

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

1 Purpose of submission

- 1.1 The submission requested a General Schedule, Authority Required listing of upadacitinib (UPA) for the treatment of adults with ankylosing spondylitis (AS) following inadequate response to at least two non-steroidal anti-inflammatory drugs (NSAIDs) combined with an exercise program. This was the first submission to the PBAC for the requested indication; UPA is currently PBS listed for rheumatoid arthritis (recommended November 2019) and was recommended by the PBAC at the March 2021 meeting for the treatment of psoriatic arthritis.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis versus adalimumab (ADA), a biologic Disease Modifying Anti-Rheumatic Drug (bDMARD) currently listed on the PBS for AS. If listed, UPA would be the first janus kinase (JAK) inhibitor and the first oral medicine available on the PBS for treatment of AS but one of eight treatment alternatives including seven bDMARDs.

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

Component	Description
Population	Patients with ankylosing spondylitis (AS) who failed to achieve an adequate response following treatment with at least 2 NSAIDs or are contraindicated to NSAIDs, while completing an appropriate exercise program, for a total of three months, as per current criteria for PBS-listed bDMARD therapies.
Intervention	Upadacitinib 15 mg tablet, administered orally once daily
Comparator	Adalimumab 40 mg subcutaneous injection, administered fortnightly; adalimumab is the most-commonly prescribed PBS-listed bDMARD used in patients with active AS. There is no listed pharmacological analogue for treatment of active AS.
Outcomes	ASAS20, ASAS40 and BASDAI 50
Clinical claim	Upadacitinib is non-inferior to adalimumab in terms of efficacy in patients with active AS for whom an adequate response has not been achieved with conventional therapies or NSAIDs. Upadacitinib is comparable to adalimumab in terms of safety.

Abbreviations: NSAID=non-steroidal anti-inflammatory drugs; bDMARD=biological disease anti-rheumatic drug; AS=Ankylosing spondylitis; ASAS20/40=Assessment of SpondyloArthritis international Society 20%/40% response criteria; BASDAI50=50% improvement in Bath ankylosing spondylitis disease activity index;

Source: Table 1.1 of the submission.

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 and ACM advice was available. The proposed TGA indication was:

‘Upadacitinib is indicated for the treatment of adults with active ankylosing spondylitis.’

3 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
UPADACITINIB					
<u>Initial 1, 2 and 3</u> 15 mg modified release tablet, 28	1	28	3	\$1,271.34 [^]	
<u>Initial – grandfathered patients</u> 15 mg modified release tablet, 28	1	28	5	\$1,271.34 [^]	RINVOQ AbbVie Pty Ltd
<u>Continuing</u> 15 mg modified release tablet, 28	1	28	5	\$1,271.34 [^]	
Category / Program:	GENERAL – General Schedule (Code GE)				
PBS Indication:	Ankylosing Spondylitis				
Treatment phase:	Initial treatment 1 (new patient)				
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing				
Treatment criteria:	<ul style="list-style-type: none"> • Must be treated by a rheumatologist; OR • Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis. 				
Clinical criteria:	<ul style="list-style-type: none"> • The condition must be radiographically (plain X-ray) confirmed Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis, AND • Patient must not have received PBS-subsidised treatment with a biological medicine for this condition, AND • Patient must have at least 2 of the following: (i) low back pain and stiffness for 3 or more months that is relieved by exercise but not by rest; or (ii) limitation of motion of the lumbar spine in the sagittal and the frontal planes as determined by a score of at least 1 on each of the lumbar flexion and lumbar side flexion measurements of the Bath Ankylosing Spondylitis Metrology Index (BASMI); or (iii) limitation of chest expansion relative to normal values for age and gender, AND • Patient must have failed to achieve an adequate response following treatment with at least 2 non-steroidal anti-inflammatory drugs (NSAIDs), whilst completing an appropriate exercise program, for a total period of 3 months, AND • 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:	<p>The following criteria indicate failure to achieve an adequate response and must be demonstrated at the time of the initial application:</p> <p>(a) a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of at least 4 on a 0-10 scale; AND</p> <p>(b) an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour or a C-reactive protein (CRP) level greater than 10 mg per L.</p> <p>The BASDAI must be determined at the completion of the 3 month NSAID and exercise trial, but prior to ceasing NSAID treatment. The BASDAI must be no more than 1 month old at the time of initial application.</p> <p>An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 12 weeks of therapy. An application for the continuing treatment must be accompanied with the assessment of response and submitted to the Department of Human Services no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.</p>				
Treatment phase:	Continuing treatment				
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing				

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Clinical criteria:	<ul style="list-style-type: none"> • Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition, AND • Patient must have demonstrated an adequate response to treatment with this drug, AND • Patient must not receive more than 24 weeks of treatment under this restriction.
Prescriber Instructions:	<p>An adequate response is defined as an improvement from baseline of at least 2 of the BASDAI and 1 of the following:</p> <p>(a) an ESR measurement no greater than 25 mm per hour; or</p> <p>(b) a CRP measurement no greater than 10 mg per L; or</p> <p>(c) an ESR or CRP measurement reduced by at least 20% from baseline.</p> <p>Where only 1 acute phase reactant measurement is supplied in the first application for PBS-subsidised treatment, that same marker must be measured and supplied in all subsequent continuing treatment applications.</p> <p>An application for the continuing treatment must be accompanied with the assessment of response following a minimum of 12 weeks of therapy with this drug and submitted to the Department of Human Services no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.</p> <p>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. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.</p> <p>A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological medicine was approved in this cycle and the date of the first application under a new cycle under the Initial 3 treatment restriction.</p>
Treatment phase:	Initial treatment - Grandfathered patients
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Clinical criteria:	<ul style="list-style-type: none"> • Patient must have previously received non-PBS-subsidised therapy with this drug for this condition prior to PBS listing of upadacitinib for ankylosing spondylitis, AND • Patient must be receiving treatment with this drug for this condition at the time of application, AND • The condition must be radiographically (plain X-ray) confirmed Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis, AND • Patient must not have received PBS-subsidised treatment with a biological medicine for this condition, AND • Patient must have at least 2 of the following: (i) low back pain and stiffness for 3 or more months that is relieved by exercise but not by rest; or (ii) limitation of motion of the lumbar spine in the sagittal and the frontal planes as determined by a score of at least 1 on each of the lumbar flexion and lumbar side flexion measurements of the Bath Ankylosing Spondylitis Metrology Index (BASMI); or (iii) limitation of chest expansion relative to normal values for age and gender, AND • Patient must have failed to achieve an adequate response following treatment with at least 2 non-steroidal anti-inflammatory drugs (NSAIDs), whilst completing an appropriate exercise program, for a total period of 3 months, AND • Patient must not receive more than 16 weeks of treatment under this restriction
Prescriber Instructions:	<p>The following criteria indicate failure to achieve an adequate response and must be demonstrated at the time of the initial application:</p> <p>(a) a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of at least 4 on a 0-10 scale; AND</p> <p>(b) an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour or a C-reactive protein (CRP) level greater than 10 mg per L.</p> <p>The BASDAI must be determined at the completion of the 3 month NSAID and exercise trial, but prior to ceasing NSAID treatment. The BASDAI must be no more than 1 month old at the time of initial application.</p>

Treatment phase:	Continuing and Initial Grandfathered patients treatment - balance of supply
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing
Clinical criteria:	<ul style="list-style-type: none"> • Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition, AND • Patient must have demonstrated an adequate response to treatment with this drug, AND • Patient must not receive more than 24 weeks of treatment under this restriction.
Prescriber Instructions:	An adequate response is defined as an improvement from baseline of at least 2 of the BASDAI and 1 of the following: <ul style="list-style-type: none"> (a) an ESR measurement no greater than 25 mm per hour; or (b) a CRP measurement no greater than 10 mg per L; or (c) an ESR or CRP measurement reduced by at least 20% from baseline.

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

- 3.1 The sponsor requested General Schedule, Authority Required (in writing) PBS listing of UPA 15 mg as a modified release tablets for initial and continuing treatment of AS, including grandfathered patients. The wording of the requested restriction was consistent with the approved criteria for ADA and bDMARDs for AS.
- 3.2 The sponsor stated that a grandfathering clause will be necessary to allow <500 patients from a planned Patient Familiarisation Program (launched upon TGA registration) and <500 trial patients (open label extension trial to be completed January 2022) to access PBS-subsidised UPA. Eligibility and continuation criteria for the Patient Familiarisation Plan will be consistent with the proposed PBS criteria. The requested quantities (including repeats) permit up to 16 weeks of initial treatment and 24 weeks of continuing treatment; 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.
- 3.3 The sponsor requested a Special Pricing Arrangement (SPA) to maintain the current published price of UPA (DPMQ = \$1,271.34 as per the current PBS listing for rheumatoid arthritis) and implement a confidential effective price. The submission presented a cost-minimisation analysis in Section 3 based on the published price of ADA (weighted across indications) as an indicative analysis corresponding to an AEMP of \$979.56.

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

4 Population and disease

- 4.1 AS is a form of axial spondyloarthritis characterised by inflammatory back pain, limited spinal mobility, enthesitis, and peripheral articular and extra-articular features. Patients with AS also have spinal inflammation visible on magnetic resonance imaging (MRI) and evidence of structural damage on X-rays that fulfil the modified New York criteria.

- 4.2 UPA is an oral, selective and reversible inhibitor of JAK1, which is important in signalling inflammatory cytokine receptors, blocking the effects of various interleukins and interferons including IL-6 and IL-23, that are elevated in AS. The recommended dose in the draft Product Information (PI) for adults with AS is UPA 15 mg once daily (D) taken orally with or without food, which is the same as the approved dose for rheumatoid arthritis.
- 4.3 If listed, UPA will offer patients a new class of treatment (i.e. JAK inhibitor) and mode of administration (oral) compared to the bDMARDs currently available on the PBS: ADA, etanercept, golimumab, infliximab, certolizumab pegol (all TNF α inhibitors), secukinumab and ixekizumab (both IL-17A inhibitors). 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 ADA as the appropriate main comparator given that ADA is the most commonly prescribed biologic treatment for AS and therefore the main drug that would be replaced. The recommended dose of ADA for AS is 40 mg every two weeks (Q2W) via subcutaneous (SC) injection. The submission also acknowledged in the utilisation and financial estimates that UPA would replace any of the bDMARDs available for AS.
- 5.2 In recent decisions for bDMARD submissions, the PBAC had previously considered all bDMARDs as relevant alternative therapies because they may be replaced in practice; and in the absence of evidence of superiority, recommended listing on a cost-minimisation basis to the lowest cost alternative (paragraph 7.1, secukinumab Public Summary Document (PSD) March 2016 PBAC meeting; paragraph 7.4, ixekizumab PSD July 2020 PBAC meeting).
- 5.3 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.

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 literature search did not identify any direct head-to-head randomised trials comparing UPA to ADA in the treatment of AS. The submission was based on six placebo controlled randomised trials:

- UPA vs placebo (SELECT-AXIS 1)
- ADA vs placebo (ATLAS, M03-606, Huang 2014, DANISH and COAST-V)

The PBAC has previously considered evidence from most of the ADA trials (all except for DANISH) in past submissions where ADA was either the intervention or comparator.

6.4 Table 2 provides details of the trials presented in the submission.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Upadacitinib vs placebo		
SELECT-AXIS 1 M16-098 NCT03178487	M16-098 CSR. A Multicenter, Randomised, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Upadacitinib in Subjects with Active Ankylosing Spondylitis. van der Heijde D, Song IH, Pangan AL, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial.	31 January 2020 Lancet 2019;394: 2108–2017
Adalimumab vs placebo		
ATLAS M03-607 NCT00085644	M03-607 CSR. A Phase 3 Multicenter Study of the Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Active Ankylosing Spondylitis. Van Der Heijde, D., Kivitz, A., Schiff, M.H., Sieper, J., Dijkmans, B.A.C., Braun, J., Dougados, M., Reveille, J.D., Wong, R.L., Kupper, H. & Davis Jr., J.C., Efficacy and safety of adalimumab in patients with ankylosing spondylitis: Results of a multicenter, randomised, double-blind, placebo-controlled trial.	23 December 2004 Arthritis and Rheumatism 2006; 54(7): 2136-2146
M03-606 NCT00195819	M03-606 CSR. A Phase 3 Multicenter Study of the Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Active Ankylosing Spondylitis. Lambert, R.G.W., Salonen, D., Rahman, P., Inman, R.D., Wong, R.L., Einstein, S.G., Thomson, G.T.D., Beaulieu, A., Choquette, D. & Maksymowych, W.P., Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: A multicenter, randomised, double-blind, placebo-controlled study.	12 October 2004 Arthritis and Rheumatism 2007; 56(12): 4005-4014
Huang 2014 M11-991 NCT01114880	M11-991. A phase 3, randomized, double-blind, placebo-controlled multicenter, efficacy and safety study of adalimumab in adult Chinese subjects with active ankylosing spondylitis. Huang, F., Gu, J., Zhu, P., Bao, C., Xu, J., Xu, H., Wu, H., Wang, G., Shi, Q., Andhivarothai, N., Anderson, J. & Pangan, A.L., Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: Results of a randomised, controlled trial.	16 February 2011 Annals of the Rheumatic Diseases 2014; 73(3): 587-594
DANISH NCT00477893	Pedersen, S.J., Poddubnyy, D., Sørensen, I.J., Loft, A., Hindrup, J.S., Thamsborg, G., Asmussen, K., Hendricks, O., Nørregaard, J., Pii, A., Møller, J.M., Jurik, A., Balding, L., Lambert, R.G., Sieper, J. & Østergaard, M., Course of Magnetic Resonance Imaging-Detected Inflammation and Structural Lesions in the Sacroiliac Joints of Patients in the Randomised, Double-Blind, Placebo-Controlled Danish Multicenter Study of Adalimumab in Spondyloarthritis, as Assessed by the Berlin and Spondyloarthritis Research Consortium of Canada Methods.	Arthritis and Rheumatology 2016; 68(2): 418-429
COAST-V NCT02696785	van der Heijde, D., Cheng-Chung Wei, J., Dougados, M., Mease, P., Deodhar, A., Maksymowych, W. P, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial.	The Lancet 2018; 392(10163): 2441-2451

Source: Table 2.3, pp29-33 of the submission.

6.5 Table 3 presents the key features of the included trials.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Bias	Treatment arms	Population	Key efficacy outcomes
UPA vs PBO						
SELECT-AXIS 1	187	R, MC, PC, DB 14wk / OL extension ^a	Low	UPA 15 mg D PBO	AS (mNY) ^b , bDMARD naive	1°: ASAS40 (Wk 14) 2°: BASDAI50 other: ASAS20
ABA vs PBO						
ATLAS	315	R, MC, PC, DB 24wk / OL extension; rescue ≥Wk 12 ^c	Low	ADA 40mg Q2W SC PBO	AS (mNY), bDMARD naive	1°: ASAS20 (Wk 12) 2°: ASAS40, BASDAI50
M03-606	82	R, MC, PC, DB 24wk / OL extension; rescue ≥Wk 12 ^d	Low	ADA 40mg Q2W SC PBO	AS (mNY), bDMARD naive	1°: ASAS20 (Wk 12) 2°: ASAS40, BASDAI50
Huang 2014	344	R, MC PC, DB 12wk / OL extension	Low	ADA 40mg Q2W SC PBO	AS (mNY), bDMARD naive	1°: ASAS20 (Wk 12) 2°: ASAS40, BASDAI50
DANISH	52	R, MC, PC, DB 12wk / OL extension ^f	Low	ADA 40mg Q2W SC PBO	AS (ESSG) ^e , bDMARD naive	1°: BASDAI50 (Wk 24) other: BASDAI50 (Wk 12)
COAST-V	341 ^h	R, MC, PC, DB# 16wk / dose-blind extension ^k	Unclear	IXE 80mg Q2W SC IXE 80mg Q4W SC ADA 40mg Q2W SC PBO	AS (mNY) ^g , bDMARD naive	1°: ASAS40 (Wk 16) 2°: ASAS20, BASDAI50

Abbreviations: ADA=adalimumab; AS=ankylosing spondylitis; ASAS= Assessment of SpondyloArthritis international Society; ASAS20/40=Assessment of SpondyloArthritis international Society 20%/40% response criteria; ASDAS= Ankylosing Spondylitis Disease Activity Score; }=axial spondyloarthritis; BASDAI(50)=50% improvement in Bath ankylosing spondylitis disease activity index; bDMARD=biologic Disease Modifying Anti-Rheumatic Drug; DB=double blind; ESSG=European Spondyloarthropathy Study Group; IXE=ixekizumab; MC=multi-centre; mNY=modified New York; MRI=magnetic resonance imaging; OL=open-label; PBO=placebo; PC=placebo control; R=randomised; SpA=spondyloarthritis; Tx=treatment; UPA=upadacitinib; D=daily; Q2W=every 2 weeks; wk=week; # COAST-V is double blind, double dummy design in which each active treatment has its own matched placebo to preserve the blind.

a At Wk 14, patients assigned to UPA received open-label UPA and patients on placebo at baseline received open-label UPA. Starting Wk 16, patients who do not achieve at least an ASAS 20 response at two consecutive visits could add or modify doses of NSAIDs, acetaminophen/paracetamol, low potency opioids, and/or modify dose of methotrexate or sulfasalazine at Wk 20 or thereafter (after assessments have been performed). Change in dose or addition of DMARDs other than methotrexate or sulfasalazine was not permitted.

b Patients must have clinical diagnosis of AS and fulfil mNY criteria for AS, which require meeting clinical criteria for AS and sacroiliitis on conventional radiographs.

c Patients who failed to achieve ASAS20 at Wks 12, 16 or 20: i) continued blinded study medication through Wk 24, ii) received early escape therapy (i.e. open-label ADA 40 mg Q2W SC prior to Wk 24) or iii) discontinued from the study.

d Patients who failed to achieve ASAS20 at Wks 12, or 16, or 20 could receive open-label ADA 40 mg Q2W SC prior to Wk 24.

e Patients were included with axSpA according to the ESSG classification criteria and presence of sacroiliitis on conventional radiography or MRI. Of the 52 enrolled patients, 45 (86.5%) patients also fulfilled the mNY criteria for radiographic damage.

f Clinical non-responders changed treatment at the discretion of the treating rheumatologist.

g Patients must have sacroiliitis on radiograph by mNY criteria for AS and ≥1 SpA feature fulfilling ASAS criteria.

h 1 patient excluded due to allocation error. The patient did not meet criteria during screening and was accidentally randomly assigned to placebo and discontinued before receiving study drug. The patient was not counted as completing Wk 16 study treatment nor discontinuing treatment.

i It was noted in the July 2020 PBAC meeting that COAST-V trial had several protocol deviations (paragraph 6.5 (Table 3), ixekizumab PSD July 2020 PBAC meeting): 4.7% of patients took incorrect study medication (6.2% in IXE Q4W arm vs. 2.2% in ADA and 4.6% in placebo), 0.6% had unqualified personnel perform assessments (1.1% in placebo and 1.1% in ADA vs. 0% in IXE Q4W arm), 5% did not have AS at screening (7.8% in ADA and 6.2% IXE Q4W vs. 4.6% in placebo), 1.5% did not have active AS (2.2% in ADA vs. 0% in IXE Q4W or placebo), and 11.7% provided improper informed consent (14.8% in IXE Q4W or 12.2% in ADA arms vs. 8% in placebo). The risk of bias was considered low for all other types of bias.

k At Wk 16, patients entered ongoing extended treatment period (Wks 16 to 52), during which time patients in IXE groups remained on their assigned treatment and patients in placebo or ADA groups were randomly reassigned to receive one of the two IXE dosing regimens. All patients continued to receive masked treatment until Wk 52.

Source: Table 2.4, pp41-44 of the submission.

6.6 All trials were multicentre, double blind, randomised placebo-controlled trials of UPA or ADA at TGA approved doses; except the COAST-V trial was designed to investigate efficacy of two doses of ixekizumab and included ADA as an active-control arm for

comparison versus placebo (to evaluate the assay sensitivity of ADA and ixekizumab concurrently in one trial).

- 6.7 The duration of the double blind phases across the trials ranged from 12 to 24 weeks, but all trials reported key clinical response outcomes at Weeks 12 to 16 either as the primary or key secondary endpoints: 50% improvement in Bath ankylosing spondylitis disease activity index (BASDAI50), and/or the Assessment of SpondyloArthritis international Society 20% (ASAS20) and 40% (ASAS40) response criteria.
- 6.8 There were some minor differences in study design across the trials in terms of:
- Population. All the trials enrolled patients with AS with sacroiliitis on radiograph meeting the mNY criteria, except for DANISH trial, which included patients with axSpA according to the ESSG classification criteria and presence of sacroiliitis on conventional radiography or MRI. However, 45 (86.5%) patients in DANISH also fulfilled the mNY criteria for radiographic damage. In addition to sacroiliitis on radiograph, COAST-V required ≥ 1 SpA feature (including inflammatory back pain, elevated C-reactive protein (CRP), family history, response to NSAIDs or extraspinal manifestations) according to ASAS criteria (Rudwaleit et al. 2009¹).
 - Rescue / early escape and concomitant medications. ATLAS and M03-606 permitted early escape /rescue during the double-blind treatment phases. Patients who failed to achieve ASAS20 response criteria at Weeks 12, 16 or 20 could receive early escape therapy with open-label ADA 40 mg Q2W SC prior to Week 24.
- 6.9 There were also some differences between enrolled patients in the trials and the proposed PBS population. For example, none of the trials required patients to complete an exercise program, although concomitant non-drug therapies (e.g. physiotherapy and hydrotherapy) were permitted in ATLAS, M03-606, Huang 2014 and COAST-V. The proportion of patients with inadequate response to prior NSAIDs was not reported in most trials, 99-100% in SELECT-AXIS 1 (inclusion criteria ≥ 2 NSAIDs) and 100% in Huang 2014 (inclusion criteria ≥ 1 NSAIDs). All the patients in the trials were bDMARD (or TNF α inhibitor) naïve whereas the requested PBS population included bDMARD naïve and experienced (inadequate responder) patients.
- 6.10 Overall the risk of bias of the included trials were low with the exception of COAST-V which reported several protocol deviations. The protocol deviations were similar between groups, but it is unclear their impact on the reliability of the trial results at 16 weeks. The submission presented results from the per-protocol analysis that excluded patients with protocol deviation as reported in the trial publication. However, the per-protocol set also excluded patients who were non-compliant, and

¹ Rudwaleit M, van der Heijde D, Landewe R, et al., The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Annals of Rheumatic Diseases* 2009; 68:777–783.

whose investigator site had significant good clinical practice issues that required a report to the regulatory agencies prior to Week 16. Nevertheless, results in the per-protocol population was consistent with the ITT (e.g. BASDAI50, risk difference (RD): 0.20, 95%CI: 0.07, 0.34 v 0.15, 95%CI: 0.02, 0.27) (paragraph 6.19 and Table 5, ixekizumab PSD July 2020 PBAC meeting).

Comparative effectiveness

- 6.11 Under PBS criteria, eligible patients for initial treatment must demonstrate failure to achieve an adequate response to NSAIDs defined as a BASDAI of at least 4 on a 0-10 scale and CRP level greater than 10 mg/L or elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour. For continuing treatment, patients must demonstrate response to therapy, which is assessed after a minimum of 12 weeks following initial therapy (and every 24 weeks thereafter). Response is defined as a reduction from baseline in the BASDAI score by 2 or more units and one of the following: an ESR measurement no greater than 25 mm per hour, a CRP measurement no greater than 10 mg/L, or an ESR or CRP measurement reduced by at least 20% from baseline.
- 6.12 The trials did not report an outcome that fully aligned to the PBS continuation criteria but given all trials enrolled patients with a BASDAI score of ≥ 4 at baseline, a 50% improvement in the BASDAI (i.e. BASDAI50) corresponded to a reduction from baseline in the BASDAI score of ≥ 2 . The PBAC had considered ASAS20, ASAS40 and BASDAI50 as clinically relevant outcomes for assessing treatment response in AS, and were used to support non-inferiority (paragraph 12, adalimumab PSD November 2006 PBAC meeting; paragraph 12, golimumab PSD March 2010 PBAC meeting; paragraph 12, certolizumab pegol PSD March 2015 PBAC meeting; paragraph 6.27, ixekizumab PSD July 2020 PBAC meeting).
- 6.13 The submission presented indirect treatment comparisons between UPA 15 mg D and ADA 40 mg Q2W for ASAS20, ASAS40 and BASDAI50 at Week 12 to 16 using a standard frequentist approach (as described by Bucher et al 1997); and nominated a non-inferiority margin of 0.43 using the relative risk (RR) for ASAS20. The PBAC had considered the same non-inferiority margin in past decisions of treatments for AS (page 4, certolizumab pegol PSD March 2014 PBAC meeting; paragraph 6.7, secukinumab PSD March 2016 PBAC meeting, paragraph 6.27 ixekizumab PSD July 2020 PBAC meeting). The submission did not nominate a non-inferiority margin for either BASDAI50 or ASAS40, and the PBAC has not clearly stated an acceptable margin for these outcomes in past decisions.
- 6.14 Table 4 and Table 5 presents the results of the indirect comparisons for ASAS20/40 and BASDAI50 respectively. For the analysis, the submission combined available results across ADA trials using a random effects model. The analysis presented in the submission used results at Week 14 for UPA and Week 12 or 16 for ADA; results at Week 12 (where reported) were calculated during the evaluation and presented as sensitivity analyses below. For COAST-V, the ASAS20/40 response rates reported

differed slightly between the trial publication and clinical study report; the submission presented results from the publication and results from the clinical study report were calculated during the evaluation as another sensitivity analysis.

Table 4: ASAS20 and ASAS40 response in patients with AS (ITT)

Trial	Drug n/N (%)	Control n/N (%)	RR (95%CI)	RD (95%CI)	NNT (95%CI)
ASAS20					
COMPARISON: UPA 15mg D v PBO					
SELECT-AXIS 1 (n=187), Wk 14	60/93 (64.5)	38/94 (40.4)	1.60 (1.20, 2.13)	0.24 (0.10, 0.38)	4 (10,3)
SA: SELECT-AXIS 1 (n=187), Wk 12 [‡]	58/93 (62.4)	37/94 (39.4)	1.58 (1.18, 2.13)	0.23 (0.09, 0.37)	4 (11,3)
COMPARISON: ADA 40mg Q2W v PBO					
ATLAS (n=315), Wk 12	121/208 (58.2)	22/107 (20.6)	2.83 (1.92, 4.18)	0.38 (0.27, 0.48)	3 (4,2)
M03-606 (n=82), Wk 12	18/38 (47.4)	12/44 (27.3)	1.74 (0.97, 3.13)	0.20 (-0.01, 0.41)	-
Huang 2014 (n=344) [#] , Wk 12	154/229 (67.2)	35/115 (30.4)	2.21 (1.65, 2.96)	0.37 (0.26, 0.47)	3 (4,2)
COAST-V (n=177) [^] , Wk 16	53/90 (58.9)	35/87 (40.2)	1.46 (1.07, 1.99)	0.19 (0.04, 0.33)	5 (25,3)
SA: COAST-V (n=177) [^] , Wk 12 [§]	53/90 (58.9)	32/87 (36.8)	1.60 (1.16, 2.22)	0.22 (0.08, 0.36)	5 (13,3)
Meta-analysis (Wk 12/16)	346/565 (61.2)	104/353 (29.5)	2.00 (1.48, 2.72)	0.30 (0.21, 0.40)	3 (5,3)
SA: Meta-analysis (Wk 12)	346/565 (61.2)	101/353 (28.6)	2.06 (1.60, 2.67)	0.32 (0.23, 0.40)	3 (4,3)
ASAS40					
COMPARISON: UPA 15mg D v PBO					
SELECT-AXIS 1 (n=187), Wk 14	48/93 (51.6)	24/94 (25.5)	2.02 (1.36, 3.01)	0.26 (0.13, 0.40)	4 (8,3)
SA: SELECT-AXIS 1 (n=187), Wk 12 [‡]	47/93 (50.5)	13/94 (13.8)	3.65 (2.12, 6.29)	0.37 (0.24, 0.49)	3 (4,2)
COMPARISON: ADA 40mg Q2W v PBO					
ATLAS (n=315), Wk 12 (publication) ^b	83/208 (39.9)	14/107 (13.1)	3.05 (1.82, 5.11)	0.27 (0.18, 0.36)	4 (6,3)
SA: ATLAS (n=315), Wk 12 (CSR) ^{bθ}	85/208 (40.9)	15/107 (14.0)	2.92 (1.77, 4.79)	0.27 (0.17, 0.36)	4 (6,3)
M03-606 (n=82), Wk 12	17/38 (44.7)	4/44 (9.1)	4.92 (1.81, 13.36)	0.36 (0.18, 0.54)	3 (6,2)
Huang 2014 (n=344), Wk 12	102/229 (44.5)	11/115 (9.6)	4.66 (2.61, 8.32)	0.35 (0.27, 0.43)	3 (4,2)
COAST-V (n=177) [^] , Wk 16	32/90 (35.6)	16/87 (18.4)	1.93 (1.15, 3.26)^a	0.17 (0.04, 0.30)	6 (25,3)
SA: COAST-V (n=177) [^] , Wk 12 [§]	32/90 (35.6)	14/87 (16.1)	2.21 (1.27, 3.85)	0.19 (0.07, 0.32)	5 (14,3)
Meta-analysis (Wk 12/16)	234/565 (41.4)	45/353 (12.7)	3.19 (2.06, 4.94)	0.29 (0.21, 0.37)	3 (5,3)
SA: Meta-analysis (Wk 12/16, ATLAS CSR)	236/565 (41.8)	46/353 (13.0)	3.15 (2.04, 4.86)	0.29 (0.21, 0.37)	3 (5,3)
SA: Meta-analysis (Wk 12, ATLAS CSR)	236/565 (41.8)	44/353 (12.5)	3.25 (2.25, 4.68)	0.29 (0.22, 0.36)	3 (5,3)
Indirect comparisons					
PBS population with AS: ASAS20					
UPA (Wk 14) v ADA (Wk 12/16)			0.80 (0.53, 1.22)	-0.06 (-0.23, 0.11)	NA
SA: UPA (Wk 12) v ADA (Wk 12)			0.77 (0.52, 1.13)	-0.09 (-0.25, 0.07)	NA
PBS population with AS: ASAS40					
UPA (Wk 14) v ADA (Wk 12/16)			0.63 (0.35, 1.14)	-0.03 (-0.19, 0.13)	NA
SA: UPA (Wk 14) v ADA (Wk 12/16, ATLAS CSR)			0.64 (0.36, 1.16)	-0.03 (-0.19, 0.13)	NA
SA: UPA (Wk 12) v ADA (Wk 12, ATLAS CSR)			1.12 (0.58, 2.16)	0.08 (-0.06, 0.22)	NA

Abbreviations: ADA=adalimumab; AS=ankylosing spondylitis; ASAS20/40=20%/40% improvement in Assessment of SpondyloArthritis international Society response criteria; BASDAI= Bath ankylosing spondylitis disease activity index; ITT=intention to treat; PBO=placebo; SA=sensitivity analysis; UPA=upadacitinib; RD=risk difference; RR=relative risk; D=daily; Q2W=every 2 weeks; wk=week;

[^] 1 patient in PBO group was excluded due to allocation error, and not counted as completing Wk 16 study treatment nor discontinuing.

[#] Huang 2014 CSR reported that the primary efficacy analysis on ASAS20 was performed in which a proportion of patients enrolled in the study prior to 26 April 2010 were administered the BASDAI using an incorrect version of the VAS line for Question 6. Additional analysis performed using an algorithm to calculate a corrected score found that this "BASDAI-corrected" score also produced results (ADA 154/229 (67.2%) v 33/115 (28.7%)) consistent with those of the primary efficacy analysis.

[‡] Sensitivity analysis was conducted during the evaluation using ASAS20/40 response at Wk 12 for UPA v PBO derived from Table 14.2_2.1.1 and Table 14.2_14.1 of Attachment 2.1 SELECT-AXIS 1 UPA M16-098 CSR.

[§] Sensitivity analysis was conducted using ASAS20/40 response at Wk 12 for ADA v PBO estimated from Figure 2, p2446 and Figure 3, p2448 of Attachment 3.6 COAST-V van der Heijde 2018 main publication.

^θ Sensitivity analysis was conducted during the evaluation using ASAS40 reported in the CSR (Attachment 2.3 ATLAS M03-607 CSR).

^a The RR for ASAS40 in COAST-V was corrected during the evaluation. The submission presented analysis based on ADA 31/90 (34.4%) v PBO 15/87 (17.2%).

^b For ATLAS, a discrepancy was noted during the evaluation between the ASAS40 results presented in the submission based on the trial publication (van der Heijde 2006) and CSR (Attachment 2.3 ATLAS M03-607 CSR).

Source: Table 2.14, p76 and Table 2.20, p87 of the submission.

Table 5: BASDAI50 response in patients with AS (ITT)

Trial	Drug n/N (%)	Control n/N (%)	RR (95%CI)	RD (95%CI)	NNT (95%CI)
BASDAI50					
COMPARISON: UPA 15mg D v PBO					
SELECT-AXIS 1 (n=187), Wk 14	42/93 (45.2)	22/94 (23.4)	1.93 (1.26, 2.96)	0.22 (0.09, 0.35)	5 (11,3)
SA: SELECT-AXIS 1 (n=187), Wk 12 [‡]	38/93 (40.9)	17/94 (18.1)	2.26 (1.38, 3.71)	0.23 (0.10, 0.35)	4 (10,3)
COMPARISON: ADA 40mg Q2W v PBO					
ATLAS (n=315), Wk 12	94/208 (45.2)	17/107 (15.9)	2.84 (1.79, 4.51)	0.29 (0.20, 0.39)	3 (5,3)
M03-606 (n=82), Wk 12	14/38 (36.8)	6/44 (13.6)	2.70 (1.15, 6.34)	0.23 (0.05, 0.42)	4 (20,2)
Huang 2014 (n=344), Wk 12	114/229 (49.8)	19/115 (16.5)	3.01 (1.96, 4.64)	0.33 (0.24, 0.43)	3 (4,2)
DANISH (n=52), Wk 12	13/25 (52.0)	6/27 (22.2)	2.34 (1.05, 5.21)	0.30 (0.05, 0.55)	3 (20,2)
COAST-V (n=177) [^] , Wk 16	29/90 (32.2)	15/87 (17.2)	1.87 (1.08, 3.24)	0.15 (0.02, 0.27)	7 (50,4)
Meta-analysis	264/590 (44.7)	63/380 (16.6)	2.60 (2.03, 3.33)	0.27 (0.20, 0.34)	4 (5,3)
Indirect comparisons					
PBS population with AS: BASDAI50					
UPA (Wk 14) v ADA (Wk 12/16)			0.74 (0.45, 1.22)	-0.05 (-0.20, 0.10)	NA
SA: UPA (Wk 12) v ADA (Wk 12/16)			0.87 (0.50, 1.51)	-0.04 (-0.18, 0.10)	NA

Abbreviations: ADA=adalimumab; AS=ankylosing spondylitis; BASDAI(50)=50% improvement in Bath ankylosing spondylitis disease activity index; PBO=placebo; SA=sensitivity analysis; UPA=upadacitinib; RD=risk difference; RR=relative risk; D=daily; Q2W=every 2 weeks; wk=week;

[^] 1 patient in PBO group was excluded due to allocation error. The patient was not counted as completing Wk 16 study treatment nor discontinuing study treatment.

[‡] Sensitivity analysis was conducted during the evaluation using BASDAI50 response at Wk 12 for UPA v PBO derived from Table 14.2_6.1 of Attachment 2.1 SELECT-AXIS 1 UPA M16-098 CSR.

Source: Table 2.14, p76 and Table 2.20, p87 of the submission.

- 6.15 The trial results for ASAS20, ASAS40 and BASDAI50 response demonstrated that UPA 15 mg D and ADA 40 mg Q2W were more effective than placebo at producing a response to treatment in patients with AS at Week 14 and Weeks 12 to 16, respectively.
- 6.16 The indirect comparisons found that there was no statistically significant difference between UPA and ADA for ASAS20, ASAS40 and BASDAI50 at Weeks 12 to 16. The sensitivity analyses conducted during the evaluation at Week 12 found similar results. There was some variation in the placebo response rates for some outcomes within trials (e.g. for ASAS40, 13.8% at Week 12 vs 25.5% at Week 14 in SELECT-AXIS) and across trials (e.g. for ASAS20, 21% to 40% across the ADA trials). The reason for these variations was unknown but may be partially due to differences in the trial design. Overall, the placebo response rates (i.e. the common reference) within the indirect treatment comparisons were similar after controlling for the time point, particularly for ASAS40 and BASDAI50. The difference in placebo response rates was larger for ASAS20, but there was insufficient evidence to indicate that the transitivity assumption of the analysis was violated.
- 6.17 The submission concluded that UPA was non-inferior to ADA given the ASAS20 response met the nominated non-inferiority margin, given the RR for ASAS20 response included the value 1.00 and the lower bound of the 95%CI was greater than 0.43. With the exception of ASAS40 at Week 12, all point estimates for all outcomes and time points favoured ADA over UPA.

- 6.18 The submission also presented a series of indirect comparisons of UPA versus other PBS-listed bDMARDs including etanercept, golimumab, secukinumab, certolizumab, infliximab and ixekizumab (and non-PBS tofacitinib) for the treatment of AS. The results of these supportive comparisons found no statistically significant differences between UPA and any of the other bDMARDs in terms of ASAS20 or ASAS40 with one exception; infliximab was more likely to lead to ASAS20 response at Weeks 12-16 than UPA. All other comparisons met the nominated non-inferiority margin for ASAS20 but like the comparison to ADA, none of the point estimates favoured UPA.
- 6.19 Despite presenting results for these supportive comparisons, the submission did not present adequate data on the inputs of these analysis (i.e. the 20 trials) to allow for a thorough evaluation and critical appraisal of results. For example, the submission did not present the literature search, selection criteria, trial designs or patient characteristics. Hence, it was unclear whether all relevant trials had been included or whether the trials/patients were adequately similar for indirect comparison. There also appeared to be some discrepancies in the submission's approach for these supportive analyses. For example, the comparison versus ixekizumab excluded one trial previously considered by the PBAC comparing ixekizumab to placebo (COAST-W, NCT02696798), and a 'supportive' indirect comparison versus ADA for ASAS20 excluded one of the included trials in the primary indirect comparison presented above (M03-606).

Comparative harms

- 6.20 In SELECT-AXIS 1, the incidence of any AEs and drug-related AEs was higher in patients treated with UPA (Week 14) and ADA (Week 12-16) compared to placebo. The majority of AEs were mild to moderate in severity. Across the trials, the incidence of serious AEs and AEs leading to discontinuations were low. The most frequently reported AEs in SELECT-AXIS 1 were blood creatine phosphokinase elevation, diarrhoea and nasopharyngitis and in the ADA trials were nasopharyngitis, headaches and upper respiratory tract infection. In the ADA trials, higher incidence of injection site reactions was experienced by patients treated with ADA compared to placebo.
- 6.21 Table 6 presents the indirect comparison of the AEs in the safety population for AS for the double-blind period of the included trials using placebo as the common reference. The indirect comparison indicated that there was no statistically significant difference in any AEs, drug related AEs between UPA and ADA. The risk of AEs leading to discontinuations and any infections were numerically lower for UPA compared to ADA.

Table 6: Adverse events (AEs) in patients with AS during the double-blind period (ITT)

Trial	Drug n/N (%)	Control n/N (%)	RR (95%CI)	RD (95%CI)
Any AEs				
UPA 15mg D v PBO				
SELECT-AXIS 1 (n=187), Wk 14	58/93 (62.4)	52/94 (55.3)	1.13 (0.89, 1.43)	0.07 (-0.07, 0.21)
ADA 40mg Q2W v PBO				
ATLAS (n=315), Wk 12	140/208 (67.3)	61/107 (57.0)	1.18 (0.98, 1.43)	0.10 (-0.01, 0.22)
M03-606 (n=82), Wk 12	31/38 (81.6)	28/44 (63.6)	1.28 (0.98, 1.68)	0.18 (-0.01, 0.37)
Huang 2014 (n=344), Wk 12	81/229 (35.4)	26/115 (22.6)	1.56 (1.07, 2.29)	0.13 (0.03, 0.23)
COAST-V (n=177) [^] , Wk 16	44/90 (49.0)	34/86 (39.5)	1.24 (0.88, 1.73)	0.09 (-0.05, 0.24)
Meta-analysis (Wk 12/16)	296/565 (52.4)	149/352 (42.3)	1.25 (1.10, 1.43)	0.12 (0.06, 0.18)
Drug-related AEs				
UPA 15mg D v PBO				
SELECT-AXIS 1 (n=187), Wk 14	27/93 (29.0)	17/94 (18.1)	1.61 (0.94, 2.74)	0.11 (-0.01, 0.23)
ADA 40mg Q2W v PBO				
ATLAS (n=315), Wk 12	59/208 (28.4)	16/107 (15.0)	1.90 (1.15, 3.13)	0.13 (0.04, 0.23)
M03-606 (n=82), Wk 12	10/38 (26.3)	13/44 (29.5)	0.89 (0.44, 1.80)	-0.03 (-0.23, 0.16)
Huang 2014 (n=344), Wk 12	0	0	-	-
COAST-V (n=177) [^] , Wk 16	NR	NR	-	-
Meta-analysis (Wk 12/16)	69/475 (14.5)	29/266 (10.9)	1.35 (0.65, 2.84)	0.04 (-0.24, 0.31)
Discontinuations due to AEs				
UPA 15mg D v PBO				
SELECT-AXIS 1 (n=187), Wk 14	2/93 (2.2)	3/94 (3.2)	0.67 (0.12, 3.94)	-0.01 (-0.06, 0.04)
ADA 40mg Q2W v PBO				
ATLAS (n=315), Wk 12	2/208 (1.0)	2/107 (1.9)	0.51 (0.07, 3.60)	-0.01 (-0.04, 0.02)
M03-606 (n=82), Wk 12	0	0	-	-
Huang 2014 (n=344), Wk 12	4/229 (1.7)	0	4.54 (0.25, 83.59)	0.02 (-0.00, 0.04)
COAST-V (n=177) [^] , Wk 16	1/90 (1.1)	0	2.87 (0.12, 69.46)	0.01 (-0.02, 0.04)
Meta-analysis (Wk 12/16)	7/565 (1.2)	2/352 (0.6)	1.25 (0.29, 5.28)	0.01 (-0.01, 0.02)
Any infections				
UPA 15mg D v PBO				
SELECT-AXIS 1 (n=187), Wk 14	19/93 (20.4)	261/94 (27.7)	0.74 (0.44, 1.24)	-0.07 (-0.19, 0.05)
ADA 40mg Q2W v PBO				
ATLAS (n=315), Wk 12	46/208 (22.1)	20/107 (18.7)	1.18 (0.74, 1.89)	0.03 (-0.06, 0.13)
M03-606 (n=82), Wk 12	11/38 (28.9)	6/44 (13.6)	2.12 (0.87, 5.20)	0.15 (-0.02, 0.33)
Huang 2014 (n=344), Wk 12	25/229 (10.9)	12/115 (10.4)	1.05 (0.55, 2.01)	0.00 (-0.06, 0.07)
COAST-V (n=177) [^] , Wk 16	19/90 (21.1)	13/86 (15.1)	1.40 (0.74, 2.65)	0.06 (-0.05, 0.17)
Meta-analysis (Wk 12/16)	101/565 (17.9)	51/352 (14.5)	1.28 (0.94, 1.74)	0.03 (-0.01, 0.08)
Indirect comparisons				
Any AEs				
UPA (Wk 14) v ADA (Wk 12/16)			0.90 (0.69, 1.19)	-0.05 (-0.20, 0.10)
Drug-related AEs				
UPA (Wk 14) v ADA (Wk 12/16)			1.19 (0.48, 2.97)	0.07 (-0.23, 0.37)
Discontinuations due to AEs				
UPA (Wk 14) v ADA (Wk 12/16)			0.54 (0.06, 5.19)	-0.02 (-0.07, 0.03)
Any infections				
UPA (Wk 14) v ADA (Wk 12/16)			0.58 (0.32, 1.06)	-0.1 (-0.23, 0.03)

Abbreviations: ADA=adalimumab; AE=adverse event; AS=ankylosing spondylitis; ITT=intention to treat; n=number of participants; N=total participants in group; PBO=placebo; UPA=upadacitinib; RD=risk difference; RR=relative risk; D=daily; Q2W=every 2 weeks; wk=week;

[^] 1 patient in PBO group was excluded due to allocation error. The patient was not counted as completing Wk 16 study treatment nor discontinuing study treatment.

Source: Table 2.15 and Table 2.16 of the submission.

- 6.22 Overall, there were no notable differences in the number/type of AEs between groups and no deaths were reported. The safety outcomes reported in the trials were consistent with the known safety profile of UPA and the anticipated effects of JAK1 inhibitor treatment as described in the proposed PI. During the double blind treatment period, no major adverse cardiovascular events (including pulmonary embolism) and venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) were reported in SELECT-AXIS. The TGA Clinical Evaluation noted that in the long-term safety set of UPA in rheumatoid arthritis, a total of 2 fatal cases of pulmonary embolisms have been reported with UPA 15 mg.
- 6.23 Long-term safety data has raised concerns regarding thrombosis risk with JAK inhibitors. In the PBAC consideration of UPA for rheumatoid arthritis, it was noted that black box warnings were issued by the FDA for i) baricitinib that included a caution related to deep venous thrombosis, pulmonary embolism and arterial thrombosis; and for ii) tofacitinib due to an increased risk of thrombosis and mortality seen in the post-marketing study (paragraph 6.12, upadacitinib PSD November 2019 PBAC meeting). UPA (and other JAK inhibitors) are part of the TGA Black Triangle Scheme and subject to additional post-market surveillance in Australia.

Clinical claim

- 6.24 The submission described UPA as non-inferior in terms of effectiveness and non-inferior (or comparable) in terms of safety compared with ADA in patients with AS.
- 6.25 Overall the clinical claim was generally supported by the evidence presented in the submission. In terms of comparative effectiveness, the indirect comparison of ASAS20 met the nominated non-inferiority margin and there were no significant differences found for ASAS40 or BASDAI50 (for which the submission did not nominate a non-inferiority margin). The only caveat was that almost all point estimates across all outcomes favoured ADA (as well as other supplementary comparators) over UPA. In terms of comparative safety, there were no notable differences in safety outcomes between ADA and UPA presented in the submission. The PBAC has also previously considered that UPA has non-inferior safety to ADA in rheumatoid arthritis (paragraph 6.25, upadacitinib PSD November 2019 PBAC meeting).
- 6.26 The PBAC considered that, on balance, the claim of non-inferior comparative effectiveness to adalimumab was reasonable.
- 6.27 The PBAC considered that the claim of non-inferior comparative safety to adalimumab was reasonable.

Economic analysis

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

- UPA 15 mg once daily = ADA 40 mg every other week

6.29 The cost-minimisation analysis calculated drug costs over the first 2 years of treatment based on published AEMP of ADA for AS (\$979.56), assuming < 500 scripts of UPA and < 500 scripts of ADA.

Table 7: Results of the cost-minimisation analysis

Component	UPA 15 mg	ADA 40 mg
AEMP / pack	\$979.56	\$979.56
Dose	UPA 15 mg oral daily	ADA 40 mg SC injection every 2 weeks
Quantity / pack	28 x 15 mg tablets	2 x 40 mg injections
Scripts / 2 years	█ ¹	█ ¹
Total cost / 2 years	\$█ ²	\$█ ²

Abbreviations: ADA=adalimumab; UPA=upadacitinib;

Source: Tables 3.5 to 3.6, p99 of the submission.

The redacted values correspond to the following ranges:

¹ < 500

² \$0 to < \$10 million

6.30 The submission stated the published price of ADA used in the cost-minimisation analysis is a weighted price across multiple indications. The indication specific price of ADA for AS was unknown to the sponsor. The sponsor requested a SPA to maintain the current published price of UPA (DPMQ = \$1,271.34 as per the current PBS listing for rheumatoid arthritis) and implement a confidential effective price.

Drug cost/patient/year: \$█

6.31 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 \$█.

Estimated PBS usage & financial implications

6.32 This submission was not considered by the DUSC. The submission estimated the financial implications of the proposed listing using a market share approach, plus treatment of < 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.

6.33 For the market share approach, the submission assumed UPA would substitute for all currently PBS listed bDMARDs for AS, 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. This approach may not be an accurate method for estimated background market growth. For grandfathered patients, the analysis assumed 0% treatment failure over the first six years.

6.34 Table 8 summarises the key inputs in the financial estimates.

Table 8: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Current market of bDMARDs in AS	Yr0: ██████ ¹ scripts (aggregate); Scripts by product presented in Attachment 4. Yr0: ██████ ² patients (aggregate); Patient-years by product presented in Attachment 4. Source: Script numbers sourced from Medicare Australia statistics; -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 (i.e. year 0) and subsequent years (i.e. years 1 to 6). The submission implicitly assumed all scripts for each drug provided for 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 doses).
Script equivalence / substitution rate	Source: 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.	Reasonable 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, 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 (█████ ³) and grandfathered patients (█████ 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).
bDMARD aggregate market growth (without UPA), patient-years	Yr0: +█████ ⁴ patient-years per annum (proposed listing of UPA will not impact growth). Source: Average annual growth in patient-years from 2015 to 2019 (patient-years calculated as scripts divided by scripts/year/patient), where (█████ ³ + ██████ ³ + ██████ ⁴ + ██████ ⁴) / 4 = ██████ ⁴ .	Poorly justified given the current market does not appear to be completely established. Annual market growth increased from 3% to 27% between 2015 and 2019. In contrast, the assumed constant growth in patient-years corresponds to declining growth of ██████% to ██████% between Yr0 and Yr6 of the financial estimates.
bDMARD market share % (without UPA), patient-years	Source: Assumption ('commercial-in-confidence' estimates').	Poorly justified given the submission did not present any of the assumptions underpinning these estimates. The estimates imply ADA and GLM lost 4.7% and 1% of the market between 2019 and 2020 (Yr0), replaced largely by SEC and CZP.
bDMARD market growth % by product (without UPA), scripts	Source: Derived from the estimated market growth (aggregate patient-years) and market share (patient-years by product) assumptions.	The submission derived the annual change in the assumed market shares (in terms of patient-years), where Yr1 growth refers to change between Yr0 and Yr1 (E473:K478, '2d. Scripts – market'). For example, the submission used Yr1 growth rate to estimate change in scripts between Yr0 and Yr1, and Yr2 growth rate to estimate change in scripts between Yr1 and Yr2, and so on.
Displacement % of bDMARDs scripts for UPA	Source: Assumption ('commercial-in-confidence' estimates').	The submission assumed that UPA would displace treatment with ADA the most, followed by ETN/SEC/GLM and few displacements of IFX/CZP. The submission assumed the same displacement rates apply equally to initial and continuing scripts.
Drug cost / script	Source: 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

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Parameter	Value applied and source	Comment
		doses/script assumed in the script relativities, and do not take into account DPMQs which provide 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: ADA=adalimumab; AS=ankylosing spondylitis; bDMARD=biologic disease modifying anti-rheumatic drug; CZP=certolizumab pegol; ETN=etanercept; GLM=golimumab; IFX=infliximab; SEC=secukinumab; UPA=upadacitinib; Yr=year;

Source: Constructed during the evaluation from pp101-108 of the submission, and parameters in the excel spreadsheet (Attachment 8.1 UCM_AnkylosingSpondylitis Workbook.xlsx2).

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

6.35 Table 9 summarises the estimated net financial implications to the PBS/RPBS for the proposed listing of UPA for AS over the first six years (assumed as 2021 to 2026).

Table 9: 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	1	2	3	3	4	4
Non-grandfather patients	1	1	2	3	4	4
Grandfathered patients	1	1	1	1	1	1
Net cost PBS/RPBS, UPA	\$ 5	\$ 5	\$ 6	\$ 7	\$ 7	\$ 8
Non-grandfather patients	\$ 5	\$ 5	\$ 6	\$ 7	\$ 7	\$ 7
Grandfathered patients	\$ 5	\$ 5	\$ 5	\$ 5	\$ 5	\$ 5
Estimation of changes in use and financial impact of bDMARDs[^]						
bDMARD scripts	1	1	2	3	4	4
ADA	9	1	2	2	3	3
ETN	9	1	1	1	1	1
IFX	9	9	9	9	9	9
CZP	9	9	9	1	1	1
SEC	9	9	1	1	1	1
GLM	9	1	1	1	1	1
Net cost PBS/RPBS, bDMARDs	-\$ 5	-\$ 5	-\$ 6	-\$ 6	-\$ 7	-\$ 7
Estimated financial implications for the PBS/RPBS and the health budget						
Net change in scripts	1	1	1	1	1	1
Net change in authorities	9	9	9	9	9	9
Written	9	9	9	9	9	9
Net cost PBS/RPBS, proposed listing	\$ 5	\$ 5	\$ 5	\$ 5	\$ 5	\$ 5
Grandfathered patients	\$ 5	\$ 5	\$ 5	\$ 5	\$ 5	\$ 5
Non-grandfather patients	\$ 5	\$ 5	\$ 5	\$ 5	\$ 5	\$ 5

Abbreviations: ADA=adalimumab; AS=ankylosing spondylitis; bDMARD=biologic disease modifying anti-rheumatic drug; CZP=certolizumab pegol; ETN=etanercept; GLM=golimumab; IFX=infliximab; SEC=secukinumab; UPA=upadacitinib; Yr=year;

[^] The financial estimates do not consider the potential change in the market share from ixekizumab which was recommended for listing on the PBS for AS in July 2020 PBAC meeting.

Source: Tables 4.9-4.11, pp108-109 of the submission.

The redacted values correspond to the following ranges:

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

6.36 The submission made a number of assumptions to simplify the calculations which impact on the accuracy of the financial 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 potentially captures patients that will be in the future Patient Familiarisation Scheme.

- 6.37 The estimated net cost to the PBS/RPBS of approximately \$20 million to < \$30 million over the first six years of listing was likely an overestimate, driven by the assumed published prices and grandfathered patients. 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 be expected to have negligible financial impact on the PBS/RPBS.

Quality Use of Medicines

- 6.38 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 adults with ankylosing spondylitis (AS). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of UPA would be acceptable if it were cost minimised to the least costly biologic disease modifying anti-rheumatic drug (bDMARD) for this indication. The PBAC noted there were seven biologics listed on the PBS for severe AS and UPA was the first janus kinase (JAK) inhibitor and oral agent for this indication.
- 7.2 The PBAC considered the nominated comparator of ADA was reasonable, however considered all other bDMARDs currently listed for AS 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 submission presented an indirect comparison of UPA and ADA based on 6 clinical trials (one trial of UPA v placebo and five of ADA v placebo). The PBAC considered the non-inferiority margin of 0.43 was reasonable and consistent with its previous considerations of bDMARDs for AS. The PBAC considered that, whilst most point estimates for ASAS20, ASAS40 and BASDAI50 outcomes favoured ADA, based on the evidence presented, a claim of non-inferior comparative effectiveness of UPA to ADA was reasonable.
- 7.4 The PBAC also noted the safety outcomes reported in the trial were consistent with the established profile of UPA (and JAK inhibitors more broadly) and also noted overall there were no notable differences in the number or type of AEs between groups. The

PBAC noted that while no major adverse cardiovascular events or venous thromboembolic events were reported in the SELECT-AXIS trial, there were emerging signals of 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 AS should be aligned with other bDMARD listings where appropriate 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 AS 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 Under section 101(3BA) of the *National Health Act 1953*, the PBAC advised that UPA and the other bDMARDs including adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab and secukinumab should be treated as interchangeable on an individual patient basis for the treatment of AS.
- 7.8 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.
- 7.9 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 (based on existing adalimumab restrictions under 9103D/9104E for AS)

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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 9530 / ToC: 9503: Authority Required	Initial 1
Restriction Summary 9412 / ToC: 9414: Authority Required	Initial 2
Restriction Summary 9427 / ToC: 9428: Authority Required	Initial 3
Restriction Summary 9535 / ToC: 9429: 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 9508 / ToC: 9430: Authority Required	Continuing treatment
Restriction Summary 9415 / ToC: 9431: Authority Required	Continuing treatment – balance of supply
Restriction Summary NEW / ToC: NEW: Authority Required	Grandfather treatment

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type / Method: <input checked="" type="checkbox"/> Authority Required - In Writing
Administrative Advice: TREATMENT OF ADULT PATIENTS WITH ANKYLOSING SPONDYLITIS
Administrative Advice: Special Pricing Arrangements apply.
Indication: Ankylosing spondylitis
Treatment phase: Transitioning from non-PBS to PBS-subsidised supply - 'Grandfather' arrangements
Clinical criteria:
Patient must have received treatment with this drug for this indication prior to [listing date],
AND
Clinical criteria:
The condition must be radiographically (plain X-ray) confirmed Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis,
AND
Clinical criteria:
Patient must have had at least 2 of the following prior to initiating treatment with this drug for this condition: (i) low back pain and stiffness for 3 or more months that is relieved by exercise but not by rest; or (ii) limitation of motion of the lumbar spine in the sagittal and the frontal planes as determined by a score of at least 1 on each of the lumbar flexion and lumbar side flexion measurements of the Bath Ankylosing Spondylitis Metrology Index (BASMI); or (iii) limitation of chest expansion relative to normal values for age and gender,
AND
Clinical criteria:

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Patient must have had failed to achieve an adequate response following treatment with at least 2 non-steroidal anti-inflammatory drugs (NSAIDs), whilst completing an appropriate exercise program, for a total 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.
Treatment criteria:
Must be treated by a rheumatologist; OR
Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis.
Prescriber Instructions: The application must include details of the NSAIDs trialled, their doses and duration of treatment. If the NSAID dose is less than the maximum recommended dose in the relevant TGA-approved Product Information, the application must include the reason a higher dose cannot be used. If treatment with NSAIDs is contraindicated according to the relevant TGA-approved Product Information, the application must provide details of the contraindication. If intolerance to NSAID treatment develops during the relevant period of use which is of a severity to necessitate permanent treatment withdrawal, the application must provide details of the nature and severity of this intolerance.
Prescriber Instructions The following criteria indicate failure to achieve an adequate response to NSAIDs and must have been demonstrated prior to initiation of non-PBS subsidised treatment with this biological medicine for this condition: (a) a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of at least 4 on a 0-10 scale; and (b) an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour or a C-reactive protein (CRP) level greater than 10 mg per L. The BASDAI must have been determined at the completion of the 3 month NSAID and exercise trial, but prior to ceasing NSAID treatment. If the above requirement to demonstrate an elevated ESR or CRP could not be met, the application must state the reason this criterion could not be satisfied. Treatment with prednisolone dosed at 7.5 mg or higher daily (or equivalent) or a parenteral steroid within the preceding 4 weeks (intramuscular or intravenous methylprednisolone or equivalent) is an acceptable reason.
Prescriber Instructions The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Ankylosing Spondylitis PBS Authority Application Form which includes the following: (i) details of the radiological report confirming Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis; and (ii) a baseline BASDAI score; and (iii) a completed Exercise Program Self Certification Form included in the supporting information form; and (iv) baseline ESR and/or CRP level
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.
Administrative Advice

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Details of the toxicities, including severity, which will be accepted for the purposes of administering this restriction can be found on the Services Australia website at www.servicesaustralia.gov.au
Administrative Advice For details on the appropriate minimum exercise program that will be accepted for the purposes of administering this restriction, please refer to the Services Australia website at www.servicesaustralia.gov.au
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 [26621]:

TREATMENT OF ADULT PATIENTS WITH ANKYLOSING SPONDYLITIS

The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, ~~and~~ secukinumab *and upadacitinib* for adult patients with ankylosing spondylitis.

Where the term 'biological medicine' appears in notes and restrictions, it refers to adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, ~~and~~ secukinumab *and upadacitinib* only.

A patient is eligible for PBS-subsidised treatment with only 1 of the ~~78~~ biological medicines at any 1 time.

Under these arrangements, within a single treatment cycle, a patient may continue to receive long-term treatment with a biological medicine while they continue to show a response to therapy.

A patient who has been receiving PBS-subsidised adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab and secukinumab treatment prior to ~~4 December 2020~~ [PBS Listing Date] is considered to start their first cycle as of ~~4 December 2020~~ [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.

Once a patient has either failed or ceased to respond to treatment 3 times, they are deemed to have completed a treatment cycle and they must have, at a minimum, a 5-year break in PBS-subsidised biological medicine therapy before they are eligible to commence the next cycle. The 5-year break is measured from the date of the last prescription for PBS-subsidised biological medicine treatment in the most recent cycle to the date of the first application for initial treatment with a biological medicine under the new treatment cycle.

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.

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.

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

(1) How to prescribe PBS-subsidised biological medicine treatment with adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, ~~and~~ secukinumab *and upadacitinib*.

(a) Initial treatment.

Applications for initial treatment should be made where:

(i) a patient has received no prior PBS-subsidised biological medicine treatment in this treatment cycle and wishes to commence such therapy (Initial 1 - New patient)

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(ii) a patient has received prior PBS-subsidised (initial or continuing) biological medicine therapy and wishes to trial an alternate agent (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 agent (Initial 2 - Change or Recommencement of treatment after a break in therapy of less than 5 years); or

(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).

A patient must be assessed for response to a course of initial PBS-subsidised treatment following a minimum of 12 weeks of therapy.

Grandfather patients (upadacitinib only)

A patient who commenced treatment with upadacitinib for ankylosing spondylitis 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.

(b) Continuing treatment.

~~For the first continuing treatment course of PBS-subsidised biological medicine, it is recommended that a patient is reviewed for response following a minimum of 12 weeks of therapy under the Initial 1, Initial 2 or Initial 3 treatment restrictions. For second and subsequent continuing courses of PBS-subsidised biological medicine it is recommended that a patient be reviewed the month prior to completing their current course of treatment to ensure uninterrupted biological medicine supply.~~

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.

Assessment of the patient's response to treatment must be conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from the cessation of the most recent course of biological medicine therapy. Where a response assessment is not conducted within the required timeframe, 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.

(2) Swapping therapy.

Once initial treatment with the first PBS-subsidised biological medicine is approved, a patient may swap to an alternate biological medicine within the same treatment cycle without having to requalify with respect to the indices of disease severity (i.e. the erythrocyte sedimentation rate (ESR), the C-reactive protein (CRP) levels and the BASDAI), or the prior NSAID therapy and exercise program requirements.

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.

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.

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.

(3) Baseline measurements to determine response.

~~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 BASDAI, ESR and/or CRP submitted with the first authority application for a biological medicine.

For a new patient, the BASDAI used to determine the baseline must be measured while the patient is receiving NSAID therapy and completing their exercise program.

To ensure consistency in determining response, the same indices of disease severity used to establish baseline must be used for all subsequent continuing treatment applications. Therefore, where only an ESR or CRP level is provided at baseline, an ESR or CRP level respectively must be used to determine response.

Prescribers may provide new baseline measurements any time an 'Initial treatment' authority application is submitted within a treatment cycle and the eligibility for continuing treatment must be assessed according to these revised baseline measurements.

(4) Recommencement 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 medicine therapy of at least 5 years, must qualify under the Initial 3 treatment restriction. The same clinical criteria and indices of disease severity (i.e. the erythrocyte sedimentation rate (ESR), the C-reactive protein (CRP) levels and the BASDAI) as for the Initial 1 (New patient) restriction will need to be met, but a re-trial of NSAID therapy and exercise therapy is not required.

Flow-on changes to Administrative Advice [26621] to the following:

Adalimumab: 9103D, 9104E, 9077R, 9078T

Certolizumab: 10137M, 10904X, 10897M, 11320T, 11318Q, 11319R.

Etanercept: 8778B, 8779C, 9085E, 9086F, 9455P, 9456Q, 11204Q, 11201M, 11196G, 11215G, 11217J.

Golimumab: 3434R, 3436W, 11361Y, 11376R.

Infliximab: 5753T, 6448J, 11486M, 11488P, 11482H, 11489Q.

Secukinumab: 10893H, 10906B, 10890E.

Ixekizumab: 12209N, 12217B.

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.