6.04 IXEKIZUMAB, Injection 80 mg in 1 mL single dose pre-filled pen, Taltz®, Eli Lilly Australia Pty. Ltd.

1 Purpose of submission

1.1 The submission requested an Authority Required listing for ixekizumab for the treatment of adult patients with active ankylosing spondylitis (AS).

1.2 The listing was requested on the basis of a cost-minimisation analysis versus adalimumab (Table 1).

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

Component	Description
Population	Adults with radiographic confirmed (active) ankylosing spondylitis
Intervention	Ixekizumab 80 mg every 4 weeks
Comparator	**Main comparator**: Adalimumab 40 mg, every 2 weeks **Secondary comparator**: Secukinumab 150 mg at weeks 0,1,2,3 and 4 followed by the same dose every month
Outcomes	Efficacy: ASAS20, ASAS40 and BASDAI 50 (or change in BASDAI from baseline [a]) Safety: Frequency of TEAE, SAE and discontinuations.
Clinical claim	In adults with active ankylosing spondylitis, ixekizumab has non-inferior [b] efficacy and comparable safety with adalimumab or secukinumab.

Source: Table 1.1.1, p30 of the submission and added during the evaluation
ASAS = Assessment of SpondyloArthritis international Society; ASAS20/40 = Assessment of SpondyloArthritis international Society 20%/40% response criteria; BASDAI = Bath ankylosing spondylitis disease activity index; BASDAI 50 = Bath ankylosing spondylitis disease activity index 50, defined as a ≥ 50% improvement in BASDAI score from baseline; PBAC = Pharmaceutical Benefits Advisory Committee; SAE = serious adverse events; TEAE = treatment-emergent adverse events
[a] For BASDAI response, the comparison of ixekizumab with adalimumab used BASDAI 50, whereas the comparison with secukinumab used the change in BASDAI from baseline.
[b] The submission reiterated that for the purpose of this submission, PBAC's clinical claim terminology "non-inferior" also has the same meaning as comparable or similar

2 Background

Registration status

2.1 Ixekizumab was registered by the Therapeutic Goods Administration (TGA) on 6 March 2020 for treatment of active AS in adult patients. At the time of evaluation for PBAC consideration, the TGA Delegate's Overview and Advisory Committee on Medicines (ACM) advice were available.

Previous PBAC consideration

2.2 Ixekizumab has previously been considered by PBAC for severe chronic plaque psoriasis (July 2016) and severe psoriatic arthritis (July 2018), and is listed on the PBS for these indications. This submission requested an extension of the current ixekizumab PBS listing to include active AS.

3 Requested listing

3.1 An abridged listing is provided below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
IXEKIZUMAB Initial-1 and initial-2 [a] 80 mg/ mL, 2 x 1 mL pen device	1	2	1	$3,412.04 published price $[redacted] effective price	Taltz® Eli Lilly Australia Pty Ltd.
Continuing treatment 80 mg/ mL, 2 x 1 mL pen device	1	2	2		

Source: Table 1.4.1, p46 of the submission

[a] Initial treatment-1 is for new patients, or patients recommencing treatment after a break of 5 years or more; and Initial treatment-2 is for those who change or recommence after a break in biological medicine treatment of less than 5 years.

Severity:	Ankylosing Spondylitis
Condition:	Active Ankylosing Spondylitis
PBS Indication:	Initial treatment 1 - new patients ~~or patients recommencing treatment after a break of 5 years or more~~ Initial treatment 2 - change or recommencement of treatment after a break in biological medicine treatment less than 5 years
Treatment phase:	Initial treatment
Restriction:	☒Authority Required - In Writing
Treatment criteria:	Must be treated by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis.
Clinical criteria:	Initial Treatment 1 (new patients ~~or patients recommencing treatment after a break of 5 years or more~~) • The condition must be radiographically (plain X-ray) confirmed Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis, AND • Patient must not have received any PBS-subsidised treatment with a biological medicine for this condition, AND • Patients 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 • *Patient must not receive more than 16 weeks of treatment under this restriction*
	Initial Treatment 2 (change or recommencement of treatment after a break in biological medicine treatment of less than 5 years) • Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle, AND • 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 • *Patient must not receive more than 16 weeks of treatment under this restriction*
Population criteria:	~~Patient must be an adult~~ *Patient must be aged 18 years or older*

Severity:	Ankylosing Spondylitis
Condition:	Active Ankylosing Spondylitis
PBS Indication:	Continuing treatment - patient that has responded to the most recent treatment cycle with ixekizumab in ankylosing spondylitis.
Treatment phase:	Continuing treatment
Restriction:	☒Authority Required - In Writing
Treatment criteria:	Must be treated by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis.
Clinical criteria:	Patient must have received this drug as their most recent course of PBS-subsidised biological disease modifying anti-rheumatic drug (bDMARD) treatment in this treatment cycle, AND Patient must have demonstrated an adequate response to treatment with this drug. *AND* *Patient must not receive more than 24 weeks of treatment under this restriction*
Population criteria:	~~Patient must be an adult~~ *Patient must be aged 18 years or older*
Definitions:	An adequate response is defined as an improvement from baseline of at least 2 of the BASDAI and 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.

Source: Table 1.4.2, pp 47-48 of the submission.
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; bDMARD = biological disease modifying anti-rheumatic drug; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; NSAID = non-steroidal anti-inflammatory drug; PBS = Pharmaceutical Benefits Scheme

3.2 The submission requested a listing consistent with the existing biological medicines for AS with an initial treatment period of 16 weeks and continuing treatment period of 24 weeks.

3.3 The submission did not request a separate Initial-3 restriction for patients recommencing treatment after a treatment break of more than 5 years (rather, this was included in the Initial-1 restriction), balance of supply restrictions, or a grandfathering restriction. The Sponsor advised in its Pre-Sub-Committee Response (PSCR) that there are currently no patients that would need to be transitioned to PBS treatment and a grandfathering restriction was not required (page 3). The Secretariat proposed wording for Initial-3 and balance of supply restrictions during the evaluation.

3.4 The Sponsor requested a Special Pricing Arrangement (SPA) for this indication. A SPA is currently in place for ixekizumab for the plaque psoriasis and psoriatic arthritis indications. The requested published price was consistent with the current published price.

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

4 Population and disease

4.1 AS is a form of progressive axial spondyloarthritis caused by chronic inflammation and enthesitis (inflammation of soft tissues like, muscles, tendons or ligaments where these enter the bones) involving the spine, sacroiliac joints and thoracic cage.

4.2 Ixekizumab is proposed as an alternative to the currently PBS-listed biological medicines (secukinumab, adalimumab, etanercept, golimumab, infliximab and certolizumab pegol) for AS.

4.3 Ixekizumab is a humanised immunoglobulin G subclass 4 (IgG4) monoclonal antibody that binds with high affinity to the proinflammatory cytokine interleukin 17 alpha (IL-17A). It is the seventh biological medicine and the second IL-17A inhibitor to be proposed for listing on the PBS for AS, following the PBS listing of secukinumab for this indication in 2016.

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

5 Comparator

5.1 The submission nominated adalimumab as the main comparator, with secukinumab as a secondary comparator. Adalimumab was nominated as the main comparator because it is the market share leader in active AS (41.4% market share), and would be the medicine most likely to be replaced in the market if the requested PBS listing of ixekizumab is recommended. Secukinumab (7.8% market share) was nominated as the secondary comparator, as the pharmacological analogue of ixekizumab.

5.2 Under Section 101(3B) of the National Health Act (1953) where therapy involving the use of a particular drug or medicinal preparation, or a class of drugs and medicinal preparations, is substantially more costly than an alternative therapy or alternative therapies, whether or not involving the use of other drugs or preparations, the Committee shall not recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part unless the Committee is satisfied that the first-mentioned therapy, for some patients, provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies.

5.3 Adalimumab and secukinumab were appropriate comparators; however, ixekizumab may replace any of the six currently PBS-listed biological medicines for AS. The PBAC noted no evidence was provided to demonstrate ixekizumab provided an improvement in efficacy or reduction of toxicity over the alternative therapies.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from one individual via the Consumer Comments facility on the PBS website. The comments described the significant negative impact of AS on quality of life and the importance of having a variety of treatment options available.

Clinical trials

6.3 The submission was based on (Table 2):

- one direct randomised trial (COAST-V, N = 341) that compared ixekizumab with adalimumab (and placebo) in biological medicine-naïve patients with AS;
- one randomised trial (COAST-W, N = 316) that compared ixekizumab with placebo in tumour necrosis factor inhibitor (TNFi)-experienced patients with AS; and
- two randomised trials (MEASURE 2, N = 219 and MEASURE 4, N = 350) that compared secukinumab with placebo in both TNFi-naïve and TNFi-experienced patients with AS.

6.4 The submission also presented an additional placebo-controlled trial of secukinumab (MEASURE 5, N = 458) as a sensitivity analysis as only an abstract was available for this trial. The submission excluded two other placebo-controlled secukinumab trials, MEASURE 1 and MEASURE 3, as they used intravenous secukinumab loading doses.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
COAST-V (NCT02696785)	A Multicenter, Randomised, Double-Blind, Active and Placebo-Controlled 16-Week Study Followed by Long Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in bDMARD-Naive Patients with Radiographic Axial Spondyloarthritis. Eli Lilly and Company. van der Heijde 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.	9 October 2018. Lancet 2018; 392: 2441-2451.
COAST-W (NCT02696798)	A Multicenter, Randomised, Double-Blind, Placebo-Controlled 16-Week Study Followed by Long-Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in TNFi-Experienced Patients with Radiographic Axial Spondyloarthritis. Eli Lilly and Company. Deodhar et al. Efficacy and Safety of Ixekizumab in the Treatment of Radiographic Axial Spondyloarthritis: Sixteen-Week Results From a Phase III Randomised, Double-Blind, Placebo-Controlled Trial in Patients With Prior Inadequate Response to or Intolerance of Tumor Necrosis Factor Inhibitors.	11 September 2018. Arthritis Rheumatol 2019; 71 (4): 599-611.
MEASURE 2 (NCT01649375)	Baeten et al. (2015) Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis.	New Engl J Med 2015; 373: 2534-2548.
MEASURE 4 (NCT02159053)	Kivitz et al. (2018) Efficacy and Safety of Secukinumab 150 mg with and Without Loading Regimen in Ankylosing Spondylitis: 104-week Results from MEASURE 4 Study.	Rheumatol Ther 2018; 5: 447-462.
MEASURE 5	Huang et al. Secukinumab provides rapid and significant improvement in the signs and symptoms of ankylosing spondylitis: primary (16-week) results from a phase 3 China-centric study, measure 5.	Ann Rheum Dis 2019; 78: 894-895.

Source: Table 2.2.1, p62 of the submission.
bDMARDS = biological disease-modifying anti-rheumatic drugs; TNFi = tumour necrosis factor inhibitor

6.5 The key features of the included trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Ixekizumab vs. adalimumab (vs. placebo)					
COAST-V	341	R, DB, MC 16 weeks	Unclear [a]	Adults, AS (ASAS [b]), biological medicine-naïve, BASDAI score ≥ 4 and total back pain ≥ 4 on an NRS, inadequate response to ≥ 2 NSAIDs or intolerance to NSAIDs, prior therapy for AS for ≥ 12 weeks	Primary ASAS40 Secondary ASAS20, BASDAI 50, change in BASDAI, ASDAS clinical improvement, ASDAS inactive disease
Ixekizumab vs. placebo					
COAST-W	316	R, DB, MC 16 weeks	Unclear [c]	Adults with AS (ASAS [b]) [d], TNFi-experienced, BASDAI score of ≥ 4 and spinal pain ≥ 4 on an NRS, inadequate response to ≥ 2 NSAIDs or history of intolerance to NSAIDs, prior therapy for ≥ 12 weeks	Primary ASAS40 Secondary [e] ASAS20, change in BASDAI
Meta-analysis	657	COAST-V and COAST-W; assessed ASAS20, ASAS40 and change in BASDAI			
Secukinumab vs. placebo					
MEASURE 2	219	R, DB, MC 16 weeks	Low	Adults with AS (mNY) [d], TNFi-experienced or naïve, BASDAI score of ≥ 4 and total back pain ≥ 4 on a 0-10 cm VAS, failed or inadequate response or intolerant to NSAIDs	Primary ASAS20 Secondary [f] ASAS40, change in BASDAI
MEASURE 4	350	R, DB, MC 16 weeks	Low		
Meta-analysis	569	MEASURE 2 and MEASURE 4; assessed ASAS20, ASAS40 and change in BASDAI			

Source: Table 2.2.3, p65 and Table 2.7.3, p101 of the submission; Table RHBV14.5, pp158-160 COAST-V CSR; Table RHBW.14.5, pp168-169 COAST-W CSR

AS = ankylosing spondylitis; ASAS = Assessment of SpondyloArthritis international Society; ASAS20/40 = Assessment of SpondyloArthritis international Society 20%/40% response criteria; ASDAS = ankylosing spondylitis disease activity score; BASDAI = Bath ankylosing spondylitis disease activity index; BASDAI 50 = Bath ankylosing spondylitis disease activity index 50, defined as a ≥ 50% improvement in BASDAI score from baseline; BASFI = Bath ankylosing spondylitis functional index; DB = double blind; MC = multi-centre; HI = health index; hsCRP = high sensitivity c-reactive protein; mNY = modified New York criteria; NRS = numeric rating scale; NSAID = non-steroidal anti-inflammatory drug; Q4W = every 4 weeks; R = randomised; SpA = spondyloarthritis; TNFi = tumour necrosis factor inhibitor; VAS = visual analogue scale; vs. = versus

[a] COAST-V had several important protocol deviations: 4.7% of patients took an incorrect study medication (6.2% in ixekizumab Q4W arm vs. 2.2% in adalimumab and 4.6% in placebo), 0.6% had unqualified personnel perform assessments (1.1% in placebo and 1.1% in adalimumab vs. 0% in ixekizumab Q4W arm) 5% did not have AS at screening (7.8% in adalimumab and 6.2% ixekizumab Q4W vs. 4.6% in placebo), 1.5% did not have active AS (2.2% in adalimumab vs. 0% in ixekizumab Q4W or placebo), and 11.7% provided improper informed consent (14.8% in ixekizumab Q4W or 12.2% in adalimumab arms vs. 8% in placebo). The risk of bias was considered low for all other domains.

[b] ASAS criteria for classification of axial spondyloarthritis. Requires sacroiliitis on imaging (COAST trials required X-ray as per mNY criteria) and ≥ 1 SpA feature

[c] COAST-W had several important protocol deviations: 4.4% had unqualified staff perform assessments (4.8% in placebo vs. 2.6% in ixekizumab Q4W), 5.4% of patients did not have AS at screening (similar between arms), 1.3% did not have active AS (1.9% in placebo vs. 0% in ixekizumab Q4W arm), and 11.7% provided improper informed consent (14.4% in placebo vs. 10.5% in ixekizumab Q4W). The risk of bias was considered low for all other domains.

[d] Requires definitive sacroiliitis on conventional x-rays (unilateral grade 3-4 or bilateral grade 2-4) and one of: low back pain (≥ 3 months) improved by exercise but not rest, limited lumbar spine motion, or decreased chest expansion

[e] Other secondary outcomes included: Proportion of patients achieving an ASAS20 response, ASDAS < 2.1; Change from baseline in ASDAS, BASDAI, BASFI, SF-36 PCS score, ASAS HI, MRI of the spine (SPARCC score)

[f] Other secondary outcomes included: change from baseline in hsCRP, BASDAI, SF-36 PCS, ASQoL and overall safety

6.6 The comparison with adalimumab was based on a post-hoc analysis of the COAST-V trial. COAST-V was powered to detect superiority with placebo and the pre-specified analyses compared ixekizumab and adalimumab with placebo.

6.7 The comparison with secukinumab was based on an indirect treatment comparison (ITC) that compared the meta-analysis of ixekizumab trials (COAST-V and COAST-W) with the meta-analysis of secukinumab trials (MEASURE 2 and MEASURE 4), with placebo as the common reference. MEASURE 4 was not considered by the PBAC at its March 2016 consideration of secukinumab for AS.

6.8 The ixekizumab and secukinumab trials used different diagnostic criteria. The secukinumab trials used the modified New York (mNY) criteria while the ixekizumab trials used the 2009 ASAS criteria for classification of axial spondyloarthritis. The ixekizumab trials required patients to have radiographic sacroiliitis on x-ray as per the mNY criteria. However, the ASAS criteria also allow identification of sacroiliitis on magnetic resonance imaging (MRI). The ASAS criteria require age of onset below 45 years, and at least one SpA features (inflammatory back pain, elevated CRP, family history, response to NSAIDs or extraspinal manifestations). An overview of the differences is presented in Table 4.

Table 4: Summary of inclusion and exclusion criteria across included trials

Criterion	COAST-V	COAST-W	MEASURE 2	MEASURE 4
AS diagnosis	ASAS criteria [a]		Modified New York criteria [b]	
sacroiliitis on radiograph	Modified New York criteria		Modified New York criteria	
SpA features [c]	≥ 1		Not required	
Back pain ≥ 3 months	Yes (Modified New York criteria)		Yes (trial criterion)	
Age < 45 years at onset	Yes		No	
ESR or CRP threshold	No [c]		No	
BASDAI ≥ 4	Yes		Yes	
Pain	≥ 4 out of 10 (NRS)		≥ 4 out of 10 (VAS)	
NSAID use	Inadequate response ≥ 2, or intolerance		Pain despite maximal dose	
Biological medicine use	No	1 – 2 TNFi [d]	Up to 1 TNFi [d]	
Duration of prior therapy	≥ 12 weeks		Not stated	
Total spinal ankylosis	Excluded		Excluded	

Source: Section 2.4, pp73-74; Section 2(i).4, pp131-132 submission; Section 9.3, pp48-49 COAST-V CSR; Section 9.3, pp47-48 COAST-V CSR; Rudwaleit et al. 2009

AS = ankylosing spondylitis; ASAS= Assessment of SpondyloArthritis international Society; BASDAI = Bath ankylosing spondylitis disease activity index; CRP = c-reactive protein; CSR = clinical study report; ESR = erythrocyte sedimentation rate; NRS = numeric rating scale; NSAID = nonsteroidal anti-inflammatory drugs; SpA = SpondyloArthritis; TNFi = tumour necrosis factor inhibitor; VAS = visual analogue scale

[a] 2009 ASAS criteria for classification of axial spondyloarthritis. Requires sacroiliitis on imaging (COAST trials required X-ray) and ≥ 1 SpA feature (Rudwaleit et al. 2009)

[b] Requires definitive sacroiliitis on conventional x-rays (unilateral grade 3-4 or bilateral grade 2-4) and one of: low back pain (≥ 3 months) improved by exercise but not rest, limited lumbar spine motion, or decreased chest expansion.

[c] SpA features include any of: inflammatory back pain, dactylitis, arthritis, enthesitis, uveitis, psoriasis, Crohn's disease/ulcerative colitis, good response to NSAIDs, family history of SpA, elevated CRP

[d] Inadequate response

6.9 The proposed PBS restrictions were better aligned with the mNY criteria. Although the mNY and ASAS criteria differed, they appear to diagnose the same patients with AS.

Boel et al. (2019)[1], a study of 4,041 people diagnosed with ax-SpA, reported that almost all patients who meet the mNY criteria met the ASAS criteria if the age criterion in the ASAS criteria was disregarded.

6.10 The submission claimed there were no trial-related factors that would reduce the internal validity of the trial or increase the risk of bias. The ixekizumab trials (COAST-V and COAST-W) were considered to have an unclear risk of bias as they had several major protocol deviations, including some which were imbalanced between treatment arms such as provision of incorrect trial medication (COAST-V only), enrolment of patients who did not have radiographically confirmed active AS, assessments performed by unqualified site personnel and problems with obtaining timely and accurate updated informed consent (both trials). All other domains were considered to have a low risk of bias. The impact of the protocol deviations on the reliability of the trial results was unclear. The results from the per-protocol results that excluded patients with significant protocol deviations and a trial site with Good Clinical Practice issues was included in the evaluation.

6.11 The ixekizumab and secukinumab trials included arms with dosing regimens that differed from the approved Product Information. The results for these arms are not presented below.

Comparative effectiveness

6.12 Under the proposed PBS criteria, continued treatment is dependent on demonstrating and maintaining response to therapy, assessed after a minimum of 12 weeks following initial therapy (and every 24 weeks ongoing thereafter). Response is defined as a reduction from baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score by 2 or more units and one of the following: an erythrocyte sedimentation rate (ESR) measurement no greater than 25 mm per hour, a c-reactive protein (CRP) measurement no greater than 10 mg/L, or an ESR or CRP or measurement reduced by at least 20% from baseline. The trials did not report an outcome that fully aligned to the PBS continuation criteria. BASDAI 50 response (≥ 50% reduction in BASDAI score) was reported in the ixekizumab trials. As both the ixekizumab and secukinumab trials recruited participants with BASDAI ≥ 4, a BASDAI 50 response corresponded to a ≥ 2-point reduction in the BASDAI score. BASDAI 50 response rates were not reported in the secukinumab trial publications. Therefore, for the comparison with secukinumab, the submission presented a comparison of the mean change in BASDAI score from baseline. However, the PBAC considered BASDAI 50 response rates from the MEASURE 2 trial at its March 2016 consideration of

[1] Boel A, Molto A, van der Heijde D, *et al.* Do patients with axial spondyloarthritis with radiographic sacroiliitis fulfil both the modified New York criteria and the ASAS axial spondyloarthritis criteria? Results from eight cohorts. Ann Rheum Dis 2019; 78:1545-9.

secukinumab (Table 2, secukinumab, Public Summary Document (PSD), March 2016 PBAC meeting).

6.13 The proportion of patients with an ankylosing spondylitis disease activity score (ASDAS) clinical improvement was included in the evaluation as the ASAS-EULAR guidelines (van der Heijde 2017) recommended that the ASDAS was favoured compared to the BASDAI for assessing disease activity and response/continuation of biological medicines. The ASDAS is a relatively new index for measuring disease activity in AS, which combines patient-reported outcomes and levels of CRP into one index. The publication stated that ASDAS is a better index than BASDAI for several reasons including better correlation with patients' and physicians' opinion of disease activity, high scores being a predictor of TNFi continuation (which can be seen as a surrogate outcome for efficacy) and use of validated cut-offs.

6.14 Tables 5 presents the results of the key effectiveness outcomes from the COAST-V trial.

Table 5: Treatment response rates at Week 16 (NRI) for ITT population in COAST-V

	IXEQ4W n/N (%)	ADA n/N (%)	PBO n/N (%)	IXEQ4W vs. ADA		
				RD (95% CI) [a]	RR (95% CI) [a]	OR (95% CI)
ASAS20						
ITT	52/81 (64)	53/90 (59)	35/87 (40)	5.3 (-9.3,19.9)	1.09 (0.86,1.38)	1.21 (0.65, 2.26) [b]
ASAS40						
ITT	39/81 (48)	32/90(36)	16/87 (18)	12.6 (-2.1, 27.3)	1.35 (0.95, 1.94)	1.63 (0.88, 3.04) [b]
BASDAI 50						
ITT	34/81 (42)	29/90 (32)	15/87 (17)	9.8 (-4.7, 24.2)	1.30 (0.88, 1.93)	1.48 (0.79, 2.79) [b]
ASDAS clinical improvement (≥ 1.1-point improvement)						
ITT	50/81 (62)	49/90 (54)	20/87 (23)	7.3 (-7.5, 22) [c]	1.13 (0.88, 1.46) [c]	1.35 (0.73, 2.49) [c]
ASDAS inactive disease (ASDAS < 1.3)						
ITT	13/81 (16)	14/90 (16)	2/87 (2)	0.5 (-10.5,11.4) [c]	1.03 (0.52, 2.06) [c]	1.04 (0.46, 2.36) [c]

Source: Table 2.6-1 to Table 2.6-3, pp92-93, Table 2.5-6, p90 of the submission; Attachment 2.1 and 2.2; Table RHBV.14.18, pp338-345, Table RHBV 14.19, pp346-347, Table RHBV 14.40, pp580-592, Table RHBV 14.34, pp542-547, Table RHBV 14.41, p598 and Table RHBV 14.42, p605 of COAST-V CSR

ADA = adalimumab 40 mg every 2 weeks; ASAS20/40 = Assessment of SpondyloArthritis international Society 20%/40% response criteria; ASDAS = ankylosing spondylitis disease activity score; BASDAI 50 = Bath ankylosing spondylitis disease activity index 50, defined as a ≥ 50% improvement in BASDAI score from baseline; CI = confidence interval; CRP = C-reactive protein; ITT = intention-to-treat; IXEQ4W = ixekizumab 80 mg every 4 weeks; NRI = non-responder imputation; OR = odds ratio; PBO = placebo; RD = risk difference; RR = relative risk; vs. = versus

[a] Risk difference and relative risk presented were unadjusted for covariates.

[b] Logistic regression analysis with treatment, geographic region and baseline CRP status as factors

[c] Calculated during the evaluation. Not adjusted for covariates

Note: Comparisons of ixekizumab with placebo are presented with the indirect treatment comparison

6.15 The response rate in terms of ASAS20, ASAS40, BASDAI 50 and ASDAS clinical improvement were not statistically different between ixekizumab and adalimumab. A numerically higher proportion of patients achieved an ASAS20, ASAS40, BASDAI 50, or ASDAS clinical improvement (≥ 1.1-point improvement) with ixekizumab than adalimumab. The proportion of patients achieving ASDAS inactive disease (ASDAS < 1.3) was similar for both biological medicines.

6.16 The submission nominated a non-inferiority margin of 0.43 for the relative risk of ASAS20 at week 16 based on the PSD for certolizumab pegol and secukinumab in AS

(certolizumab pegol PSD, March 2014 PBAC meeting; secukinumab PSD, March 2016 PBAC meeting). The submission considered that non-inferiority was supported as the lower bounds of the 95% confidence interval (CI) of the relative risk estimates for ASAS20 was larger than 0.43 and showed no statistically significant difference between ixekizumab and adalimumab.

6.17 The submission did not nominate a non-inferiority margin for BASDAI 50 or ASAS40. The 95% CI for BASDAI 50 were similar to those presented in the March 2016 consideration of secukinumab (Table 4, secukinumab PSD, March 2016 PBAC meeting).

6.18 The proportion of patients achieving an improvement in ASDAS (≥ 1.1 point-improvement) was considered a clinically important improvement in the ASAS-EULAR guidelines. The rate of ASDAS clinical improvement was numerically higher with ixekizumab than adalimumab. The proportion of patients with inactive disease according to the ASDAS was similar for both drugs.

6.19 The results of the per-protocol analysis for ASAS20 and ASAS40 were consistent with the intention to treat (ITT) analysis. The PBAC considered the consistency between the ITT and per-protocol analyses of ASAS20 and ASAS40 response rates supported the reliability of the ITT outcomes, regardless of the protocol deviations in the two trials.

6.20 The submission presented a meta-analysis of the COAST-V (biological medicine-naïve) and COAST-W (TNFi-experienced) ixekizumab trials to examine the effect of prior TNFi use. The submission considered the results of the meta-analyses (Tables 6 and 7) showed a consistent treatment effect across both populations with no heterogeneity observed for ASAS20 and ASAS40 response and change in BASDAI score. However, the evaluation considered this may not be appropriate, and the results of this meta-analyses should be interpreted with caution especially in relation to the comparison of IXEQ4W versus adalimumab in treatment-experienced patients. While there was statistical homogeneity based on the I^2 statistics (i.e. the relative risks for IXEQ4W vs placebo appeared reasonably consistent across the studies) there was considerable difference in the response rate in both populations. The ASAS40 response and change in BASDAI results were numerically worse for TNFi-experienced patients than biological medicine-naïve patients for both IXEQ4W and placebo. The TNFi-experienced cohort in COAST-W also had slightly worse BASDAI and ASDAS scores at baseline compared to the biological medicine-naïve cohort in COAST-V.

Table 6: Meta-analysis of ASAS20 and ASAS40 response in the ixekizumab trials

Outcome	Trial ID	IXEQ4W n/N (%)	Placebo n/N (%)	RD (95% CI)	RR (95% CI)
ASAS20	COAST-V	52/81 (64.2)	35/87 (40.2)	0.24 (0.09, 0.39)	1.60 (1.18, 2.16)
	COAST-W	55/114 (48.2)	31/104 (29.8)	0.18 (0.06, 0.31)	1.62 (1.14, 2.30)
	Meta-analysis of overall trial results			0.21 (0.11, 0.30)	1.61 (1.28, 2.02)
	Tau (heterogeneity)			0	0
	I^2 (95% CI)			0 (NA, NA)	0 (NA, NA)
	Test of heterogeneity: Q (df))			0.31 (1) p = 0.58	0 (1) p = 0.95
ASAS40	COAST-V	39/81 (48.1)	16/87 (18.4)	0.30 (0.16, 0.43)	2.6 (1.59, 4.30)
	COAST-W	29/114 (25.4)	13/104 (12.5)	0.13 (0.03, 0.23)	2.04 (1.12, 3.70)
	Meta-analysis of overall trial results			0.21 (0.04, 0.37)	2.36 (1.61, 3.46)
	Tau (heterogeneity)			0.0107	0
	I^2 (95% CI)			74 (0, 94.1)	0 (NA, NA)
	Test of heterogeneity: Q (df))			3.85 (1) p = 0.05	0.4 (1) p = 0.53

Source: Table 2.7-3, p101 of the submission.
ASAS20/40 = Assessment of SpondyloArthritis international Society 20/40% response criteria; CI = confidence interval; df = degrees of freedom; IXEQ4W= ixekizumab 80 mg every four weeks; NA = not applicable; OR = odds ratio; RD = risk difference; RR = relative risk

Table 7: Meta-analysis of change in BASDAI score in the ixekizumab trials

Trial ID	IXEQ4W			Placebo			Mean difference (95% CI)
	Mean baseline (SD)	Mean end point (SD)	Mean change (SE)	Mean baseline (SD)	Mean end point (SD)	Mean change (SE)	
COAST-V	6.75 (1.32)	*3.71 (2.01)*	-2.92 (0.22)	*6.79* (1.22)	*5.28 (2.05)*	-1.39 (0.22)	**-1.54 (-2.14, -0.93)**
COAST-W	7.54 (1.34)	*5.18 (2.16)*	-2.17 (0.20)	7.32 (1.26)	*6.37 (2.03)*	-0.92 (0.21)	**-1.24 (-1.81, -0.67)**
Pooled ixekizumab							**-1.38 (-1.80, -0.96)**
Tau (heterogeneity)							0
I^2 (95% CI)							0 (NA, NA)
Test of heterogeneity: Q (df))							0.43 (1) P = 0.513

Source: Table 2.7-3, p104 of the submission; *Table RHBV.14-32, p501 of COAST-V CSR*; *Table RHBW.14-32, p495 of COAST-W CSR*
BASDAI = Bath ankylosing spondylitis disease activity index; CI = confidence interval; CSR = clinical study report; IXEQ4W= ixekizumab 80 mg every four weeks; NA = not applicable; SD = standard deviation; SE = standard error; ***Bold*** = *statistically significant; Italics* = added/corrected during evaluation

6.21 The submission also suggested that ixekizumab may perform better than adalimumab in TNFi-experienced patients, as the RHAPSODY trial of adalimumab in AS showed numerically lower rates of ASAS20 and BASDAI 50 response in TNFi-experienced compared with TNFi-naïve patients, implicitly suggesting ixekizumab would perform better, as the response rates were consistent across ixekizumab-treated TNFi-naïve and TNFi-experienced patients in the COAST trials. This was not supported by the formal comparison presented in the submission.

6.22 The submission presented an ITC of the ixekizumab (COAST-V and COAST-W) and secukinumab trials (MEASURE 2 and MEASURE 4) (presented in Tables 8 and 9). The submission conducted unadjusted meta-analyses in the combination of the individual trials. The evaluation considered this may not have been appropriate and may lead to transitivity concerns in the ITC; however, it was noted that adjusted relative risk and odds ratio were not available for the MEASURE trials. The submission presented unadjusted, pairwise indirect comparisons of the meta-analyses using standard frequentist methods as described by Bucher et al. (1997). However, as unadjusted meta-analyses were conducted it should be noted that the Bucher method does not

account for treatment effect modifiers which were not balanced between treatment arms (such as concomitant therapies).

6.23 The submission presented risk differences, relative risks and odds ratios of the response outcomes for the meta-analysis; however, only relative risks and odds ratios are presented below.

6.24 The publications for the secukinumab trials did not report BASDAI 50 or ASDAS outcomes. The BASDAI 50 outcomes from the MEASURE 2 trial were presented to the PBAC in the secukinumab submission for AS (paragraph 6.10, secukinumab PSD, March 2016 PBAC meeting).

Table 8: Indirect comparison of ixekizumab and secukinumab ASAS20 and ASAS40 response

Outcome Trial ID	Drug n/N (%)	Placebo n/N (%)	RR (95% CI)	OR (95% CI)
ASAS20 [a]				
COAST-V	52/81 (64.2)	35/87 (40.2)	**1.60 (1.18, 2.16)**	**2.66 (1.43, 4.97)**
COAST-W	55/114 (48.2)	31/104 (29.8)	**1.62 (1.14, 2.30)**	**2.20 (1.26, 3.84)**
Meta-analysis (ixekizumab)			**1.61 (1.28, 2.02)**	**2.39 (1.58, 3.63)**
I^2 (95% CI)			0 (NA, NA)	0 (NA, NA)
MEASURE 2	44/72 (61.1)	21/74 (28.4)	**2.15 (1.43, 3.23)**	**3.97 (1.98, 7.93)**
MEASURE 4	69/116 (59.5)	55/117 (47.0)	1.27 (0.99, 1.62)	1.65 (0.99, 2.78)
Meta-analysis (secukinumab)			1.61 (0.95, 2.72)	**2.48 (1.06, 5.83)**
I^2 (95% CI)			79.8 (12.9, 95.3)	74.5 (0, 94.2)
ITC: Ixekizumab vs. secukinumab			1.00 (0.56, 1.77)	0.96 (0.37, 2.49)
ITC: ixekizumab vs. MEASURE 2			0.75 (0.47, 1.19)	0.60 (0.27, 1.35)
ITC: ixekizumab vs. MEASURE 4			1.27 (0.91, 1.77)	1.45 (0.74, 2.81)
ASAS40 [a]				
COAST-V	39/81 (48.1)	16/87 (18.4)	**2.62 (1.59, 4.30)**	**4.12 (2.05, 8.26)**
COAST-W	29/114 (25.4)	13/104 (12.5)	**2.04 (1.12, 3.70)**	**2.39 (1.16, 4.90)**
Meta-analysis (ixekizumab)			**2.36 (1.61, 3.46)**	**3.16 (1.85, 5.39)**
I^2 (95% CI)			0 (NA, NA)	12.6 (NA, NA)
MEASURE 2	26/72 (36.1)	8/74 (10.8)	**3.34 (1.62, 6.88)**	**4.66 (1.94, 11.21)**
MEASURE 4	45/116 (38.8)	33/117 (28.2)	1.38 (0.95, 1.99)	1.61 (0.93, 2.79)
Meta-analysis (secukinumab)			2.03 (0.85, 4.87)	2.59 (0.92, 7.29)
I^2 (95% CI)			78.8 (8.2, 95.1)	75.3 (0, 94.4)
ITC: Ixekizumab vs. secukinumab			1.16 (0.45, 3.03)	1.22 (0.38, 3.91)
ITC: Ixekizumab vs. MEASURE 2			0.71 (0.31, 1.60)	0.68 (0.24, 1.89)
ITC: Ixekizumab vs. MEASURE 4			**1.72 (1.01, 2.92)**	1.96 (0.91, 4.22)

Source: Table 2(i).6-12 and Table 2(i).6-13 of the submission

ASAS20/40 = Assessment of SpondyloArthritis international Society 20/40% response criteria; CI = confidence interval; df = degrees of freedom; ITC = indirect treatment comparison; IXEQ4W= ixekizumab 80 mg every four weeks; NA = not applicable; OR = odds ratio; RD = risk difference; RR = relative risk; vs. = versus; Bold = statistically significant;

[a] ASAS20 was the primary outcome for the secukinumab trials (MEASURE 2 and MEASURE 4). ASAS40 was the primary outcome for the ixekizumab trials (COAST-V and COAST-W).

Table 9: Indirect comparison of ixekizumab and secukinumab change in BASDAI score from baseline

Trial ID	IXEQ4W or secukinumab			Placebo			Mean difference (95% CI)
	mean baseline (SD)	mean end point (SD)	mean change (SE)	mean baseline (SD)	mean end point (SD)	mean change (SE)	
Ixekizumab							
COAST-V	6.75 (1.32)	3.71 (2.01)	-2.92 (0.22)	6.79 (1.22)	5.28 (2.05)	-1.39 (0.22)	**-1.54 (-2.14, -0.93)**
COAST-W	7.54 (1.34)	5.18 (2.16)	-2.17 (0.20)	7.32 (1.26)	6.37 (2.03)	-0.92 (0.21)	**-1.24 (-1.81, -0.67)**
Meta-analysis ixekizumab							**-1.38 (-1.80, -0.96)**
I^2 (95% CI)							0 (NA, NA)
Secukinumab							
MEASURE 2	6.6 (1.5)	NR	-2.19 (0.25)	6.8 (1.3)	NR	-0.85 (0.25)	**-1.34 (-2.03, -0.65)**
MEASURE 4	7.0 (1.23)	NR	-2.39 (0.20)	7.1 (1.27)	NR	-1.86 (0.20)	-0.53 (-1.08, 0.02)
Meta-analysis secukinumab							**-0.91 (-1.70, -0.12)**
I^2 (95% CI)							68.8 (0, 93)
ITC: Ixekizumab vs. secukinumab							-0.47 (-1.37, 0.42)
ITC: Ixekizumab vs. MEASURE 2							-0.04 (-0.85, 0.77)
ITC: Ixekizumab vs. MEASURE 4							**-0.85 (-1.55, -0.16)**

Source: Table 2(i).6-14, p175 of the submission; Table 3, p4 of A2.18 sensitivity analysis for IDC.pdf; Table RHBV.14-32, p501, Table RHBV 14.33, p509 and p522 of COAST-V CSR; Table RHBW.14-32, p495, Table RHBW 14.33, p512 and p530 of COAST-W CSR; Table 1, p2450 and Table 2, p2544 of Baeten et al. 2015; Table 1, p452 and Table 2, p454 Kivitz et al. 2018.

BASDAI = Bath ankylosing spondylitis disease activity index; CI = confidence interval; CSR = clinical study report; ITC = indirect treatment comparison; IXEQ4W= ixekizumab 80 mg every four weeks; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error; vs. = versus; **Bold** = statistically significant;

6.25 The MEASURE 2 trial reported significantly higher rates of ASAS20 and ASAS40 response and change in BASDAI score compared with placebo. MEASURE 4 did not find a significant difference in terms ASAS20 or ASAS40 response or change in BASDAI score compared with placebo.

6.26 The meta-analyses of the secukinumab trials had a high level of heterogeneity. The submission considered that this was due to the differences in placebo response between the trials. This may suggest there was underlying clinical heterogeneity in the secukinumab meta-analyses as the placebo response for all measures presented was considerably higher in MEASURE 4 than in any of the other trials presented. However, Kivitz et al. (2018), which reported the 104-week results of MEASURE 4, did not report any reason for the increased placebo response. The publication reported the treatment groups were balanced in terms of demographic and baseline disease characteristics, and considered that geographic region did not show any unexpected patterns in efficacy.

6.27 The main ITC compared the meta-analysis of the ixekizumab trials (COAST-V and COAST-W) with the meta-analysis of the secukinumab trials (MEASURE 2 and MEASURE 4). The main ITC found no statistically significant difference in ASAS20 and ASAS40 response or change in BASDAI score. The submission considered that non-inferiority was supported as the lower bounds of 95% confidence interval of the relative risk estimates for ASAS20 crossed 1 and the lower bound was larger than 0.43. The submission did not nominate a non-inferiority margin for the change in BASDAI

score. Kviatkovsky et al. (2016)[2] estimated a minimally clinically important difference of 0.7 (95% CI: 0.4, 1.0) for change in BASDAI score. The upper confidence limit of the mean difference was less than 0.7 in the main ITC, the minimally clinically important difference (MCID) estimated by Kviatkovsky et al. (2016).

6.28 The submission presented ITC sensitivity analyses that compared ixekizumab with each of the secukinumab trials separately. The ITC with MEASURE 2 was broadly consistent with the main ITC, however the point estimates and confidence intervals for ASAS20/40 responses shifted towards favouring secukinumab. The lower bound of the 95% confidence interval of the relative risk estimates for ASAS20 was larger than 0.43 non-inferiority margin previously accepted by the PBAC. The upper bound of the 95% CI for change in BASDAI score of 0.77 in the comparison with MEASURE 2 was greater than the MCID of 0.7 estimated by Kviatkovsky et al. (2016). The ITC with the MEASURE 4 trial shifted the point estimates and confidence intervals in favour of ixekizumab, with ixekizumab having a higher likelihood of ASAS40 response in terms of relative risk and a larger reduction in BASDAI score.

Comparative harms

6.29 Table 10 summarises a post-hoc comparison of the key AEs for ixekizumab versus adalimumab (the active reference arm) for the safety population of the COAST-V trial at the end of week 16.

Table 10: Summary of key adverse events in the ixekizumab trials

	IXEQ4W n/N (%)	ADA n/N (%)	RR (95% CI)
Any TEAE[a]	34/81 (42.0)	44/90 (48.9)	0.86 (0.62, 1.2)
Severe AEs	0/81	2/90 (2.2)	NA
Drug-related AEs	10/81 (12.3)	11/90 (12.2)	1.01 (0.45, 2.25)
Serious AEs	1/81 (1.2)	3/90 (3.3)	0.37 (0.04, 3.49)
Withdrawal due to AEs	0/81 (0)	1/90 (1.1)	NA
Hepatic	1/81 (1.2)	2/90 (2.2)	0.56 (0.05, 6.01)
Infections	16/81 (19.8)	19/90 (21.1)	0.94 (0.52, 1.69)
Injection site reactions	3/81 (3.7)	7/90 (7.8)	0.48 (0.13, 1.78)
Inflammatory bowel disease	0/81	0/90	NA

Source: Table 2.6-5, p94 and Table 2(i).5-9, p153 of the submission; AEs *post-hoc* analyses, pp1-5 (attachment 2.20-A2.20_ad48_t_aesm_safety_db); Calculated during evaluation

ADA = adalimumab 40 mg every 2 weeks; AE = adverse event; CI = confidence interval; IXEQ4W = ixekizumab 80 mg every 4 weeks; NA = not applicable; RR = relative risk; SAE = serious adverse event; TEAE = treatment emergent adverse event

[a] Patients with multiple occurrences of the same event are counted under the highest severity

6.30 In the COAST-V trial, there were no significant differences between ixekizumab and adalimumab for the safety outcomes. There were no statistically significant differences between ixekizumab and placebo in the occurrence of TEAEs, drug related TEAEs, SAEs, treatment discontinuation due to AEs or TEAEs of special interest. The submission noted that the COAST-W trial has more patients experiencing SAEs and

[2] Kviatkovsky, M. J., et al. (2016). The Minimum Clinically Important Improvement and Patient-acceptable Symptom State in the BASDAI and BASFI for Patients with Ankylosing Spondylitis. *J Rheumatol, 43*(9), 1680-1686. doi:10.3899/jrheum.151244

discontinuing treatment across the treatment arms than the COAST-V trial. In the COAST-W trial the ixekizumab arm had more treatment-emergent AEs, more discontinuations due to AEs, but fewer drug-related AEs compared with placebo. The ixekizumab arm also had more infections than placebo. This may be due to differences in baseline patient demographics between the two COAST trials in terms of treatment experience and concomitant treatments.

6.31 The submission presented an ITC of the two ixekizumab trials (COAST-V and COAST-W) with the secukinumab trials (MEASURE 2 and MEASURE 4) using placebo as the common comparator. Table 11 presents the results of the indirect comparison of safety.

Table 11: Indirect comparison of ixekizumab and secukinumab AEs

	Ixekizumab trials [a]		Secukinumab trials [b]		ITC
	IXEQ4W n/N (%)	Placebo n/N (%)	Secukinumab n/N (%)	Placebo n/N (%)	Relative risk (95% CI)
Any AE	107/195 (54.9)	85/190 (44.7)	119/188 (63.3)	111/191 (58.1)	1.13 (0.87, 1.46)
SAE	5/195 (2.6)	5/190 (2.6)	6/188 (3.2)	7/191 (3.7)	1.01 (0.20, 5.12)

Source: Table 2(i).6-15 to 2(i).6-16, pp178-179 of the submission
AE = adverse event; CI = confidence interval; ITC = indirect treatment comparison; IXEQ4W= ixekizumab 80 mg every four weeks; SAE = serious adverse event;
[a] COAST-V and COAST-W
[b] MEASURE 2 and MEASURE 4 trials

6.32 The submission stated that there was no significant difference in the risk of AEs or SAEs between ixekizumab and secukinumab. This was reasonable.

6.33 The PBAC previously considered ixekizumab to have non-inferior safety to other biological medicines (including adalimumab and secukinumab) in its July 2016 consideration of ixekizumab for psoriasis (paragraph 6.21, ixekizumab PSD, July 2016 PBAC meeting). At its July 2018 consideration of ixekizumab for psoriatic arthritis, the PBAC considered that the claim of non-inferior safety with other biological medicine comparators appeared to be reasonably supported (paragraph 7.3, ixekizumab PSD, July 2018 PBAC meeting).

Clinical claim

6.34 The submission described ixekizumab as non-inferior in terms of efficacy and safety compared with adalimumab for the treatment of AS.

6.35 The submission described ixekizumab as non-inferior in terms of efficacy and safety compared with secukinumab for the treatment of AS.

6.36 The PBAC considered that the claim that ixekizumab is non-inferior to adalimumab and secukinumab in terms of comparative effectiveness and safety was reasonable.

Economic analysis

6.37 The submission presented a cost-minimisation analysis (CMA) between ixekizumab and adalimumab based on the published approved ex-manufacturer price (AEMP). The equi-effective doses were estimated as ixekizumab 80 mg every four weeks and

adalimumab 40 mg every two weeks and the CMA was conducted over two years. This was based on the recommended doses in the Product Information and is consistent with the clinical data presented above.

6.38 Table 12 presents the corrected CMA recalculated during evaluation based on the cost up to 104 weeks' treatment (where treatment coverage is the same for both drugs) and the April 2020 published price of adalimumab (which included a 5% anniversary statutory price reduction).

Table 12: Cost minimisation analysis (corrected)

Component	CMA with adalimumab	
	Ixekizumab	Adalimumab
Doses per pack	2	2
Doses up to 104 weeks [a]	26	52
Cost of treatment over 2 years	$[redacted]	$27,408.16
Revised AEMP per pack	$[redacted]	$1,054.16 [b]

Source: Table 3.4.2, p193 of the submission; April 2020 ex-manufacturer pricing spreadsheet; and calculated during the evaluation
AEMP = approved ex-manufacturer price; CMA = cost-minimisation analysis
[a] Based on treatment coverage of up to 104 weeks. The submission calculated costs for 105 weeks of treatment (from Week 0 to Week 104, inclusive) and included 26 doses of ixekizumab and 53 doses of adalimumab; however, this provides treatment coverage of 104 weeks for ixekizumab and 106 for adalimumab and hence the doses are not equi-effective.
[b] AEMP of $1,054.16 (per pack of 2 pens) as at April 2020

6.39 The corrected analysis based on up to 104 weeks of treatment and the updated April 2020 published AEMP of adalimumab resulted in an AEMP of $[redacted].

Drug cost/patient/year

6.40 Ixekizumab was estimated to cost $[redacted] per year based on the revised effective DPMQ ($[redacted]) and 6.5 prescriptions per year. Adalimumab was estimated to cost $15,192 based on the current published DPMQ ($1,168.62) and 13 prescriptions per year.

Estimated PBS usage & financial implications

6.41 This submission was not considered by DUSC. The submission used a market-share approach to estimate the financial implications of the proposed listing. The key inputs used to estimate the financial estimates are presented in Table 13. The submission assumed there would be 0% uptake in Year 1 (2020) as ixekizumab would not be listed until December 2020. The Sponsor provided revised financial estimates in the PSCR with 5% uptake in Year 1 (2021) and 8% in Year 3 (2023) onwards.

Table 13: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Current market share	PBS & RPBS items processed from December 2018 to November 2019	The evaluation considered this was appropriate
Market growth up	12.61% and 22.59% for initial and continuing items, respectively based on growth from 2014 to 2017.	Potentially underestimated. Data from 2014 to 2019 resulted in higher growth rates: 15.65% (initial) and 35.22% continuing.
Ixekizumab uptake	0% in Year 1 (2020) increasing to 8% for Year 4 (2025) onwards. Based on secukinumab uptake.	The Sponsor provided revised financial estimates in the PSCR with 5% uptake in Year 1 (2021) and 8% in Year 3 (2023) onwards.
Replaced biological medicines	Existing biological medicines replaced in proportion to 2019 market share. Prices from March 2020 PBS schedule.	The evaluation considered this was reasonable.
MBS item 14245	$99.50 (100% schedule fee) for replaced infliximab infusions.	Should be calculated at 85% schedule fee (corrected in evaluation)

Source: Table 4.1-2, pp196-197 of submission; Section 4 spreadsheet
DPMQ = dispensed price for maximum quantity; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits

6.42 The submission estimated that the AS biological medicine market would grow at 12.61% and 22.59% for initial and continuing items, respectively based on market growth rates from 2014 to 2017. This may have been underestimated, as more recent data from June 2014 to June 2019 estimated annual growth of 15.65% for initial items and 35.22% for continuing items. The submission assumed ixekizumab would gain maximum market share of 8% in Year 4 (2023), based on the uptake of secukinumab. The submission assumed that ixekizumab would take market share from all biological medicines in proportion to their 2019 market share. The submission converted the number of replaced biological medicine prescriptions into ixekizumab prescriptions using a "script-equivalence" conversion factor, which accounted for the different lengths of treatment provided by a single prescription. The approach was reasonable but did not account for infliximab and certolizumab pegol having longer durations of initial treatment. A summary of the financial implications is presented in Table 14. During the evaluation, the cost of infliximab was corrected to allow 4.87 vials per dose (rather than one vial for several items) and Medicare Benefits Schedule (MBS) administration costs were calculated at 85% of the Schedule Fee. The PSCR identified a calculation error in how uptake rates were applied in the model provided with the submission. Revised financial estimates are presented in Table 14.

Table 14: Estimated use and financial implications (based on uptake corrected for error as advised in PSCR)

	Year 1 (2021)	Year 2 (2022)	Year 3 (2023)	Year 4 (2024)	Year 5 (2025)	Year 6 (2026)
Estimated extent of use						
Number of scripts dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of ixekizumab [a]						
Cost to PBS/RPBS less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for other biological medicines [b]						
Cost to PBS/RPBS less co-payments [b]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS (85% schedule fee)	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Tables 4.1-2 to 4.5-3, pp196-219 of the submission and calculated during the evaluation

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits

[a] Based on a recalculated ixekizumab effective DPMQ of $[redacted], PBS co-payment of $29.87 and RPBS co-payment of $5.34. The financial estimates provided in the PSCR incorrectly used a DPMQ of $[redacted].

[b] Based on the corrected infliximab costs (dispensed price changed to $1,561.86 (public) and $1,609.15 (private) for 4.87 vials per dose) and updated dispensed price of adalimumab ($1,168.62 as at April 2020). The financial estimates provided in the PSCR did not correct the infliximab error or use the April 2020 price for adalimumab.

The redacted table shows that at Year 6, the estimated number of scripts dispensed was 10,000 < 20,000.

6.43 The total cost to the PBS/RPBS of listing ixekizumab was estimated to be $0 to < $10 million in Year 6, and a total of $0 to < $10 million in the first six years of listing. The total cost to the PBS/RPBS was inaccurate as it was based on the published prices of other biological medicines replaced.

6.44 The small net cost was mostly due to 12 months continuing treatment with ixekizumab ($[redacted]) costing more than secukinumab ($9,626), etanercept ($13,646), certolizumab pegol ($13,192) and infliximab ($13,588 [public] and $13,994 [private] when corrected). Assuming ixekizumab were to be listed on a cost-minimisation basis to the least costly alternative therapy and current market growth was unchanged, then the requested listing would be expected to have negligible financial impact on the PBS/RPBS.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of ixekizumab on a cost-minimisation basis to the least costly biological medicine for ankylosing spondylitis (AS). In making this recommendation, the PBAC accepted any of the current PBS listed biological medicines for AS could be an alternative therapy to ixekizumab.

7.2 The PBAC considered the equi-effective doses between ixekizumab (at a dose of 80 mg every four weeks) and the alternative biological medicines could be derived from the product information and with reference to the previously recommended equi-effective doses collated in the PBS Therapeutic Relativity Sheets. The cost

minimisation analysis should be conducted over two years using approved ex-manufacturer prices consistent with methodology previously accepted by the PBAC for biological medicines.

7.3 The PBAC noted that six alternative therapies were listed on the PBS for the treatment of AS at the time of consideration. The PBAC considered that while the clinical need for an additional treatment was low, the addition of another option may be useful for some patients.

7.4 The PBAC considered the nominated comparators of adalimumab and secukinumab were reasonable; however, noted any of the biological medicines currently listed on the PBS for AS were relevant alternative therapies.

7.5 The PBAC considered the claim that ixekizumab is non-inferior to adalimumab and secukinumab in terms of effectiveness and safety was adequately supported by the clinical evidence presented in the submission. The PBAC noted no evidence demonstrating superiority against any of the other alternative therapies was provided.

7.6 The PBAC considered that the listing of ixekizumab for AS based on a cost minimisation basis with the least costly biological medicine using effective prices would result in no additional cost to the PBS.

7.7 The PBAC advised that the restriction is simple and that the listing of ixekizumab would result in flow-on changes to the Prescriber Instructions regarding the treatment of adult patients with AS.

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

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

Outcome:
Recommended

8 Recommended listing.

Add new PBS indication /recommended listing as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer	
IXEKIZUMAB ixekizumab 80 mg/mL injection, 2 x 1 mL pen devices	NEW	1	2	1	TALTZ	Eli Lilly Australia Pty Ltd

Restriction Summary 9530 / ToC: 9503

Category/ Program: GENERAL – General Schedule (Code GE)
Prescriber type : ☒Medical Practitioners
Restriction type: ☒Authority Required - In Writing
Indication: Ankylosing spondylitis
Treatment Phase: Initial treatment - Initial 1 (new patient)
Clinical criteria:
The condition must be radiographically (plain X-ray) confirmed Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis
AND
Clinical criteria:
Patient must not have received PBS-subsidised treatment with a biological medicine for this condition
AND
Clinical criteria:
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
Clinical criteria:
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
Clinical criteria:
Patient must not receive more than 16 weeks of treatment under this restriction
AND
Population criteria:
Patient must be aged 18 years or older
AND
Treatment criteria:
Must be treated by a rheumatologist; or
Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis
Prescribing Instructions: The application must include details of the NSAIDs trialled, their doses and duration of treatment. If the NSAID dose is less than the maximum recommended dose in the relevant TGA-approved Product Information, the application must include the reason a higher dose cannot be used. If treatment with NSAIDs is contraindicated according to the relevant TGA-approved Product Information, the application must provide details of the contraindication. If intolerance to NSAID treatment develops during the relevant period of use which is of a severity to necessitate permanent treatment withdrawal, the application must provide details of the nature and severity of this intolerance.
Prescribing Instructions: 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. The BASDAI must be determined at the completion of the 3 month NSAID and exercise trial, but prior to ceasing NSAID treatment. The BASDAI must be no more than 1 month old at the time of initial application. Both ESR and CRP measures should be provided with the initial treatment application and both must be no more than 1 month old. 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.
Prescribing Instructions: The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Ankylosing Spondylitis PBS Authority Application - Supporting Information Form which includes the following: (i) a copy of the radiological report confirming Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis; and (ii) a completed BASDAI Assessment Form; and (iii) a completed Exercise Program Self Certification Form included in the supporting information form.
Prescribing Instructions: 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.
Prescribing Instructions: Where the response assessment is not submitted within this timeframe, the patient will be deemed to have failed to respond to treatment with this drug.
Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
Administrative Advice: Details of the toxicities, including severity, which will be accepted for the purposes of administering this restriction can be found on the Services Australia website at www.servicesaustralia.gov.au
Administrative Advice: For details on the appropriate minimum exercise program that will be accepted for the purposes of administering this restriction, please refer to the Services Australia website at www.servicesaustralia.gov.au
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

Restriction Summary 9412 / ToC: 9414

Indication: Ankylosing spondylitis
Treatment Phase: Initial treatment - Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years)
Clinical criteria:
Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle
AND
Clinical criteria:
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
AND
Clinical criteria:
Patient must not receive more than 16 weeks of treatment under this restriction
AND
Population criteria:
Patient must be aged 18 years or older
AND
Treatment criteria:
Must be treated by a rheumatologist; or
Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis
Prescribing Instructions: The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Ankylosing Spondylitis PBS Authority Application - Supporting Information Form.
Prescribing Instructions: 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.
Prescribing Instructions: 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.
Prescribing Instructions: 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.
Prescribing Instructions: An adequate response is defined as an improvement from baseline of at least 2 of the BASDAI and 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.
Prescribing Instructions: All measurements provided must be no more than 1 month old at the time of application.
Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
Prescribing Instructions: A 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.
Administrative Advice:

Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au
Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos
Or mailed to:
Services Australia
Complex Drugs
Reply Paid 9826
HOBART TAS 7001

Restriction Summary 9427 / ToC: 9428

Indication: Ankylosing spondylitis
Treatment Phase: Initial treatment - Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)
Clinical criteria:
Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition
AND
Clinical criteria:
Patient must have a break in treatment of 5 years or more from the most recently approved PBS-subsidised biological medicine for this condition
AND
Clinical criteria:
The condition must be radiographically (plain X-ray) confirmed Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis
AND
Clinical criteria:
Patient must have 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
Clinical criteria:
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
AND
Clinical criteria:
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
AND
Clinical criteria:
Patient must not receive more than 16 weeks of treatment under this restriction
AND
Population criteria:
Patient must be aged 18 years or older
AND
Treatment criteria:
Must be treated by a rheumatologist; or
Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis
Prescribing Instructions: The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Ankylosing Spondylitis PBS Authority Application - Supporting Information Form which includes the following: (i) a copy of the radiological report confirming Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis; and (ii) a completed BASDAI Assessment Form.
Prescribing Instructions: 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.
Prescribing Instructions:

Where the response assessment is not submitted within this timeframe, the patient will be deemed to have failed to respond to treatment with this drug.
Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

Restriction Summary 9535 / ToC: 9429

Category/ Program: GENERAL – General Schedule (Code GE)
Prescriber type : ☒Medical Practitioners
Restriction type: ☒Authority Required - Telephone
Indication: Ankylosing spondylitis
Treatment Phase: 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
Clinical criteria:
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
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
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
AND
Clinical criteria:
The treatment must provide no more than the balance of up to 16 weeks treatment available under the above restrictions
AND
Treatment criteria:
Must be treated by a rheumatologist; or
Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis
Administrative Advice: Authority approval for sufficient therapy to complete the balance of supply may be requested by telephone by contacting ~~the~~ Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer	
IXEKIZUMAB ixekizumab 80 mg/mL injection, 2 x 1 mL pen devices	NEW	1	2	2	TALTZ	Eli Lilly Australia Pty Ltd

Restriction Summary 9508 / ToC: 9430

Category/ Program: **GENERAL – General Schedule (Code GE)**
Prescriber type : ☒**Medical Practitioners**
Restriction type: ☒Authority Required - In Writing
Indication: Ankylosing spondylitis
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition
AND
Clinical criteria:
Patient must have demonstrated an adequate response to treatment with this drug
AND
Clinical criteria:
Patient must not receive more than 24 weeks of treatment under this restriction
AND
Population criteria:
Patient must be aged 18 years or older
AND
Treatment criteria:
Must be treated by a rheumatologist; or
Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis
Prescribing Instructions: The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Ankylosing Spondylitis PBS Authority Application - Supporting Information Form.
Prescribing Instructions: An adequate response is defined as an improvement from baseline of at least 2 of the BASDAI and 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.
Prescribing Instructions: All measurements provided must be no more than 1 month old at the time of application.
Prescribing Instructions: 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.
Prescribing Instructions: Where the response assessment is not submitted within this timeframe, the patient will be deemed to have failed to respond to treatment with this drug.
Prescribing Instructions:

If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
Prescribing Instructions: A 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.
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

Restriction Summary 9415 / ToC: 9431

Category/ Program: GENERAL – General Schedule (Code GE)
Prescriber type : ☒Medical Practitioners
Restriction level: ☒Authority Required - Telephone
Indication: Ankylosing spondylitis
Treatment phase: Continuing treatment – balance of supply
Clinical criteria:
Patient must have received insufficient therapy with this drug under the Continuing treatment restriction to complete 24 weeks treatment
AND
Clinical criteria:
The treatment must provide no more than the balance of up to 24 weeks treatment available under the above restriction
AND
Treatment criteria:
Must be treated by a rheumatologist; or
Must be treated by a clinical immunologist with expertise in the management of ankylosing spondylitis
Administrative Advice: Authority approval for sufficient therapy to complete the balance of supply may be requested by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Flow on changes required.

The note for all AS item codes for infliximab, adalimumab, secukinumab, golimumab, certolizumab pegol and etanercept will need to be amended to include ixekizumab as a biological medicine for the purposes of a treatment cycle.

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

The sponsor had no comment.