

## 6.04 TOFACITINIB, Tablet 5 mg, Xeljanz<sup>®</sup>, Pfizer Australia Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule, Authority Required (in writing) listing for tofacitinib for the treatment of ankylosing spondylitis (AS).
- 1.2 Listing was requested on the basis of a cost-minimisation approach versus adalimumab, with a secondary comparison with upadacitinib.

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

Component	Description
Population	Patients with 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.
Intervention	Tofacitinib 5 mg orally twice daily
Comparator	Primary: adalimumab 40 mg by subcutaneous injection every two weeks Secondary: upadacitinib 15 mg orally once daily
Outcomes	Primary: ASAS20 Secondary: ASAS40, BASDAI50 Safety
Clinical claim	Tofacitinib is non-inferior to adalimumab and upadacitinib in terms of efficacy in patients with active AS for whom an adequate response has not been achieved with NSAIDs Tofacitinib is non-inferior to upadacitinib and is comparable to adalimumab in terms of safety.

Source: Table 1.1.1, p3 of the submission.

AS = ankylosing spondylitis; NSAID = non-steroidal anti-inflammatory drug; ASAS20/40 = assessment of spondyloarthritis international society 20%/40% response criteria; BASDAI50 = 50% improvement in Bath ankylosing spondylitis disease activity index

### 2 Background

#### **Registration status**

- 2.1 TGA registration for the ankylosing spondylitis indication was finalised on 25 January 2023. In the Pre-Sub-Committee Response (PSCR), the Sponsor advised the Australian registered indication for TOF for AS was:
- ‘Xeljanz (tofacitinib) is indicated for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy.’
- 2.2 The approved US FDA indication restricts use to patients who have failed treatment with or cannot be given a tumour necrosis factor- $\alpha$  (TNF) inhibitor, because of concerns about the safety of tofacitinib. The EMA updated the regulatory advice for all JAK inhibitors to include a note that these medicines should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years

or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer.

- 2.3 The PSCR stated the European Pharmacological Risk Assessment Committee (PRAC) considered the results of the safety signals identified in the long-term safety study (Study A3921133/ORAL Surveillance, discussed further in the ‘Comparative Harms’ section) to be a class effect, with recommendations and warnings to be implemented for all JAK inhibitors. The PSCR also stated that whilst updates to the Australian Product Information(s) are not finalised, it is the Sponsor’s understanding the TGA also considers these results to be a JAK inhibitor class effect, and noted the Pharmacovigilance Branch of the TGA has conducted a post-market safety assessment of JAK inhibitors and is currently liaising with relevant sponsors about updating their respective product information documents.

### Previous PBAC consideration

- 2.4 Tofacitinib has not previously been considered for listing for AS, but is currently PBS listed for rheumatoid arthritis (RA) (listed October 2015), psoriatic arthritis (PsA) (listed April 2019) and moderate to severe ulcerative colitis (MSUC) (listed July 2021).

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

## 3 Requested listing

- 3.1 The essential elements of the requested listing and an abridged proposed restriction are presented below.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
TOFACITINIB					
Tofacitinib 5 mg tablet, 56 (initial)	\$1,211.08 published price \$ [REDACTED] effective price	1	56	3	Xeljanz
Tofacitinib 5 mg tablet, 56 (continuing)	\$1,211.08 published price \$ [REDACTED] effective price	1	56	5	Xeljanz
<b>Category / Program:</b>	GENERAL – General Schedule (Code GE)				
<b>Prescriber type:</b>	<input checked="" type="checkbox"/> Medical Practitioners				
<b>Severity:</b>					
<b>Condition:</b>	Ankylosing spondylitis				
<b>PBS Indication:</b>	Ankylosing spondylitis				
<b>Treatment phase:</b>	<b>Initial treatment 1 (new patient)</b>				
<b>Restriction:</b>	<input checked="" type="checkbox"/> Authority Required – In Writing				
<b>Treatment criteria:</b>	Must be treated by a rheumatologist; or Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis				
<b>Clinical criteria:</b>	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				

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	<p>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</p>
<b>Population criteria:</b>	Patient must be at least 18 years of age.
<b>Prescriber Instructions:</b>	<p>The application must include details of the NSAIDs trialled, their doses and duration of treatment.</p> <p>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.</p> <p>The following criteria indicate failure to achieve an adequate response and must be demonstrated at the time of the initial application:            (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.</p> <p>The baseline BASDAI score and ESR or CRP level must be determined at the completion of the 3 month NSAID and exercise trial, but prior to ceasing NSAID treatment. All measurements must be no more than 4 weeks old at the time of initial application.            If the above requirement to demonstrate an elevated ESR or CRP cannot be met, the application must state the reason this criterion cannot be satisfied.</p> <p>The authority application must be made in writing and must include:</p> <p>(1) a completed authority prescription form; and            (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) 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.</p> <p>An assessment of a patient's response to this initial course of treatment must be conducted following a minimum of 12 weeks of therapy and no later than 4 weeks prior the completion of this course of treatment.            An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from the date of completion of the most recent course of treatment.</p>

<b>Treatment phase:</b>	<b>Continuing treatment</b>
<b>Restriction:</b>	<input checked="" type="checkbox"/> Authority Required - In Writing
<b>Treatment criteria:</b>	Must be treated by a rheumatologist OR undergoing treatment under the supervision of a paediatric rheumatology treatment centre.
<b>Clinical criteria:</b>	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 per continuing treatment course authorised under this restriction.
<b>Prescriber Instructions:</b>	An adequate response is defined as an improvement from baseline of at least 2 units (on a scale of 0-10) in the BASDAI score combined with at least 1 of the following:  (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.  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.

3.2 The submission requested a Special Pricing Arrangement. The submission noted that four products on the PBS for AS have such arrangements.

3.3 The submission proposed restrictions for initial and continuing treatment as well as a grandfathering restriction for approximately 150 patients to continue treatment. The restriction details were proposed to be consistent with other biologic products for AS (See Section 8 'Recommended listing' for more detail).

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

## 4 Population and disease

4.1 AS is a subtype of spondyloarthritis (SpA), an umbrella term that encompasses several chronic rheumatic disorders that share similar clinical features. The disease is characterised by pain and stiffness in the spine and neck, progressive spinal rigidity, and inflammation of the hips, shoulders, peripheral joints and fingers/toes which can result in serious impairment of spinal mobility and reduced quality of life (QoL).

4.2 There are eight medicines available on the PBS for AS patients who demonstrate an inadequate response to NSAIDs and an exercise program. The most recent listing is upadacitinib, which was recommended for listing by the PBAC on a cost minimisation basis to adalimumab in March 2021.

4.3 The clinical management algorithms were based on the current PBS restrictions for the other molecules that are currently PBS listed for AS and were also guided by APLAR, EULAR and ACR recommendations.

4.4 The key factors presented in the submission for the rationale for PBS listing were to provide an additional choice of oral treatment for the management of AS, with

upadacitinib as the only other oral treatment currently listed for use after failing NSAID treatment (and meeting other eligibility criteria).

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

## **5 Comparator**

- 5.1 The submission nominated adalimumab as the comparator, as it is the most commonly prescribed product for AS, and has previously been accepted by the PBAC as the comparator for upadacitinib as well as for ixekizumab (July 2020). The submission also presented a secondary comparison with upadacitinib, as tofacitinib is of the same pharmacological class. These comparators were appropriate.
- 5.2 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. The alternative therapies include adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, ixekizumab, secukinumab and upadacitinib.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the results of the ORAL Surveillance study (see 'Clinical trials' and 'Long-term safety data' sections). In interpreting the results, the clinician stated the risk of cardiovascular events were higher in both the tofacitinib and tumour necrosis factor alfa (TNF) inhibitor group in the over 65 years old cohort, and stratifying the results by current smoker status, this also conferred increased cardiovascular risk across study groups. Overall, the clinician stated that given the ORAL Surveillance study was undertaken in particular subgroups, the results should not be considered representative of the Australian AS population.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments from the individual outlined the patient experience of living with AS, the practical challenges of using the injected therapies, including the need for dexterity to self-administer and the need to refrigerate these agents, and described the safety profile of tofacitinib as manageable.
- 6.3 The PBAC noted the advice received from Musculoskeletal Australia, which described

the burden of AS on everyday life, and highlighted the benefits of oral treatment options for patients. The advice also noted that due to the high cost and storage requirements of the injectable AS treatments to pharmacies, these are often not held in stock and patients experience delays getting prescriptions filled, which can lead to flaring of symptoms.

### **Clinical trials**

- 6.4 The submission was based on a series of indirect comparisons based on seven RCTs: there were two trials of tofacitinib vs. placebo and five trials of adalimumab vs. placebo. For the secondary comparison with upadacitinib there was one trial of upadacitinib vs. placebo.
- 6.5 Details of the trials presented in the submission are provided in Table 2.
- 6.6 A claim of non-inferiority was made on the outcomes of change in scores on the Assessment in Ankylosing Spondylitis Scale (ASAS) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
- 6.7 The outcomes used in the comparisons were ASAS20 and ASAS40. ASAS20 was defined as at least 20% improvement and an absolute improvement of at least one unit on a numerical rating scale of 0–10 from baseline in at least three of the following four domains, with no worsening in the remaining domain: patient global assessment of disease activity, patient assessment of back pain, Bath Ankylosing Spondylitis Functional Index (BASFI), and inflammation defined as the mean of the BASDAI questions on severity and duration of morning stiffness.
- 6.8 ASAS40 was defined as at least 40% improvement and an absolute improvement of at least two units on a numerical rating scale of 0–10 from baseline in at least three of the four domains, with no worsening in the remaining domain. BASDAI50 was defined as Improvement of at least 50 % in the BASDAI score or an absolute change of 2 units (on a 0 to 10 scale) after at least 3 months of treatment, together with an expert opinion compatible with improvement.
- 6.9 These outcomes have previously been accepted by the PBAC. PBS criteria require patients for initial treatment to demonstrate an inadequate 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.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Tofacitinib vs. placebo</b>		
Study A3921120 NCT03502616	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Study of the Efficacy and Safety of Tofacitinib in Subjects with Active Ankylosing Spondylitis (AS) Deodhar, A., Sliwinska-Stanczyk, P., Xu, H., et al. Tofacitinib for the treatment of ankylosing spondylitis: a phase III, randomised, double-blind, placebo-controlled study. Navarro-Compan, V., Wei, J.C.C., Van Den Bosch, F., et al. Effect of tofacitinib on patient-reported outcomes in patients with active ankylosing spondylitis: Results from a phase 3 trial. <i>Annals of the Rheumatic Diseases</i> .	April 2019  Ann Rheum Dis 2021; 80:1004–1013.  European Congress of Rheumatology, EULAR 2021. Virtual. 80(Suppl 1) (pp 704)
Study A3921119 NCT01786668	A Phase 2, Randomized, Double-Blind, Placebo- Controlled, Dose-Ranging Study of the Efficacy and Safety of Tofacitinib in Subjects with Active Ankylosing Spondylitis (AS) van der Heijde, A., Deodhar, A., Wei, J. C., et al. Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. Maksymowych, W.P., Van Der Heijde, D., Baraliakos, X., et al. Tofacitinib treatment is associated with attainment of the minimally important reduction in axial MRI inflammation in patients with ankylosing spondylitis. <i>Annals of the Rheumatic Diseases</i> .	April 2013  Ann Rheum Dis 2017;76: 1340–1347.  Annual European Congress of Rheumatology, EULAR 2017. Madrid Spain. 76(Supplement 2) (pp 337).
<b>Adalimumab vs. placebo</b>		
ATLAS NCT00085644	Van Der Heijde, D., Kivitz, A., Schiff, M.H., et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: Results of a multicenter, randomised, double-blind, placebo-controlled trial. Van Der Heijde, D., Revicki, D. A., Gooch, K.L., et al. Physical function, disease activity, and health-related quality-of-life outcomes after 3 years of adalimumab treatment in patients with ankylosing spondylitis. Davis, J.C., Revicki D., van der Heijde, D., et al. Health-related quality of life outcomes in patients with active ankylosing spondylitis treated with adalimumab: results from a randomized controlled study. Van Der Heijde, D., Schiff, M. H., Sieper, J., et al Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. Scott D.G., Van Der Heijde D., Schiff M.H., et al. Improvement in long-term spinal mobility in patients with ankylosing spondylitis (AS) is sustained during up to 3 years of adalimumab treatment: 3-Year atlas results. Revicki, D.A.; Luo, M.P.; Wordsworth, P., et al. Adalimumab reduces pain, fatigue, and stiffness in patients with ankylosing spondylitis: results from the adalimumab trial evaluating long-term safety and efficacy for ankylosing spondylitis (ATLAS).	Arthritis Rheum 2006; 54(7): 2136-2146  Arthritis Res Ther 2009, 11(4):R124  Arthritis Rheum 2007, 57 (6): 1050–1057  Ann Rheum Dis 2009; 68:922–929.  BSR and BHPR Annual Meetings 2009, 48 (Suppl.1) (pp i56)  J Rheumatol. 2008 35(7):1346-53
M03-606 NCT00195819	Lambert, R.G.W., Salonen, D., Rahman, P., et al. Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: A multicenter, randomised, double-blind, placebo-controlled study.	Arthritis Rheum 2007; 56(12): 4005-4014
Huang 2014 NCT01114880	Huang, F., Gu, J., Zhu, P., Bao, C., et al. Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: Results of a randomised, controlled trial.	Ann Rheum Dis 2014; 73(3): 587-594
DANISH NCT00477893	Pedersen, S.J., Poddubnyy, D., Sørensen, I.J., et al. 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	Arthritis Rheumatol 2016; 68(2): 418-429

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Trial ID	Protocol title/ Publication title	Publication citation
	assessed by the Berlin and Spondyloarthritis Research Consortium of Canada methods.	
COAST-V NCT02696785	van der Heijde, D., Cheng-Chung Wei, J., Dougados, M., 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.	Lancet 2018; 392(10163): 2441-2451
<b>Upadacitinib vs. placebo</b>		
SELECT-AXIS 1 NCT03178487	<p>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.</p> <p>Deodhar, A., van der Heijde, D., Sieper, J., et al. Safety and efficacy of upadacitinib in patients with active ankylosing spondylitis and an inadequate response to nonsteroidal antiinflammatory drug therapy: one-year results of a double-blind, placebo-controlled study and open-label extension.</p> <p>van der Heijde D., Deodhar A., Maksymowych, W., et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis: 2-year results from a randomized, double-blind, placebo-controlled study with open-label extension.</p> <p>Van den Bosch, F., Poddubnyy, D., Stigler J., et al. Influence of baseline demographics on improvements in disease activity measures in patients with ankylosing spondylitis receiving upadacitinib: A post hoc subgroup analysis (abstract).</p>	<p>Lancet 2019; 394: 2108–2117</p> <p>Arthritis Rheumatol 2022, Vol. 74 (1): 70–80</p> <p>Arthritis Rheumatol 2021; 73 (Suppl 9): 1925-1928</p> <p>Arthritis Rheumatol 2021; 73 (Suppl 9): 1914-1916</p>

Source: Table 2.2.1, pp33-35 of the submission.

6.10 The key features of the randomised trials are summarised in Table 3.

**Table 3: Key features of the included evidence – indirect comparisons**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
<b>Tofacitinib vs. placebo</b>					
A3921119	52 TOF 52 placebo	R, DB, dose ranging (TOF 2, 5, 10 mg bd), 12 wk	Low	AS by mNY, $\geq 18$ , active disease despite NSAID	ASAS20 at 12 wk
A3921120	270	R, DB, TOF 5 mg bd, 16 wk	Low	AS by mNY, $\geq 18$ , active disease despite NSAID	ASAS20 at 16 wk
<b>Adalimumab vs. placebo</b>					
ATLAS	311	R, DB, 12 wk, ADA 40 mg sci q2wk; 2:1 ADA vs placebo	Low	AS by mNY, $\geq 18$ , active disease despite NSAID, bDMARD naive	ASAS20 at 12 wk; mean change in mSASSS
M03-606	82	R, DB, 12 wk, ADA 40 mg sci q2wk	Low	AS by mNY, $\geq 18$ , active disease despite NSAID, bDMARD naive	ASAS20 at 12 wk
Huang 2014	344	R, DB, 12 wk, ADA 40 mg sci q2wk; 2:1 ADA vs placebo	Low	AS by mNY, $\geq 18$ , active disease despite NSAID, bDMARD naive	ASAS20 at 12 wk
DANISH	52	R, DB, 12 wk, ADA 40 mg sci q2wk	Low	AS by ESSG, $\geq 18$ , active disease despite NSAID, bDMARD naive	BASDAI50 at 12 wk
COAST-V	90 ADA 87 placebo	R, DB, 16 wk, ixekizumab 80 mg q2wk or q4wk, ADA 40 mg sci q2wk	Unclear <sup>a</sup>	AS by mNY, $\geq 18$ , active disease despite NSAID, bDMARD naive	ASAS40 at 16 wk
<b>Upadacitinib vs. placebo</b>					
SELECT-AXIS 1	187	R, DB, 14 wk, UPA 15 mg daily	Low	AS by mNY, $\geq 18$ , active disease despite $\geq 2$ NSAID, bDMARD and JAK inhibitor naive	ASAS40 at 14 wk

Source: Table 2.2.2, pp39-40; Table 2.3.1, Appendix A of the submission.

ADA = adalimumab; AS = ankylosing spondylitis; ASAS = Assessment in Ankylosing Spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; bd = twice daily; bDMARD = biological disease-modifying anti-rheumatic drug; DB = double blind; ESSG = European Spondyloarthritis Study Group; JAK = Janus kinase; mNY = modified New York criteria; mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score; NSAID = nonsteroidal anti-inflammatory drug; q2wk = once every two weeks; q4wk = once every 4 weeks; R = randomized; SC = subcutaneous; TOF = tofacitinib; UPA = upadacitinib; wk = week.

<sup>a</sup> It was noted in the July 2020 PBAC meeting that COAST-V trial had several protocol deviations (paragraph 6.5 (Table 3), ixekizumab Public Summary Document (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).

- 6.11 Overall, the risk of bias in the trials was low, except in COAST-V, as previously noted by the PBAC in its considerations of upadacitinib and ixekizumab.
- 6.12 The doses of the drugs used in the trials were: tofacitinib 5 mg bd (Study A3921120) and 2 mg or 5 mg or 10 mg bd (Study A3921119); adalimumab 40 mg Q2W; upadacitinib 15 mg QD. Only data for the 5 mg bd dose in Study A3921119 were used in the submission.

## **Comparative effectiveness**

### **Indirect comparison - adalimumab**

- 6.13 The results of the indirect treatment comparisons are presented in

6.14 Table 4, Table 5 and Table 6. The submission nominated a non-inferiority margin only for ASAS20: a lower bound of the 95% CI of the relative risk greater than 0.43. The submission noted that this non-inferiority margin has been used in submissions for other medicines for AS, such as ixekizumab, considered by the PBAC in July 2020.

**Table 4: ASAS20 at week 12/16 (double-blind period) - indirect comparison**

Comparison	Trial ID	Tofacitinib or adalimumab n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)
Tofacitinib vs. placebo	A3921119	42/52 (80.8)	21/51 (41.2)	<b>6.00 (2.47, 14.57)</b>	<b>1.96 (1.38, 2.79)</b>
	A3921120	75/133 (56.4)	40/136 (29.4)	<b>3.10 (1.88, 5.13)</b>	<b>1.92 (1.42, 2.59)</b>
	Pooled	117/185 (63.2)	61/187 (32.6)	<b>3.88 (2.11, 7.16)</b>	<b>1.94 (1.54, 2.43)</b>
Adalimumab vs. placebo	ATLAS	121/208 (58.2)	22/107 (20.6)	<b>5.37 (3.12, 9.26)</b>	<b>2.83 (1.92, 4.18)</b>
	M03-606	18/38 (47.4)	12/44 (27.3%)	2.40 (0.96, 6.02)	1.74 (0.97, 3.13)
	Huang 2014	154/229 (67.2)	35/115 (30.)	<b>4.69 (2.89, 7.61)</b>	<b>2.21 (1.65, 2.96)</b>
	COAST-V	53/90 (58.9)	35/87 (40.2)	<b>2.13 (1.17, 3.88)</b>	<b>1.46 (1.07, 1.99)</b>
	Pooled	346/565 (61.2)	104/353 (29.5)	<b>3.57 (2.25, 5.65)</b>	<b>2.00 (1.48, 2.72)</b>
<b>Tofacitinib vs. adalimumab:</b>				1.09 (0.51, 2.34)	0.97 (0.66, 1.42)

Source: Table 2.6.9, p117 of the submission.

CI = confidence interval; OR = odds ratio; RR = relative risk. Statistically significant effects are in **bold**.

**Table 5: ASAS40 at week 12/16 (double-blind period) - indirect comparison**

Comparison	Trial ID	Tofacitinib or adalimumab n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)
Tofacitinib vs. placebo	A3921119	24/52 (46.2)	10/51 (19.6)	<b>4.93 (2.52, 9.65)</b>	<b>2.35 (1.26, 4.41)</b>
	A3921120	54/133 (40.6)	17/136 (12.5)	<b>4.78 (2.59, 8.85)</b>	<b>3.25 (1.99, 5.30)</b>
	Pooled	78/185 (42.2)	27/187 (14.4)	<b>4.32 (2.61, 7.16)</b>	<b>2.88 (1.95, 4.23)</b>
Adalimumab vs. placebo	ATLAS	83/208 (39.9)	14/107 (13.1)	<b>4.41 (2.36, 8.25)</b>	<b>3.05 (1.82, 5.11)</b>
	M03-606	17/38 (44.7)	4/44 (9.1)	<b>8.10 (2.41, 27.16)</b>	<b>4.92 (1.81, 13.36)</b>
	Huang 2014	102/229 (44.5)	11/115 (9.6)	<b>7.59 (3.87, 14.90)</b>	<b>4.66 (2.61, 8.32)</b>
	COAST-V	32/90 (35.6)	16/87 (18.4)	<b>2.45 (1.22, 4.90)</b>	<b>1.93 (1.15, 3.26)</b>
	Pooled	234/565 (41.4)	45/353 (12.7)	<b>4.77 (2.77, 8.22)</b>	<b>3.19 (2.06, 4.94)</b>
<b>Tofacitinib vs. adalimumab:</b>				0.91 (0.43, 1.9)	0.90 (0.5, 1.62)

Source: Table 2.6.10, p118 of the submission.

CI = confidence interval; OR = odds ratio; RR = relative risk. Statistically significant effects are in **bold**.

**Table 6: BASDAI50 at week 12/16 (double-blind period) - indirect comparison**

Comparison	Trial ID	Tofacitinib or adalimumab n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)
Tofacitinib vs. placebo	A3921119	22/52 (42.3)	12/51 (21.2)	<b>2.38 (1.02, 5.57)</b>	1.80 (1.00, 3.24)
	A3921120	57/133 (42.9)	24/136 (17.6)	<b>3.50 (2.00, 6.12)</b>	<b>2.43 (1.61, 3.67)</b>
	Pooled	79/185 (42.7)	36/187 (19.3)	<b>3.12 (1.95, 4.97)</b>	<b>2.20 (1.57, 3.08)</b>
Adalimumab vs. placebo	DANISH	13/25 (52.0)	6/27 (22.2)	<b>3.79 (1.14, 12.58)</b>	<b>2.34 (1.05, 5.21)</b>
	ATLAS	94/208 (45.2)	17/107 (15.9)	<b>4.37 (2.43, 7.84)</b>	<b>2.84 (1.79, 4.51)</b>
	M03-606	14/38 (36.8)	6/44 (13.6)	<b>3.69 (1.25, 10.93)</b>	<b>2.70 (1.15, 6.34)</b>
	Huang 2014	114/229 (49.8)	19/115 (16.5)	<b>5.01 (2.87, 8.73)</b>	<b>3.01 (1.96, 4.64)</b>
	COAST-V	29/90 (32.2)	15/87 (17.2)	<b>2.28 (1.12, 4.64)</b>	<b>1.87 (1.08, 3.24)</b>
	Pooled	264/590 (44.7)	63/380 (16.6)	<b>4.77 (2.77, 8.22)</b>	<b>3.19 (2.06, 4.94)</b>
<b>Tofacitinib vs. adalimumab:</b>				0.8 (0.45, 1.41)	0.85 (0.56, 1.29)

Source: Table 2.6.12, p119 of the submission.

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = confidence interval; OR = odds ratio; RR = relative risk. Statistically significant effects are in **bold**.

6.15 These results showed no significant differences between tofacitinib and adalimumab.

### Indirect comparison – upadacitinib

6.16 The results of the indirect comparison with upadacitinib are shown in Table 7, Table 8 and Table 9.

**Table 7: ASAS20 at week 12/14/16 (double-blind period) - indirect comparison**

Comparison	Trial ID	Tofacitinib or upadacitinib n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)
Tofacitinib vs. placebo	A3921119 <sup>a</sup>	42/52 (80.8)	21/51 (41.2)	<b>6.00 (2.47, 14.57)</b>	<b>1.96 (1.38, 2.79)</b>
	A3921120	75/133 (56.4)	40/136 (29.4)	<b>3.10 (1.88, 5.13)</b>	<b>1.92 (1.42, 2.59)</b>
	Pooled	117/185 (63.2)	61/187 (32.6)	<b>3.88 (2.11, 7.16)</b>	<b>1.94 (1.54, 2.43)</b>
Upadacitinib vs. placebo	SELECT-AXIS 1	60/93 (64.5)	38/94 (40.4)	<b>2.68 (1.48, 4.84)</b>	<b>1.60 (1.20, 2.13)</b>
<b>Tofacitinib vs. upadacitinib:</b>				1.45 (0.62, 3.39)	1.21 (0.84, 1.75)

Source: Table 2.6.9, p117 of the submission.

ASAS = Ankylosing Spondylitis Assessment Score; CI = confidence interval; OR = odds ratio; RR = relative risk. Statistically significant effects are in **bold**.

<sup>a</sup> Patients receiving 5 mg bd only.

**Table 8: ASAS40 at week 12/14/16 (double-blind period) - indirect comparison**

Comparison	Trial ID	Tofacitinib or upadacitinib n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)
Tofacitinib vs. placebo	A3921119 <sup>a</sup>	24/52 (46.2)	10/51 (19.6)	<b>3.51 (1.46, 8.48)</b>	<b>2.35 (1.26, 4.41)</b>
	A3921120	54/133 (40.6)	17/136 (12.5)	<b>4.78 (2.59, 8.85)</b>	<b>3.25 (1.99, 5.30)</b>
	Pooled	78/185 (42.2)	27/187 (14.4)	<b>4.32 (2.61, 7.16)</b>	<b>2.88 (1.95, 4.23)</b>
Upadacitinib vs. placebo	SELECT-AXIS 1	48/93 (51.6)	24/94 (25.5)	<b>3.11 (1.68, 5.76)</b>	<b>2.02 (1.36, 3.01)</b>
<b>Tofacitinib vs. upadacitinib:</b>				1.39 (0.63, 3.08)	1.43 (0.82, 2.48)

Source: Table 2.6.9, p117 of the submission.

ASAS = Ankylosing Spondylitis Assessment Score; CI = confidence interval; OR = odds ratio; RR = relative risk. Statistically significant effects are in **bold**.

<sup>a</sup> Patients receiving 5 mg bd only.

**Table 9: BASDAI50 at week 12/14/16 (double-blind period) - indirect comparison**

Comparison	Trial ID	Tofacitinib or upadacitinib n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)
Tofacitinib vs. placebo	A3921119 <sup>a</sup>	22/52 (42.3)	12/51 (21.2)	<b>2.38 (1.02, 5.57)</b>	<b>1.80 (1.00, 3.24)</b>
	A3921120	57/133 (42.9)	24/136 (17.6)	<b>3.50 (2.00, 6.12)</b>	<b>2.43 (1.61, 3.67)</b>
	Pooled	79/185 (42.7)	36/187 (19.3)	<b>3.12 (1.95, 4.97)</b>	<b>2.20 (1.57, 3.08)</b>
Upadacitinib vs. placebo	SELECT-AXIS 1	42/93 (45.2)	22/94 (23.4)	<b>2.70 (1.44, 5.05)</b>	<b>1.93 (1.26, 2.96)</b>
<b>Tofacitinib vs upadacitinib.</b>				1.16 (0.53, 2.53)	1.14 (0.66, 1.96)

Source: Table 2.6.3, Appendix A of the submission.

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = confidence interval; OR = odds ratio; RR = relative risk. Statistically significant effects are in **bold**.

<sup>a</sup> Patients receiving 5 mg bd only.

## Comparative harms

### Indirect comparison - adalimumab

6.17 The results of the indirect comparison of key safety outcomes from the trials are shown in Table 10 and Table 11.

**Table 10: Any AE to week 12/16 (double-blind period) - indirect comparison**

Comparison	Trial ID	Tofacitinib or adalimumab n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)
Tofacitinib vs. placebo	A3921119	28/52 (53.8)	22/51 (43.1)	1.54 (0.71, 3.35)	1.25 (0.83, 1.87)
	A3921120	73/133 (54.9)	70/136 (51.5)	1.15 (0.71, 1.85)	1.07 (0.85, 1.33)
	Pooled	101/185 (54.6)	92/187 (49.2)	1.24 (0.83, 1.87)	1.11 (0.91, 1.35)
Adalimumab vs. placebo	ATLAS	140/208 (67.3)	61/107 (57.0)	1.55 (0.96, 2.51)	1.18 (0.98, 1.43)
	M03-606	31/38 (81.6)	28/44 (63.6)	2.53 (0.91, 7.05)	1.28 (0.98, 1.68)
	Huang 2014	81/229 (35.4)	26/115 (22.6)	<b>1.87 (1.12, 3.13)</b>	<b>1.56 (1.07, 2.29)</b>
	COAST-V	44/90 (49.0)	34/86 (39.5)	1.46 (0.80, 2.66)	1.24 (0.88, 1.73)
	Pooled	296/565 (52.4)	149/352 (42.3)	<b>1.69 (1.26, 2.26)</b>	<b>1.25 (1.10, 1.43)</b>
<b>Tofacitinib vs. adalimumab:</b>				0.73 (0.44, 1.21)	0.89 (0.7, 1.13)

Source: Table 2.6.13, p120-1 of the submission.

AE = adverse event; CI = confidence interval; OR = odds ratio; RR = relative risk. Statistically significant effects are in bold.

**Table 11: AE leading to discontinuation to week 12/16 (double-blind period) - indirect comparison**

Comparison	Trial ID	Tofacitinib or adalimumab n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)
Tofacitinib vs. placebo	A3921119	1/52 (1.9)	3/51 (5.9)	0.31 (0.03, 3.12)	0.33 (0.04, 3.04)
	A3921120	3/133 (2.3)	1/136 (0.7)	3.12 (0.32, 30.34)	3.07 (0.32, 29.12)
	Pooled	4/185 (2.2)	4/187 (2.1)	0.99 (0.10, 9.43)	1.00 (0.11, 8.94)
Adalimumab vs. placebo	ATLAS	2/208 (1.0)	2/107 (1.9)	0.51 (0.07, 3.67)	0.51 (0.07, 3.60)
	M03-606	0	0	NE	NE
	Huang 2014	4/229 (1.7)	0	4.61 (0.25, 86.36)	4.54 (0.25, 83.59)
	COAST-V	1/90 (1.1)	0	2.90 (0.12, 72.15)	2.87 (0.12, 69.46)
	Pooled	7/565 (1.2)	2/352 (0.6)	1.26 (0.29, 5.41)	1.25 (0.29, 5.28)
<b>Tofacitinib vs. adalimumab:</b>				0.79 (0.05, 11.73)	0.8 (0.06, 11.15)

Source: Table 2.6.13, p120-1 of the submission.

AE = adverse event; CI = confidence interval; NE = not evaluated; OR = odds ratio; RR = relative risk. Statistically significant effects are in bold.

### Indirect comparison – upadacitinib

6.18 The results of the indirect comparison with upadacitinib with respect to adverse events are shown in Table 12 and Table 13.

**Table 12: Any AE to week 12/14/16 (double-blind period) - indirect comparison**

Comparison	Trial ID	Tofacitinib or upadacitinib n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)
Tofacitinib vs. placebo	A3921119 <sup>a</sup>	28/52 (53.8)	22/51 (43.1)	1.54 (0.71, 3.35)	1.25 (0.83, 1.87)
	A3921120	73/133 (54.9)	70/136 (51.5)	1.15 (0.71, 1.85)	1.07 (0.85, 1.33)
	Pooled	101/185 (54.6)	92/187 (49.2)	1.24 (0.83, 1.87)	1.11 (0.91, 1.35)
Upadacitinib vs. placebo	SELECT-AXIS 1	58/93 (62.4)	52/94 (55.3)	1.34 (0.75, 2.40)	1.13 (0.89, 1.43)
<b>Tofacitinib vs. upadacitinib:</b>				0.93 (0.46, 1.88)	0.98 (0.72, 1.34)

Source: Table 2.6.4, Appendix A of the submission.

AE = adverse event; CI = confidence interval; OR = odds ratio; RR = relative risk. Statistically significant effects are in **bold**.<sup>a</sup> Patients receiving 5 mg bd only.**Table 13: Discontinuations due to AE to week 12/14/16 (double-blind period) - indirect comparison**

Comparison	Trial ID	Tofacitinib or upadacitinib n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)
Tofacitinib vs. placebo	A3921119 <sup>a</sup>	1/52 (1.9)	3/51 (5.9)	0.31 (0.03, 3.12)	0.33 (0.04, 3.04)
	A3921120	3/133 (2.3)	1/136 (0.7)	3.12 (0.32, 30.34)	3.07 (0.32, 29.12)
	Pooled	4/185 (2.2)	4/187 (2.1)	0.99 (0.10, 9.43)	1.00 (0.11, 8.94)
Upadacitinib vs. placebo	SELECT-AXIS 1	2/93 (2.2)	3/94 (3.2)	0.67 (0.11, 4.08)	0.67 (0.12, 3.94)
<b>Tofacitinib vs. upadacitinib</b>				1.48 (0.08, 26.95)	1.49 (0.09, 24.73)

Source: Table 2.6.6, Appendix A of the submission.

AE = adverse event; CI = confidence interval; OR = odds ratio; RR = relative risk. Statistically significant effects are in **bold**.<sup>a</sup> Patients receiving 5 mg bd only.

6.19 These comparisons did not identify any significant differences between tofacitinib and upadacitinib but do not address the question of whether the adverse effects of tofacitinib found in Study A3921133 (discussed below) are potentially a class effect of JAK-1 inhibitors. Given that tofacitinib and upadacitinib have different selectivity for JAK receptor subtypes, there may be differences in the adverse event profiles.

### Long-term safety data

6.20 The submission provided information about Study A3921133 (ORAL Surveillance), a Phase 3b/4 randomised, parallel-arm, open-label, safety study in patients with rheumatoid arthritis and one or more risk factors for cardiovascular (CV) events, evaluating the safety of tofacitinib at 2 doses (5 mg bd and 10 mg bd) versus TNFi (adalimumab 40 mg every other week by subcutaneous injection or etanercept 50 mg once weekly by subcutaneous injection). Interim analyses showed a higher risk of thromboembolic events and of death in patients receiving tofacitinib 10 mg bd, and all patients were switched to 5 mg bd. Final results of the study did not show that tofacitinib 5 mg bd was non-inferior for safety, and are shown in Table 14.

6.21 The submission stated that the TGA has reviewed the results and explanations from the sponsor. The Delegate Overview concluded that the benefit-risk balance of the use of tofacitinib in the treatment of adults with active AS is positive, and the Delegate was inclined to approve tofacitinib for the treatment of adult patients with active AS who have responded inadequately to conventional therapy.

- 6.22 The evaluation considered the results of the ORAL Surveillance study was noteworthy and would merit further consideration as to whether this impacted the cost-effectiveness proposition of tofacitinib.

Table 14: Safety data from A3921133

	Tofacitinib 5 mg bd	Tofacitinib 10 mg bd <sup>b</sup>	TNF Inhibitor
<b>MACE<sup>a</sup></b>			
IR per 100 py (95% CI)	0.91 (0.67, 1.21)	1.05 (0.78, 1.38)	0.73 (0.52, 1.01)
HR vs TNFI (95% CI)	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	-
<b>Fatal MI<sup>a</sup></b>			
IR per 100 py (95% CI)	0.00 (0.00, 0.07)	0.06 (0.01, 0.18)	0.06 (0.01, 0.17)
HR vs TNFI (95% CI)	0.00 (0.00, infinity)	1.03 (0.21, 5.11)	-
<b>Non-fatal MI<sup>a</sup></b>			
IR per 100 py (95% CI)	0.37 (0.22, 0.57)	0.33 (0.19, 0.53)	0.16 (0.07, 0.31)
HR vs TNFI (95% CI)	<b>2.32 (1.02, 5.30)</b>	2.08 (0.89, 4.86)	-
<b>Malignancies excluding NMSC</b>			
IR per 100 py (95% CI)	1.13 (0.87, 1.45)	1.13 (0.86, 1.45)	0.77 (0.55, 1.04)
HR vs TNFI (95% CI)	<b>1.47 (1.00, 2.18)</b>	<b>1.48 (1.00, 2.19)</b>	-
<b>Lung cancer</b>			
IR per 100 py (95% CI)	0.23 (0.12, 0.40)	0.32 (0.18, 0.51)	0.13 (0.05, 0.26)
HR vs TNFI (95% CI)	1.84 (0.74, 4.62)	<b>2.50 (1.04, 6.02)</b>	-
<b>Lymphoma</b>			
IR per 100 py (95% CI)	0.07 (0.02, 0.18)	0.11 (0.04, 0.24)	0.02 (0.00, 0.10)
HR vs TNFI (95% CI)	3.99 (0.45, 35.70)	6.24 (0.75, 51.86)	-

Source: <https://www.ema.europa.eu/en/medicines/dhpc/xeljanz-tofacitinib-increased-risk-major-adverse-cardiovascular-events-malignancies-use-tofacitinib> published 6 July, 2021; accessed 22 November, 2022.

CI = confidence interval; IR = incidence rate; HR = hazard ratio; MACE = major adverse cardiovascular events; MI = myocardial infarction; NMSC = non-melanoma skin cancer; py = patient year; TNFI = tumour necrosis factor inhibitor

<sup>a</sup> Events occurring on treatment or within 60 days of treatment discontinuation.

<sup>b</sup> Patients randomised to 10 mg bd but switched to 5 mg bd.

- 6.23 The Pre-PBAC Response argued the population in the ORAL Surveillance study was different to the AS population for which PBS listing was being sought, and noted the safety study population were at higher baseline risk due to the design of study, which recruited patients with rheumatoid arthritis aged 50 years and over who had at least one additional cardiovascular risk factor. The Response argued that rheumatoid arthritis as a condition carries additional risk features by the nature of the disease, and given the study also recruited only patients with additional risk factors, it was not reasonable to extrapolate the results of the study to the AS population.

### Benefits/harms

- 6.24 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

### Clinical claim

- 6.25 The submission described tofacitinib as non-inferior in terms of effectiveness and safety compared to adalimumab and upadacitinib.
- 6.26 The PBAC considered that the claim of non-inferior comparative effectiveness compared to adalimumab and upadacitinib was reasonable.

6.27 The PBAC considered that the claim of non-inferior comparative safety was overall likely to be reasonable, and considered the long-term safety data from the ORAL Surveillance study should be interpreted with caution in the context of the specific submission for AS (discussed further in Section 7 ‘PBAC Outcome’).

### **Economic analysis**

6.28 The submission presented a cost minimisation approach. The key components are presented in Table 15.

**Table 15: Key components and assumptions of the cost-minimisation approach**

<b>Component</b>	<b>Claim or assumption</b>
Therapeutic claim: effectiveness	Based on evidence presented in the submission, the effectiveness of TOF 5 mg twice daily is assumed to be non-inferior to ADA 40 mg every 2 weeks.
Therapeutic claim: safety	Based on evidence presented in the submission, the safety of TOF 5 mg twice daily is assumed to be non-inferior to ADA 40 mg every 2 weeks.
Evidence base	Indirect comparison of randomised trials
Equi-effective doses	TOF 5 mg twice daily is equivalent to ADA 40 mg every 2 weeks.
Direct medicine costs	The costs of TOF 5 mg twice daily per patient are equivalent to the cost of ADA 40 mg every two weeks.
Other costs or cost offsets	nil

Source: Table 3.1.1, p131 of the submission.

ADA = adalimumab; TOF = tofacitinib

6.29 The equi-effective doses were estimated as tofacitinib 5 mg twice daily and adalimumab 40 mg subcutaneous injection every 2 weeks, based on the indirect treatment comparison.

6.30 The submission proposed that the effective AEMP for tofacitinib 5 mg x 56 tablets is \$1,211.08, equivalent to the published AEMP of adalimumab two 40mg pre-filled syringes.

### **Drug cost/patient/4 weeks**

6.31 Assuming a DPMQ of \$1,211.08 (i.e. requested published price) and 13 scripts required per year inclusive of initial and continuing therapy with TOF 10 mg daily, the cost per patient per year is \$15,744.04.

### **Estimated PBS usage & financial implications**

6.32 This submission will not be considered by DUSC.

6.33 The submission used a market share approach to estimate use and the financial implications of listing tofacitinib for AS, outlined in Table 16.

Table 16: Key inputs for financial estimates

Parameter	Source	Estimate						Justification		
		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6			
Estimated annual growth rate of all bDMARDs + upadacitinib	Services Australia - PBS data	3.7%	3.0%	2.5%	2.2%	1.9%	1.6%	Projected from PBS utilisation data.		
Projected scripts for AS	Sponsor forecast	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	Historical PBS bDMARD use		
Market share of tofacitinib	Sponsor patient forecast model	█%	█%	█%	█%	█%	█%	Observed from PBS 1:10 data.		
Proportion of substitution of each medicine affected by tofacitinib	Calculated using 1:10 PBS data for PsA indication observed for years 2019-2021	<b>Substitution rates for each medicine (%)</b>		<b>Proportion of each medicine substituted (%)</b>				See paragraph below.		
				Year 1	Year 2	Year 3	Year 4		Year 5	Year 6
		ADA	█	█						
		INF	█	█						
		GOL	█	█						
		ETA	█	█						
		SEC	█	█						
		UPA	█	█						
		CER	█	█						
IXE	█	█								
Calculation of substituted scripts	Projected market numbers were multiplied by the assumed market share in each year to determine the estimated script volume per year (Table 17). The estimated script volume was then multiplied by the substitution rate for each medicine to estimate the number of substituted scripts for each medicine. Table 17 provides the number of scripts substituted for each bDMARD.									
Grandfathered patients	Sponsor patient familiarisation program: N = █ <sup>1</sup> . The scripts for these patients were included in the estimated number of tofacitinib scripts.									
Costs (published DPMQ's)	Tofacitinib: \$1,211.08		Infliximab: \$1,014.08, \$1,061.90			Adalimumab: \$885.56				
	Golimumab: \$1,160.64		Secukinumab: \$709.71			Etanercept: \$1,050.20				
	Ixekizumab: \$3,258.28		Certolizumab: \$1,025.83							
Patient copayment	PBS: \$29.75; RPBS: \$5.21 for all medicines except infliximab, which had a PBS copayment of \$30.46 and RPBS \$6.60. All copayments were calculated using a general copayment of \$41.30 and concessional copayment of \$6.60, which were 2021 values.									

Source: Table 4.1.2, p139; Table 4.2.6, p143 of the submission; Excel workbook 'Tofacitinib\_AS\_UCM-FINAL\_01NOV2022'.

ADA = adalimumab; AS = ankylosing spondylitis; bDMARD = biological disease modifying antirheumatic drug; CER = certolizumab; ETA = etanercept; GOL = golimumab; INF = infliximab; IXE = ixekizumab; Jan = January; PsA = psoriatic arthritis; SEC = secukinumab; Sept = September; UPA = upadacitinib

The redacted values correspond to the following ranges:

<sup>1</sup> <500

<sup>2</sup> 100,000 to < 200,000

6.34 The submission assumed that tofacitinib will substitute each of the PBS listed medicines for AS at different rates but in a similar manner to the substitution assumed for PsA. PBS data for PsA was analysed between 2019 and 2021, the first three years of tofacitinib PBS listing for PsA in order to estimate the substitution rates for the current PBS listed bDMARDs. The submission proposed that as there are currently a total of eight medicines listed on the PBS for AS, and one is UPA which is the same

class of medicine as tofacitinib and has a once daily dosing regimen, the listing of tofacitinib on the PBS would not drive additional future market growth, and that tofacitinib would be expected to displace current PBS listed medicines. This assumption was reasonable.

- 6.35 The submission stated that since the existing treatments and tofacitinib have differing dosage and administration requirements, there was no consistent relationship between patient numbers and script numbers for all treatments. Thus, the estimates provided were based on prescription numbers.
- 6.36 The submission proposed that projections of the future prescriptions should be based on logarithmic extrapolations of current estimates rather than linear, although the latter were provided as a sensitivity analysis.
- 6.37 The submission considered whether conversion factors were needed due to the different treatment regimens for the currently listed PBS medicines for AS but this was only necessary for infliximab.
- 6.38 The submission assumed there would be < 500 grandfathered patients who would be receiving tofacitinib through a Patient Familiarisation Programme and will require grandfathering onto PBS-reimbursed tofacitinib treatment. Scripts for these patients were included as part of the estimated number of tofacitinib scripts, see Table 18. The submission also assumed that approximately  $\frac{1}{2}$ % of these patients will discontinue treatment each year, starting at Year 2. The grandfathered patients account for close to 60% of the estimated net cost to the PBS/RPBS (see para 6.44).
- 6.39 The estimated number of substituted scripts for each bDMARD is listed in Table 17 as well as the estimated cost offset. All estimates are for initial and continuing scripts combined. To estimate the number of scripts to be substituted by tofacitinib, the submission applied the following steps:
- Calculated an estimated script volume. This was based on the expected tofacitinib market share (e.g.  $\frac{1}{2}$ % in Year 1, see Table 16) multiplied by the projected number of scripts for that year (e.g. 100,000 to < 200,000 in Year 1). This resulted in an estimated number of scripts that will be used by tofacitinib patients (e.g.  $\frac{1}{2}$ %  $\times$  100,000 to < 200,000 = 5,000 to < 10,000 in Year 1).
  - The estimated number of scripts to be used for tofacitinib (Year 1: 5,000 to < 10,000) was then used to calculate the number of substituted scripts for each medicine as follows:
    - The estimated script volume (e.g. 5,000 to < 10,000 in Year 1) was multiplied by the substitution rate for each medicine. To illustrate, for adalimumab in Year 1,  $\frac{1}{2}$ %  $\times$  5,000 to < 10,000 = 500 to < 5,000 adalimumab scripts to be substituted. The number of substituted scripts for all medicines is reported in Table 17.

Table 17: Estimated scripts of all bDMARDs substituted by tofacitinib and estimated cost offsets

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Projected market size (scripts) for AS	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Estimated tofacitinib market share	4.3%	6.0%	7.5%	7.8%	8.0%	8.2%
Estimated scripts <sup>a</sup> for bDMARDs to be substituted	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>
<b>Adalimumab</b>						
Number substituted	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Cost	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Infliximab (all adjusted for script equivalence: estimated scripts × proportion × 1.5)</b>						
Number substituted	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Cost	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Golimumab</b>						
Number substituted	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Cost	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Etanercept</b>						
Number substituted	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Cost	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Secukinumab</b>						
Number substituted	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Cost	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Upadacitinib</b>						
Number substituted	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Cost	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Certolizumab</b>						
Number substituted <sup>b</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Cost	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Ixekizumab</b>						
Number substituted	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Cost	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Total substituted scripts</b>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Net cost offset PBS/RPBS</b>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
Tofacitinib patient numbers <sup>c</sup>	█ <sup>3</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>

Source: Table 4.2.8, p144; Table 4.3.1, p152-153; Table 4.3.2, p154; Table 4.3.3, p154-155 of the submission; Excel workbook 'Tofacitinib\_AS\_UCM-FINAL\_01NOV2022'.

bDMARD = biological disease modifying antirheumatic drug

<sup>a</sup> Calculated by multiplying projected market size by estimated tofacitinib market share e.g. in Year 1, 100,000 to < 200,000 × █% = 5,000 to < 10,000.

<sup>b</sup> The number of substituted scripts for certolizumab presented here matches those in Table 4.3.1 of the submission and was used in the submission's Excel workbook for calculation of cost offsets.

<sup>c</sup> Calculated as substituted scripts/13; e.g. 5,000 to < 10,000scripts/13 scripts per year = < 500 patients.

The redacted values correspond to the following ranges:

<sup>1</sup> 100,000 to < 200,000

<sup>2</sup> 5,000 to <10,000

<sup>3</sup> <500

<sup>4</sup> Net cost saving

<sup>5</sup> 500 <5,000

<sup>6</sup> 10,000 to <20,000

6.40 The estimated net cost of tofacitinib to the PBS/RPBS based on published prices is shown in Table 18.

6.41 The submission included cost offsets for MBS item 14245 for the intravenous administration of infliximab. There was only a small drop in the number of infliximab scripts, and the corresponding decrease in usage and cost of the MBS item was small (net cost saving in Year 1 and net cost saving in Year 6). The submission did not include this cost offset in its determination of net cost to the PBS/RPBS, and it has not been included during the evaluation.

**Table 18: Estimated use and cost of tofacitinib to the PBS/RPBS – based on published prices**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of scripts	1	1	6	6	6	6
Net cost <sup>a</sup> PBS/RPBS	2	5	5	5	5	5
<b>Estimated changes in use and financial impact of currently listed treatments</b>						
Adalimumab	3	3	3	3	3	3
Infliximab	3	3	3	3	3	3
Golimumab	3	3	3	3	3	3
Etanercept	3	3	3	3	3	3
Secukinumab	3	3	3	3	3	3
Upadacitinib	3	3	3	3	3	3
Certolizumab	3	3	3	3	3	3
Ixekizumab	3	3	3	3	3	3
Total	3	3	3	3	3	3
Cost PBS/RPBS	4	4	4	4	4	4
Net cost <sup>a</sup> PBS/RPBS	4	4	4	4	4	4
<b>Estimated change in use and cost of MBS items</b>						
MBS item 14245	3	3	3	3	3	3
MBS cost (\$103.55)	4	4	4	4	4	4
<b>Net financial implications to PBS/RPBS</b>						
Total cost PBS/RPBS	2	5	5	5	5	5
<b>Total net cost<sup>b</sup> PBS/RPBS</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>2</b>

Source: Table 4.3.2, p154; Table 4.5.2, p157 of the submission; Excel workbook 'Tofacitinib\_AS\_UCM-FINAL\_01NOV2022'.

<sup>a</sup> Net of patient copayments.

<sup>b</sup> Net of substituted medicines and patient copayments.

The redacted values correspond to the following ranges:

<sup>1</sup> 5,000 to < 10,000

<sup>2</sup> \$0 to < \$10 million

<sup>3</sup> <500

<sup>4</sup> net cost saving

<sup>5</sup> \$10 million to <\$20 million

<sup>6</sup> 10,000 to < 20,000

6.42 The estimated net cost to the PBS/RPBS for the listing of tofacitinib for AS was from \$0 to < \$10 million to \$0 to < \$10 million, for a total of approximately \$10 million to < \$20 million over the first 6 years of listing (based on published prices).

6.43 The submission stated that the additional cost was mainly driven by the group of <500 grandfathered patients. If all grandfathered patients were removed from the estimates (**Error! Reference source not found.**), there remained cost to the PBS/RPBS in every year of listing, with an estimated total of \$0 to < \$10 million over the first 6 years of listing, 41% of the total net cost. The evaluation noted there remained considerable additional cost associated with the requested listing, however considered if TOF were listed on a cost minimisation basis with the least costly

alternative, the listing would likely be cost neutral or modestly cost saving to the PBS as it would only replace therapies that were the same or more costly.

- 6.44 The Pre-PBAC Response noted the utilisation and financial estimates were based on the published prices of the alternative therapies and stated a more accurate estimated of the financial implications of the listing of TOF cannot be made until the effective prices of these alternatives are revealed following a PBAC recommendation.

### **Quality Use of Medicines**

- 6.45 The submission noted the post marketing surveillance studies that are outlined in the Risk Management Plan.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the General Schedule listing of tofacitinib (TOF) for the treatment of ankylosing spondylitis (AS). The PBAC's recommendation was based on, among other matters, its assessment the cost-effectiveness of TOF would be acceptable if it were cost minimised to the least costly alternative therapy of adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, ixekizumab, secukinumab and upadacitinib.
- 7.2 The PBAC considered the equi-effective doses of TOF and the alternative therapies could be derived with reference to the therapeutic relativity sheets and relevant Product Information documents, noting the TOF equi-effective dose component was 5 mg twice daily (total daily dose 10 mg).
- 7.3 The PBAC considered it was reasonable for the listing of TOF to be consistent with other biologic or targeted synthetic disease modifying anti-rheumatic drugs (bDMARDs/tsDMARDs), with prescribing limited to eligible medical practitioners, an initial treatment period of 16 weeks, followed by maintenance therapy with re-assessment at 24-week intervals. The Committee noted the flow-on changes to other AS bDMARD/tsDMARD listings to include TOF in the list of eligible therapies.
- 7.4 The PBAC noted the input from individuals and organisations supported the listing of TOF for AS and highlighted the benefits of an additional oral treatment option for AS.
- 7.5 The PBAC noted that eight treatments were currently PBS listed for AS, including an alternative oral janus kinase inhibitor (upadacitinib) and considered the clinical need for additional therapies was low; however, the PBAC considered an additional oral therapy option may be beneficial for some patients.
- 7.6 The submission nominated adalimumab as the main comparator as the therapy most used in practice, and upadacitinib as a supplementary comparator with a similar mechanism of action. The PBAC considered the nominated comparators were reasonable but noted TOF may substitute for any of the PBS listed bDMARDs/tsDMARDs for AS (described in paragraph 7.1). The PBAC noted the clinical

claim for TOF was one of non-inferior comparative effectiveness and safety to adalimumab and upadacitinib. These claims are discussed further below.

- 7.7 The PBAC noted no direct trials comparing TOF to adalimumab or upadacitinib were available, and the submission relied on indirect treatment comparisons (ITCs) with placebo as the common comparator to support the clinical claims. The PBAC noted the submission also presented the long-term safety trial Study A3921133 (ORAL Surveillance), a Phase IIIb/IV, randomised controlled trial of patients with rheumatoid arthritis and one or more risk factors for cardiovascular (CV) events.
- 7.8 The PBAC noted the results of the indirect comparisons versus adalimumab and upadacitinib for the outcomes of ASAS20, ASAS40 and BASDAI50 found no statistically significant differences between TOF and either of those therapies. The PBAC noted the nominated non-inferiority margin of 0.43 had been previously accepted for upadacitinib, based on numerous previous bDMARD/tsDMARD submissions for AS (paragraph 6.13, upadacitinib Public Summary Document (PSD), March 2021 PBAC meeting). Overall, the PBAC considered, based on the available evidence, that the claim of non-inferior comparative effectiveness to adalimumab and upadacitinib was adequately supported, and noted no evidence of superiority versus any of the alternative bDMARDs/tsDMARDs was presented.
- 7.9 With respect to comparative safety, the PBAC noted the ITCs did not identify any significant differences between tofacitinib and either adalimumab or upadacitinib, however noted the wide 95% confidence intervals on the comparison of adverse events leading to discontinuation and considered this was likely due to the low number of observed events in the clinical trials. Overall, the PBAC considered, based on the evidence presented, that the claim of non-inferior comparative safety to adalimumab and upadacitinib, and by extension the other alternative bDMARDs/tsDMARDs, was adequately supported.
- 7.10 The PBAC noted the evaluation highlighted the results of the ORAL Surveillance study (in RA patients), which indicated an increased risk of non-fatal myocardial infarction events and malignancies in the long-term study population, and further noted additional regulatory action had been taken by the US FDA to restrict the use of janus kinase (JAK) inhibitors to later-line use, and by the EMA to add a caution about use in patients aged over 65 or with specific risk factors for these events. The PBAC also noted the Pre-PBAC Response reiterated the ORAL Surveillance population were at a heightened risk of these events than the broader AS population as they had increased underlying risk of these events as part of the design of the trial. The PBAC accepted that the ORAL Surveillance population was essentially an enriched population at higher baseline risk of these events, and was of the view that if the increased safety risk is a therapeutic class effect, these issues were most appropriately managed at the regulatory level by the TGA. The PBAC agreed with the Pre-PBAC Response and considered the results of the ORAL Surveillance study should not be extrapolated to draw conclusions about the comparative safety claim in AS (to the alternative therapies), however advised it would consider any regulatory changes to the JAK

inhibitors undertaken by the TGA in the future and would consider any necessary changes to these PBS listings should the need arise.

- 7.11 The PBAC considered that a listing based on a cost minimisation approach, with costs over two years, consistent with the approach previously used for bDMARDs/tsDMARDs, was appropriate to determine the cost-minimised price of TOF. The PBAC considered the cost of TOF should be no greater than the alternative therapies.
- 7.12 The PBAC noted the utilisation and financial estimates appeared to result in an incremental cost for the listing of TOF, even after accounting for grandfather patients. The PBAC considered this estimated cost was likely to be unrealistic as TOF would be the ninth bDMARD/tsDMARD and second oral agent listed for AS and therefore was unlikely to growth market. On that basis the PBAC considered the listing of TOF, if listed on a cost minimisation basis with the least costly alternative therapy, would most likely be cost neutral or modestly cost saving to the PBS as it will only replace therapies that are either of equivalent cost or more expensive.
- 7.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because tofacitinib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over the alternative therapies, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.14 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:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer
TOFACITINIB					
5 mg tablet, 56 (initial)	New	1	56	3	Xeljanz® Pfizer Australia Pty Ltd
5 mg tablet, 56 (continuing)	New	1	56	5	

**Variant of benefit type 49240 (Restrictions 10996, 11060, 11039, 11040; ToC 11061, 10997, 11054, 9429)**

<b>Concept ID</b>	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners

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	<p><b>Restriction Level / Method:</b>  <input checked="" type="checkbox"/> Authority Required – In Writing</p>
	<p><b>Administrative Advice:</b>          (See end of this document for common administrative advice)</p>
	<p><b>Condition:</b> Ankylosing spondylitis</p>
	<p><b>Indication:</b> Ankylosing spondylitis</p>
	<p><b>Treatment Phase:</b> Initial treatment - Initial 1 (new patient)</p>
	<p><b>Clinical criteria:</b></p>
	<p>The condition must be radiographically (plain X-ray) confirmed Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis</p>
	<p><b>AND</b></p>
	<p><b>Clinical criteria:</b></p>
	<p>Patient must not have received PBS-subsidised treatment with a biological medicine for this condition</p>
	<p><b>AND</b></p>
	<p><b>Clinical criteria:</b></p>
	<p>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</p>
	<p><b>AND</b></p>
	<p><b>Clinical criteria:</b></p>
	<p>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</p>
	<p><b>AND</b></p>
	<p><b>Clinical criteria:</b></p>
	<p>Patient must not receive more than 16 weeks of treatment under this restriction</p>
	<p><b>AND</b></p>
	<p><b>Treatment criteria:</b></p>
	<p>Must be treated by a rheumatologist; or          Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis</p>
	<p><b>AND</b></p>
	<p><b>Population criteria:</b></p>
	<p>Patient must be at least 18 years of age</p>
	<p><b>Prescribing Instructions:</b>          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.</p>
	<p><b>Prescribing Instructions:</b>          The following criteria indicate failure to achieve an adequate response and must be demonstrated at the time of the initial application:          (a) a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of at least 4 on a 0-10 scale; and</p>

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	<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 baseline BASDAI score and ESR or CRP level must be determined at the completion of the 3 month NSAID and exercise trial, but prior to ceasing NSAID treatment. All measurements must be no more than 4 weeks old at the time of initial application.</p> <p>If the above requirement to demonstrate an elevated ESR or CRP cannot be met, the application must state the reason this criterion cannot be satisfied.</p>
	<p><b>Prescribing Instructions:</b></p> <p>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Ankylosing Spondylitis PBS Authority Application Form which includes the following:</p> <p>(i) details of the radiological report confirming Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis; and</p> <p>(ii) a baseline BASDAI score; and</p> <p>(iii) a completed Exercise Program Self Certification Form included in the supporting information form; and</p> <p>(iv) baseline ESR and/or CRP level</p>
	<p><b>Prescribing Instructions:</b></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 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>
	<p><b>Prescribing Instructions:</b></p> <p>Where a response assessment is not conducted within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.</p>
	<p><b>Prescribing Instructions:</b></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 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.</p>
	<p><b>Administrative Advice:</b></p> <p>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 <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a></p>
	<p><b>Administrative Advice:</b></p> <p>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 <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a></p>
	<p><b>Administrative Advice:</b></p> <p>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. Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a></p> <p>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a></p> <p>Or mailed to:</p> <p>Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
	<p><b>Administrative Advice:</b></p> <p>No increase in the maximum quantity or number of units may be authorised.</p>

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	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Treatment Phase:</b> Initial treatment - Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years)
	<b>Clinical criteria:</b>
	Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with this drug for this condition during the current treatment cycle
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not receive more than 16 weeks of treatment under this restriction
	<b>AND</b>
	<b>Treatment criteria:</b>
	Must be treated by a rheumatologist; or Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must be at least 18 years of age
	<b>Prescribing Instructions:</b> 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.
	<b>Prescribing Instructions:</b> An application for a patient who has received PBS-subsidised biological medicine treatment for this condition who wishes to change or recommence therapy with this drug, must be accompanied by evidence of a response to the patient's most recent course of PBS-subsidised biological medicine treatment, within the timeframes specified below.
	<b>Prescribing Instructions:</b> Where the most recent course of PBS-subsidised biological medicine treatment was approved under either Initial 1, Initial 2, Initial 3 or continuing treatment restrictions, an assessment of a patient's response must have been conducted following a minimum of 12 weeks of therapy and submitted no later than 4 weeks from the date of completion of treatment.
	<b>Prescribing Instructions:</b> 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 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.
	<b>Prescribing Instructions:</b> An adequate response is defined as an improvement from baseline of at least 2 units (on a scale of 0-10) in the BASDAI score combined with at least 1 of the following: (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.

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	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.
	<b>Prescribing Instructions:</b> All measurements provided must be no more than 4 weeks old at the time of application.
	<b>Prescribing Instructions:</b> 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.
	<b>Prescribing Instructions:</b> 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.
	<b>Administrative Advice:</b> 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. Monday to Friday).  Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a>  Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a>  Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Treatment Phase:</b> Initial treatment - Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)
	<b>Clinical criteria:</b> Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition
	<b>AND</b>
	<b>Clinical criteria:</b> Patient must have a break in treatment of 5 years or more from the most recently approved PBS-subsidised biological medicine for this condition
	<b>AND</b>
	<b>Clinical criteria:</b> The condition must be radiographically (plain X-ray) confirmed Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis
	<b>AND</b>
	<b>Clinical criteria:</b> 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

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	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
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of at least 4 on a 0-10 scale that is no more than 4 weeks old at the time of application
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour that is no more than 4 weeks old at the time of application; or
	Patient must have a C-reactive protein (CRP) level greater than 10 mg per L that is no more than 4 weeks old at the time of application; or
	Patient must have a clinical reason as to why demonstration of an elevated ESR or CRP cannot be met and the application must state the reason
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not receive more than 16 weeks of treatment under this restriction
	<b>AND</b>
	<b>Treatment criteria:</b>
	Must be treated by a rheumatologist; or
	Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must be at least 18 years of age
	<b>Prescribing Instructions:</b> 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 BASDAI score.
	<b>Prescribing Instructions:</b> 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 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.
	<b>Prescribing Instructions:</b> Where a response assessment is not conducted within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.
	<b>Prescribing Instructions:</b> 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.
	<b>Administrative Advice:</b> 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. Monday to Friday).

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	<p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a></p> <p>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a></p> <p>Or mailed to:                  Services Australia                  Complex Drugs                  Reply Paid 9826                  HOBART TAS 7001</p>
	<p><b>Administrative Advice:</b>                  No increase in the maximum quantity or number of units may be authorised.</p>
	<p><b>Administrative Advice:</b>                  No increase in the maximum number of repeats may be authorised.</p>
	<p><b>Administrative Advice:</b>                  Special Pricing Arrangements apply.</p>
	<p><b>Treatment Phase:</b> Initial treatment - Initial 1 (new patient), Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) or Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) - balance of supply</p>
	<p><b>Clinical criteria:</b></p>
	<p>Patient must have received insufficient therapy with this drug for this condition under the Initial 1 (new patient) restriction to complete 16 weeks treatment; or</p> <p>Patient must have received insufficient therapy with this drug for this condition under the Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) restriction to complete 16 weeks treatment; or</p> <p>Patient must have received insufficient therapy with this drug for this condition under the Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) restriction to complete 16 weeks treatment</p>
	<p><b>AND</b></p>
	<p><b>Clinical criteria:</b></p>
	<p>The treatment must provide no more than the balance of up to 16 weeks treatment available under the above restrictions</p>
	<p><b>AND</b></p>
	<p><b>Treatment criteria:</b></p>
	<p>Must be treated by a rheumatologist; or                  Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis</p>
	<p><b>Prescribing Instructions:</b>                  None proposed</p>
	<p><b>Administrative Advice:</b>                  Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p>
	<p><b>Administrative Advice:</b>                  Special Pricing Arrangements apply.</p>

**Restriction summary: Variant of 11062; ToC: Variant of 11030**

<b>Concept ID</b>	<b>Category / Program:</b>
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	GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – In Writing
	<b>Administrative Advice:</b> (See end of this document for common administrative advice)
	<b>Condition:</b> Ankylosing spondylitis
	<b>Indication:</b> Ankylosing spondylitis
	<b>Treatment Phase:</b> Continuing treatment
	<b>Clinical criteria:</b>
	Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have demonstrated an adequate response to treatment with this drug
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not receive more than 24 weeks of treatment under this restriction
	<b>AND</b>
	<b>Treatment criteria:</b>
	Must be treated by a rheumatologist; or Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must be at least 18 years of age
	<b>Prescribing Instructions:</b> 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.
	<b>Prescribing Instructions:</b> An adequate response is defined as an improvement from baseline of at least 2 units (on a scale of 0-10) in the BASDAI score combined with at least 1 of the following: (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. 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.
	<b>Prescribing Instructions:</b> All measurements provided must be no more than 4 weeks old at the time of application.
	<b>Prescribing Instructions:</b> 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 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.
	<b>Prescribing Instructions:</b> Where a response assessment is not conducted within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.
	<b>Prescribing Instructions:</b>

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	If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsided 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.
	<b>Prescribing Instructions:</b> A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsided biological medicine was approved in this cycle and the date of the first application under a new cycle under the Initial 3 treatment restriction.
	<b>Administrative Advice:</b> 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. Monday to Friday).  Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a>  Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a>  Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Treatment Phase:</b> Continuing treatment – balance of supply
	<b>Clinical criteria:</b>
	Patient must have received insufficient therapy with this drug under the Continuing treatment restriction to complete 24 weeks treatment
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must provide no more than the balance of up to 24 weeks treatment available under the above restriction
	<b>AND</b>
	<b>Treatment criteria:</b>
	Must be treated by a rheumatologist; or Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis
	<b>Prescribing Instructions:</b> None proposed.
	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.

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Restriction summary: New; ToC: New

<b>Concept ID</b>	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – In Writing
	<b>Administrative Advice:</b> (See end of this document for common administrative advice)
	<b>Condition:</b> Ankylosing spondylitis
	<b>Indication:</b> Ankylosing spondylitis
	<b>Treatment Phase:</b> Grandfather patients
	<b>Clinical criteria:</b>
	The condition must be radiographically (plain X-ray) confirmed Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have had at least 2 of the following prior to commencing non-PBS subsidised treatment: (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
	<b>AND</b>
	<b>Clinical criteria:</b>
	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 prior to commencing non-PBS subsidised treatment
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have demonstrated an adequate response to treatment with this drug
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not receive more than 24 weeks of treatment under this restriction
	<b>AND</b>
	<b>Treatment criteria:</b>
	Must be treated by a rheumatologist; or Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must be at least 18 years of age
	<b>Prescribing Instructions:</b> The application must include details of the NSAIDs trialed, 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.
	<b>Prescribing Instructions:</b>

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	<p>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:</p> <p>(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.</p> <p>The baseline BASDAI score and ESR or CRP level must be 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 cannot be met, the application must state the reason this criterion cannot be satisfied.</p>
	<p><b>Prescribing Instructions:</b>          The authority application must be made in writing and must include:</p> <p>(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</p>
	<p><b>Prescribing Instructions:</b>          An adequate response is defined as an improvement from baseline of at least 2 units (on a scale of 0-10) in the BASDAI score combined with at least 1 of the following:          (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.</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><b>Prescribing Instructions:</b>          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 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>
	<p><b>Prescribing Instructions:</b>          Where a response assessment is not conducted within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.</p>
	<p><b>Prescribing Instructions:</b>          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.</p>
	<p><b>Prescribing Instructions:</b>          A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.</p>
	<p><b>Administrative Advice:</b>          This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</p>
	<p><b>Administrative Advice:</b>          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 <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a></p>
	<p><b>Administrative Advice:</b>          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 <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a></p>
	<p><b>Administrative Advice:</b>          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. Monday to Friday).</p>

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	<p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a></p> <p>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a></p> <p>Or mailed to:          Services Australia          Complex Drugs          Reply Paid 9826          HOBART TAS 7001</p>
	<p><b>Administrative Advice:</b>          No increase in the maximum quantity or number of units may be authorised.</p>
	<p><b>Administrative Advice:</b>          No increase in the maximum number of repeats may be authorised.</p>
	<p><b>Administrative Advice:</b>          Special Pricing Arrangements apply.</p>
<p><b>OVERARCHING ADMINISTRATIVE ADVICE</b></p>	
	<p><b>Administrative Advice:</b></p> <p>TREATMENT OF ADULT PATIENTS WITH ANKYLOSING SPONDYLITIS</p> <p>The following information applies to Pharmaceutical Benefits Scheme (PBS) benefits listed for adult patients with the indication of ankylosing spondylitis (AS).</p> <p>Where the term 'biological medicine' appears in notes and restrictions, it refers to any PBS benefit where the PBS indication specifies: Ankylosing spondylitis. Some benefits are not biological medicines, but are small molecules. However, for administrative purposes, these benefits are included within the term "biological medicine".</p> <p>Treatment cycles:</p> <p>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 1 October 2021 is considered to start their first cycle as of 1 October 2021.</p> <p>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.</p> <p>Where treatment has resulted in an inadequate response on 3 occasions a treatment cycle is considered to have been completed and there must be a 5-year break in PBS-subsidy from all medicines with the PBS indication: 'Ankylosing spondylitis' before starting a new treatment 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.,</p> <p>Where treatment has resulted in an inadequate response on fewer than 3 occasions in a treatment cycle and where a break in therapy of less than 5 years has occurred, a further course of treatment may be commenced within the same treatment cycle.</p> <p>There is no limit to the number of treatment cycles a patient may undertake in their lifetime.</p>

<p>Prescribing under the correct 'Treatment phase' listing for the authority application:</p> <p>(1) Initial treatment. Apply under the 'Initial 1' treatment listing where the patient has never received a biological medicine for ankylosing spondylitis</p> <p>(2) Grandfather patients (tofacitinib only) A patient who commenced treatment with tofacitinib for ankylosing spondylitis prior to [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.</p> <p>(3) Continuing treatment. Apply under the 'Continuing treatment' listing where the patient is experiencing an adequate response as defined in the restriction where there has been no change in prescribed biological medicine. Under no circumstance is continuing treatment to proceed initial treatment. An authority application for continuing treatment is not to be made on the same day as initial treatment.</p> <p>(4) Changing therapy., Apply under the 'Initial 2' treatment listing. 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 will not need to be restated. 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 change to a particular biological medicine if it has failed to provide the patient with an adequate response within the same treatment cycle., A response assessment to the preceding supply of biological medicine must accompany this initial 2 treatment authority application.</p> <p>(5) Baseline measurements to determine response., A response to treatment is to be determined by comparison of current disease activity measurements relative to the baseline measurements of the BASDAI, ESR and/or CRP submitted with the first authority application for a biological medicine. 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. 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.,</p> <p>(6) Recommencement of treatment after a 5-year break in PBS-subsidised therapy., Apply under the 'Initial 3' treatment listing. Prior NSAID and exercise therapies need not be re-trialled.</p>
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***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**

Pfizer Australia welcomes the PBAC recommendation to list Xeljanz on the PBS for patients with Ankylosing Spondylitis and is working with the Department of Health and Aged Care to achieve the earliest possible listing.