remission’ in OCTAVE SUSTAIN with ‘clinical remission’ in U-ACHIEVE-S3, but the definition of remission is slightly stricter than clinical remission. The results presented below were updated during the evaluation based on the clinical remission outcome in OCTAVE SUSTAIN, but this did not impact on the conclusions of the analysis.

Table 4: Indirect comparisons comparing UPA versus PBS-listed comparators (TOF, IFX, ADA, GOL and VDZ) for clinical remission and clinical response at Week 6/8/10, ITT population

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI)	RD (95% CI)	NNT (95%CI)
Clinical remission, FMS Wk6/8/10 (ITT)					
UPA 45mg v PBO (MA: U-ACHIEVE-S1/S2, U-ACCOMPLISH)	177/716 (24.7)	8/374 (2.1)	10.60 (5.39, 20.86)	0.22 (0.19, 0.26)	5 (4,5)
TOF 10mg v PBO (MA: OCTAVE-1, OCTAVE-2)	160/905 (17.7)	14/234 (6.0)	2.95 (1.46, 5.95)	0.12 (0.08, 0.16)	8 (6,13)
IFX 5mg/kg v PBO (MA: ACT 1/2, Jiang, REMICADE, Kobayashi)	142/437 (32.5)	50/438 (11.4)	2.72 (1.90, 3.88)	0.20 (0.12, 0.29)	5 (3,8)
GOL 200->100mg v PBO (PURSUIT-SC)	45/253 (17.8)	16/251 (6.4)	2.79 (1.62, 4.8)	0.11 (0.06, 0.17)	9 (6,17)
ADA 160->80mg v PBO (MA: ULTRA-1, ULTRA-2, Suzuki)	74/468 (15.8)	46/472 (9.7)	1.58 (1.05, 2.4)	0.05 (-0.00, 0.11)	NS
VDZ 300mg v PBO (MA: GEMINI-1, Motoya)	68/389 (17.5)	18/231 (7.8)	2.14 (1.03, 4.43)	0.10 (0.05, 0.15)	10 (7,20)
Clinical response, FMS Wk6/8/10 (ITT)					
UPA 45mg v PBO (MA: U-ACHIEVE-S1/S2, U-ACCOMPLISH)	516/716 (72.1)	86/374 (23.0)	3.10 (2.56, 3.75)	0.49 (0.43, 0.54)	2 (2,2)
TOF 10mg v PBO (MA: OCTAVE-1, OCTAVE-2)	521/905 (57.5)	72/234 (30.7)	1.87 (1.53, 2.28)	0.27 (0.20, 0.33)	4(3,5)
IFX 5mg/kg v PBO (MA: ACT 1/2, Jiang, REMICADE, Kobayashi)	283/437 (64.8)	152/438 (34.7)	1.86 (1.61, 2.15)	0.3 (0.23, 0.37)	3(3,4)
GOL 200->100mg v PBO (PURSUIT-SC)	129/253 (51.0)	76/251 (30.3)	1.68 (1.35, 2.11)	0.21 (0.12, 0.29)	5(3,8)
ADA 160->80mg v PBO (MA: ULTRA-1, ULTRA-2, Suzuki)	241/468 (51.4)	177/472 (37.5)	1.36 (1.18, 1.58)	0.14 (0.08, 0.20)	7(5,13)
VDZ 300mg v PBO (MA: GEMINI-1, Motoya)	171/389 (44.0)	65/231 (28.1)	1.51 (0.99, 2.29)	0.15 (0.002, 0.29)	7(3,500)
Indirect comparison, clinical remission, ITT					
UPA 45mg v TOF 10mg			3.59 (1.36, 9.53)	0.10 (0.05, 0.15)	10 (6,20)
UPA 45mg v IFX 5mg/kg			3.90 (1.81, 8.38)	0.02 (-0.07, 0.11)	NS
UPA 45mg v GOL 200->100mg			3.80 (1.60, 9.05)	0.11 (0.04, 0.18)	9 (6,20)
UPA 45mg v ADA 160->80mg			6.71 (3.04, 14.83)	0.17 (0.10, 0.24)	6 (4,9)
UPA 45mg v VDZ 300mg			4.95 (1.83, 13.40)	0.12 (0.06, 0.18)	8 (6,17)
Indirect comparison, clinical response, ITT					
UPA 45mg v TOF 10mg			1.66 (1.26, 2.19)	0.22 (0.13, 0.31)	5 (3,8)
UPA 45mg v IFX 5mg/kg			1.67 (1.31, 2.12)	0.19 (0.10, 0.28)	5 (4,10)
UPA 45mg v GOL 200->100mg			1.85 (1.38, 2.48)	0.28 (0.18, 0.38)	4 (3,6)
UPA 45mg v ADA 160->80mg			2.28 (1.79, 2.90)	0.35 (0.27, 0.43)	3 (2,4)
UPA 45mg v VDZ 300mg			2.05 (1.30, 3.25)	0.34 (0.18, 0.50)	3 (2,6)

Source: Table 2-32, pp107-108 of the submission; Table 2-33, pp111-112 of the submission; Table 2-35, pp119-120 of the submission, Table 2-36, pp120-121 of the submission; Figure 2, p1208 of the submission.

ADA = adalimumab; GOL = golimumab; IFX = infliximab; TOF = tofacitinib; UPA = upadacitinib; VDZ = vedolizumab; FMS=full Mayo score; MA = meta-analysis; NS=not significant.

Table 5: Indirect comparison comparing UPA versus PBS-listed comparators (TOF, GOL, VDZ) for clinical remission and clinical response at Week 52 | clinical response following induction treatment[^], ITT population

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI)	RD (95% CI)	NNT (95%CI)
Clinical remission, FMS Wk52/54/60					
UPA 15mg v PBO (U-ACHIEVE-S3)	60/148 (40.5)	16/149 (10.7)	3.78 (2.28, 6.24)	0.30 (0.20, 0.39)	3 (3,5)
UPA 30mg v PBO (U-ACHIEVE-S3)	73/154 (47.4)	16/149 (10.7)	4.41 (2.70, 7.22)	0.37 (0.27, 0.46)	3 (2,4)
UPA 15,30mg pooled v PBO (U-ACHIEVE-S3)	133/302 (44.0)	16/149 (10.7)	4.10 (2.54, 6.63)	0.33 (0.26, 0.41)	3 (2,4)
TOF 5mg v PBO (OCTAVE-SUSTAIN)	68/198 (34.3)	22/198 (11.1)	3.09 (1.99, 4.79)	0.23 (0.15, 0.31)	4 (3,7)
TOF 10mg v PBO (OCTAVE-SUSTAIN)	81/197# (41.1)	22/198 (11.1)	3.70 (2.41, 5.68)	0.30 (0.22, 0.38)	3 (3,5)
TOF 5,10mg pooled v PBO (OCTAVE-SUSTAIN)	149/395# (37.7)	22/198 (11.1)	3.39 (2.24, 5.14)	0.27 (0.20, 0.33)	4 (3,5)
GOL 100mg v PBO (MA: PURSUIT-M, PURSUIT-J)	67/183 (36.6)	36/185 (19.5)	3.01 (0.60, 15.12)	0.27 (0.05, 0.58)	4 (2,20)
VDZ IV 300mg, SC 108mg pooled v PBO (MA: GEMINI-1, VISIBLE, Motoya)	146/323 (45.2)	41/224 (18.3)	2.41 (1.78, 3.27)	0.28 (0.20, 0.35)	4 (3,5)
Clinical response, FMS Wk52					
UPA 15mg v PBO (U-ACHIEVE-S3)	89/148 (60.1)	28/149 (18.8)	3.20 (2.24, 4.58)	0.41 (0.31, 0.51)	2 (2,3)
UPA 30mg v PBO (U-ACHIEVE-S3)	106/154 (68.8)	28/149 (18.8)	3.66 (2.58, 5.20)	0.50 (0.40, 0.60)	2 (2,3)
UPA pooled (U-ACHIEVE-S3)	195/302 (64.6)	28/149 (18.8)	3.44 (2.44, 4.85)	0.46 (0.38, 0.54)	2 (2,3)
TOF 5mg v PBO (OCTAVE-SUSTAIN)	102/198 (51.5)	40/198 (20.2)	2.55 (1.87, 3.47)	0.31 (0.22, 0.40)	3 (3,5)
TOF 10mg v PBO (OCTAVE-SUSTAIN)	122/197 (61.9)	40/198 (20.2)	3.07 (2.28, 4.13)	0.42 (0.33, 0.51)	2 (2,3)
TOF pooled v PBO (OCTAVE-SUSTAIN)	224/395 (56.7)	40/198 (20.2)	2.81 (2.10, 3.75)	0.37 (0.29, 0.44)	3 (2,3)
Indirect comparison, clinical remission, ITT					
UPA 15mg v TOF 5mg			1.22 (0.63, 2.39)	0.07 (-0.05, 0.19)	NS
UPA 30mg v TOF 10mg			1.19 (0.62, 2.29)	0.07 (-0.05, 0.19)	NS
UPA 15,30mg pooled v TOF 10mg			1.11 (0.58, 2.11)	0.03 (-0.08, 0.14)	NS
UPA 15mg v GOL 100mg			1.26 (0.23, 6.81)	0.03 (-0.25, 0.31)	NS
UPA 30mg v GOL 100mg			1.47 (0.27, 7.91)	0.10 (-0.18, 0.38)	NS
UPA 15,30mg pooled v GOL 100mg			1.36 (0.25, 7.33)	0.06 (-0.22, 0.34)	NS
UPA 15mg v VDZ IV 300mg / SC 108mg			1.57 (0.87, 2.82)	0.02 (-0.10, 0.14)	NS
UPA 30mg v VDZ IV 300mg / SC 108mg			1.83 (1.03, 3.26)	0.09 (-0.03, 0.21)	NS
UPA 15,30mg pooled v VDZ IV 300mg / SC 108mg			1.70 (0.96, 3.00)	0.05 (-0.06, 0.16)	NS
Indirect comparison, clinical response, ITT					
UPA 15mg v TOF 5mg			1.26 (0.78, 2.01)	0.10 (-0.03, 0.23)	NS
UPA 30mg v TOF 10mg			1.19 (0.75, 1.89)	0.08 (-0.05, 0.21)	NS
UPA 15,30mg pooled v TOF 10mg			1.12 (0.71, 1.77)	0.04 (-0.08, 0.16)	NS

Source: Table 2-34, pp115-116 of the submission; Table 2-36, pp120-121 of the submission; Figure 3, Sands et al 2019.

ADA = adalimumab; GOL = golimumab; IFX = infliximab; TOF = tofacitinib; UPA = upadacitinib; VDZ = vedolizumab; FMS=full Mayo score; IV = intravenous; SC = subcutaneous; MA=meta-analysis; NS=not significant.

[^] Clinical response using adapted Mayo score in U-ACHIEVE 3 and the full Mayo score in the other trials

Result for clinical remission reported in main trial publication by Sandborn et al 2017, Supplementary Table S4.

- 6.20 For induction therapy, the indirect comparisons indicated that UPA was more effective than the nominated comparators (TOF, IFX, ADA, GOL and VDZ) with significantly more patients achieving clinical remission and clinical response at Week 6, 8 or 10. For maintenance therapy, the indirect comparisons indicated that UPA was similar to the nominated comparators (TOF, GOL, and VDZ) with no statistically significant differences between treatments in terms of clinical remission.
- 6.21 Interpretation of the results requires consideration given that the indirect treatment comparisons conducted do not control for any differences across the trials that may explain differences in the outcomes observed across the trials. This is particularly relevant for the induction trials as patients enrolled in the randomised withdrawal trials had already demonstrated a response to treatment (and were generally more comparable). As discussed above, there are a number of differences across the induction trials in terms of baseline characteristics such as baseline Mayo score, age, and prior biologic exposure, as well as concomitant use of corticosteroids and immunosuppressant drugs. The PBO response rates in the UPA trials were much lower than the PBO response rates observed across the other trials (2.1% versus 6.0% to 11.4% respectively), clinical response (23.0% versus 30.3% to 37.5% respectively) and mucosal healing (7.0% v 13.7% respectively), indicating that these differences likely influenced outcomes.
- 6.22 For comparison versus TOF, the submission argued that despite some variation across UPA and TOF trials (e.g. in proportions of patients with prior exposure to biologics and in the proportions of patients using corticosteroids at baseline), any differences were unlikely to bias (relative) results because none were considered to be treatment effect modifiers. The submission did not present any subgroup data to support this argument. Ignoring issues related to power and confounding from other factors, subgroup data retrieved during the evaluation suggests some patient characteristics are at least prognostic factors and some may be associated with a different relative treatment effect. For the comparisons versus the other treatments, the submission relied on the assumption that the PBAC had previously considered that the trials were similar enough to conduct an indirect treatment comparison and inform decision making, which may not be reasonable.
- 6.23 Overall, the trials may not be sufficiently comparable to conduct a reliable (unadjusted) indirect comparison between UPA and other PBS-listed comparators for decision making. Although the results indicated that UPA may be superior to other PBS-listed treatments for induction treatment, there is considerable uncertainty around the magnitude and clinical significance of any benefit.
- 6.24 The Pre-Sub-Committee Response (PSCR) presented an additional Bayesian network meta-analysis (NMA) for the outcome of clinical remission in the induction phase, which included adjustments to account for between-study heterogeneity and for patient characteristics which were thought to be treatment effect modifiers, (however the ESC noted no information on what adjustments were done was provided). The

PSCR also included several additional published NMAs in MSUC^{4,5,6}, which reported similar findings that UPA performed better than most other PBS-listed therapies for the outcomes of clinical remission and response. The PSCR argued the results of the NMA continued to demonstrate that UPA demonstrated superiority versus the other PBS-listed therapies for induction therapy.

- 6.25 The ESC noted the NMA had not been independently evaluated, and was concerned the approach did not adjust for the lower PBO response rates observed in the UPA trials and this key uncertainty with the indirect comparisons remained unresolved. Based on the evidence presented, the ESC considered there was a highly uncertain level of support for the claim of superior comparative effectiveness over other biologics in the induction phase (8 weeks), and considered further analyses to investigate the impact of the low PBO response rates in the UPA trials would be required to substantiate this claim.
- 6.26 The Pre-PBAC Response noted the advice of the ESC and undertook additional analyses examining the impact of differing PBS response rates between the included clinical trials, including a baseline risk adjustment (fixed effects adjusted) model, and an additional NMA based on the risk difference (RD) statistic for the outcome of clinical remission in induction treatment. The sponsor stated these methods were recognised by the UK National Institute for Health Care Excellence (NICE) as a valid framework for statistical analysis. The sponsor did not present the results of the baseline risk adjustment model, however argued the results of that analysis did not improve the estimation of the effect size and its goodness-of-fit was lower than for the unadjusted models. For the NMA based on the RD statistic, the Pre-PBAC Response stated that rather than calculating relative effects on the log-odds scale, which may inflate or deflate relative effects in treatments with particularly high or low associated placebo efficacy, this approach means absolute probabilities of treatment response are subtracted across interventions, yielding estimates of treatment effect as the linear difference in absolute rate to a reference treatment; thus, the sponsor argued this approach accounts for placebo rate heterogeneity. The results of the RD NMA were broadly similar to the unadjusted indirect comparisons, producing statistically

⁴Lasa, J. S., Olivera, P. A., Danese, S., & Peyrin-Biroulet, L. (2022). Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. *The lancet. Gastroenterology & hepatology*, 7(2), 161–170. [https://doi.org/10.1016/S2468-1253\(21\)00377-0](https://doi.org/10.1016/S2468-1253(21)00377-0)

⁵ Burr NE, Gracie DJ, Black CJ, et al Efficacy of biological therapies and small molecules in moderate to severe ulcerative colitis: systematic review and network meta-analysis *Gut* Published Online First: 22 December 2021. doi: 10.1136/gutjnl-2021-326390

⁶ R Panaccione, E B Collins, G Y Melmed, S Vermeire, S Danese, P D R Higgins, W Zhou, D Ilo, D Sharma, Y Sanchez Gonzalez, S T Wang, OP34 Efficacy and safety of advanced induction and maintenance therapies in patients with moderately to severely active Ulcerative Colitis: An indirect treatment comparison using Bayesian network meta-analysis, *Journal of Crohn's and Colitis*, Volume 16, Issue Supplement_1, January 2022, Pages i037–i041, <https://doi.org/10.1093/ecco-jcc/jjab232.033>

significant results in favour of UPA over GOL, TOF, VDZ and ADA for the outcome of clinical remission in the induction phase. The RD NMA found no statistically significant difference between UPA and IFX for this outcome. The PBAC noted these had not been independently evaluated.

- 6.27 The submission also conducted a similar indirect comparison between UPA and the near-market comparator OZA; an indirect treatment comparison between UPA and UST was conducted during the evaluation for completeness. The results significantly favoured UPA over the near market comparators for both induction and maintenance treatment; however, like the comparisons versus the PBS-listed comparators, the trials may not be sufficiently comparable and the PBO response rates in the UPA trials were lower than those observed in the OZA and UST trials, indicating that the main exchangeability assumption of the indirect treatment comparisons may have been violated.

Comparative harms

- 6.28 Table 6 summarises adverse events (AEs) reported in the UPA induction and maintenance trials. A slightly higher proportion of patients treated with UPA experienced any AE compared to PBO but the incidence of serious AEs was low. The most frequently reported AEs with UPA in the induction period (worsening of ulcerative colitis, headache, acne, nasopharyngitis, anaemia and blood CPK increased) and maintenance period (nasopharyngitis and blood CPK increased) were consistent with the known safety profile of UPA.

Table 6: Summary of adverse events in UPA induction trials and maintenance trial

Trial	UPA n/N (%)	PBO n/N (%)	RR (95% CI)	RD (95% CI)
UPA induction trials[^]				
UPA 45 mg versus PBO (MA: U-ACHIEVE 1, U-ACHIEVE 2, U-ACCOMPLISH) at Week 8				
Any AE	398/719 (55.4)	199/378 (52.6)	1.03 (0.79, 1.35)	0.01 (-0.13, 0.15)
Serious adverse event	22/719 (3.1)	22/378 (5.8)	0.55 (0.30, 0.98)	-0.02 (-0.05, 0.00)
Discontinuation due to adverse event	17/719 (2.4)	27/378 (7.1)	0.39 (0.16, 0.92)	-0.04 (-0.08, -0.01)
Serious Infections	9/719 (1.3)	5/378 (1.3)	1.03 (0.34, 3.10)	0.00 (-0.01, 0.01)
Adjudicated MACE/CV events	1/719 (0.1)	0/378 (0)	2.47 (0.10, 59.32)	0.00 (-0.01, 0.01)
UPA maintenance trial				
UPA 15 mg or 30 mg pooled versus PBO (U-ACHIEVE 3 maintenance trial Safety C population*) at Week 52				
Any AE	377/501 (75.2)	180/245 (73.5)	1.02 (0.94, 1.11)	0.02 (-0.05, 0.08)
Serious AE	40/501 (8.0)	23/245 (9.4)	0.85 (0.52, 1.39)	-0.01 (-0.06, 0.03)
Discontinuation due to AE	22/501 (4.4)	25/245 (10.2)	0.43 (0.25, 0.75)	-0.06 (-0.10, -0.02)
Serious Infection	14/501 (2.8)	8/245 (3.3)	0.85 (0.35, 2.06)	0.00 (-0.03, 0.02)
Malignancy	6/501 (1.2)	1/245 (0.4)	2.93 (0.36, 24.24)	0.01 (-0.00, 0.02)
Adjudicated MACE/CV	1/501 (0.2)	1/245 (0.4)	0.49 (0.03, 7.79)	0.00 (-0.01, 0.01)

Source: Tables 2-21 to 2-22, pp.72-74 of the submission.

AE=adverse event; CV=cardiovascular; MACE=major adverse cardiovascular events; CI=confidence interval; MA=meta-analysis; n=number of participants with event; N=total participants in group, NE=not estimable, RD=risk difference, RR=risk ratio, PBO=placebo; UPA=upadacitinib.

[^] The UPA induction trials had no malignancies in UPA or PBO treatment arms and hence not reported in this table.

* Patients who were UPA 45mg responders at Week 8 and enrolled for the 44-week or 52-week maintenance treatment period with UPA 15mg, UPA 30mg or PBO.

- 6.29 To compare the safety of UPA versus TOF, the submission conducted indirect treatment comparisons across comparable outcomes of adverse events (AEs). Overall, the indirect treatment comparisons of safety outcomes found no statistically significant differences between UPA and TOF.
- 6.30 To compare the safety of UPA versus other comparators, the submission conducted: (i) a naïve comparison versus the PBS-listed comparators (GOL, VDZ, IFX and ADA) similar to the analysis presented in the GOL PSD (Tables 10 and 11, GOL PSD, November 2017); and (ii) an indirect comparison versus the near market comparator OZA. The naïve comparison relied on the same data presented in the GOL PSD and included comparable data from the more recent VDZ trials. The submission stated serious AEs and serious infection rates were comparable across the treatments, and that there was a trend for lower discontinuation due to AEs with active treatments likely due to worsening disease in the PBO arms.
- 6.31 Interpretation of the naïve comparison of safety data is problematic due to inadequate power to detect differences in safety outcomes, differences in the durations of exposure (i.e. unadjusted for exposure time) and differences in the maintenance trial designs (i.e. control patients in the treat-through trials only received PBO throughout, whereas controls in the randomised withdrawal trials received active induction treatment). However, the PBAC had previously considered it reasonable that GOL is non-inferior to IFX, ADA and VDZ in terms of comparative safety based on naïve comparisons of safety data (paragraph 6.24, GOL PSD, November 2017).

- 6.32 The submission noted that the FDA recently completed a review of a large post-marketing safety clinical trial for TOF (ORAL Surveillance). The trial found an increased risk of blood clots and death with TOF 5 mg or 10 mg compared to TNF inhibitors in rheumatoid arthritis patients on concomitant methotrexate 50 years of age and older with at least one cardiovascular risk factor. The FDA required updated warnings for JAK inhibitor class products including UPA. The FDA believed that UPA (and other JAK inhibitors) may have similar risks as they share mechanisms of action with TOF.

Benefits/harms

- 6.33 Table 7 presents a summary of the comparative benefits in induction therapy for UPA versus the PBS-listed comparators, based on the indirect treatment comparisons for clinical remission. A summary of comparative benefit in maintenance treatment or comparative harms is not presented given the trial results indicated no significant differences between treatments. As discussed above, the induction trials may not be sufficiently comparable to support conducting unadjusted indirect treatment comparisons and the results should therefore be interpreted with caution.

Table 7: Summary of comparative benefits for UPA versus comparators

	UPA n/N	PBO n/N	Comparator n/N	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					UPA	PBO	Comparator	
Clinical remission in induction at Weeks 6/8/10: indirect comparisons								
UPA 45mg v PBO (MA: U-ACHIEVE- S1/S2, U- ACCOMPLISH)	177/716	8/374	-	10.60 (5.39, 20.86)	24.7	2.1	-	0.22 (0.19, 0.26)
TOF 10mg v PBO (MA: OCTAVE-1, OCTAVE-2)	-	14/234	160/905	2.95 (1.46, 5.95)	-	6.0	17.7	0.12 (0.08, 0.16)
IFX 5mg/kg v PBO (MA: ACT 1/2, Jiang, REMICADE, Kobayashi)	-	50/438	142/437	2.72 (1.90, 3.88)	-	11.4	32.5	0.20 (0.12, 0.29)
GOL 200->100mg v PBO (PURSUIT- SC)	-	16/251	45/253	2.79 (1.62, 4.8)	-	6.4	17.8	0.11 (0.06, 0.17)
ADA 160->80mg v PBO (MA: ULTRA-1, ULTRA-2, Suzuki)	-	46/472	74/468	1.58 (1.05, 2.4)	-	9.7	15.8	0.05 (-0.00, 0.11)
VDZ 300mg v PBO (MA: GEMINI-1, Motoya)	-	18/231	68/389	2.14 (1.03, 4.43)	-	7.8	17.5	0.10 (0.05, 0.15)
Indirect comparison: UPA 45mg v TOF 10mg				3.59 (1.36, 9.53)				0.10 (0.05, 0.15)
Indirect comparison: UPA 45mg v IFX 5mg/kg				3.90 (1.81, 8.38)				0.02 (-0.07, 0.11)
Indirect comparison: UPA 45mg v GOL 200->100mg				3.80 (1.60, 9.05)				0.11 (0.04, 0.18)
Indirect comparison: UPA 45mg v ADA 160->80mg				6.71 (3.04, 14.83)				0.17 (0.10, 0.24)
Indirect comparison: UPA 45mg v VDZ 300mg				4.95 (1.83, 13.40)				0.12 (0.06, 0.18)

Source: Table 2-32, pp107-108 of the submission; Table 2-33, pp111-112 of the submission; Table 2-35, pp119-120 of the submission, Table 2-36, pp120-121 of the submission; Figure 2, p1208 of the submission.

ADA = adalimumab; GOL = golimumab; IFX = infliximab; TOF = tofacitinib; UPA = upadacitinib; VDZ = vedolizumab; FMS=full Mayo score; MA=meta-analysis; HR = hazard ratio; PBO = placebo; RD = risk difference; RR = risk ratio.

6.34 On the basis of indirect evidence presented by the submission, for every 100 patients treated with UPA over the induction treatment period (of between 6 to 10 weeks), in comparison with:

- TOF – Approximately 10 additional patients would achieve clinical remission.
- GOL – Approximately 11 additional patients would achieve clinical remission.
- ADA – Approximately 17 additional patients would achieve clinical remission.
- VDZ – Approximately 12 additional patients would achieve clinical remission.
- IFX – No significant difference (*based on the risk difference statistic).

Clinical claim

6.35 For induction therapy, the submission described UPA as superior in terms of efficacy and non-inferior in terms of safety when compared with all PBS-listed treatments

(TOF, IFX, VDZ, GOL and ADA). For maintenance therapy, the submission described UPA as non-inferior in terms of efficacy and safety when compared with TOF, VDZ and GOL. The submission did not compare UPA to IFX and ADA in maintenance due to fundamental differences across trial designs.

- 6.36 The therapeutic claim of superior effectiveness between UPA and the PBS-listed comparators for induction treatment requires consideration because the UPA trials may not be sufficiently similar to the comparator trials to conduct a reliable (unadjusted) indirect treatment comparison. Although the results indicated that UPA may be superior to all PBS-listed comparators, the ESC considered there was considerable uncertainty around the robustness of the claim, given the uncertainty as to the exchangeability of the trials. Furthermore, the ESC was particularly concerned by the uncertainty arising from the lower placebo response rates observed in the UPA trials and implications for the comparisons, and noted there was no evidence this issue was adjusted for in the NMA presented in the PSCR. No head-to-head evidence was available for UPA vs. any of the comparators for the treatment of MSUC.
- 6.37 The PBAC considered that the claim of superior comparative effectiveness in induction therapy was adequately supported versus ADA, and also considered the claim may be supported versus TOF, VDZ and GOL (but was of uncertain clinical significance), however was likely not supported versus IFX. The PBAC considered the claim of non-inferior comparative effectiveness in maintenance therapy was adequately supported.
- 6.38 The PBAC considered that the claim of non-inferior comparative safety was adequately supported by the clinical evidence presented in the submission.

Economic analysis

- 6.39 The submission conducted: (i) a cost-per-responder analysis for initial treatment (Week 0 to Week 16) based on the claim of superior effectiveness for induction treatment; (ii) a cost-minimisation analysis for continuing treatment (Week 16 to Week 104) based on the claim of non-inferior effectiveness for maintenance treatment (see Clinical claim). The submission argued that it was appropriate to consider the induction and maintenance separately because it was ‘impractical’ to conduct a cost-utility analysis. The ESC noted the clinical trials assessed induction treatment at week 8, which was inconsistent with the cost per responder model assumption of induction by week 16.
- 6.40 The results presented in the submission used the published prices of comparators because the effective prices were unknown to the Sponsor. Hence, the submission stated that the results were only indicative and the analyses will need to be repeated with effective prices.
- For initial treatment, the submission estimated an induction price of UPA based on the average cost-per-incremental-responder with IFX IV, VDZ IV, GOL and TOF

relative to PBO (i.e. to achieve the average gradient on the cost-effectiveness plane). The submission stated that ADA was excluded because the PBAC recommended listing based on cost-effectiveness in the Southwest quadrant of the cost-effectiveness plane versus IFX (i.e. less effective, less costly).

- For continuing treatment, the submission estimated a maintenance price of UPA based on a cost-minimisation analysis with TOF over 88 weeks, assuming an equi-effective dose of UPA 15 mg or 30 mg daily = TOF 5 mg or 10 mg twice daily.

6.41 Irrespective of the clinical claim, separating the induction and maintenance periods for the economic evaluation is not reasonable. To understand the potential value of UPA, it is important to estimate the total costs and benefits over the entire treatment time (including the induction and maintenance periods) compared to the nominated comparators. Given a relatively low proportion of patients maintain an adequate response following induction treatment and assuming the treatment effect for maintenance is the same across treatments, then any absolute difference in responders observed at Week 16 would quickly decrease over time. The costs of UPA are also likely to be higher over time because there would be more patients using maintenance therapy. The submission's approach also does not adequately adjust for differences in the dosing frequencies for the induction and maintenance phases between UPA (i.e. constant dosing frequency) and the comparators (i.e. more frequent dosing for induction treatment), which has flow on implications for costs, given the prices of the comparators reflect an average price over the induction and maintenance periods. Table 8 presents the results of the cost-per-responder analysis.

Table 8: Results of the incremental cost per responder analysis for induction treatment (based on published AEMP)

	UPA	TOF	GOL	VDZ IV ^d	IFX IV ^d
Costs					
PBS item, max qty	45mg, 30mg or 15mg (1 pack / 28 tablets)	5mg or 10mg (1 pack / 56 tablets)	100mg injection (single use pen)	300mg powder for injection (vial)	100mg powder for injection (vial)
AEMP	\$5,032.48	\$1,092.47	\$1,044.43	\$2,949.93	\$320.71
Units / 16 weeks	4 (16 weeks)	4 (16 weeks)	6 ^a (18 weeks)	4 ^b (22 weeks)	4*4.41 vials (22 weeks)
Drug costs / 16 weeks	\$20,129.93	\$4,369.88	\$6,266.58	\$11,799.72	\$5,659.46
Admin costs / 16 weeks	-	-	-	\$319.00	\$407.60
Total Cost / 16 weeks	\$20,129.93	\$4,369.88	\$6,266.58	\$12,118.72	\$6,067.06
% Clinical remission					
Active	24.7%	17.7%	17.8%	17.5%	32.5%
PBO	2.1%	6.0%	6.4%	7.8%	11.4%
Risk difference	22.0%	12.0%	11.4%	10.0%	20.0%
Incremental cost per responder versus PBO	\$91,500	\$36,416	\$54,970	\$121,187	\$30,335
Derived UPA total cost (16 weeks) ^c	\$20,129.93	\$8,011.45	\$12,093.40	\$26,661.18	\$6,673.77
Derived UPA AEMP	NA	\$2,022.86	\$3,023.35	\$6,665.30	\$1,668.44
Market share: utilisation	NA	3.9%	5.3%	65.6%	25.1%
Average UPA AEMP	\$5,032.48	\$5,032.48			

Source: Table 3-6, p133 of the submission.

Abbreviations: AEMP = approved ex-manufacturer price; BD=twice daily, GOL=golimumab; IFX=infliximab; PBO = placebo; QD=once daily, Qty=quantity, TOF=tofacitinib; UPA=upadacitinib; VDZ=vedolizumab.

^a The PBS listing for GOL limits induction treatment to 14 weeks of treatment, consisting of 5 *100mg injections (2*100mg at Wk 0 and 1*100mg at Wks 2, 6 and 10). The submission included an additional 100mg injection at Week 14, with the next dose due Wk18.

^b The PBS listings for VDZ IV and IFX IV limit induction treatment to 3 doses of treatment at Wk0, Wk2 and Wk6, which permits a maximum of 14 weeks of induction treatment. The submission included an additional dose at Wk14, with the next dose due Wk22.

^c Derived as risk difference for UPA versus PBO x incremental cost per responder for comparator versus PBO (for each comparator).

^d The analysis assumed dosing for VDZ and IFX based on the IV only regimens; however, patients can switch to SC dosing of either VDZ or IFX from Week 6. The SC regimens were PBS-listed on a cost-minimisation basis to the IV regimens. In the cost per responder analysis, IV administration costs were included for VDZ and IFX, but assumed no SC administration costs with GOL. The derivation of comparator weights also excluded PBS items numbers for VDZ SC but inconsistently included PBS item numbers for IFX SC (Remsima®).

6.42 Notwithstanding the concerns related to the submission's overall approach (or the use of published prices), the following key issues were identified with the cost per responder analysis:

- The submission costed one too many doses of GOL, VDZ IV and IFX IV. Initial treatment is limited to 14 weeks of treatment corresponding to a total of five SC injections with GOL or 3 IV infusions with VDZ and IFX. Patients can receive up to 16 weeks of initial treatment with VDZ and IFX if they switch to the SC formulations, but the submission excluded the VDZ SC and IFX SC doses from the analysis. By setting a time horizon of 16 weeks for all treatments rather than simply the duration of initial treatment on the PBS, the submission included the first dose of continuing treatment and hence overestimated costs for GOL, VDZ IV and IFX IV. The submission also assumed no administration costs for SC injections with GOL despite some 10% of patients requiring medical assistance or training

(paragraph 7.16, VDZ PSD, November 2020). The PSCR acknowledged the evaluation's calculation of the number of doses of GOL, VDZ IV and IFX IV due to the 16-week horizon and agreed it was reasonable to correct these.

- The methodology for conducting the cost per responder analysis was inappropriate. The submission estimated the cost per responder for each treatment separately versus placebo, calculating the corresponding price for UPA assuming an equal cost per responder with each comparator, then finally combining these prices using utilisation weights. Under this approach, comparators with larger market shares are more heavily weighted without properly accounting for the corresponding number of responders. In contrast, under a standard evaluation framework the analysis would estimate the cost per responder of a mixed treatment comparator taking account of both the relative effectiveness and proportional use of each comparator in the one step.
 - The analysis used the point estimates of the RD statistic from the ITT populations of the corresponding trials, which ignores any uncertainty around the treatment effects and assumes that the absolute treatment effects are constant across trials. Given the PBO response rate in the UPA trials (2.1%) was different/lower than the other trials (range: 6.0% to 11.4%), indicating that there were likely prognostic differences across trials, the assumption of constant absolute effects across trials is less likely to be true.
 - The rationale to exclude ADA from the analysis was unclear and may not be reasonable; the submission also excluded IFX SC and VDZ SC dosing regimens, which may have implications for total costs.
- 6.43 The ESC advised there was sufficient clinical evidence to justify a cost minimisation approach to the least costly alternative therapy across both the induction and maintenance phases. As the ESC considered the cost per responder analysis was inappropriate as it attempted to capture benefits over only a short induction period for a treatment which is intended to be ongoing, the ESC advised that if a cost minimisation to the least costly alternative therapy were not accepted by the sponsor, the new model would require evaluation in conjunction with further clinical analyses noted in paragraph 6.23.
- 6.44 The PSCR argued the superiority of UPA in inducing remission in the induction phase was a clinically meaningful benefit and disagreed with the evaluation position that it was more important to consider the total costs and benefits over the induction and maintenance periods. The ESC agreed with the evaluation and considered, given the treatment objective of UPA in MSUC was the ongoing management of the condition over a long period, that if a claim of superior comparative effectiveness in the induction phase were accepted, a cost utility model over a longer time period would better capture the costs and benefits of UPA over the full treatment period (induction and maintenance). The ESC noted the Sponsor had indicated it would be 'impractical' to undertake a formal cost utility analysis; however the ESC considered that such an

approach would be more informative than the cost per responder approach used in the submission, if a cost-minimisation analysis was not accepted by the sponsor.

6.45 Table 9 presents the results of the cost-minimisation analysis, between UPA and TOF for maintenance treatment.

Table 9: Results of the cost-minimisation analysis for maintenance treatment (based on published AEMP)

Component	UPA		TOF	
	15mg	30mg	5mg	10mg
PBS item, max qty	15mg (1 pack / 28 tablets)	30mg (1 pack / 28 tablets)	10mg (1 pack / 56 tablets)	5mg (1 pack / 56 tablets)
AEMP	\$1,092.47 (flat pricing proposed)		\$1,092.47 (flat priced)	
Units / 88 weeks	22 packs		22 packs	
Total Cost / 88 weeks	\$24,034.34		\$24,034.34	

Source: Table 3-7, p134 of the submission.

Abbreviations: AEMP = approved ex-manufacturer price; BD=twice daily, QD = once daily, Qty=quantity, TOF=tofacitinib; UPA=upadacitinib.

6.46 The Pre-PBAC Response reiterated the sponsor’s view that the evidence demonstrated UPA was of superior comparative effectiveness to other PBS listed therapies in the induction phase, however also acknowledged the challenges in valuing the benefits UPA offered over alternative therapies. The sponsor indicated it was amenable to accepting the listing of UPA on a cost minimisation basis with IFX, TOF or VDZ, however argued ADA and GOL would be inappropriate comparators due to inferior efficacy, based on the PBAC’s prior advice that IFX, TOF and VDZ should be treated as interchangeable on an individual patient basis, but not ADA or GOL (paragraph 4.17, TOF interchangeability PSD, November 2020).

Drug cost/patient/year

6.47 Based on the proposed indicative effective prices from economic analyses (\$5,032.48 in induction, and \$1,092.47 in maintenance), the drug cost for UPA per patient over the first year of treatment is \$29,962, assuming \$20,130 for initial treatment (Week 0 to 16) and \$9,832 for continuing treatment (Week 16 to 52). This is likely an overestimate given the calculations were based on the published prices of the comparators.

Estimated PBS usage & financial implications

6.48 This submission was not considered by DUSC. The submission used a market share approach to the financial estimates based on the published prices of the nominated comparators and the proposed published prices for UPA. Table 10 summarises the inputs used for the financial estimates.

Table 10: Key inputs for financial estimates

Component	Data source
Market share	
Current market	<p><u>Usage of TOF, GOL, VDZ, IFX and ADA:</u> Medicare (PBS) statistics for 2017 to 2021. This was reasonable.</p> <p><u>Projected script usage for substituted treatments:</u> The submission indicated that since there are more than 40 items on the PBS for treatment of MSUC, where possible and appropriate, the submission combined individual items. Similarly, as some item numbers include initiation and continuing treatment, the submission disaggregated combined items into scripts for initiation only and continuing only to model the substitution. It was also assumed that usage would follow a linear trend of growth reflecting 2017 to 2021 usage, and that UPA would not impact on the current growth of the market. The current market was estimated to be [redacted]¹ scripts in Year 1, increasing to [redacted]² scripts in Year 6. Given the claim of superior effectiveness for initiation treatment, it is possible that UPA may delay the average time to treatment failure and hence delay the time to the mandatory break from PBS listed treatment. This would have the effect of growing the total market in the years after listing.</p>
Substitution	<p><u>Substitution rate:</u> The submission assumed a substitution rate of 10% in Year 1, 12% in Year 2, 14% in Year 3, 16% in Year 4, 18% in Year 5 and 20% in Year 6. The same rate of substitution was used for all treatments. This did not concur with the submission's claim that UPA would be used preferentially among patients who would otherwise be prescribed TOF, and therefore relatively limited substitution with other treatments was expected.</p> <p><u>Determination of script equivalence:</u> dosing regimens for UPA and those in the PBS listings for TOF, GOL, IFX, VDZ and ADA were assessed by the submission, along with existing therapeutic relativities and dosing information in the PIs. The submission estimated script equivalence separately for initial and continuing script.</p>
Utilisation	
Number of scripts	<p><u>Reconfiguration of initiation/continuation scripts:</u> The submission indicated that the proportion of initiation packs in overall usage would be greater in the early years of listing, and then gradually overtaken by continuation packs as more patients stay on treatment over time. To account for this, reconfiguration of the initiation/continuation usage split was done, based on ADA data. The reconfiguration assumed that in Year 1, 32% of scripts were for initiation, decreasing to 18% in Year 2, 12% in Year 3, and 10% in Years 4 to 6.</p> <p><u>Number of UPA scripts:</u> Estimated UPA script numbers were: [redacted]³ in Year 1; [redacted]⁴ in Year 2, [redacted]⁴ in Year 3; [redacted]⁵ in Year 4; [redacted]⁵ in Year 5; and [redacted]⁶ in Year 6.</p> <p><u>Grandfathered patients:</u> The submission stated that the sponsor requested a grandfather clause to allow approximately [redacted]⁷ patients from a patient familiarisation program and [redacted]⁷ patients in the OL extension trial to transition to PBS-subsidised UPA. The estimates presented by the submission did not include these patients and their estimated script usage.</p>
Cost of medicines	
UPA, TOF, GOL, VDZ, IFX and ADA (published prices)	<p>UPA: requested published DPMQs (UPA 15 mg \$1,271.40; UPA 30 mg \$2,076.38; UPA 45 mg \$ [redacted]). Errors with mark-ups in the Section 4 Excel workbook were identified during the evaluation and corrected numbers are presented in this section. Costs presented in the commentary are based on the requested DPMQs for UPA 15 mg, 30 mg and 45 mg formulations.</p> <p>TOF, GOL, VDZ, IFX, ADA: published DPMQs</p>
Impact on other medicines	
Other agents	Cost offsets for TOF, GOL, VDZ, IFX and ADA were applied, based on the substitution rates listed above and published prices for each agent.
MBS usage and costs	
MBS items	The submission indicated that the IV formulations of IFX and VDZ require MBS-funded administration procedures, and provided estimates of cost offsets for these infusion costs. MBS item 14245 for IV infusion of IFX and item 116 for VDZ infusion were used, at 80% benefit (\$81.52 and \$63.80, respectively).

Source: Table 4-16, p152; Table 4-20, p154; Table 4-21, p155; Section 4.1.2, p142-143 of the submission; worksheet '7. Net changes – MBS' of the Excel workbook 'Attachment 4 Workbook section 4'.

ADA = adalimumab; GOL = golimumab; IFX = infliximab; PI = product information; TOF = tofacitinib; UPA = upadacitinib; VDZ = vedolizumab

The redacted values correspond to the following ranges:

- ¹ 60,000 to < 70,000
- ² 100,000 to < 200,000
- ³ 5,000 to < 10,000
- ⁴ 10,000 to < 20,000
- ⁵ 20,000 to < 30,000
- ⁶ 30,000 to < 40,000
- ⁷ < 500

6.49 The estimated script numbers and costs for the PBS listing of UPA for the treatment of MSUC in adult patients are presented in Table 11. The table reflects updated results that correct for three programming/parameter errors identified in the submission’s Section 4 Excel workbook (see table footnotes for details).

Table 11: Estimated use and financial implications (updated for programming errors*)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Initiation scripts 45 mg	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Continuation scripts 15 mg	█ ¹	█ ²	█ ³	█ ³	█ ³	█ ³
Continuation scripts 30 mg	█ ¹	█ ¹	█ ¹	█ ²	█ ²	█ ²
Total number of scripts dispensed ^a	█ ²	█ ³	█ ³	█ ⁴	█ ⁴	█ ⁵
Estimated financial implications of upadacitinib for MSUC						
Cost to PBS/RPBS less copayments	\$ █ ⁶	\$ █ ⁷	\$ █ ⁷	\$ █ ⁸	\$ █ ⁹	\$ █ ⁹
Estimated financial implications of ADA, VDZ, TOF, IFX and GOL						
Cost to PBS/RPBS less copayments	-\$ █ ⁶	-\$ █ ⁶	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁸	-\$ █ ⁸
Net financial implications						
Net cost to PBS/RPBS	\$ █ ¹⁰	\$ █ ¹⁰	\$ █ ¹⁰	\$ █ ¹⁰	\$ █ ⁶	\$ █ ⁶
Net cost to MBS	-\$ █ ¹⁰	-\$ █ ¹⁰	-\$ █ ¹⁰	-\$ █ ¹⁰	-\$ █ ¹⁰	-\$ █ ¹⁰
Net cost to Government	\$ █¹⁰	\$ █¹⁰	\$ █¹⁰	\$ █¹⁰	\$ █¹⁰	\$ █⁶

Source: Table 4-20, p154; worksheet ‘5. Impact - net’; worksheet ‘7. Net changes - MBS’ of the Excel workbook ‘Attachment 4 Workbook section 4’.

ADA = adalimumab; GOL = golimumab; IFX = infliximab; MSUC = moderate to severe ulcerative colitis; TOF = tofacitinib; VDZ = vedolizumab

* Updated results correct for three programming/parameter errors: the published price for UPA 45 mg (the submission assumed a published price of \$ █ instead of the requested published price of \$ █); the published prices for UPA 15 mg and 30 mg (the submission applied the requested published price for UPA 15 mg to UPA 30 mg scripts, and vice versa); the patient copayment values (the submission did not use the current values).

^a As the proportion of initiation packs in overall usage would be greater during the early years of listing, and then use of continuation packs would increase as more patients stay on treatment over time, the submission reconfigured the initiation/continuation split to address this. For continuation it was assumed that 70% of scripts would be for the 15 mg, and 30% for the 30 mg.

The redacted values correspond to the following ranges:

- ¹ 500 to < 5,000
- ² 5,000 to < 10,000
- ³ 10,000 to < 20,000
- ⁴ 20,000 to < 30,000
- ⁵ 30,000 to < 40,000
- ⁶ \$10 million to < \$20 million
- ⁷ \$20 million to < \$30 million
- ⁸ \$30 million to < \$40 million
- ⁹ \$40 million to < \$50 million
- ¹⁰ \$0 to < \$10 million

6.50 The estimated net cost to the PBS/RPBS was \$0 to < \$10 million in Year 1, increasing to approx. \$10 million to < \$20 million in Year 6, for a total of \$40 million to < \$50 million over the first 6 years of listing. The incremental cost to the PBS/RPBS is driven

by the relatively higher published prices UPA for both initiation treatment and continuation treatment compared to PBS-listed comparators (after adjusting for script relativities). The estimates presented in the submission are not reliable for the following reasons:

- The analysis used the published rather than effective prices;
- The assumed linear growth trend (from close to market inception) potentially overestimates the size of the total MSUC market;
- The estimates did not consider differences in the costs to government related to different fees and mark ups for General Schedule and Section 100 drugs (paragraph 7.16, VDZ PSD, November 2020) which is relevant for substitution with VDZ and IFX IV.
- The analysis assumed no additional growth above the assumed (linear) trend with the proposed listing of UPA. Based on the claim of superior effectiveness for induction treatment, there may be more patients on treatment over time (due to longer persistence and potentially higher uptake); and
- The proportional use of the UPA 30 mg tablets for continuation treatment may be higher than assumed (i.e. more than 30%); however, although this parameter would not impact on an analysis of effective prices, where there is a flat pricing structure between UPA 15 mg and 30 mg formulations.

- 6.51 The submission also provided estimates of net cost to the PBS/RPBS using the estimated indicative effective prices for UPA (based on the cost-per-responder analysis and cost-minimisation analysis, totalling \$50 million to < \$60 million of the first six years of listing. These estimates were also unreliable for similar reasons above; however, the requested listing of UPA would likely lead to a moderate net cost to the PBS given the relative price premium requested for initial treatment (i.e. approximately double the total cost per person).
- 6.52 If recommended on a cost minimisation basis with the least costly alternative, the listing of UPA for MSUC would be expected to be cost neutral (or modestly cost saving if it replaced more expensive alternatives).

Quality Use of Medicines

- 6.53 The submission indicated that the sponsor has a risk management plan, which includes an Australian-specific annex that has been submitted to the TGA as part of the regulatory dossier. The submission also stated that the sponsor's patient support program will be available to provide support regarding the use of UPA to prescribers and patients. Alongside the PSCR, the sponsor provided an updated version of the Periodic Safety Update Report (PSUR) dated April 2022.

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation to list upadacitinib (UPA) for the treatment of moderate-to-severe ulcerative colitis (MSUC) in adult patients, as the TGA Delegate’s Overview was not available at time of PBAC consideration. However, the PBAC was of a mind to recommend listing upadacitinib for MSUC on the basis the cost-effectiveness of UPA would likely be acceptable if it were cost minimised to the least costly alternative therapy out of infliximab (IFX), tofacitinib (TOF), vedolizumab (VDZ) and golimumab (GOL). The PBAC considered, based on the evidence presented, that UPA is likely to be of non-inferior comparative effectiveness and safety to these agents in MSUC and considered there is also likely sufficient evidence that UPA, for some patients, provides a significant improvement in effectiveness in the induction phase compared to adalimumab (ADA).
- 7.2 The PBAC considered the equi-effective doses of UPA and the alternative therapies could be derived (if/when UPA is recommended for listing for MSUC) with reference to the therapeutic relativity sheet and relevant Product Information documents, noting the UPA equi-effective dose component includes treatment with UPA 45 mg once daily for 8 or 16 weeks in initial therapy, with an option for a dose reduction to 15 mg or 30 mg UPA once daily for the second 8 weeks of initial therapy, followed by either 15 mg or 30 mg UPA once daily thereafter.
- 7.3 The PBAC considered it was reasonable for the listing of UPA to be consistent with other biological or targeted synthetic disease modifying anti-rheumatic drugs (b/tsDMARDs) for MSUC, with prescribing restricted to specific specialists, an initial treatment period of 16 weeks, followed by maintenance therapy with re-assessment at 24 week intervals.
- 7.4 The PBAC noted that five b/tsDMARDs are currently listed for MSUC (with an additional two treatments either recommended or under consideration) and considered the clinical need for additional therapies is low. The Committee noted UPA would be the second janus kinase (JAK) inhibitor listed for this indication.
- 7.5 The PBAC considered the nominated main comparator of tofacitinib was reasonable, however also noted the submission nominated other PBS listed b/tsDMARDs for MSUC, including GOL, IFX, ADA and VDZ as supplementary comparators. The PBAC noted the clinical claim was that UPA was of superior comparative effectiveness to all currently listed b/tsDMARDs in induction therapy and of non-inferior comparative to GOL, TOF and VDZ in maintenance therapy. The PBAC noted a clinical effectiveness claim was not made versus ADA or IFX in maintenance therapy due to differences in the clinical trial designs. These claims are discussed further below.
- 7.6 The PBAC noted no direct trials comparing UPA to TOF or any of the supplementary comparators were available, and the submission relied on indirect treatment comparisons with placebo as the common comparator to support the clinical claims. The PBAC noted there were potential transitivity issues with the indirect comparisons

and specifically noted differences in the population recruited in the UPA trials compared to TOF and the supplementary comparator trials outlined in paragraph 6.11. The PBAC considered these differences introduced additional uncertainty to the comparisons, however was unsure of the potential magnitude of any potential bias introduced by these issues. The PBAC also specifically noted the low placebo response results observed in the induction phase of the UPA trials (compared to other bDMARD trials the Committee had previously assessed) and considered this difference was likely to bias in favour of UPA in the unadjusted indirect comparisons. The PBAC noted the Pre-PBAC Response presented a fixed effects network meta-analysis (NMA) for the outcome of clinical remission in the induction phase based on the risk difference statistic (paragraph 6.24 refers), however noted this analysis was not independently evaluated. The PBAC considered it was appropriate to consider the totality of the available evidence when drawing conclusions on the comparative effectiveness of UPA to the other PBS-listed b/tsDMARDs for MSUC.

- 7.7 For induction treatment, the PBAC noted the results of the unadjusted indirect comparisons showed statistically significant results favouring UPA for both clinical remission and clinical response versus TOF, GOL, ADA and VDZ, however noted this result was not demonstrated over infliximab for all outcomes. For the comparison versus IFX, the unadjusted indirect comparison statistically significantly favoured UPA for the outcome of clinical response, but was not sustained for clinical remission across both the relative risk and risk difference statistics (clinical remission UPA vs IFX RR = 3.90 (95% CI 1.81, 8.38) and RD = 0.02 (95% CI -0.07, 0.11)). For the comparison versus TOF, GOL, ADA and VDZ, the PBAC considered the clinical relevance of the difference in the proportion of patients achieving remission and clinical response was uncertain, given the transitivity issues discussed in the paragraph above, wide confidence intervals and short induction treatment period (6 to 10 weeks). Overall, the PBAC considered UPA was likely to be of non-inferior comparative effectiveness to IFX for induction therapy, and considered the evidence presented may support a conclusion that UPA is statistically significantly superior to other PBS-listed b/tsDMARDs for induction therapy for both clinical remission and response but the clinical relevance was uncertain.
- 7.8 For maintenance treatment, the PBAC noted the results of the indirect comparisons did not demonstrate statistically significant differences between UPA and any of TOF, VDZ or GOL for clinical remission or clinical response (with the exception of the comparison of UPA 30mg vs. VDZ, which favoured UPA) and considered based on the results of the unadjusted indirect comparisons that the claim of non-inferior comparative effectiveness to these therapies was reasonable. The PBAC noted no indirect comparisons versus IFX and ADA were presented, however considered this was acceptable due to differences in the trial designs.
- 7.9 The PBAC noted the submission originally requested listing at a higher price than the alternative therapies, based on the claim of superior comparative effectiveness in induction therapy, with the requested price supported by a cost per responder

analysis for this phase of treatment. The Committee noted the submission requested price was based on a weighted price proposal combining the results of the cost per responder analysis for induction therapy, and the results of a cost minimisation approach to tofacitinib for maintenance therapy. The PBAC considered the approach in the submission was inappropriate, and agreed with the ESC that the cost per responder model attempted to capture benefits over only a short induction period for a treatment which is intended to be ongoing, and therefore it would have been preferable to model both benefits and costs over a duration reflective of the likely duration of treatment. This issue notwithstanding, the PBAC noted the sponsor indicated in its pre-PBAC response that they would accept listing on a cost minimisation basis with the alternative therapies (excluding ADA and GOL). The PBAC noted UPA was significantly better than ADA at achieving clinical remission and clinical response across both the relative risk and risk difference statistics (clinical remission UPA vs ADA RR = 6.71 (95% CI 3.04, 14.83) and RD = 0.17 (95% CI 0.10, 0.24) and clinical response UPA vs ADA RR 2.28 (95% CI 1.79, 2.90) and RD = 0.35 (95% CI 0.27, 0.43)). Based on the totality of the evidence presented in Table 4, the PBAC is satisfied that UPA provides, for some patients, a significant improvement in efficacy compared to ADA in the induction period.

- 7.10 The PBAC considered that a listing based on a cost minimisation approach with costs over two years, consistent with the approach previously used for b/tsDMARDs, was appropriate to determine the cost minimised price of UPA and agreed the cost of UPA should be no greater than the alternative therapies (excluding ADA).
- 7.11 The PBAC considered that, under the parameters of its recommended listing on a cost minimisation with the least costly of VDZ, IFX, GOL and TOF, the listing of UPA would likely be cost neutral to the PBS or result in a modest net save as it will predominantly replace therapies that are either of equivalent cost or more expensive.

Outcome:

Deferred

8 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.

9 Sponsor's Comment

The sponsor had no comment.

Addendum to the July 2022 Public Summary Document:

4.03 UPADACITINIB,

**Tablet 15 mg, Tablet 30 mg, Tablet 45 mg,
Rinvoq[®],
AbbVie Pty Ltd.**

10 Background

10.1 At its July 2022 meeting, the PBAC deferred making a recommendation for the listing of upadacitinib (UPA) for the treatment of moderate to severe ulcerative colitis (MSUC) as the TGA Delegate's Overview was not available at the time of PBAC consideration. The PBAC was of a mind to recommend the General Schedule, Authority Required (in writing) listing of UPA for MSUC on the basis the cost-effectiveness of UPA would likely be acceptable if it were cost minimised to the least costly alternative therapy out of infliximab (IFX), tofacitinib (TOF), vedolizumab (VDZ) and golimumab (GOL). The PBAC considered, based on the evidence presented, that UPA is likely to be of non-inferior comparative effectiveness and safety to these agents in MSUC and considered there is also likely sufficient evidence that UPA, for some patients, provides a significant improvement in effectiveness in the induction phase compared to adalimumab (ADA).

10.2 The TGA Delegate's Overview, ACM advice and finalised TGA registration were provided prior to the November 2022 PBAC meeting. The finalised TGA indication for UPA for MSUC is as follows:

'RINVOQ [upadacitinib] 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 medicine.'

11 PBAC outcome

11.1 The PBAC recommended the General Schedule, Authority Required (in writing) listing of upadacitinib (UPA) for the treatment moderate to severe ulcerative colitis (MSUC). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of UPA would be acceptable if it were cost minimised to the least costly alternative therapy out of infliximab (IFX), tofacitinib (TOF), vedolizumab (VDZ), ustekinumab (UST) and golimumab (GOL).

11.2 The PBAC reaffirmed its view, based on the evidence presented, that UPA is likely to be of non-inferior comparative effectiveness and safety to these agents in MSUC and considered there is also likely sufficient evidence that UPA, for some patients, provides

a significant improvement in effectiveness in the induction phase compared to adalimumab (ADA) (paragraphs 7.1 and 7.10).

- 11.3 The Committee also reaffirmed its view that a listing based on a cost minimisation approach with costs over two years, consistent with the approach previously used for b/tsDMARDs, was appropriate to determine the cost minimised price of UPA and agreed the cost of UPA should be no greater than the alternative therapies (excluding ADA) (paragraph 7.10). The PBAC considered the equi-effective doses of UPA and the alternative therapies could be derived per its view expressed in July 2022, noting the UPA equi-effective dose component includes treatment with UPA 45 mg once daily for 8 or 16 weeks in initial therapy, with an option for a dose reduction to 15 mg or 30 mg UPA once daily for the second 8 weeks of initial therapy, followed by either 15 mg or 30 mg UPA once daily thereafter.
- 11.4 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because UPA is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity over the alternative therapies, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 11.5 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

Outcome:

Recommended

12 Recommended listing

12.1 Add new item(s):

For brevity reasons, a shortened version of the restriction is presented. Administrative notes and prescribing instructions common to all MSUC listings are noted by their corresponding concept code and not reproduced in full. Changes to the single large administrative advice (code 27221) are noted once at the end of this overview.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
UPADACITINIB					
upadacitinib 45 mg modified release tablet, 28	NEW	1	28	3	Rinvoq
Restriction Summary [11954 attached to tofacitinib] / Treatment of Concept: [11940]					
Concept ID (for internal Dept. use)	Category / Program: 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)				

	<p>Administrative Advice: TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS Changes to common administrative advice concept 27221 at the end of this section.</p>
	<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>
	<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
	<p>Administrative Advice: Special Pricing Arrangements apply.</p>
	<p>Indication: Moderate to severe ulcerative colitis</p>
	<p>Treatment Phase: Initial treatment - Initial 1 (new patient)</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>
	<p>AND</p>
	<p>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 months or have intolerance necessitating permanent treatment withdrawal</p>
	<p>AND</p>
	<p>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 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 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 months of treatment of an appropriately dosed thiopurine agent,</p>
	<p>AND</p>
	<p>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).</p>
	<p>AND</p>
	<p>Population criteria: Patient must be aged 18 years or older</p>
	<p>Prescribing Instructions: Concepts 27219, 24856, 24883, 27220, 23934, 26614, 14943, 10418 and 11162 not displayed here for brevity reasons.</p>
	<p>Administrative advice: Concepts 27176 and 28664 [Retired text] [CAR flag] not displayed here for brevity reasons.</p>
	<p>Restriction Summary: 11830 as per tofacitinib / ToC: 11915</p>
	<p>Indication: Moderate to severe ulcerative colitis</p>
	<p>Treatment Phase: Initial treatment - Initial 2 (change or re-commencement of treatment after a break in biological medicine of less than 5 years)</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)].
	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:
	Items 27220, 23934, 26614, 24713 and 11162 should apply.
	Administrative advice:
	Item 28664 should apply.
Restriction Summary 11881 as per tofacitinib / ToC: 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

Public Summary Document – July 2022 PBAC Meeting with Addendum November 2022

	Prescribing Instructions: Items 27470, 24883, 27220, 23934, 26614 and 11162 should apply.
	Administrative advice: Item 28664 [Retired text] [CAR] should apply.
Restriction Summary 11976 as attached to tofacitinib / ToC 11976	
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Initial 1 (new patient) or Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) or Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) - balance of supply
	Treatment criteria:
	Must be treated by a gastroenterologist (code 87); OR
	Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR
	Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
	AND
	Clinical criteria:
	Patient must have received insufficient therapy with this drug for this condition under the Initial 1 (new patient) restriction to complete 16 weeks treatment; or
	Patient must have received insufficient therapy with this drug for this condition under the Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) restriction to complete 16 weeks treatment; or
	Patient must have received insufficient therapy with this drug for this condition under the Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) restriction to complete 16 weeks treatment
	AND
	Clinical criteria:
	The treatment must provide no more than the balance of up to 16 weeks treatment available under the above restrictions
	Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Restriction Summary New (based on 12279 tofacitinib's GF listing underneath Continuing treatment, but with 3 variations) / Treatment of Concept: New (based on 12317)	
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements
	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 be receiving treatment with this drug for this condition at the time of application
	AND
	Clinical criteria:

Public Summary Document – July 2022 PBAC Meeting with Addendum November 2022

	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [<<PBS listing date]
	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 16 weeks of treatment under this restriction
	AND
	Population criteria:
	Patient must be aged 18 years or older
	Prescribing Instructions: Items 27842, 12980, 17110, 23637, 23643, 17150, 17047 and 19535 should apply.
	Administrative advice: Item 28644 should apply.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
UPADACITINIB					
upadacitinib 15 mg modified release tablet, 28	NEW	1	28	1	Rinvoq
upadacitinib 30 mg modified release tablet, 28	NEW	1	28	1	Rinvoq

Restriction Summary [new] / Treatment of Concept: [new]

Concept ID (for internal Dept. use)	Category / Program: General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
	Administrative Advice: Changes to common administrative advice concept 27221 at the end of this section.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Initial treatment Dose modification
	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)].

Public Summary Document – July 2022 PBAC Meeting with Addendum November 2022

AND
Treatment criteria:
Patient must be undergoing existing PBS-subsidised treatment with this therapy
Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m Monday to Friday).
Administrative advice: Any further authority applications occurring immediately after access through this dose modification listing are not to occur through any of the following Treatment phase listings: (i) Balance of Supply, (ii) Initial Treatment

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
UPADACITINIB					
upadacitinib 15 mg modified release tablet, 28	NEW	1	28	5	Rinvoq
upadacitinib 30 mg modified release tablet, 28	NEW	1	28	5	Rinvoq

Restriction Summary based on 11942 as attached to tofacitinib/ Treatment of Concept:11883

Concept ID (for internal Dept. use)	Category / Program: 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 telephone/online PBS Authorities system)
	Administrative Advice: Changes to common administrative advice concept 27221 at the end of this section.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Continuing treatment
	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
	Prescribing Instructions: Items 17150, 17047, 19535, 26394, 23934, 26614 and 23943 should apply.
	Administrative advice:

Public Summary Document – July 2022 PBAC Meeting with Addendum November 2022

	Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Restriction Summary New (based on 12279 tofacitinib's GF listing underneath Continuing treatment, but with 3 variations) / Treatment of Concept: New (based on 12317)	
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements
	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 be receiving treatment with this drug for this condition at the time of application
	AND
	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [insert PBS listing date]
	AND
	Clinical criteria:
	Patient must have had a Mayo clinic score greater than or equal to 6 prior to commencing non-PBS-subsidised treatment with this drug for this condition; OR
	Patient must have had a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores were both greater than or equal to 2 (endoscopy subscore is not required for a partial Mayo score) prior to commencing non-PBS-subsidised treatment with this drug for this condition; OR
	Patient must have a documented history of moderate to severe refractory ulcerative colitis prior to having commenced non-PBS-subsidised treatment with this drug for this condition where a Mayo clinic or partial Mayo clinic baseline assessment is not available
	AND
	Population criteria:
	Patient must be aged 18 years or older
	Prescribing Instructions: Items 27842, 12980, 17110, 23637, 23643, 17150, 17047 and 19535 should apply.
	Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Public Summary Document – July 2022 PBAC Meeting with Addendum November 2022

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
UPADACITINIB					
upadacitinib 45 mg modified release tablet, 28	NEW	1	28	0	Rinvoq
upadacitinib 30 mg modified release tablet, 28	NEW	1	28	0	Rinvoq
upadacitinib 15 mg modified release tablet, 28	NEW	1	28	0	Rinvoq

Restriction Summary based on 11882 as attached to tofacitinib/ Treatment of Concept:11882

Concept ID (for internal Dept. use)	Category / Program: General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
	Administrative Advice: Changes to common administrative advice concept 27221 at the end of this section.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Moderate to severe ulcerative colitis
	Treatment Phase: 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:
	The treatment must provide no more than the balance of up to 16 weeks therapy available under Initial 1, 2 or 3 treatment; or
	The treatment must provide no more than the balance of up to 24 weeks therapy available under Continuing treatment.
	Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
	Administrative advice: Seek an increase in repeat prescriptions to that stated (zero) only where applicable.

	<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.</p> <p>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. 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> <p>(6) Dose modification Where the drug's Product Information indicates variable dosing regimens based on the individual's response/tolerance, apply under this listing to continue treatment with the new strength. Mark any remaining repeat prescriptions for the discontinued strength with the word 'cancelled'. This treatment phase listing recognises that a patient's optimal dose may not always be immediately apparent at the time of treatment initiation and therefore does not require confirmation of an objective, adequate response to the preceding supply of drug.</p>
--	---

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

13 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.

14 Sponsor's Comment

The sponsor had no comment.