6.12 UPADACITINIB, Tablet 15 mg, Rinvoq®, AbbVie Pty Ltd.

1 Purpose of submission

1.1 The submission requested a General Schedule, Authority Required listing for upadacitinib (UPA) for the treatment of severe active psoriatic arthritis (PsA) in patients who have failed to achieve an adequate response to conventional disease modifying anti rheumatic drugs (cDMARDs). This was the first submission to the PBAC for the requested indication; UPA is currently PBS listed for rheumatoid arthritis and was recommended by the PBAC at the March 2021 meeting for the treatment of ankylosing spondylitis.

1.2 Listing was requested on the basis of a cost-minimisation analysis versus tofacitinib (TOF), which is the only other Janus kinase (JAK) inhibitor currently listed on the PBS for PsA. If listed, UPA would be one of ten treatment alternatives including TOF and eight biologic disease modifying anti rheumatic drugs (bDMARDs).

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

Component	Description
Population	Patients with severe PsA in whom an adequate response has not been achieved with at least 6 months of intensive treatment with cDMARDs
Intervention	Upadacitinib 15mg tablet, orally once daily
Comparator	Tofacitinib 5mg tablet, orally twice daily
Outcomes	Disease activity outcomes: clinical responses (ACR20, ACR50, ACR70) reported as the percentage of patients achieving 20%, 50% or 70% functional improvement in the American College of Rheumatology response criteria at week 12/3 months; PASI75 improvement from baseline at week 12/3 months. Patient reported outcomes: improvement in physical function measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) from baseline to week 12/3 months.
Clinical claim	Upadacitinib is non-inferior to tofacitinib in terms of efficacy and safety in patients with severe PsA for whom an adequate response has not been achieved with conventional therapies.

Source: Table1-1, p13 of the submission.
Abbreviations: ACR, American College of Rheumatology; ACR20/50/50, ≥20/50/70% improvement in tender and swollen joint counts and ≥20/50/70% improvement in 3 of 5 remaining ACR core set measures; PASI, Psoriasis Area and Severity Index; PASI75, ≥75% improvement from baseline; cDMARD = conventional disease modifying anti-rheumatic drugs; PsA = psoriatic arthritis.

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. At time of PBAC consideration: The TGA Delegate's Overview was available.

2.2 The TGA Delegate was supportive of registration for the following indication:

'Upadactinib is indicated for the treatment of moderate to severe active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to, one or more DMARDs. Upadactinib may be used as monotherapy or in combination with a non-biological DMARD'.

3 Requested listing

Name, Restriction, Manner of administration and form	Maximum quantity (packs)	Maximum quantity (units)	№.of Rpts	Dispensed price for maximum quantity (DPMQ)	Proprietary Name and Manufacturer
UPADACITINIB					
Initial 1, 2, 3 15 mg modified release tablet, 28	1	28	3	$1,271.34^	RINVOQ, AbbVie Pty Ltd
Initial – grandfathered patients 15 mg modified release tablet, 28	1	28	5	$1,271.34^	
Continuing treatment 15 mg modified release tablet, 28	1	28	5	$1,271.34^	

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☒Medical Practitioners
Severity:	Severe
Condition:	Psoriatic arthritis
PBS Indication:	Severe Psoriatic Arthritis
Treatment phase:	Initial treatment
Restriction:	☒Authority Required - In Writing
Treatment criteria:	Must be treated by a rheumatologist OR a clinical immunologist with expertise in the management of psoriatic arthritis.
Clinical criteria:	As per other PBS-listed JAK inhibitor/bDMARDs, where: Patient must not receive more than 16 weeks of treatment under this restriction.
Population criteria:	Patient must be aged 18 years or older.
Prescriber Instructions:	As per other PBS-listed JAK inhibitor/bDMARDs, where: An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 12 weeks of therapy.
Treatment phase:	Initial treatment: grandfathered patients
Restriction:	☒Authority Required - In Writing
Treatment criteria:	Must be treated by a rheumatologist OR a clinical immunologist with expertise in the management of psoriatic arthritis.
Clinical criteria:	As per other PBS-listed JAK inhibitor/bDMARDs, where: Patient must have demonstrated an adequate response following at least 12 weeks of non-PBS-subsidised treatment with this drug for this condition. Patient must not receive more than 24 weeks of treatment under this restriction.
Population criteria:	Patient must be aged 18 years or older.
Prescriber Instructions:	As per other PBS-listed JAK inhibitor/bDMARDs, where: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
Treatment phase:	Continuing treatment
Restriction:	☒Authority Required - In Writing
Clinical criteria:	As per other PBS-listed JAK inhibitor/bDMARDs, where: Patient must have demonstrated an adequate response to treatment with this drug. Patient must not receive more than 24 weeks of treatment under this restriction.
Prescriber Instructions:	As per other PBS-listed JAK inhibitor/bDMARDs.

Source: Table 1-7 p23 of the submission and Attachment: 03-Resctriction_Upadacitinib PsA, located in key documents folder alongside the submission.

^Requested published DPMQ (effective from 1 January 2021 based on the 7th Community Pharmacy Agreement); confidential effective price to be determined.

Abbreviations: JAK=janus kinase; bDMARD=biological disease modifying anti-rheumatic drug.

3.1 The sponsor requested General Schedule, Authority Required (in writing) PBS listing of UPA 15mg tablets for initial and continuing treatment of severe active PsA,

including for grandfathered patients. The wording of the requested restriction was consistent with approved criteria for TOF and bDMARDs.

3.2 The submission stated that a grandfather clause will be necessary to allow < 500 patients from a planned Patient Familiarisation Program (launched upon TGA registration) and < 500 patients who are enrolled in the long-term extension phases of UPA clinical trials to transition to PBS-subsidised treatment.

3.3 The requested quantities (including repeats) permit up to 16 weeks of initial treatment (4 packs) followed by 24 weeks of continuing therapy (6 packs). Grandfathered patients would be eligible for a maximum of 24 weeks of initial PBS treatment (before assessment under the continuing treatment restriction). Patients treated with UPA must meet the response criteria after at least 12 weeks of initial treatment, and maintain that response thereafter, to be eligible for continuing treatment.

3.4 The sponsor requested a Special Pricing Arrangement that would maintain the current published DPMQ for UPA (DPMQ = $1,271.34 as per the current PBS listing for rheumatoid arthritis), and an effective price based on a cost-minimisation analysis to TOF 5mg twice daily. The submission stated that the effective price for TOF 5mg was unknown and therefore an effective price was not calculated.

3.5 The sponsor also requested that the PBAC does not treat UPA as interchangeable on an individual basis with bDMARDs for PsA according to Section 101(3BA) of the *National Health Act 1953*, given UPA is not a biologic and has a different mode of action and method of administration (i.e. JAK inhibitor with oral administration compared to the bDMARDs administered via subcutaneous injection or intravenous infusion). In November 2020, the PBAC reaffirmed that TOF, another JAK inhibitor, should be treated as interchangeable with certolizumab pegol, guselkumab, ustekinumab, secukinumab for PsA (Tofacitinib Outcome Statement November 2020 PBAC meeting).

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

4 Population and disease

4.1 PsA is a chronic inflammatory musculoskeletal disease associated with psoriasis. PsA consists of the coexisting progression of joint disease and skin inflammation. Patients with PsA experience pain, swelling, joint tenderness and joint deformity, which results in a loss of function and limited movement, impacting productivity and quality of life. The population targeted in the submission was patients with severe active PsA in whom an adequate response had not been achieved with at least 6 months of intensive treatment with cDMARDs, as per the requested PBS criteria.

4.2 UPA is an oral, selective and reversible inhibitor of JAK1, which is important in transmitting inflammatory cytokine signals active in PsA. The recommended dose in the draft product information (PI) for PsA is UPA 15mg orally once daily which is the same as the approved dose for rheumatoid arthritis.

4.3 If listed, UPA will become an alternative treatment option to TOF and eight bDMARDs available on the PBS: etanercept, infliximab, adalimumab, golimumab, certolizumab pegol, ustekinumab, secukinumab, and ixekizumab. Under current PBS criteria, patients may fail or cease to respond to three PBS-subsidised treatments during a 'treatment cycle' before being required to undergo a five-year break.

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

5 Comparator

5.1 The submission nominated TOF 5mg twice daily as the main comparator. TOF is the only other JAK inhibitor currently PBS listed for PsA and shares the same route of administration. The submission also acknowledged in the utilisation and financial estimates that UPA would replace any of the bDMARDs available for PsA.

5.2 The PBAC has previously considered ustekinumab, secukinumab, certolizumab pegol and TOF to be 'lower tier' medicines (i.e., less effective) and etanercept, adalimumab, infliximab, ixekizumab and golimumab to be 'higher tier' medicines (i.e., more effective) for the treatment of PsA.

5.3 In recent decisions, the PBAC had considered all currently listed treatments for PsA including TOF and bDMARDs (irrespective of their effectiveness 'tier') as relevant alternative therapies because they may be replaced in practice; and in the absence of evidence of a significant improvement in efficacy or reduction of toxicity, recommended listing on a cost-minimisation basis to the lowest cost alternative (paragraph 7.1, Tofacitinib Public Summary Document (PSD) November 2018; paragraph 7.1, Ixekizumab, PSD July 2018). For guselkumab, to account for the lack of evidence to support non-inferiority to the higher tier medicines, the PBAC considered the price must be less than the higher tier bDMARDs and could not be any more costly than any of the lower tier bDMARDs (guselkumab PSD, November 2020 PBAC meeting).

5.4 Under Section 101(3B) of the National Health Act (1953), the PBAC cannot recommend listing a therapy that is substantially more costly than an alternative therapy unless it is satisfied that the therapy provides, for some patients, a significant improvement in efficacy and/or reduction in toxicity. The submission did not present any evidence that UPA provided a significant improvement in efficacy and/or reduction in toxicity compared to any alternative, and therefore there was no basis for UPA to have a price advantage over any relevant alternative for an equivalent treatment period. Direct evidence presented in the submission supported non-inferior effectiveness between UPA and adalimumab (a higher tier drug); whereas the indirect evidence, on which the clinical claim was based, supported non-inferior effectiveness between UPA and TOF (a lower tier drug).

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 that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on two randomised trials comparing UPA to adalimumab (ADA) and/or placebo (PBO), and two randomised trials comparing TOF to ADA and/or PBO:

- UPA versus ADA and PBO (SELECT-PsA 1)
- UPA versus PBO (SELECT-PsA 2)
- TOF versus ADA and PBO (OPAL-BROADEN)
- TOF versus PBO (OPAL-BEYOND)

The PBAC had previously considered evidence from the OPAL-BROADEN trial, comparing TOF to PBO and ADA, during consideration of TOF in November 2018 (paragraph 6.3-4, TOF, PSD, November 2018). That submission excluded data from OPAL-BEYOND, comparing TOF to PBO, because the nominated comparator was ADA.

6.4 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission (main publications only)

Trial ID	Protocol title/ Publication title	Publication citation
UPA trials		
SELECT-PsA 1	A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug (DMARD) – SELECT – PsA 1.	CSR, April 2020
SELECT PsA 2	A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease Modifying Anti-Rheumatic Drug (bDMARD) – SELECT – PsA 2.	CSR, April 2020
TOF trials		
OPAL-BROADEN	Mease P, Hall S, FitzGerald O et al. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis.	NEJM 2017; 377(16):1537-1550.
OPAL-BEYOND	Gladman D, Rigby W, Azevedo VF et al. Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors.	NEJM 2017; 377(16):1525-1536.

Source: Table 2-5, pp32-34 of the submission.
Abbreviations: UPA = upadacitinib; TOF = tofacitinib; PsA=psoriatic arthritis; CSR = Clinical Study Report.

6.5 Table 3 summarises the key features of the included randomised trials, categorised by prior treatment failure: patients with an inadequate response to cDMARDs or an inadequate response to bDMARDs. The submission presented comparison arms with

the relevant doses only (excluding data for UPA 30mg and TOF 10mg dosing regimens reported across the four trials).

Table 3: Key features of the included evidence

Trial	N	Design/duration	Bias	Relevant comparison	Patient population	Primary outcome(s)
POPULATION: cDMARD-IR						
SELECT-PsA 1	1282*	P3, MC, R, DB, DD, 56wk; AC, PC 24 wk; SOC rescue >wk16	*Low*	UPA 15mg D ± cDMARDs ADA 40mg Q2W ± cDMARDs PBO ± cDMARDs	Active PsA cDMARD-IR	ACR20 Wk12
OPAL-BROADEN	318*	P3, MC, R, DB, DD 12mth; AC, PC 3mth; SOC rescue >3mth	*Low*	TOF 5mg BD + cDMARDs ADA 40mg Q2W + cDMARDs PBO + cDMARDs	Active PsA cDMARD-IR	ACR20 3mth & ΔHAQ-DI 3mth
POPULATION: bDMARD-IR						
SELECT-PsA 2	423*	P3, MC, R, DB 56wk, PC 24 wk; SOC rescue >wk16	*Low*	UPA 15mg D ± cDMARDs PBO ± cDMARDs	Active PsA bDMARD-IR	ACR20 Wk12
OPAL-BEYOND	262*	P3, MC, R, DB,6mth; PC 3mth; SOC rescue >3mth	*Low*	TOF 5mg BD + cDMARDs PBO + cDMARDs	Active PsA bDMARD-IR	ACR20 3mth & ΔHAQ-DI 3mth

Source: Table 2-7, pp46-49, text on pp38-45 of the submission and related publications/CSRs.
P3=phase 3; DB=double blind; DD=double dummy; MC=multi-centre; R=randomised; PC=placebo-controlled; AC=active control; SOC=standard-of-care; wk=week; ACR20= ≥20% improvement on the American College of Rheumatology response criteria; UPA=upadacitinib; TOF=tofacitinib; ADA=adalimumab; PBO=placebo; D=once daily; Q2W=once every 2weeks; BD=twice daily; c/bDMARD=conventional/biologic disease-modifying anti-rheumatic drug; IR=inadequate response; HAQ-DI= Health Assessment Questionnaire-Disability Index; Δ = change from baseline.
* excluding patients randomised to UPA 30mg or TOF 10mg treatment arms.

6.6 All trials were phase 3, multicentre, randomised, placebo and/or active controlled, with a double-blind phase of at least 12 weeks. Patients had severe active PsA, no prior exposure to JAK inhibitors and were required to have experienced inadequate response to cDMARDs or bDMARDs. Aside from prior treatment failure, the selection criteria were similar across the trials and patient characteristics at baseline were generally balanced across treatment arms and similar across trials. A key difference across the trials was the use of concomitant cDMARDs during the trial period, with use being mandatory in the TOF trials and optional in the UPA trials (~80% received concomitant cDMARDs).

6.7 The primary endpoint in all trials was American College of Rheumatology (ACR) 20% response criteria (ACR20) at Week 12/3 months and a co-primary endpoint of change from baseline to 3 months in Health Assessment Questionnaire Disability Index (HAQ-DI) for the OPAL-BROADEN and OPAL-BEYOND trials. Rescue therapy with local standard of care was allowed after the primary endpoint in all trials, from week 12 (OPAL-BROADEN, OPAL-BEYOND) or week 16 (SELECT PsA 1 and SELECT PsA 2). Patients who received rescue therapy were considered non-responders for categorical endpoints. The overall risk of bias was low across the trials for primary and secondary endpoints at Week 12 / 3 months.

6.8 Both SELECT-PsA 1 and OPAL-BROADEN included ADA as an active control arm, but the OPAL-BROADEN trial was not designed (or powered) to evaluate the non-inferiority or superiority of TOF versus ADA. In contrast, the statistical analysis plan for SELECT-PsA 1 included (multiplicity-controlled) secondary analyses to test non-

inferiority and superiority of UPA versus ADA for ACR20 (and superiority for other outcomes). The sample size in SELECT-PsA 1 provided at least 85% power for evaluating non-inferiority of UPA versus ADA in ACR20 response at Week 12 (assuming 50% response rates for UPA and ADA, and 30% response rates for PBO).

Comparative effectiveness

6.9 Under PBS criteria, continued treatment is dependent on demonstrating and maintaining response to therapy, assessed after a minimum of 12 weeks following initiation (and every 24 weeks ongoing thereafter). The response criteria are a composite outcome requiring a 50% improvement from baseline in tender joint counts (TJC) and swollen joint counts (SJC), and 20% (or below absolute thresholds) improvement in acute phase reactants erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

6.10 The response criteria on the PBS are similar to the ACR 50% and 20% response criteria, which were primary and secondary outcomes at Week 12 / 3 months in the included trials. Assessment of response at Week 12 / 3 months corresponds with assessment of response to initial treatment on the PBS. The PBAC had previously considered that ACR50 was more relevant than ACR20 because it better reflected the PBS criteria for response to initial therapy; but ACR20 had also been used to support non-inferiority (paragraph 6.8, tofacitinib PSD Nov 2018; paragraph 6.10, ixekizumab PSD, July 2018).

6.11 The submission presented indirect treatment comparisons by prior treatment failure for ACR50 and ACR20 at Week 12 / 3 months using a standard frequentist approach (as described by Bucher et al 1997), summarised in Tables 4 and 5 respectively. The submission nominated non-inferiority margins of 0.29 for ACR50 and 0.46 for ACR20 using the relative risk (RR) statistic, where non-inferiority was concluded if the lower bound of the 95% CI was larger than the nominated margin. The PBAC has considered the same non-inferiority margins in past decisions (paragraph 6.14, ixekizumab PSD, July 2018; paragraph 6.9, tofacitinib PSD, November 2018).

Table 4: ACR50 response at Week 12 / 3 months at recommended doses of UPA 15mg D, TOF 5mg BD and ADA 40mg Q2W, and indirect comparisons presented by the submission

Trial	Drug, n/N (%)	Control, n/N (%)	OR (95%CI)	RR (95% CI)	RD (95%CI)
cDMARD-IR population					
UPA v PBO					
SELECT-PsA 1	161/429 (37.5)	56/423 (13.2)	**3.94 (2.80, 5.54)**	**2.83 (2.16, 3.72)**	**24.3 (18.7, 29.9)**
TOF v PBO					
OPAL-BROADEN	30/107 (28.0)	10/105 (9.5)	**3.70 (1.70, 8.04)**	**2.94 (1.52, 5.71)**	**18.5 (8.3, 28.7)**
UPA v ADA					
SELECT PsA 1	161/429 (37.5)	161/429 (37.5)	1.00 (0.76, 1.32)	1.00 (0.84, 1.19)	0.00 (-6.5, 6.5)
TOF v ADA					
OPAL-BROADEN	30/107 (28.0)	35/106 (33.0)	0.79 (0.44, 1.42)	0.85 (0.57, 1.28)	-5.0 (-17.3, 7.4)
bDMARD-IR population					
UPA v PBO					
SELECT PsA 2	67/211 (31.8)	10/212 (4.7)	**9.40 (4.68, 18.89)**	**6.73 (3.56, 12.72)**	**27.0 (20.1, 33.9)**
TOF v PBO					
OPAL-BEYOND	39/131 (29.8)	*19/131 (14.5)**	***2.49 (1.30, 4.89)***	***2.05 (1.26, 3.36)***	***15.3 (5.3, 25.2)***
Indirect Comparisons					
cDMARD-IR population					
UPA v TOF					
UPA (SELECT PsA 1) v TOF (OPAL-BROADEN) via PBO			1.06 (0.46,2.48)	0.96 (0.47, 1.97)	5.8 (-5.9, 17.4)
UPA (SELECT PsA 1) v TOF (OPAL-BROADEN) via ADA			1.27 (0.66, 2.42)	1.18 (0.76, 1.83)	5.0 (-9.0, 18.9)
bDMARD-IR population					
UPA v TOF					
UPA (SELECT PsA 2) v TOF (OPAL-BEYOND) via PBO			***3.08 (1.19, 7.97)***	***3.28 (1.47, 7.33)***	*11.7 (-0.41, 23.8)*

Source: Compiled during evaluation from Tables 2-18, 2-21, 2-29 and 2-32, pp78, 82, 93 and 96 of the submission.
CI=confidence interval; n=number of participants with event; N=total participants in group; OR=odds ration; RR=relative risk; RD=response rate difference. **Bold** indicates statistically significant results.
*incorrect value of 16 (12.2%) was reported in the submission; re-calculated results are indicated in *italics.*

Table 5: ACR20 response at Week 12 / 3 months at recommended doses of UPA 15mg D, TOF 5mg BD and ADA 40mg Q2W, and indirect comparisons presented by the submission

Trial	Drug, n/N (%)	Control, n/N (%)	OR (95%CI)	RR (95% CI)	RD (95%CI)
cDMARD-IR population					
UPA v PBO					
SELECT-PsA 1	303/429 (70.6)	153/423 (36.2)	**4.24 (3.18, 5.66)**	**1.95 (1.70, 2.25)**	**34.5 (28.2, 40.7)**
TOF v PBO					
OPAL-BROADEN	54/107 (50.5)	35/105 (33.3)	**2.04 (1.17, 3.55)**	**1.51 (1.09, 2.10)**	**17.1 (4.1, 30.2)**
UPA v ADA					
SELECT PsA 1	303/429 (70.6)	279/429 (65.0)	1.29 (0.97, 1.72)	1.09 (0.99, 1.19)	5.6 (-0.6, 11.8)
TOF v ADA					
OPAL-BROADEN	54/107 (50.5)	55/106 (51.9)	0.94 (0.55, 1.62)	0.97 (0.75, 1.26)	-1.4 (-14.8, 12.0)
bDMARD-IR population					
UPA v PBO					
SELECT PsA 2	120/211 (56.9)	51/212 (24.1)	**4.16 (2.75, 6.31)**	**2.36 (1.81, 3.09)**	**32.8 (24.0, 41.6)**
TOF v PBO					
OPAL-BEYOND	65/131 (49.6)	31/131 (23.7)	**3.18 (1.87, 5.39)**	**2.10 (1.47, 2.98)**	**26.0 (14.7, 37.2)**
Indirect Comparisons					
cDMARD-IR population					
UPA v TOF					
UPA (SELECT PsA 1) v TOF (OPAL-BROADEN) via PBO			**2.08 (1.11, 3.89)**	1.29 (0.90, 1.84)	**17.3 (2.8, 31.8)**
UPA (SELECT PsA 1) v TOF (OPAL-BROADEN) via ADA			1.37 (0.74, 2.52)	1.12 (0.85, 1.47)	7.0 (-7.8, 21.8)
bDMARD-IR population					
UPA v TOF					
UPA (SELECT PsA 2) v TOF (OPAL-BEYOND) via PBO			1.31 (0.67, 2.57)	1.13 (0.72, 1.75)	6.9 (-7.4, 21.1)

Source: Compiled during evaluation from Tables 2-18, 2-21, 2-29 and 2-32, pp78, 82, 93 and 96 of the submission.
CI=confidence interval; n=number of participants with event; N=total participants in group; OR=odds ration; RR=relative risk; RD=response rate difference. **Bold** indicates statistically significant results.

6.12 The trials demonstrated that UPA and TOF were more effective than PBO at achieving ACR20 and ACR50 responses at Week 12 / 3 months in patients with an inadequate response to cDMARDs or bDMARD, and had similar response rates versus ADA in patients with an inadequate response to cDMARDs. The submission did not make a clinical claim between UPA and ADA, but results for ACR20 in the SELECT-PsA 1 trial (RD=5.6, 95%CI: -0.6, 11.8) met the pre-specified test of non-inferiority (p-value < 0.0001) but not superiority (p-value = 0.0815).

6.13 In patients with an inadequate response to cDMARDs, the indirect treatment comparisons did not show any significant difference between UPA vs TOF for ACR50 response at Week 12 / 3 months using PBO or ADA as common reference. There were similar results for ACR20 at Week 12 / 3 months, but the OR and RD favoured UPA using PBO as the common reference.

6.14 In patients with an inadequate response to bDMARDs, the indirect treatment comparison generally favoured UPA versus TOF for ACR50 response at Week 12 / 3 months, with significant differences observed for the OR and RR statistics but not the RD. However, the assumption of transitivity may have been violated in this analysis given the difference in PBO response rates across the two trials (4.7% in SELECT-PsA 2 versus 14.5% OPAL-BEYOND). The SELECT-PsA 2 trial enrolled patients with more advanced / severe disease, a larger proportion of patients had an inadequate response to ≥2 bDMARDs and fewer used concomitant cDMARDs during the trial, which may

have caused heterogeneity in treatment responses. The indirect treatment comparison found no significant difference between UPA vs TOF for ACR20 response at Week 12 / 3 months and PBO response rates for ACR20 were similar.

6.15 Based on the nominated non-inferiority margins, the submission concluded that UPA was non-inferior to TOF for both ACR50 and ACR20 in both patients with an inadequate response to cDMARDs and bDMARDs. Despite minor differences across the trials, the results reasonably supported a conclusion of non-inferior efficacy between UPA and TOF.

Comparative harms

6.16 Table 6 summarises key adverse events (AEs) for UPA reported in SELECT-PsA 1 and SELECT-PsA 2. The submission presented AEs for TOF but did not present an indirect treatment safety comparison between UPA and TOF because safety results were reported at different time points across trials (UPA trials at 24 weeks, TOF trials at 3 and 12 months).

Table 6: Summary of key adverse events in the UPA trials up to Week 24.

	SELECT-PsA 1			SELECT-PsA 2		Pooled results, RE model: RR (95%CI)	
	UPA 15mg	PBO	ADA 40mg	UPA 15mg	PBO	UPA vs PBO	UPA vs ADA
N	429	423	429	211	212	-	-
Summary of any adverse events							
Any AE	287 (66.9)	252 (59.6)	278 (64.8)	135 (64.0)	139 (65.6)	1.06 (0.92,1.21)	1.03 (0.94,1.14)
Any serious AE	14 (3.3)	13 (3.1)	16 (3.7)	12 (5.7)	4 (1.9)	1.64 (0.60,4.51)	0.88 (0.43,1.78)
Any severe AE	21 (4.9)	16 (3.8)	27 (6.3)	13 (6.2)	8 (3.8)	1.41 (0.84,2.34)	0.78 (0.45,1.35)
Any AE leading to discontinuation	13 (3.0)	13 (3.1)	22 (5.1)	15 (7.1)	11 (5.2)	1.16 (0.68,1.98)	0.59 (0.30,1.16)
Death[a]	0	1 (0.2)	0	0	1 (0.5)	0.33 (0.03,3.18)	-
Treatment emergent adverse events of special interest							
Serious infection	5 (1.2)	4 (0.9)	3 (0.7)	1 (0.5)	1 (0.5)	1.19 (0.36,3.87)	1.25 (0.34,4.62)
Herpes zoster	4 (0.9)	3 (0.7)	0	3 (1.4)	2 (0.9)	1.39 (0.44,4.36)	9.00 (0.49,166.65)
Adjudicated MACE[b]	0	1 (0.2)	2 (0.5)	1 (0.5)	0	1.00 (0.10,9.55)	0.20 (0.01,4.15)
Adjudicated VTE[c]	0	1 (0.2)	2 (0.5)	1 (0.5)	0	1.00 (0.10,9.55)	0.20 (0.01,4.15)
Malignancy	1 (0.2)	1 (0.2)	3 (0.7)	3 (1.4)	0	2.47 (0.33,18.6)	0.33 (0.04,3.19)
Adjudicated NMSC	0	1 (0.2)	0	1 (0.5)	0	1.00 (0.10,9.55)	-

Source: Table 2-24 and 2-25, pp85-86 of the submission.

CI=confidence interval; n=number of participants reporting data; N=total participants in group; RR=relative risk; UPA=upadacitinib; PBO=placebo; ADA=adalimumab; AE=adverse event; MACE=major adverse cardiovascular event; NMSC=non-melanoma skin cancer; VTE=venous thromboembolic event.

[a] Includes non-treatment emergent deaths.

[b] MACE was defined as cardiovascular death (includes acute myocardial infarction, sudden cardiac death, heart failure, cardiovascular procedure-related death, death due to cardiovascular haemorrhage, fatal stroke, pulmonary embolism and other cardiovascular causes), non-fatal myocardial infarction and non-fatal stroke.

[c] Venous thromboembolic events include fatal and non-fatal deep vein thrombosis and pulmonary embolism.

6.17 Overall, the trial evidence found no increased risk for any safety outcomes at Week 24 in pooled results for UPA vs PBO or UPA vs ADA using a random effects model. In SELECT PsA 1, the incidence of any AE rates was numerically higher for UPA compared ADA, but numerically lower for serious AEs and severe AEs. Similar findings were

reported in the TOF trials at 3 months and 12 months, with the incidence of safety outcomes being similar for patients randomised to TOF, ADA and PBO.

6.18 The most common AEs reported for UPA 15mg included upper respiratory tract infection (URTI), increased blood creatinine phosphokinase (CPK), nasopharyngitis and urinary tract infection. The most common AEs reported in the TOF trials included URTI, nasopharyngitis and headache. Patients treated with either UPA or TOF were more likely to experience herpes zoster infection compared to PBO. The safety outcomes reported in the trials were consistent with the known safety profiles of UPA and TOF.

6.19 Long-term safety data has raised concerns regarding thrombosis risk with JAK inhibitors, with a black box warning issued by the FDA for i) baricitinib that included a caution related to deep venous thrombosis, pulmonary embolism and arterial thrombosis; and for ii) TOF due to an increased risk of thrombosis and mortality seen in the post-marketing study (paragraph 6.12, UPA PSD in Rheumatoid Arthritis, November 2019). In SELECT-PsA 1 and SELECT PsA 2, the incidence of venous thromboembolism was low and the TGA Clinical Evaluation Report (Round 1) noted that events were not observed more frequently than anticipated.

Clinical claim

6.20 The submission described UPA as non-inferior in terms of efficacy and safety compared with TOF (main comparator). The clinical claim was reasonable and adequately supported by the evidence presented. The indirect comparisons for ACR50 and ACR20 at Week 12 / 3 months met the nominated non-inferiority margins and the safety profiles of UPA and TOF appear to be similar based on the available data.

6.21 The PBAC considered that the claim of non-inferior comparative effectiveness to tofacitinib was reasonable.

6.22 The PBAC considered that the claim of non-inferior comparative safety to tofacitinib was reasonable.

Economic analysis

6.23 The submission presented a cost-minimisation analysis between UPA and TOF and nominated the following equi-effective doses based on the recommended doses for PsA in the respective PIs (and used in the trials):

- UPA 15mg orally once daily = TOF 5mg orally twice daily

6.24 The analysis used the published price for TOF and assumed equivalent costs (drug cost only) over the first 12 months of treatment. The submission stated that the effective price for TOF was not available to the Sponsor, but the same effective price is requested for UPA.

6.25 As discussed in paragraph 5.4, there was no basis for UPA to have a price advantage over any of the relevant alternatives for an equivalent treatment period, whether that is TOF or one of the bDMARDs PBS listed for PsA. The treatment period accepted by

the PBAC for similar treatments is the first 2 years of treatment, rather than the first 12 months assumed in the submission.

Drug cost/patient/year: $[redacted]

6.26 Assuming a DPMQ of $1,271.34 (i.e. requested published price) and < 500 scripts required for the first year of treatment inclusive of initial and continuing therapy with UPA 15 mg once daily, the cost per patient per year is $[redacted].

Estimated PBS usage & financial implications

6.27 This submission was not considered by DUSC. The submission estimated the financial implications of the proposed listing using a market share approach, plus treatment of approximately < 500 grandfathered patients enrolled in a Patient Familiarisation Program and long-term extension phases of clinical trials. The analysis used published DPMQs because the sponsor was not aware of the confidential effective or indication specific prices of substituted treatments.

6.28 For the market share approach, the submission assumed UPA would substitute for all currently PBS listed bDMARDs for PsA, and that the proposed listing would not affect future overall market growth. The submission estimated the annual background growth of the market by converting scripts dispensed in the past five years to 'patient-years' and future market share based on a number of assumptions. For grandfathered patients, the analysis assumed 0% treatment failure over the first six years.

6.29 Table 7 summarises the key inputs in the financial estimates.

Table 7. Data sources and parameter values applied in the utilisation and financial estimates of UPA

Data	Value and Source	Comment
Eligible population		
Current market of JAK/bDMARDs in PsA	Yr 0: [redacted][1] scripts (aggregate); Yr 0: [redacted][2] patient-years (aggregate); Script numbers sourced from Medicare Australia statistics; Patient-years calculated as scripts divided by scripts / year.	In deriving patient-years, the submission calculated patient-years in 2019 from scripts in 2019, and applied the growth rate (see below) to estimate patient-years in 2020 and subsequent years. For scripts, the submission inappropriately (and inconsistently) used scripts dispensed in 2019 as an estimate for scripts in both 2020 (Yr0) and 2021 (Yr1). That is, the submission did not apply the growth rate to scripts until Yr2 in the model. This likely underestimated the aggregate market in terms of script numbers over the first 6 years of listing. The submission also implicitly assumed all scripts for each drug provided the same number of doses, based on the assumed script relativities (see below), which is not true for IFX, CZP and SEC (due to the loading dose).
Script equivalence / substitution rate	Scripts / year calculated as the number of scripts required over the first two years of treatment divided by 2, based on TGA approved dosing regimens. Script equivalence vs UPA calculated as scripts / year for drug divided by scripts / year for UPA.	Appropriate approximation, given the PBAC has accepted the same implied assumptions in the cost-minimisation analysis (i.e. same response and continuation rates over the first two years). The submission however did not distinguish between initial and continuing scripts (which isn't possible for IXE), or the different number of doses provided by each. There is a slight discrepancy in the assumed number of UPA scripts per year for substituted therapies ([redacted][3]) and grandfathered patients ([redacted][3]). The submission also assumed 'monthly' dosing of SEC after the loading doses (corresponding to 14 / year), rather than 'every 4 weeks' (corresponding to 14.5 / year).
JAK/bDMARD aggregate market growth (without UPA), patient-years	Yr 0 + [redacted][4] patient-years per annum. (proposed listing of UPA will not impact growth) Average annual growth in patient-years from 2015 to 2019 (patient-years calculated as scripts divided by scripts/year/patient), where ([redacted][3] + [redacted][4] + [redacted][4] + [redacted][4]) / 4 = [redacted][4].	Poorly justified given the current market does not appear to be completely established. Annual market growth increased from 10% to 31% between 2015 and 2019. In contrast, the assumed constant growth in patient-years corresponds to declining growth of [redacted]% to [redacted]% between Yr0 and Yr6 of the financial estimates.
JAK/bDMARD market share % (without UPA), patient-years	Assumption ('commercial-in-confidence' estimates').	Poorly justified given the submission did not present any of the assumptions underpinning the estimates. The estimates imply ADA, ETN and UST lost 7.7%, 4.3% and 2.0% of the market between 2019 and 2020 (Yr0), replaced largely by TOF, SEC and CZP.
JAK/bDMARD market growth % (without UPA), scripts	Derived from the estimated market growth (aggregate patient-years) and market share (patient-years by product) assumptions.	The submission correctly derived the annual change in the assumed market shares (in terms of patient-years), where the Yr1 growth refers to change between Yr0 and Yr1 but did not apply the estimates correctly. The submission assumed no growth in scripts between 2019 and 2021 (Yr1), and then used the 'Yr1' growth rate to estimate change in scripts between Yr1 and Yr2, and the 'Yr2' growth rate to estimate change in scripts between Yr2 and Y3, and so on.

Data	Value and Source	Comment
Displacement of JAK/bDMARDs scripts % by UPA	Assumption ('commercial-in-confidence' estimates').	The submission assumed that UPA would displace treatment with TOF the most, followed by treatment with ADA/ETN/SEC/CZP/GOL, and very little displacement of IFX/UST/IXE. The submission assumed the same displacement rates apply equally to initial and continuing scripts.
Drug cost / script	Published DPMQ for corresponding item numbers (see above), based on new mark-ups/fees applicable from Jan 2021.	The 'published' DPMQs reflect wholesale/pharmacy mark-ups and dispensing fees based on the 7th Community Pharmacy Agreement. The DPMQs do not reflect the effective prices for many of the substituted medications, which are subject to Special Pricing Arrangements (and weighted prices across multiple indications). The DPMQs correspond to the number of doses/script assumed in the script relativities, and do not take into account DPMQs which provide for larger quantities. The cost per script for IFX assumed (i.e. 1 x 100mg vial) was inappropriate, as it did not take into account the average number of vials required per dose (i.e. 5mg/kg corresponding to at least 4 to 5 vials per dose).

Abbreviations: JAK=janus kinase; bDMARD=biologic disease modifying anti-rheumatic drug; PBS=Pharmaceutical Benefits Scheme; RPBS=Repatriation Pharmaceutical Benefits Scheme; UPA=upadacitinib; ADA=adalimumab; ETN=etanercept; IFX=infliximab; UST=ustekinumab; SEC=secukinumab; IXE=ixekizumab; CZP=certolizumab pegol; GOL=golimumab; TOF=tofacitinib; Yr=year; DPMQ=Dispensed Price Maximum Quantity; PBAC=Pharmaceutical Benefits Advisory Committee; TGA=Therapeutic Goods Administration.

Source: Constructed during the evaluation from pp111-126 of the submission, and from parameters in the excel spreadsheet ('Attachment 6_UCM-Release 3-Workbook-v105_UPA PsA(1).xlsx').

The redacted values correspond to the following ranges:

[1] *100,000 to < 200,000*

[2] *5,000 to < 10,000*

[3] *< 500*

[4] *500 to < 5,000*

6.30 Table 8 summarises the estimated net financial implications for the proposed listing of UPA on the PBS/RPBS for PsA.

Table 8: Estimated use and financial implications to the PBS/RPBS for the proposed listing of UPA

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of the use and financial impact of UPA						
UPA scripts	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]
Non-grandfather patients	[redacted][4]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]
Grandfathered patients	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net cost PBS/RPBS, UPA	[redacted][6]	[redacted][7]	[redacted][8]	[redacted][8]	[redacted][9]	[redacted][9]
Non-grandfather patients	[redacted][6]	[redacted][7]	[redacted][7]	[redacted][8]	[redacted][8]	[redacted][9]
Grandfathered patients	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Estimation of changes in use and financial impact of JAK inhibitors / bDMARDs						
JAK / bDMARD scripts	[redacted][4]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]
ADA	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][1]	[redacted][1]	[redacted][1]
ETN	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][1]
IFX	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
UST	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
SEC	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][1]
IXE	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
CZP	[redacted][10]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
GOL	[redacted][10]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
TOF	[redacted][10]	[redacted][10]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net cost PBS/RPBS, JAK/bDMARDs	-[redacted][6]	-[redacted][7]	-[redacted][7]	-[redacted][8]	-[redacted][8]	-[redacted][8]
Estimated financial implications for the PBS/RPBS and the health budget						
Net change in scripts	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net change in authorities	[redacted][10]	[redacted][10]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Streamlined	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][4]	[redacted][4]
Written	[redacted][10]	[redacted][10]	[redacted][10]	[redacted]	[redacted][4]	[redacted][4]
Net cost PBS/RPBS, proposed listing	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Grandfathered patients	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Non-grandfather patients	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]

Abbreviations: JAK=janus kinase; bDMARD=biologic disease modifying anti-rheumatic drug; PBS=Pharmaceutical Benefits Scheme; RPBS=Repatriation Pharmaceutical Benefits Scheme; UPA=upadacitinib; ADA=adalimumab; ETN=etanercept; IFX=infliximab; UST=ustekinumab; SEC=secukinumab; IXE=ixekizumab; CZP=certolizumab pegol; GOL=golimumab; TOF=tofacitinib.

Source: Tables 4.7-4.14, pp117-125 of the submission.

The redacted values correspond to the following ranges:

[1] 5,000 to < 10,000

[2] 10,000 to < 20,000

[3] 20,000 to < 30,000

[4] 500 to < 5,000

[5] $0 to < $5,000

[6] $0 to < $10 million

[7] $10 million to < $20 million

[8] $20 million to < $30 million

[9] $30 million to < $40 million

[10] < 500

6.31 The utilisation and financial estimates spreadsheet included an error in applying the estimated annual change of each JAK inhibitor / bDMARD without UPA (derived from patient-years) to the correct corresponding number of scripts in each year and there was an apparent error/discrepancy in the number of JAK/bDMARD scripts dispensed in 2019 presented on different tabs of the utilisation and financial estimates spreadsheet.

6.32 Aside from these errors, the submission also made a number of assumptions to simplify the calculations that affect the accuracy of the estimates. For example, the submission assumed the same displacement rates for initial and continuing scripts, did not differentiate between public/private hospital scripts, assumed constant market growth in patient-years, did not account for number of vials per script of infliximab, and used published rather than effective prices. The estimated scripts for grandfathered patients was also likely conservative given the market share analysis likely captures patients that will be in the future Patient Familiarisation Scheme.

6.33 The estimated net cost to the PBS/RPBS of listing UPA was approximately $30 million to < $40 million over the first six years. This was likely an overestimate, driven by the assumed published prices and grandfathered patients. Assuming upadacitinib were to be listed on a cost-minimisation basis to the least costly alternative therapy and current market growth was unchanged, then the requested listing would be expected to have negligible financial impact on the PBS/RPBS.

Quality Use of Medicines

6.34 The submission stated that the sponsor has a risk management plan including an Australian annex, and will be providing a patient support program for help managing treatment with UPA.

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

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required listing of upadacitinib (UPA) for the treatment of severe psoriatic arthritis (PsA). 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 lowest cost biologic disease modifying anti-rheumatic drug (bDMARD) for this indication.

7.2 The PBAC considered the nominated comparator of tofacitinib (TOF) was reasonable, however considered all other bDMARDs currently listed for PsA were also relevant alternative therapies. The PBAC considered the equi-effective doses of UPA (at a dose of one 15mg tablet once daily) and alternative bDMARDs could be derived from the product information and with reference to previously recommended equi-effective doses collated in the PBS Therapeutic Relativity Sheets. The cost minimisation analysis should be conducted over two years using approved ex-manufacturer prices consistent with methodology previously accepted by the PBAC for bDMARDs.

7.3 The PBAC noted the indirect comparison of UPA and TOF support a conclusion that UPA is of non-inferior comparative effectiveness to TOF, both in terms of ACR20 and ACR50 response. Further, the PBAC also noted that the pivotal UPA PsA study (SELECT PsA 1) included adalimumab (ADA) as a third study arm and a multiplicity-adjusted direct comparison was included in the statistical analysis plan as a secondary outcome

and considered the analysis provided additional supportive evidence that UPA may also be of non-inferior effectiveness to ADA.

7.4 The PBAC noted that while pairwise safety comparisons of UPA and TOF were not possible due to differences in timing of data collection, the Committee also noted the available evidence did not raise any specific safety issues that would indicate UPA is of inferior safety to TOF and therefore considered the claim of non-inferior comparative safety was reasonable. The PBAC also noted there were emerging signals thrombotic events associated with treatment with TOF and baricitinib (BAR) and that UPA was included in the TGA Black Triangle Scheme and subject to additional post-market surveillance. The PBAC noted this issue was being monitored in multiple jurisdictions and may be a class effect for the janus kinase inhibitor family.

7.5 The PBAC recommended the UPA restriction for PsA should be aligned with other bDMARD listings and should include a grandfather restriction for a period of 12 months, for patients transitioning from the clinical trial and patient familiarisation program. The PBAC noted the flow-on restriction changes to the administrative notes and prescriber instructions common to all bDMARDs for PsA that specify the lists of eligible treatments.

7.6 The PBAC noted the estimated costs to the PBS were driven by the use of published rather than effective prices and considered that if the listing of UPA for PsA were on a cost minimisation basis with the least costly bDMARD (as recommended in paragraph 7.2) using effective prices should result in no increase in net cost to the PBS. The PBAC noted patients who move from existing PBS medicines to the patient familiarisation program and then to PBS subsidised UPA will not be in addition to the current market, however noted that the limited number of patients in extended clinical trials will incur a small incremental cost as they transition to PBS subsidised therapy.

7.7 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because upadacitinib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over tofacitinib or other bDMARDs for severe psoriatic arthritis and not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.

7.8 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item/s as follows:

Restrictions to be the same as TOF with the following changes and relevant flow-on

amendments to common administrative notes.

Abbreviated restriction summary (new, based on 11675L/11690G)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
UPADACITINIB upadacitinib 15mg modified release tablet, 28	NEW	1	28	3	Rinvoq®

Restriction Summary	Treatment phase
Restriction Summary 9142 / ToC: 9155: Authority Required	Initial 1
Restriction Summary 9171 / ToC: 9157: Authority Required	Initial 2
Restriction Summary 9061 / ToC: 9069: Authority Required	Initial 3
Restriction Summary 9106 / ToC: 9064: Authority Required	Initial 1, Initial 2 or Initial 3 balance of supply

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

Restriction Summary	Treatment phase
Restriction Summary 9117 / ToC: 9116: Authority Required	Continuing treatment
Restriction Summary 9077 / ToC: 9141: Authority Required	Continuing treatment or Grandfathered patients - balance of supply
Restriction Summary NEW / ToC: NEW: Authority Required	Grandfather treatment

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type / Method: ☒Authority Required - In Writing
Administrative Advice: TREATMENT OF ADULT PATIENTS WITH SEVERE ACTIVE PSORIATIC ARTHRITIS
Administrative Advice: Special Pricing Arrangements apply.
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.
Indication: Severe psoriatic arthritis
Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - 'Grandfather' arrangements
Treatment criteria:
Must be treated by a rheumatologist; or
Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis
AND

Clinical criteria:
Patient must have received treatment with this drug for this indication prior to [listing date],
AND
Clinical criteria:
Patient must have failed to achieve an adequate response to methotrexate at a dose of at least 20 mg weekly for a minimum period of 3 months prior to initiating non-PBS subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have failed to achieve an adequate response to sulfasalazine at a dose of at least 2 g per day for a minimum period of 3 months prior to initiating non-PBS subsidised treatment with this drug for this condition; or
Patient must have failed to achieve an adequate response to leflunomide at a dose of up to 20 mg daily for a minimum period of 3 months prior to initiating non-PBS subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not receive more than 24 weeks of treatment under this restriction
AND
Population criteria:
Patient must be aged 18 years or older
Prescribing Instructions: The following criteria indicate failure to achieve an adequate response to the conventional therapies specified under this restriction and must have been demonstrated prior to initiation of non-PBS subsidised treatment with this biological medicine for this condition: an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour or a C-reactive protein (CRP) level greater than 15 mg per L; and either (a) an active joint count of at least 20 active (swollen and tender) joints; or (b) at least 4 active joints from the following list of major joints: (i) elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or (ii) shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth). If the above requirement to demonstrate an elevated ESR or CRP cannot be met, the application must state the reasons why this criterion cannot be satisfied.
Prescribing Instructions: The same indices of disease severity used to establish baseline at the commencement of treatment with each initial treatment application must be used to determine response for all subsequent continuing treatments.
Prescribing Instructions: The assessment of the patient's response to the initial course of treatment must be conducted following a minimum of 12 weeks of treatment and no later than 4 weeks from the cessation of that treatment course. If the response assessment is not conducted within these timeframes, the patient will be deemed to have failed this course of treatment in this treatment cycle.

Prescriber Instructions If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within this treatment cycle. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
Prescribing Instructions: A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the continuing treatment criteria.
Administrative advice: This Grandfather restriction will cease to operate 12 months after the date specified in the clinical criteria.
Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed Severe Psoriatic Arthritis PBS Authority Application - Supporting Information Form; and (3) the date of commencement of this drug; and (4) results of the baseline patient assessment prior to initiation of non-PBS subsidised therapy with this drug.
Administrative Advice Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

EDIT ADMINISTRATIVE ADVICE [24357]:

TREATMENT OF ADULT PATIENTS WITH SEVERE ACTIVE PSORIATIC ARTHRITIS

The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological medicines adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab, tofacitinib*, upadacitinib* and ustekinumab for adult patients with severe active psoriatic arthritis. Therefore, where the term 'biological medicine' appears in notes and restrictions, it refers to adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab, tofacitinib*, upadacitinib* and ustekinumab only.

A patient is eligible for PBS-subsidised treatment with only 1 of the above biological medicines at any 1 time.

A patient receiving PBS-subsidised treatment for psoriatic arthritis is able to commence a treatment cycle where they may trial biological medicines without having to experience a disease flare when swapping to the alternate biological medicine. Under these arrangements, within a single cycle, a patient may receive long-term treatment with a biological medicine as long as they sustain a response to therapy.
A patient who received PBS-subsidised adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab*, tofacitinib, upadacitinib* or ustekinumab treatment prior to ~~1 May 2019~~ [*PBS listing date]* is considered to start their first cycle as of ~~1 May 2019~~ [*PBS listing date]*.

Within the same treatment cycle, a patient cannot trial and fail, or cease to respond to, the same PBS-subsidised biological medicine more than once. Therefore, once a patient fails to meet the response criteria for a PBS-subsidised biological medicine, they must change to an alternate biological medicine if they wish to continue PBS-subsidised biological treatment.

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.

Once a patient has either failed or ceased to sustain a response to treatment 3 times, they are deemed to have completed a single cycle and they must have, at a minimum, a 5-year break in PBS-subsidised biological medicine therapy before they are eligible to commence another cycle [further details are under '(5) Recommencement of treatment after a 5-year break in PBS-subsidised therapy' below].

The duration of the break in therapy will be measured from the date the last prescription for PBS-subsidised treatment was approved in the most recent cycle to the date of the first application for initial treatment with a biological medicine under the new cycle.

A patient who has failed fewer than 3 biological medicines in a treatment cycle and who has a break in therapy of more than 5 years may commence a new treatment cycle under Initial 3 treatment restriction.

A patient who has failed fewer than 3 biological medicines in a treatment cycle and who has a break in therapy of less than 5 years may commence a further course of treatment within the same treatment cycle under Initial 2 treatment restriction.

There is no limit to the number of treatment cycles a patient may undertake in their lifetime.

How to prescribe PBS-subsidised biological medicine treatment for severe active psoriatic arthritis.

(1) Initial treatment.
Applications for initial treatment should be made where:

(i) a patient has not received prior PBS-subsidised biological medicine treatment and wishes to commence such therapy (Initial 1 - New patient); or

(ii) a patient has received prior PBS-subsidised biological medicine therapy (initial or continuing) and wishes to trial an alternate medicine (Initial 2 - Change or Recommencement of treatment after a break in therapy of less than 5 years) [further details are under 'Swapping therapy' below]; or

(iii) a patient wishes to recommence treatment with a specific biological medicine following a break in PBS-subsidised therapy of less than 5 years with the same medicine (Initial 2 - Change or Recommencement of treatment after a break in biological medicine of less than 5 years).

(iv) a patient wishes to recommence treatment with a biological medicine following a break in PBS-subsidised therapy of more than 5 years (Initial 3 - Recommencement of treatment after a break in biological medicine of more than 5 years) or

An application for initial treatment will be limited to provide for a maximum of 16 weeks of therapy for adalimumab, etanercept, golimumab secukinumab, ~~and~~ tofacitinib~~,~~ and *upadacitinib,* 18 to 20 weeks of therapy for certolizumab pegol (depending upon the dosing regimen), 20 weeks of therapy for ixekizumab, 22 weeks of therapy for infliximab, and 28 weeks of therapy for ustekinumab. It is recommended that a patient be reviewed in the ~~month~~ *4 weeks* prior to completing their course of initial treatment to ensure uninterrupted biological medicine supply.

A patient must be assessed for response to a course of PBS-subsidised initial treatment following a minimum of 12 weeks of therapy and conducted no later than 4 weeks from the cessation of the treatment course. If the response assessment is not ~~submitted~~ *conducted* within these timeframes, the patient will be deemed to have failed this course of treatment.

~~Grandfather patients (ixekizumab only).~~
~~A patient who commenced treatment with ixekizumab for severe psoriatic arthritis prior to 1 March 2019 and who continues to receive treatment at the time of application, may qualify for treatment under the 'Grandfather' treatment restriction.~~
~~A patient may only qualify for PBS-subsidised treatment under this restriction once. A maximum of 24 weeks of treatment will be authorised under this criterion. Following completion of the initial PBS-subsidised course, further subsidised treatment must be prescribed under the continuing treatment restriction of the relevant drug. 'Grandfather' arrangements will only apply for the first treatment cycle.~~
~~For the second and subsequent cycles, a 'grandfather' patient must qualify for continuing treatment under the criteria that apply to a continuing patient.~~

~~Grandfather patients (tofacitinib only).~~
~~A patient who commenced treatment with Tofacitinib for severe psoriatic arthritis prior to 1 May 2019 and who continues to receive treatment at the time of application, may qualify for treatment under the 'Grandfather' treatment restriction.~~
~~A patient may only qualify for PBS-subsidised treatment under this restriction once. A maximum of 24 weeks of treatment will be authorised under this criterion. Following completion of the initial PBS-subsidised course, further subsidised treatment must be prescribed under the continuing treatment restriction of the relevant drug. 'Grandfather' arrangements will only apply for the first treatment cycle.~~
~~For the second and subsequent cycles, a 'grandfather' patient must qualify for continuing treatment under the criteria that apply to a continuing patient.~~

Grandfather patients (upadacitinib only)
A patient who commenced treatment with upadacitinib for severe psoriatic arthritis prior to [PBS listing date] and who continues to receive treatment at the time of application, may qualify for treatment under the 'Grandfather' treatment restriction.

A patient may only qualify for PBS-subsidised treatment under this restriction once. A maximum of 24 weeks of treatment will be authorised under this criterion. Following completion of the initial PBS-subsidised course, further subsidised treatment must be prescribed under the continuing treatment restriction of the relevant drug. 'Grandfather' arrangements will only apply for the first treatment cycle.

For the second and subsequent cycles, a 'grandfather' patient must qualify for continuing treatment under the criteria that apply to a continuing patient.

(2) Continuing treatment.
Following the completion of an initial treatment course with a specific biological medicine, a patient may qualify to receive up to 24 weeks of continuing treatment with that drug providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing biological medicine treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response. It is recommended that a patient be reviewed *for response following a minimum of 12 weeks of therapy and no later than* the ~~month~~ *4 weeks from the completion of the most recent course of treatment* ~~prior to completing their current course of treatment to ensure uninterrupted biological medicine supply~~.

A patient must be assessed for response to a course of continuing therapy, and the assessment must be submitted to ~~the Department of Human~~ Services *Australia* where applicable. Where a response assessment is not submitted where applicable, the patient will be deemed to have failed to respond to treatment with that biological medicine, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.

Infliximab and etanercept only:
For the first continuing treatment course of PBS-subsidised biological medicine treatment, it is recommended that a patient is reviewed for response following a minimum of 12 weeks of therapy and no later than 4 weeks from the completion of the most recent course of treatment under the Initial 1*,* ~~or~~ Initial 2 *or Initial 3* treatment restrictions.

For the second and subsequent continuing courses of PBS-subsidised biological medicine treatment, it is recommended that an assessment of a patient's response is conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from the completion of the most recent course of treatment.

(3) Swapping therapy.
Once initial treatment with the first PBS-subsidised biological medicine is approved, a patient may swap to an alternate biological medicine without having to re-qualify with respect to either the indices of disease severity (i.e. erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, and active joint count) or the prior non-biological therapy requirements, except if the patient has had a break in therapy of more than 5 years who would need to requalify under the Initial 3 treatment restriction with respect to the indices of disease severity.
A patient who is not able to complete a minimum of 12 weeks of an initial treatment course will be deemed to have failed treatment with that biological medicine unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.

A patient may trial an alternate biological medicine at any time, regardless of whether they are receiving therapy (initial or continuing) with a biological medicine at the time of the application.
However, they cannot swap to a particular biological medicine if they have failed to respond to prior treatment with that drug within the same treatment cycle.

Within a treatment cycle a patient may alternate between therapy with any biological medicine of their choice (1 at a time) providing:
(i) they have not received PBS-subsidised treatment with that particular biological medicine previously; or

(ii) they have demonstrated an adequate response to that particular biological medicine if they have previously trialled it on the PBS; and

(iii) they have not previously failed to respond to treatment 3 times in this treatment cycle with ~~that~~ biological medicines.
To ensure a patient receives the maximum treatment opportunities allowed under these arrangements, it is important that they are assessed for response to every course of treatment.

(4) Baseline measurements to determine response.
~~The Department of Human Services *Australia* will determine whether a~~ *A* response to treatment ~~has been demonstrated based~~ *is to be determined by comparison of current disease activity measurements* ~~on~~ *relative to* the baseline measurements of the indices of disease severity submitted with the first authority application for a biological medicine. However, prescribers may provide new baseline

measurements any time that an initial or change or recommencement treatment application is submitted within a treatment cycle and these revised baseline measurements will be used to assess response to the PBS-subsidised treatment.

To ensure consistency in determining response, the same indices of disease severity used to establish baseline at the commencement of treatment with each initial treatment application must be used to determine response for all subsequent continuing treatments. Therefore, where only an ESR or CRP level is provided at baseline, an ESR or CRP level respectively must be used to determine response. Similarly, where the baseline active joint count is based on total active joints (i.e. 20 or more active joints), response will be determined according to a reduction in the total number of active joints.

(5) Re-commencement of treatment after a 5-year break in PBS-subsidised therapy.
A patient who wishes to trial a second or subsequent course of treatment following a break in PBS-subsidised biological therapy of at least 5 years, must qualify under Initial 3 treatment restriction according to the criteria of the relevant restriction and index of disease severity. The application must include a joint count and ESR and/or CRP measurement that is no more than ~~one month~~ *4 weeks* old at the time of application.

Flow-on changes to Administrative Advice [24357] to the following:

Golimumab: 3430M, 3432P, 11365E, 11373N.

Etanercept: 9035M, 9036N, 9087G, 9088H, 9457R, 9458T, 11207W, 11198J, 11208X, 11216H, 11202N.

Infliximab: 5756Y, 6496X, 11514B, 11515C, 11497D, 11498E.

Certolizumab: 10238W, 10909E, 10896L, 11324B, 11326D, 11323Y.

Ustekinumab: 10774C, 10767Q.

Secukinumab: 10900Q, 10895K, 10898N, 10901R, 10894J, 10899P.

Ixekizumab: 11623R

Tofacitinib: 11690G, 11675L.

Adalimumab: 9033K, 9034L, 9101B, 9102C

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

9 Context for Decision

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

10 Sponsor's Comment

AbbVie welcomes the decision of the PBAC and is working with the Department of Health on the earliest possible PBS listing.