

7.10 UPADACITINIB, Tablet 15 mg, Rinvoq[®], AbbVie Pty Ltd

1 Purpose of Application

- 1.1 The minor submission requested that PBAC review its November 2019 finding that upadacitinib (UPA) is non-inferior to adalimumab (ADA) in terms of effectiveness when used in the treatment of severe active Rheumatoid Arthritis (RA).
- 1.2 The minor submission did not seek a review of PBAC's finding that UPA is non-inferior to baricitinib (BAR).
- 1.3 The minor submission proposed no changes to the current UPA listing for RA in terms of the circumstances¹ (restriction), price or risk share arrangement (public versus effective price).
- 1.4 The minor submission requested the outcomes of PBAC's consideration of this minor submission be published as an addendum to the public summary document (PSD) for UPA from November 2019.

2 Background

Registration and subsidy status

- 2.1 UPA was TGA registered on 7 January 2020 for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to, one or more disease-modifying anti-rheumatic drugs (DMARDs). It may be used as monotherapy or in combination with methotrexate or other conventional synthetic DMARDs.
- 2.2 UPA is currently listed on the PBS as a General Schedule Authority Required benefit for the treatment of severe active RA.

November 2019 upadacitinib PBAC consideration

- 2.3 UPA was recommended for PBS listing for severe RA by the PBAC at its November 2019 meeting.

¹ Subsection 85(7) of the *National Health Act 1953* allows the Minister to determine by legislative instrument the circumstances in which a prescription for the supply of a pharmaceutical benefit may be written. These circumstances are more commonly referred to as the "PBS restriction".

- 2.4 It was the twelfth biologic medicine² to be listed on the PBS with the same circumstances. Australian patients can trial up to five of the twelve PBS listed biologic medicines in a treatment cycle.
- 2.5 The sponsor's November 2019 superiority claim against 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%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.
- 2.6 The Sponsor's November 2019 pre-PBAC response included a statistical report to support the claim of UPA's superior efficacy over ADA in the SELECT-COMPARE trial. The report stated that UPA meets the requirements for statistical superiority as defined by global statistical norms through the ICH-E9 EMA guidelines and FDA guidelines.

Baricitinib for RA - PBAC considerations

- 2.7 BAR for treatment of severe RA was deferred by the PBAC at its July 2017 and November 2017 meetings under the TGA-PBAC parallel process arrangements, before being recommended for PBS listing at the March 2018 PBAC meeting.
- 2.8 In its July 2017 consideration, the PBAC did not accept the submission's claim that BAR was superior in terms of effectiveness compared with ADA. Specifically, the PBAC noted that the major secondary endpoint of ACR20 at week 12 failed to demonstrate an improvement of greater than 12%, when the pre-specified non-inferiority margin was -12%. Further, noting that only short-term comparative outcomes were available, the PBAC considered there was no clear evidence that demonstrated that BAR provided a significant improvement in effectiveness over ADA (paragraph 7.5, baricitinib Public Summary Document (PSD), July 2017).

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Current situation

- 3.1 The UPA minor submission based its request on advice received from Professor [REDACTED] and Professor [REDACTED]

² In line with the convention followed in the PBS restrictions for these drugs, for the purposes of these minutes the "biologics" group of drugs includes abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, sarilumab, tofacitinib and upadacitinib, where they are subsidised under the PBS for CPP MSUC PsA and RA.

Table 1 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: Table 6, PBSC minutes UPA, Nov 2019, compiled during the evaluation: Table 2.16, p84; Table 2.20, p89; Table 2.24, p94 of the submission

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of evidence

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

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

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC reaffirmed its view that overall UPA, BAR and ADA are non-inferior in terms of effectiveness when used for the treatment of severe active RA.

5.2 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.

5.3 The PBAC requested corrigenda to the UPA minutes and PSD from November 2019 be issued.

Outcome:

Advised

6 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.

7 Sponsor's Comment

As outlined in the published agenda for the November 2020 meeting, the primary purpose of AbbVie's resubmission was to request a review of the statistical basis upon which a claim of superior effectiveness of upadacitinib versus adalimumab in severe active RA was not accepted by the PBAC in November 2019. AbbVie is pleased that the PBAC recognised the inappropriate application of an unrecognised statistical methodology where the lower limit of the 95% confidence interval around the point estimate was required to exceed the inverse

of the non-inferiority margin in order for superiority to be demonstrated. In recognition of this error, corrigenda to the November 2019 Public Summary Document for upadacitinib removing reference to such a methodology are to be published. AbbVie considers that a copy of the original Public Summary Document with an addendum outlining the history and content of the corrigenda should be made available on the PBS website in the interests of transparency.