

5.13 UPADACITINIB, Tablet (modified release) 15 mg, Rinvoq®, AbbVie Pty Ltd.

1 Purpose of Application

- 1.1 The Sponsor requested Authority Required (Section 85) listing of upadacitinib (UPA) 15 mg tablets for the treatment of severe rheumatoid arthritis (RA). This was the first application to list UPA on the PBS.
- 1.2 The basis for the requested listing was cost-minimisation to baricitinib (BARI) 4 mg tablets, which is a pharmacological analogue to UPA. The submission nominated adalimumab (ADA) 40 mg subcutaneous (SC) injection as a secondary comparator.

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

Component	Description
Population	Patients with severe active RA in whom an adequate response has not been achieved with at least 6 months of intensive treatment with cDMARDs, as per current criteria for PBS-listed bDMARD and tsDMARD therapies
Intervention	Upadacitinib 15 mg tablet, administered orally, once daily
Comparator	Primary: Baricitinib 4 mg tablet, administered orally, once daily Secondary: Adalimumab 40 mg SC injection, administered fortnightly
Outcomes	Disease activity endpoints: ACR20, ACR50, ACR70 Clinical remission endpoints: DAS28(CRP) <2.6 Patient reported outcome: HAQ-DI
Clinical claim	Upadacitinib is non-inferior to baricitinib in terms of efficacy and safety in patients with severe active RA for whom an adequate response has not been achieved with conventional therapies. Upadacitinib is superior to adalimumab in terms of efficacy and is non-inferior to adalimumab in terms of safety.

Abbreviations: ACRn=American College of Rheumatology n% response criteria; bDMARD=biological disease modifying anti-rheumatic drug; cDMARD=conventional disease modifying anti-rheumatic drugs; DAS=disease activity score; HAQ-DI=Health assessment questionnaire disability index; RA=rheumatoid arthritis; SC=subcutaneous; tsDMARD=targeted synthetic disease modifying anti-rheumatic drugs.

Source: Table 1.1, p11 of the submission

2 Requested listing

- 2.1 An abridged listing is provided below.

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Table 2: Essential elements of the requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (nits)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Initial treatment					
Upadacitinib 15 mg oral tablet	1	28	3	Published: \$1,267.64* Effective: NR#	Rinvoq®, AbbVie
Continuing treatment					
Upadacitinib 15 mg oral tablet	1	28	5	Published: \$1,267.64*Effective: NR#	Rinvoq®, AbbVie
Severity:	Severe				
Condition:	Active Rheumatoid Arthritis				
PBS Indication:	Severe active Rheumatoid Arthritis				
Treatment phase:	Initial treatment and continuing treatment as per other PBS-listed JAK inhibitors/bDMARDs.				
Restriction:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined				
Treatment criteria:	Must be treated by a rheumatologist OR Clinical immunologist with expertise in the management of rheumatoid arthritis.				
Clinical criteria:	As per other PBS-listed JAK inhibitors/bDMARDs				
Population criteria:	Patient must be aged 18 years or older				
Prescriber Instructions:	As per other PBS-listed JAK inhibitors/bDMARDs.				
Administrative Advice:	As per other PBS-listed JAK inhibitors/bDMARDs.				

NR = not reported

Requested same effective price as baricitinib 4mg tablets.

* Current published DPMQ for BARI is \$1267.79

Source: Table 1.5, p20; Table 1.6, p21 of the submission.

- 2.2 The Sponsor requested PBS listing of UPA 15 mg tablets for initial and continuing treatment restrictions, which were consistent with the current PBS criteria of other Janus Kinase (JAK) inhibitors and biological disease modifying anti-rheumatic drugs (bDMARDs) listed on the PBS for RA. The requested maximum quantities and repeats provided for 16 weeks of initial treatment (4 packs) and 24 weeks of continuing treatment (6 packs).
- 2.3 The Sponsor requested a Special Pricing Arrangement that would maintain the published dispensed price for maximum quantity (DPMQ) at the same level as BARI 4 mg tablets, and an effective price based on a cost-minimisation analysis to BARI.
- 2.4 The submission stated that the requested listing included a grandfathering clause to allow approximately <500 patients from a planned UPA Patient Familiarisation Program and <500 patients enrolled in the long-term extension phases of the UPA clinical trials to transition to PBS-subsidised treatment.

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

3 Background

- 3.1 The submission was made under the TGA/PBAC Parallel Process, and was not registered at the time of PBAC consideration. At the time of the evaluation, the first round clinical evaluation report (CER) was available and the following indication was recommended: “Rinvoq is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients when the response to 1 or more disease modifying anti-rheumatic drugs (DMARDs) has been inadequate. Rinvoq can be given as monotherapy or in combination with methotrexate. Therapy with Rinvoq should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of RA.”
- 3.2 At the time of PBAC consideration the Clinical Evaluation Report (Round 2) and, Delegate’s overview were available. The TGA Delegate was supportive of the registration for Rinvoq. The PBAC noted the relevant Advisory Committee on Medicines (ACM) meeting was scheduled for 6 December 2019.
- 3.3 The PBAC noted the following issues were raised by the TGA Delegate::

- Upadacitinib studies have identified

[REDACTED]

[REDACTED]

[REDACTED]

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

4 Population and disease

- 4.1 RA is a chronic, progressive, debilitating autoimmune disease characterised by chronic inflammation of the synovium (i.e. lining of the joints), which over time results in irreversible joint damage, loss of physical function, disability, and is associated with significant pain and morbidity. RA is also associated with comorbid conditions affecting vascular, bone, metabolic and psychologic domains. The submission requested listing in patients with severe active RA in whom an adequate response has not been achieved with conventional disease modifying anti-rheumatic drugs (cDMARDs).
- 4.2 UPA is an oral, reversible, selective JAK1 inhibitor. JAK1 is important in transmitting many of the inflammatory cytokine signals that are active in RA. UPA would become one of several bDMARDs and the third JAK inhibitor, following BARI and tofacitinib (TOF), listed on the PBS for patients with severe active RA. The recommended dose in the draft PI is 15 mg orally, once daily. UPA may be used as monotherapy or in combination with methotrexate or other cDMARDs, and no dose adjustment is required in patients with renal impairment.

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

5 Comparator

- 5.1 The submission nominated BARI 4 mg orally once a day as the main comparator and ADA 40 mg SC injection every two weeks as a secondary comparator. UPA and BARI are both JAK inhibitors, and share the same route of administration and dosing frequency. ADA is a widely used bDMARD (a tumour necrosis factor alpha (TNF α) inhibitor) and there is head-to-head evidence comparing UPA to ADA.
- 5.2 The recommended dose for BARI in the TGA-approved PI is 4 mg once daily or 2 mg for patients with moderate renal impairment. Both BARI 2 mg and 4 mg tablets are listed on the PBS with the same published price, however the submission only focused on BARI 4 mg tablets. Trial results indicated that BARI 4 mg provided a more rapid onset and a numerically higher clinical response than the 2 mg dose (BARI Public Summary Document (PSD), paragraph 3.5, March 2018).
- 5.3 Under Section 101(3B) of the National Health Act (1953) where therapy involving the use of a particular drug or medicinal preparation, or a class of drugs and medicinal preparations, is substantially more costly than an alternative therapy or alternative therapies, whether or not involving the use of other drugs or preparations, the Committee shall not recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part unless the Committee is satisfied that the first-mentioned therapy, for some patients, provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies.

- 5.4 The PBAC agreed with the Economics Sub-Committee (ESC) that BARI and ADA were appropriate comparators; however, UPA may replace any of the eleven JAK inhibitors/bDMARDs currently PBS listed for severe RA. The PBAC recalled that, in recent decisions, it considered all JAK inhibitors/bDMARDs listed for severe RA represented alternative therapies and in the absence of evidence of superiority recommended listing to the lowest cost alternative (BARI PSD, paragraph 5.1, July 2017; Tocilizumab PSD, paragraph 6.5, March 2016; Sarilumab PSD, paragraph 7.1, November 2018).

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 four trials comparing UPA to placebo (PBO) or ADA (SELECT-COMPARE, SELECT-NEXT, SELECT-BEYOND, SELECT-MONOTHERAPY), and four trials comparing BARI to PBO or ADA (RA-BEAM/JADV, RA-BUILD/JADX, RA-BEACON/JADW, JADA), presented in Table 3. The PBAC previously considered evidence from the BARI trials (including one excluded trial, JADN) in March 2018.
- 6.4 The submission appropriately excluded two trials on the basis of 'incorrect population', given patients were methotrexate-naïve (SELECT-EARLY and RA-BEGIN/JADZ), but inappropriately excluded three trials on the basis of 'foreign population' (SELECT-SUNRISE and JADN conducted in Japanese patients, and RA-BALANCE/JAGS conducted in Argentina, Brazil and China). However, results were not sensitive to their exclusion.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Upadacitinib trials		
SELECT-COMPARE (M14-465)	A Phase 3, randomized, double-blinded study comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in subjects with moderately to severely active rheumatoid arthritis who are on a stable background of methotrexate (MTX) and who have had an inadequate response to MTX (MTX-IR); Protocol M14-465 Fleischmann, Roy; Pangan, Aileen L.; Mysler, Eduardo; et al. Upadacitinib versus Placebo or Adalimumab in Patients with Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase 3, Double-Blind, Randomized Controlled Trial.	CSR, August 2018 Arthritis Rheumatol. 2019 Jul 9. [Epub ahead of print]
SELECT-NEXT (M13-549)	A Phase 3, randomized, double-blinded study comparing Upadacitinib (ABT-494) to Placebo b in subjects with moderately to severely active rheumatoid arthritis who are on a stable dose of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and have an inadequate response to csDMARDs; Protocol M13-549 Burmester GR, Kremer JM, Van den Bosch F, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial.	CSR, April 2017 Lancet. 2018 Jun 23;391(10139): 2503-2512.
SELECT-BEYOND (M13-542)	A Phase 3, randomized, double-blinded study comparing Upadacitinib (ABT-494) to Placebo on a stable dose of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) in subjects with moderately to severely active rheumatoid arthritis with an inadequate response or intolerance to biologic DMARDs (bDMARDs); Protocol M13-542 Genovese, MC; Fleischmann, R; Combe, B; et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial.	CSR, June 2017 Lancet. 2018 Jun 23;391(10139):2513-2524.
SELECT-MONOTHERAPY (M15-555)	A Phase 3, randomized, double-blind study comparing upadacitinib (ABT-494) monotherapy to methotrexate (MTX) in subjects with moderately to severely active rheumatoid arthritis with inadequate response to MTX; Protocol M15-555 Smolen, JS; Pangan, AL; Emery P; et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study.	CSR, Oct 2017 Lancet 2019; 393: 2303–11
Baricitinib trials		
RA-BEAM; JADV (NCT01710358)	Taylor PC, Keystone EC, van der Heijde D et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis.	N Engl J Med. 2017 Feb 16;376(7):652-662.
RA-BUILD; JADX; (NCT01721057)	Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study.	Ann Rheum Dis. 2017; 76(1):88-95.
RA-BEACON; JADW; (NCT01721044)	Genovese MC, Kremer J, Zamani O, et al. Baricitinib in Patients with Refractory Rheumatoid Arthritis.	N Engl J Med. 2016; 374(13):1243-52.
JADA; (NCT01185353)	Keystone EC, Taylor PC, Drescher E, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate.	Ann Rheum Dis. 2015; 74(2):333-40.

Source: Table 2.3, pp 28-33 of the submission

6.5 The key features of the direct randomised trials are summarised in Table 4. The submission only presented evidence for UPA and BARI at the main recommended

doses, excluding data for UPA 30 mg and BARI 1 mg, 2 mg and 8 mg dosing regimens reported across six trials (SELECT-NEXT, SELECT-BEYOND, SELECT-MONOTHERAPY, RA-BUILD/JADX, RA-BEACON/JADW, and JADA).

Table 4: Key features of the included evidence

Trial	N	Design / duration	Relevant comparison	Risk of bias	Patient population	Key outcomes
POPULATION: cDMARD-IR						
SELECT-COMPARE ^{a, b}	1629	P3, MC, R, DD, DB 48wk+5y extension; bDMARD rescue wk14/18/22/26	UPA 15mg QD+MTX, ADA 40mg Q2W +MTX, PBO+MTX,	Low	Active RA (M-S); MTX-IR	ACR response
SELECT-NEXT ^a	661 (442) [#]	P3,MC,R, DB 12wk +5y extension; bDMARD rescue wk12	UPA 15mg QD+cDMARD, PBO+cDMARD	Low	Active RA (M-S); cDMARD-IR	ACR response
SELECT-MONOTHERAPY	648 (433) [#]	P3,MC,R, DB 14wk +5y extension; bDMARD rescue wk14	UPA 15mg QD, MTX (alone)	Low	Active RA (M-S); MTX-IR	ACR response
RA-BEAM/ JADV ^c	1305	P3,MC,R, DD, DB 52wk; bDMARD rescue wk14/16 (after that at physician's discretion)	BARI 4mg QD+cDMARD, ADA 40mg Q2W+cDMARD, PBO+cDMARD,	Low	Active RA (M-S); MTX-IR	ACR response
RA-BUILD/ JADX	684 (455) [^]	P3,MC,R, DB 24wk; bDMARD rescue after wk16 at physician's discretion	BARI 4mg QD+cDMARD, PBO+cDMARD,	Low	Active RA (M-S); cDMARD-IR	ACR response
JADA ^d	301 (150) [*]	P3,MC,R, DB 12wk	BARI 4mg QD+cDMARD, PBO+cDMARD,	Low	Active RA (M-S); MTX-IR	ACR response
POPULATION: bDMARD-IR						
SELECT-BEYOND	499 (333) [#]	P3,MC,R, DB 12wk +5y extension	UPA 15mg QD+cDMARD, PBO+cDMARD	Low	Active RA (M-S); bDMARD-IR	ACR response
RA-BEACON/JADW	527 (353) [^]	P3,MC,R, DB 24wk; bDMARD rescue after wk16 at physician's discretion	BARI 4mg QD+cDMARD, PBO+cDMARD	Low	Active RA (M-S); bDMARD-IR	ACR response

^a Allowed prior exposure to one bDMARDs in up to 20% of patients

^b 26 wks PBO-controlled and 48-wks ADA-controlled.

^c At week 24, patients in the PBO group were blindly switched to BARI

^d Patients were randomised to BARI 1, 2, 4, 8 mg or PBO, then re-randomised at wk12 for another 12 weeks to BARI 2, 4mg or PBO

[#] excluding patients randomised to UPA 30mg regimen

[^] excluding patients randomised to BARI 2mg regimen

^{*} excluding patients randomised to BARI 1mg, 2mg and 8mg regimens

Abbreviations: ACR=American College of Rheumatology response criteria; ADA=adalimumab; bDMARD=biologic disease modifying anti-rheumatic drug; cDMARD=conventional disease-modifying anti-rheumatic drug; DB=double blind; DD=double dummy; IR=inadequate response MC=multicentre; MTX=methotrexate; OL=open label; P=phase; PBO=placebo; QD=once daily; R=randomised; RA (M-S)=rheumatoid arthritis (moderate to severe); wk=week; y=year

Source: Table 2.5, pp47-51 of the submission, and trial publications.

6.6 All trials were phase 3, multicentre, randomised, PBO or ADA controlled, with a double-blind phase of at least 12 weeks; and enrolled adults with moderate to severe RA without prior exposure to JAK inhibitors. The selection criteria were similar across the trials, requiring patients to have ≥ 6 or 8 swollen joints (based on 66 joint counts),

≥ 6 or 8 tender joints (based on 68 joint counts), and high-sensitivity C-reactive protein ≥ 3 mg/L to ≥ 6 mg/L. Six trials required inadequate response to cDMARDs whereas two required inadequate response to bDMARDs.

- 6.7 All trials longer than 12 weeks permitted early escape or rescue from week 12 to 16, and classified those patients as non-responders for subsequent assessments. The overall risk of bias was low across the trials. Discontinuation rates were low across the trials and the groups were generally balanced.

Comparative effectiveness

- 6.8 Under PBS restrictions of JAK inhibitors/bDMARDs for RA, 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 is a composite outcome requiring a 50% improvement from baseline in tender joint counts and swollen joint counts, and 20% (or below absolute thresholds) improvement in acute phase reactants erythrocyte sedimentation rate or C-reactive protein. The response criteria on the PBS are similar to the American College of Rheumatology (ACR) 50% and 20% response criteria. ACR20 response at week 12 or 14 was the primary outcome in all trials.
- 6.9 The submission presented indirect comparisons between UPA and BARI (via PBO or ADA as common reference), and a direct comparison between UPA and ADA reported in SELECT-COMPARE, across several outcomes primarily at Week 12. The PBAC has previously considered outcomes ACR20 and ACR50 for the treatment of RA; and accepted that ACR50 response represents a reasonable treatment target and reflects to a greater degree the current PBS criteria for continuing treatment compared to ACR20. Assessment of response at Week 12 corresponds with assessment of response to initial treatment on the PBS (BARI PSD, paragraph 6.12, July 2017; Sarilumab PSD, paragraph 6.10, November 2018).
- 6.10 The SELECT-COMPARE trial was designed to test non-inferiority and superiority between UPA and ADA for several outcomes including ACR50 at Week 12. The trial used a stepped testing procedure to control for multiplicity. Non-inferiority on ACR50 was assessed by comparing the 95%CI of the treatment difference against the non-inferiority margin of 10%. That is, if the lower bound of the 95% CI for the risk difference (RD) was below -10%, then non-inferiority was not demonstrated. However, if the lower bound was larger than 0%, then superiority was demonstrated.
- 6.11 The RA-BEAM trial had a similar design to test non-inferiority and superiority between BARI and ADA for several outcomes including ACR20 at Week 12. That trial nominated a non-inferiority margin of 12% for ACR20. In July 2017, the PBAC rejected a claim of superior efficacy between BARI and ADA for several reasons. It was noted that “the selection of 0% as a threshold for superiority allowed any marginal statistically significant improvement over ADA to be judged as superiority, in the absence of

demonstrating this was a clinically meaningful difference. Applying the additive inverse of the non-inferiority margin (+12%) to determine superiority may be useful” (BARI PSD, paragraph 6.13, July 2017).

- 6.12 For indirect comparisons, the PBAC has previously assessed non-inferiority between JAK inhibitors/bDMARDs based on a non-inferiority margin of 0.4 for the relative risk (RR) statistic for ACR20. That is, if the lower bound of the 95%CI was larger than 0.4, then non-inferiority was concluded (Sarilumab PSD, paragraph 6.12, November 2018).
- 6.13 ACR20 and ACR50 response at Week 12 in the trials are summarised in Tables 5 and 6, respectively. The submission categorised the trials by prior treatment failure (cDMARDs and bDMARDs) and appropriately excluded SELECT-MONOTHERAPY from the indirect comparisons because it did not include a placebo-controlled treatment arm.

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Table 5: ACR20 response at Week 12 at the recommended doses of UPA, BARI and ADA, and indirect comparisons presented by the submission

Trial	Drug n/N (%)	Control n/N (%)	RR (95%CI)	RD (95%CI)	NNT (95%CI)
cDMARD IR population					
UPA v PBO or MTX					
SELECT COMPARE	459/651 (70.5)	237/651 (36.4)	1.94 (1.73,2.17)	0.34 (0.29,0.39)	3 (3, 11)
SELECT NEXT	141/221 (63.8)	79/221 (35.7)	1.78 (1.46,2.19)	0.28 (0.19,0.37)	4 (3, 5)
SELECT MONOTHERAPY ^a	147/217 (67.7)	89/216 (41.2)	1.64 (1.37,1.98)	0.27 (0.17,0.36)	4 (3, 6)
Meta-analysis (excl. MONO)	600/872 (68.8)	316/872 (36.2)	1.90 (1.72,2.10)	0.33 (0.28,0.37)	3 (3, 4)
Meta-analysis (incl. MONO)	747/1089 (68.6)	405/1088 (37.2)	1.84 (1.69,2.01)	0.31 (0.27,0.35)	3 (3, 4)
BARI v PBO					
RA-BEAM/JADV	339/487 (69.6)	196/488 (40.2)	1.73 (1.53,1.96)	0.29 (0.23,0.35)	3 (3, 4)
RA-BUILD/JADX	140/227 (61.7)	90/228 (39.5)	1.56 (1.29,1.89)	0.22 (0.13,0.31)	5 (3, 8)
JADA	39/52 (75.0)	41/98 (41.8)	1.79 (1.35,2.37)	0.33 (0.18,0.48)	3 (2, 6)
Meta-analysis	518/766 (70.5)	327/814 (40.2)	1.69 (1.53,1.86)	0.28 (0.23,0.32)	4 (3, 4)
UPA v ADA					
SELECT COMPARE	459/651 (70.5)	206/327 (63.0)	1.12 (1.02,1.23)	0.08 (0.01,0.14)	13 (7, 100)
BARI v ADA					
RA-BEAM/JADV	339/487 (69.6)	202/330 (61.2)	1.14 (1.02,1.26)	0.08 (0.02,0.15)	13 (7, 50)
bDMARD IR population					
UPA v PBO					
SELECT BEYOND	106/164 (64.6)	48/169 (28.4)	2.28 (1.75,2.97)	0.36 (0.26,0.46)	3 (2, 4)
BARI v PBO					
RA-BEACON/JADW	98/177 (55.4)	48/176 (27.3)	2.03 (1.54,2.67)	0.28 (0.18,0.38)	4 (3, 6)
Indirect Comparisons					
cDMARD IR population					
UPA (meta-analysis excl. MONO) v BARI (meta-analysis) via PBO			1.12 (0.98,1.29)	0.05 (-0.01, 0.11)	NA
UPA (meta-analysis incl. MONO) v BARI (meta-analysis) via PBO			1.09 (0.96,1.24)	0.03 (-0.03,0.09)	NA
UPA (SELECT COMPARE) v BARI (RA-BEAM/JADV) via ADA			0.98 (0.85,1.13)	0 (-0.07,0.07)	NA
bDMARD IR population					
UPA (SELECT BEYOND) v BARI (RA-BEACON/JADW) via PBO			1.12 (0.77,1.65)	0.08 (-0.06,0.22)	NA

^aPBO arm is receiving MTX. Response measured at Wk14.

Abbreviations: ADA=adalimumab; BARI=baricitinib; CI=confidence interval; IR=inadequate response; NNT = number needed to treat; OR=odds ratio; PBO=placebo; RD=risk difference; RR=risk ratio; UPA=upadacitinib

Source: compiled during the evaluation: Table 2.16, p84; Table 2.20, p89; Table 2.24, p94 of the submission

Table 6: ACR50 response at Week 12 at the recommended doses of UPA, BARI and ADA, and indirect comparisons presented by the submission

Trial	Drug n/N (%)	Control n/N (%)	RR (95%CI)	RD (95%CI)	NNT (95%CI)
cDMARD IR population					
UPA v PBO or MTX					
SELECT COMPARE	294/651 (45.2)	97/651 (14.9)	3.03 (2.48, 3.71)	0.30 (0.26, 0.35)	3 (3, 4)
SELECT NEXT	84/221 (38.0)	33/221 (14.9)	2.55 (1.78, 3.64)	0.23 (0.15, 0.31)	4 (3, 7)
SELECT MONOTHERAPY ^a	91/217 (41.9)	33/216 (15.3)	2.74 (1.93, 3.90)	0.27 (0.19, 0.35)	4 (3, 5)
Meta-analysis (excl. MONO)	378/872 (43.3)	130/872 (14.9)	2.91 (2.44, 3.46)	0.27 (0.21, 0.34)	4 (3, 5)
Meta-analysis (incl. MONO)	469/1089 (43.1)	163/1088 (14.9)	2.87 (2.46, 3.36)	0.28 (0.24, 0.32)	4 (3, 4)
BARI v PBO					
RA-BEAM/JADV	219/487 (45.0)	82/488 (16.8)	2.68 (2.15, 3.34)	0.28 (0.23, 0.34)	4 (3, 4)
RA-BUILD/JADX	76/227 (33.5)	29/228 (12.7)	2.63 (1.79, 3.87)	0.21 (0.13, 0.28)	5 (4, 7)
JADA	18/52 (34.6)	10/98 (10.2)	3.39 (1.69, 6.80)	0.24 (0.10, 0.39)	4 (3, 10)
Meta-analysis	313/766 (40.8)	121/814 (14.8)	2.71 (2.25, 3.26)	0.26 (0.21, 0.30)	4 (3, 5)
UPA v ADA					
SELECT COMPARE	294/651 (45.2)	95/327 (29.1)	1.55 (1.29, 1.88)	0.16 (0.10, 0.22)	6 (5, 10)
BARI v ADA					
RA-BEAM/JADV	219/487 (45.0)	115/330 (34.8)	1.29 (1.08, 1.54)	0.10 (0.03, 0.17)	10 (6, 33)
bDMARD IR population					
UPA v PBO					
SELECT BEYOND	56/164 (34.1)	20/169 (11.8)	2.89 (1.82, 4.59)	0.22 (0.14, 0.31)	5 (3, 7)
BARI v PBO					
RA-BEACON/JADW	50/177 (28.2)	14/176 (8.0)	3.55 (2.04, 6.18)	0.20 (0.13, 0.28)	5 (4, 8)
Indirect Comparisons					
cDMARD IR population					
UPA (meta-analysis excl. MONO) v BARI (meta-analysis) via PBO			1.07 (0.83, 1.38)	0.02 (-0.04, 0.08)	NA
UPA (meta-analysis incl. MONO) v BARI (meta-analysis) via PBO			1.06 (0.83, 1.35)	0.02 (-0.04, 0.08)	NA
UPA (SELECT COMPARE) v BARI (RA-BEAM/JADV) via ADA			1.20 (0.93, 1.56)	0 (-0.09, 0.09)	NA
bDMARD IR population					
UPA (SELECT BEYOND) v BARI (RA-BEACON/JADW) via PBO			0.81 (0.40, 1.68)	0.08 (-0.06, 0.22)	NA

^aPBO arm is receiving MTX

Abbreviations: ADA=adalimumab; BARI=baricitinib; CI=confidence interval; IR=inadequate response; NNT = number needed to treat; OR=odds ratio; PBO=placebo; RD=risk difference; RR=risk ratio; UPA=upadacitinib

Source: compiled during the evaluation: Table 2.16, p84; Table 2.20, p89; Table 2.24, p94 of the submission

- 6.14 The results demonstrated both UPA and BARI were more effective than PBO at achieving ACR20 and ACR50 response at Week 12, and the magnitude of the treatment effect for UPA was similar with or without concomitant MTX (demonstrated in SELECT-MONOTHERAPY). The results of the indirect comparisons did not show any statistically significant differences between UPA and BARI in patients with an inadequate response to either cDMARDs or bDMARDs. The results for ACR20 met the non-inferiority margin previously accepted by the PBAC given the lower bound of RR 95%CI for the indirect comparisons was larger than 0.4.
- 6.15 Overall, the ESC considered that the results supported a conclusion of non-inferior efficacy between UPA and BARI. The results were not sensitive to the inclusion of SELECT-MONOTHERAPY or the three excluded trials (JADN, SELECT-SUNRISE, RA-BALANCE/JAGS) conducted in 'foreign' populations. Similar findings were reported for

other outcomes (ACR70, DAS28 (CRP)<2.6, HAQ-DI) and time points (Week 12 and 24) presented in the submission.

- 6.16 Results of the head-to-head trials demonstrated that UPA and BARI were statistically more effective than ADA at achieving ACR20 and ACR50 response at Week 12. In SELECT-COMPARE, the comparison between UPA and ADA met the pre-specified non-inferiority margin for ACR50 (RD = 0.16, 95%CI: 0.10, 0.22) because the lower bound of the 95%CI was larger than -0.10. The result also met the multiplicity-controlled conclusion of superiority. In RA-BEAM/JADV, the comparison between BARI and ADA met the pre-specified non-inferiority margin for ACR20 and BARI was considered to be superior to ADA according to the statistical analysis plan.
- 6.17 Despite the trial conclusions, it was unclear whether the results adequately supported a claim of superior efficacy for UPA over ADA. The submission argued SELECT-COMPARE (and RA-BEAM/JADV) were powered for non-inferiority and then assessed superiority to ADA; therefore, any statistically significant difference should be considered clinically important. However, the ESC recalled that the PBAC previously rejected a claim of superior efficacy between BARI and ADA based on the evidence reported in RA-BEAM/JADV.

Comparative harms

- 6.18 The submission did not conduct an indirect comparison for any safety outcomes; estimates presented below were calculated during the evaluation. Table 7 presents a comparison of (pooled) safety outcomes for UPA, BARI and PBO at Week 12. Safety outcomes at week 24/26 were consistent with Week 12 results.

Table 7: Summary of key adverse events in the randomised trials at Wk12 (PBO common reference)

Table 1. Summary of key adverse events in the randomised trials at W12 (PBO common reference)					
Pooled results	UPA trials ^a		BARI trials ^b		Indirect comparison RD (95% CI)
	UPA 15mg N=1035 n events (%)	PBO, N=1042 n events (%)	BARI 4mg N=456 n events (%)	PBO N=507 n events (%)	
Any Adverse events					
AEs	564 (54.4)	506 (48.5)	276 (60.5)	274 (54.6)	0.01 (-0.06, 0.08)
SAEs	35 (3.4)	19 (1.8)	15 (3.3)	18 (3.6)	0.01 (-0.02, 0.04)
AEs leading to discontinuation	29 (2.8)	28 (2.7)	18 (3.9)	17 (3.4)	0.01 (-0.02, 0.04)
Death	0 (0)	2 (0.2)	2 (0.4)	7 (1.4)	0.01 (-0.01, 0.03)
TEAE of special interest					
Serious infection	12 (1.2)	6 (0.6)	5 (1.1)	6 (1.2)	0.00 (-0.02, 0.02)
Herpes zoster infections	7 (0.7)	3 (0.3)	7 (1.5)	1 (0.2)	-0.01 (-0.03, 0.01)
MACE ^c	1 (0.1)	3 (0.3)	1 (0.2)	2 (0.5)	0.00 (-0.01, 0.01)
Malignancy ^c	1 (0.1)	2 (0.2)	1 (0.2)	0 (0)	0.00 (-0.01, 0.01)
NMSC ^c	0 (0)	1 (0.1)	1 (0.2)	0 (0)	0.00 (-0.01, 0.01)

Abbreviations: AE=adverse event; CI=confidence interval; MACE=major adverse cardiovascular events; n=number of participants reporting data; N=total participants in group; NMSC=non-melanoma skin cancer; PBO=placebo; RD=risk difference; SAE=serious adverse event; UPA=upadacitinib

^a UPA trials included SELECT COMPARE, SELECT NEXT, and SELECT BEYOND

^b BARI trials included JADA, RA-BUILD/JADX, and RA-BEACON/JADW

^c not reported in the JADA trial, total N in the pooled BARI trials is 404.

Source: Tables 2.27, 2.29, 2.31, pp97-102 of the submission.

- 6.19 Overall, UPA 15 mg was not significantly different from BARI 4 mg for any of the key safety outcomes. There was a statistically lower risk of serious adverse events (SAE) and adverse events (AEs) leading to discontinuation when ADA was the common reference arm; however, this result was driven by the higher proportion of these events for ADA in SELECT-COMPARE but lower proportion in the ADA arm of RA-BEAM, compared to the UPA and BARI respectively.
- 6.20 Long-term safety data has raised concerns regarding the risk of thrombosis with JAK inhibitors, but it is not yet understood whether or how the inhibition of JAK subtypes may contribute to this risk. In 2018, the U.S. Food and Drug Administration (FDA) only approved the BARI 2 mg once daily (i.e. BARI 4 mg was not approved) with a black box warning that includes a caution related to deep venous thrombosis, pulmonary embolism and arterial thrombosis. In July 2019, the FDA also approved a black box warning for TOF 10 mg due to an increased risk of thrombosis and mortality¹ seen in the post-marketing study.
- 6.21 Based on pooled trial evidence for UPA (N=4443), there was not an increased risk of venous thromboembolism or mortality for UPA 15 mg compared to placebo. However, the TGA clinical evaluation report stated “there is limited long-term safety data ... to assess the risk of some types of AEs such as malignancy and MACE [major adverse cardiovascular events], which will require additional longitudinal safety follow-up.

¹ <https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and>
<https://www.pfizermedicalinformation.com/en-us/xeljanz/boxed-warning>

From the assessment of the safety dataset, there are some significant safety concerns with UPA therapy including the risk of infection, opportunistic infection (mainly, oral herpes and zoster infection), increased serum CPK values, anaemia, neutropenia, abnormal liver function tests (raised serum transaminases) and dyslipidaemia. These safety concerns are consistent with the known profile of JAK inhibitor therapy in adult patients with RA.”

Benefits/harms

- 6.22 There are no expected clinically meaningful differences between UPA and BARI in efficacy and safety when used for the treatment of RA.

Clinical claim

- 6.23 The submission described UPA as non-inferior in terms of effectiveness and safety compared with BARI, as well as superior in terms of effectiveness and non-inferior in terms of safety compared to ADA. The evidence presented in the submission supported the clinical claim of non-inferior effectiveness versus BARI, and non-inferior safety versus BARI and ADA. However, both the PBAC and the ESC considered that the claim of superior effectiveness versus ADA was not adequately supported for the following reasons:
- The claim was based on ACR50 results in the SELECT-COMPARE trial meeting the pre-specified tests for non-inferiority and then superiority of UPA versus ADA. That is, the lower bound of the 95%CI for the RD was larger than the nominated non-inferiority margin of -10%, and then larger than 0% (i.e. statistically significant) in accordance with the sequential testing procedure.
 - The PBAC noted the Sponsor’s pre-PBAC response included a statistical report to support the claim of UPA’s superior efficacy over ADA in the SELECT-COPMARE trial. The report stated that UPA meets the requirements for statistical superiority as defined by global statistical norms through the ICH-E9 guidelines EMA guidelines and FDA guidelines. The PBAC noted these were regulatory guidelines focused on statistical superiority and not necessarily relevant to the assessment of clinical superiority.
 - Finally, Australian patients can receive and fail up to five of the eleven PBS listed JAK inhibitors/bDMARDs. There was no evidence that adding UPA as a twelfth treatment alternative provided a significant improvement in long-term outcomes over the treatment algorithm.
- 6.24 The PBAC considered that the claim of non-inferior comparative effectiveness compared with BARI was reasonable and that the claim of superior comparative effectiveness compared with ADA was not reasonable.

- 6.25 The PBAC considered that the claim of non-inferior comparative safety compared with BARI and ADA was reasonable.

Economic analysis

- 6.26 The submission presented a cost-minimisation analysis comparing UPA with BARI over 12 months, based on published DPMQ prices. The nominated equi-effective doses were reasonably based on the recommended doses for RA (UPA 15 mg daily = BARI 4 mg daily). Given there is no difference in dosing schedule (one tablet daily) or pack size (28 tablets) between UPA and BARI, the analysis was insensitive to time horizon and the DPMQs were identical.
- 6.27 The submission stated that the effective price was not available to the sponsor for the cost-minimisation analysis, but requested the same effective price as BARI 4 mg tablets.

Drug cost/patient/year

- 6.28 \$ [REDACTED] per year based on the requested published DPMQ of \$ [REDACTED] and 13 scripts per year. As discussed above, the Sponsor requested a Special Pricing Arrangement for UPA 15 mg tablets including the same effective price (unknown) as BARI 4 mg tablets.

Estimated PBS usage & financial implications

- 6.29 This submission was not considered by DUSC. A market share approach was used to estimate the financial implications of the proposed listing, summarised in Table 8, assuming UPA would substitute for the most commonly prescribed PBS-listed JAK inhibitors/bDMARDs and the listing will not affect current market growth. The PBAC considered that the market share approach was appropriate. The analysis used the published DPMQ values given the sponsor did not have knowledge of special pricing arrangements.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
4.2 Estimation of use and financial impact of the proposed medicine						
Total scripts PBS						
Total scripts RPBS						
Net Cost PBS/RPBS (less co-pay)	\$	\$	\$	\$	\$	\$
4.3 Estimation of changes in use and financial impact of other bDMARDs						
ABA SC						
ADA						
BARI						
ETA						
TOC SC						
TOF						
Total other bDMARDs						
ABA SC	-\$	-\$	-\$	-\$	-\$	-\$
ADA	-\$	-\$	-\$	-\$	-\$	-\$
BARI	-\$	-\$	-\$	-\$	-\$	-\$
ETA	-\$	-\$	-\$	-\$	-\$	-\$
TOC SC	-\$	-\$	-\$	-\$	-\$	-\$
TOF	-\$	-\$	-\$	-\$	-\$	-\$
Net cost PBS/RPBS (less co-pay), bDMARDs	-\$	-\$	-\$	-\$	-\$	-\$
4.4 Estimated financial implications for the PBS/RPBS#						
Net Cost PBS/RPBS (less co-payment)	\$	\$	\$	\$	\$	\$
4.5 Estimated financial implications for the health budget						
Net cost to health budget (less co-payment)	\$	\$	\$	\$	\$	\$

Abbreviations: ABA=abatacept, ADA=adalimumab, BARI=baricitinib, bDMARDs=biological disease modifying antirheumatic drug, ETA=etanercept, TOC=tocilizumab, TOF=tofacitinib, SC=subcutaneous

The submission made some coding errors in the calculation of the Net cost to PBS/RPBS (less co-payments)

Source: Compiled during the evaluation from Section 4 workbook

The redacted table shows that at year 6, the estimated number of scripts was 50,000-100,000 per year and the net cost to the PBS would be \$20 - \$30 million.

- 6.30 The PBAC noted that the estimated net cost to the government of \$20-\$30 million over six years was not reliable and an artefact of using published rather than effective prices of substituted therapies. Assuming UPA 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 likely be cost neutral to the PBS/RPBS, however it was noted that there may be additional cost to the PBS from grandfathering of patients in the first 12 months of listing.

Quality Use of Medicines

- 6.31 The submission provided a risk management plan, including an Australian-specific annex. This included pharmacovigilance activities, risk minimisation plan, and the

responsible contact person for important and identified risks (e.g. serious infections, herpes zoster and MACE). The sponsor will provide the AbbVie Care patient support program to support patients with managing their RA and treatment with UPA.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of upadacitinib (UPA) on a cost-minimisation basis against the least costly biological disease modifying anti-rheumatic drug (bDMARD) for rheumatoid arthritis (RA). In making this recommendation, the PBAC accepted any of the current PBS listed bDMARDs for RA could be an alternative therapy to UPA.
- 7.2 The PBAC considered the equi-effective doses between UPA (at a dose of 15 mg daily) and the alternative bDMARDs could be derived from the product information and with reference to the 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 that 10 alternative therapies were listed on the PBS for the treatment of RA at the time of consideration. The PBAC considered that while the clinical need for an additional treatment was low, the addition of another option may be useful for some patients
- 7.4 The PBAC considered the nominated comparators of baricitinib (BARI) and adalimumab (ADA) were reasonable; however, noted any of the bDMARDs currently listed on the PBS for RA were relevant alternative therapies.
- 7.5 The PBAC considered the claims that UPA is non-inferior to BARI in terms of effectiveness and safety and non-inferior in terms of safety compared to ADA, were adequately supported by the clinical evidence presented in the submission. The PBAC considered the claim of superior effectiveness versus ADA was not fully supported by the evidence. The PBAC noted no evidence demonstrating superiority against any of the other alternative therapies was provided.
- 7.6 The PBAC noted that the claim of superior effectiveness versus ADA was based on ACR50 results in the SELECT-COMPARE trial meeting the pre-specified tests for non-inferiority and then superiority of UPA versus ADA. That is, the lower bound of the 95% confidence interval for the risk difference was larger than the nominated non-inferiority margin of -10%, and then larger than 0% (i.e. statistically significant) in accordance with the sequential testing procedure.
- 7.7 The PBAC noted that the 12 week ACR50 response rate in the SELECT-COMPARE trial was 16% higher (with 95%CI 10-22%) for UPA versus ADA, which met the convention for statistical significance. However, the PBAC considered that a clinically relevant

difference in effectiveness of one agent over another requires consideration of the totality of evidence, which involves consideration of the quality of the relevant studies, durability of treatment effect and all relevant outcomes. As such, the PBAC considered that a statistically significant result for ACR50 at 12-weeks in the SELECT-COMPARE trial was not sufficient, in isolation, to demonstrate/establish clinical superiority of UPA over ADA.

- 7.8 The PBAC noted that the submission proposed a grandfather clause to be incorporated into the listing for approximately <500 patients from a planned UPA Patient Familiarisation Program (PFP) and <500 patients enrolled in the long-term extension phases of the UPA clinical trials who may not be eligible for PBS-subsidised treatment under the initial treatment criteria. The PBAC considered that the proposed grandfather clause was appropriate, and that its wording should align with the current listings for BARI that the grandfather restriction be removed from the listing after 12 months in line with standard procedure.
- 7.9 The PBAC considered that listing of UPA for RA based on a cost minimisation basis with the least costly bDMARD using effective prices would be cost-neutral to the PBS, noting the potential for additional cost from the inclusion of grandfathered patients from the first 12 months of listing.
- 7.10 The PBAC considered that UPA is not suitable for prescribing by nurse practitioners.
- 7.11 The PBAC considered that the Early Supply Rule should apply to UPA.
- 7.12 The PBAC advised that the restriction is complex and that the listing of upadacitinib would result in flow-on changes to the Prescriber Instructions regarding the treatment of adult patients with severe active rheumatoid arthritis.
- 7.13 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.
- 7.14 Under section 101(3BA) of the National Health Act 1953, the PBAC advised that upadacitinib should be treated as interchangeable on an individual patient basis with abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, sarilumab and tofacitinib for the treatment of RA.
- 7.15 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 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 2009 for Pricing Pathway A were not met.

Outcome:

Recommended

8 Recommended listing

Add new item:

The submission requested the same restriction wording for upadacitinib as for the currently listed bDMARDS for rheumatoid arthritis; these restrictions have not been duplicated in full here.

The listing of upadacitinib would result in flow-on changes to include upadacitinib in the administrative notes for other bDMARDS regarding the treatment of adult patients with severe active rheumatoid arthritis.

The PBAC recommended that the wording for the proposed grandfather restriction should align with that of the BARI listings; this restriction has not been duplicated here.

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 in recommending upadacitinib for the treatment of patients with severe RA. AbbVie maintains that upadacitinib is superior to adalimumab as demonstrated in head-to-head clinical trials and strongly disagrees with the methodology of using the inverse of the non-inferiority margin to determine superiority. This methodology is not supported by international literature or experts. Further use of this methodology would have profound trial design, patient access and industry impacts. AbbVie will continue to seek further dialogue on this issue with the PBAC.