

## 6.03 IXEKIZUMAB, Injection 80 mg in 1 mL single dose pre-filled pen, Taltz<sup>®</sup>, Eli Lilly Australia Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 2 submission requested extending the existing General Schedule Authority Required ixekizumab (IXE) listing to include the treatment of non-radiographic axial spondyloarthritis (nr-axSpA) in adult patients.
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus golimumab (GLM), the nominated primary comparator (Table 1).

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

Component	Description
Population	Adults with non-radiographic axial spondyloarthritis
Intervention	Ixekizumab 80 mg every 4 weeks administered by a subcutaneous injection
Comparator	Main comparator: Golimumab 50 mg administered by a subcutaneous injection once a month Secondary comparator: Secukinumab 150 mg at weeks 0,1,2,3 and 4 and every four weeks thereafter [loading dose] and Secukinumab 150 mg every four weeks [no loading dose]
Outcomes	Efficacy: proportion of patients achieving ASAS20, ASAS40 and BASDAI50 response Safety: frequency of treatment emergent adverse events (TEAE), serious adverse events (SAE) and discontinuations.
Clinical claim	In adults with nr-axSpA, ixekizumab is non-inferior* to golimumab or secukinumab at improving ASAS20, ASAS40 and BASDAI50 with comparative safety.

Source: Table 1.1-1, p15 of the submission.

ASAS=Assessment of Spondyloarthritis International Society; BASDAI=Bath ankylosing spondylitis disease activity index; nr-axSpA=non-radiographic axial spondyloarthritis

\* The submission stated that “For the purpose of this submission, PBAC’s clinical claim terminology “non-inferior” has the same meaning as comparable or similar.”

ASAS20 - derived from patient-reported assessments; an ASAS20 response was defined as ≥20% improvement and an absolute improvement from baseline of ≥1 unit (range 0 to 10) in at least three of the four ASAS criteria domains (Patient Global, Spinal Pain, Function, and Inflammation), and no worsening of ≥20% and ≥1 unit (range 0 to 10) in the remaining domain.

ASAS40 - derived from patient-reported assessments; an ASAS40 response was defined as ≥40% improvement and an absolute improvement from baseline of ≥2 units (range 0 to 10) in at least three of the four ASAS criteria domains (Patient Global, Spinal Pain, Function, and Inflammation), without any worsening in the remaining domain.

BASDAI50 represents an improvement of ≥50% of the BASDAI score from baseline. The BASDAI is a patient-reported assessment consisting of six questions that relate to five major symptoms relevant to axial spondyloarthritis: fatigue, spinal pain, peripheral arthritis, enthesitis, intensity, and duration of morning stiffness. Patients needed to score each item with a score from 0 to 10 (numeric rating scale).

## 2 Background

### Registration status

- 2.1 IXE was TGA-approved on 28 May 2021 and included in the Australian Register of Therapeutic Goods on 6 July 2021 for the treatment of adult patients with active nr-axSpA with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have responded inadequately to, or are intolerant to, nonsteroidal anti-inflammatory drugs (NSAIDs).

- 2.2 Other TGA indications are: (a) adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy; (b) active psoriatic arthritis in adult patients who have responded inadequately, or who are intolerant, to previous disease-modifying antirheumatic disease (DMARD) therapy; and (c) active ankylosing spondylitis in adult patients.

### Previous PBAC consideration

- 2.3 This was the first submission of IXE for the requested indication. IXE is currently listed on the Pharmaceutical Benefits Scheme (PBS) for ankylosing spondylitis, severe psoriatic arthritis, and severe chronic plaque psoriasis.
- 2.4 There are currently three biologic disease-modifying anti-rheumatic drugs (bDMARDs) available on the PBS for the treatment of nr-axSpA: secukinumab (SEC), GLM and certolizumab pegol (CZP). If listed, IXE would be the fourth listed bDMARD available on the PBS for the treatment of nr-axSpA.

## 3 Requested listing

- 3.1 For readability reasons, a shortened version of the requested listing is presented below.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max. Qty. (units)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IXEKIZUMAB Initial treatment 1, 2 and 3 Injection 80 mg in 1 mL single use pre-filled pen	1	2	1	\$3,411.04 published price Effective price not stated	Taltz Eli Lilly Australia Pty Ltd.
Continuing treatment Injection 80 mg in 1 mL single use pre-filled pen	1	2	2	\$3,411.04 published price Effective price not stated	Taltz Eli Lilly Australia Pty Ltd.

<b>Category/Program:</b> General Schedule
<b>Indication:</b> Non-radiographic axial spondyloarthritis
<b>Restriction type:</b> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)
<b>Treatment phase:</b> Initial treatment
<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. <i>Non-radiographic axial spondyloarthritis</i>
<b>Clinical criteria:</b> Initial Treatment 1 (New Patients) <ul style="list-style-type: none"> <li>• Patient must not have received PBS-subsidised treatment with a biological medicine for this condition, AND</li> <li>• Patient must have had chronic lower back pain and stiffness for 3 or more months that is relieved by exercise but not rest, AND</li> </ul>

<ul style="list-style-type: none"> <li>• 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</li> <li>• Patient must have one or more of the following: (a) enthesitis (heel); (b) uveitis; (c) dactylitis; (d) psoriasis; (e) inflammatory bowel disease; or (f) positive for Human Leukocyte Antigen B27 (HLA-B27), AND</li> <li>• The condition must not be radiographically evidenced on plain x-ray of Grade II bilateral sacroiliitis or Grade III or IV unilateral sacroiliitis, AND</li> <li>• The condition must be non-radiographic axial spondyloarthritis, as defined by Assessment of Spondyloarthritis International Society (ASAS) criteria, AND</li> <li>• The condition must be sacroiliitis with active inflammation and/or oedema on non-contrast Magnetic Resonance Imaging (MRI), AND</li> <li>• The condition must have presence of Bone Marrow Oedema (BMO) depicted as a hyperintense signal on a Short Tau Inversion Recovery (STIR) image (or equivalent), AND</li> <li>• The condition must have BMO depicted as a hypointense signal on a T1 weighted image (without gadolinium), AND</li> <li>• The treatment must not exceed a maximum of 16 weeks with this drug under this restriction.</li> </ul> <p>Initial Treatment 2 (Change or re-commencement of treatment after a break of less than 5 years)</p> <ul style="list-style-type: none"> <li>• Patient must have received PBS-subsidised treatment with a biological medicine for this condition, AND</li> <li>• Patient must not have failed, or ceased to respond to, PBS subsidised treatment with biological medicines more than three times for this PBS indication during the current treatment cycle,</li> <li>• The treatment must not exceed a maximum of 16 weeks with this drug under this restriction.</li> </ul> <p>Initial Treatment-3 (Recommencement of treatment after a break in biological medicine of more than 5 years)</p> <ul style="list-style-type: none"> <li>• Identical to Initial Treatment 1 except that the patient may have previously received treatment for this condition with a PBS listed biological agent.</li> </ul>
<p><b>Population criteria:</b> Patient must be 18 years or older</p>
<p><b>Prescriber instructions:</b> Initial Treatment 1 (New Patients) The following criteria indicate failure to achieve an adequate response and must be demonstrated at the time of the initial application:</p> <ol style="list-style-type: none"> <li>a) a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of at least 4 on a 0-10 scale; and</li> <li>b) C-reactive protein (CRP) level greater than 10 mg per L.</li> </ol> <p>The assessment of the patient's response to the initial course of treatment must be conducted following a minimum of 12 weeks of treatment and no later than 4 weeks from the cessation of that treatment course. If the response assessment is not conducted within these timeframes, the patient will be deemed to have failed this course of treatment in this treatment cycle.</p> <p>Initial Treatment 2 (Change or re-commencement of treatment after a break of less than 5 years) An adequate response to therapy with this biological medicine is defined as a reduction from baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score by 2 or more units (on a scale of 0-10) and 1 of the following:</p> <ol style="list-style-type: none"> <li>a) a CRP measurement no greater than 10 mg per L; or</li> <li>b) a CRP measurement reduced by at least 20% from baseline.</li> </ol> <p>The assessment of the patient's response to the most recent supply of biological medicine must be conducted following a minimum of 12 weeks of treatment.</p>
<p><b>Treatment phase: Continuing treatment</b></p>
<p><b>Clinical criteria:</b></p> <ul style="list-style-type: none"> <li>• Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition, AND</li> <li>• Patient must have demonstrated an adequate response to treatment with this drug for this condition, AND</li> <li>• The treatment must not exceed a maximum of 24 weeks with this drug per authorised course under this restriction.</li> </ul>
<p><b>Prescribing instructions:</b></p>

An adequate response to therapy with this biological medicine is defined as a reduction from baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score by 2 or more units (on a scale of 0-10) and 1 of the following:

- a) a CRP measurement no greater than 10 mg per L; or
- b) a CRP measurement reduced by at least 20% from baseline.

The patient remains eligible to receive continuing treatment with the same biological medicine in courses of up to 24 weeks providing they continue to sustain an adequate response. It is recommended that a patient be reviewed in the month prior to completing their current course of treatment.

Source: Tables ES.2-ES.4, pp.iii-v of the submission

- 3.2 The submission requested a special pricing arrangement (SPA) for the nr-axSpA therapeutic indication of IXE. The submission proposed to work with the Department of Health “to incorporate the final negotiated price for patients with the nr-axSpA indication into the weighted price calculation that currently exists for ixekizumab across the plaque psoriasis, psoriatic arthritis and active ankylosing spondylitis indications”.
- 3.3 The requested restriction is similar to other currently listed bDMARDs. However, the maximum treatment duration allowed under initial treatment is different: 16 weeks for IXE and GLM, 20 weeks for SEC and 18-20 weeks for CZP. Identical initial treatment durations are not specified in the PBS restrictions due to the non-identical dosing regimens and duration of effect for each biological medicine. The intent of the duration of ‘Initial treatment’ is to reflect the treatment duration upon which a response assessment was first conducted in the supporting clinical trial.
- 3.4 No restriction for grandfather treatment was proposed.
- 3.5 IXE is currently listed as a pack containing 2 injections, equivalent to 2 months’ therapy per pack, which is inconsistent with the basis of most other bDMARD listings which typically provide for approximately a 1 month supply per pack (with some exceptions, such as some infusible therapies). The PBAC has previously expressed a view (in July 2018 and again in 2021) that the sponsor should make a single injection pack available to align the treatment durations per pack of IXE with other bDMARD listings. The sponsor, in its Pre-PBAC response, stated it is currently considering the commercial feasibility of making a pack of one injection available.

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

## 4 Population and disease

- 4.1 Spondyloarthritis refers to a group of related inflammatory disorders involving chronic joint pain. Spondyloarthritis is axial when the spine, sacroiliac joints and thoracic cage are primarily affected, and peripheral when the peripheral joints are affected. Axial spondyloarthritis with radiographic evidence of structural sacroiliac joint damage is known as ankylosing spondylitis. Non-radiographic axial spondyloarthritis (nr-axSpA) refers to axial spondyloarthritis without radiographic evidence of damage.

- 4.2 Some patients with nr-axSpA progress to ankylosing spondylitis. The radiographic changes of sacroiliitis develop around six to ten years after the onset of symptoms. MRI allows earlier detection of sacroiliitis.
- 4.3 Patients with ankylosing spondylitis or nr-axSpA suffer from pain, fatigue, morning stiffness, physical impairments, as well as reduced physical function, productivity, and quality of life.
- 4.4 IXE is an interleukin-17A inhibitor. Of the three other bDMARDs available on the PBS for the treatment of nr-axSpA, one is also an interleukin-17A inhibitor (SEC), while the other two are tumour necrosis factor alpha (TNF $\alpha$ ) inhibitors (GLM and CZP).

## **5 Comparator**

- 5.1 The submission nominated GLM as the primary comparator and SEC as the secondary comparator. GLM was nominated as the main comparator because: it was the market share leader (76% in 2020-2021) of bDMARDs for nr-axSpA; and would be the medicine most likely to be replaced in the market if the requested PBS listing of IXE is recommended. SEC was nominated as the secondary comparator, as the pharmacological analogue of IXE (listed on the PBS from 1 April 2021). GLM and SEC were appropriate comparators; however, IXE may also replace CZP in practice.
- 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 satisfied, it must make a statement to this effect. The PBAC noted the submission did not present any evidence that IXE provided a significant improvement in efficacy and/or reduction in toxicity compared to any alternative, and therefore there was no basis for IXE to have a price advantage over any relevant alternative for an equivalent treatment period.
- 5.3 For the requested population, GLM, SEC and CZP may be considered alternative therapies because they could be replaced in practice.

*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.



Trial ID	Protocol title/ Publication title	Publication citation
	Sieper J, Van Der Heijde D, Maksymowych WP, et al. Efficacy of golimumab for nonradiographic axial spondyloarthritis: Subgroup analysis by baseline MRI and c-reactive protein status [abstract] <i>Van der Heijde D, Dougados M, Maksymowych W, et al. Long-term Tolerability and Efficacy of Golimumab in Active Non-Radiographic Axial Spondyloarthritis: Results From Open-Label Extension</i>	Annals of the Rheumatic Diseases 2016; 75:813-814 <i>Rheumatology (Oxford). 2021 Apr 20. Epub ahead of print.</i>
PREVENT (NCT02696031)	Clinical Trial Protocol: A randomized, double-blind, placebo-controlled multicenter study of secukinumab 150 mg in patients with active non-radiographic axial spondyloarthritis to evaluate the safety, tolerability and efficacy up to 2 years, followed by an optional phase of either 150 mg or 300 mg randomized dose escalation for up to another 2 years Statistical analysis Plan-Amendment 2: A randomized, double-blind, placebo-controlled multicenter study of secukinumab 150 mg in patients with active non-radiographic axial spondyloarthritis to evaluate the safety, tolerability and efficacy up to 2 years, followed by an optional phase of either 150 mg or 300 mg randomized dose escalation for up to another 2 years Deodhar A, Blanco R, Dokoupilová E, et al. Improvement of Signs and Symptoms of Nonradiographic Axial Spondyloarthritis in Patients Treated With Secukinumab: Primary Results of a Randomized, Placebo-Controlled Phase III Study.	2018  2019  Arthritis and Rheumatology 2021a; 73(1):110-120.
	Braun J, Blanco R, Marzo-Ortega H, et al. Secukinumab Improved Signs and Symptoms in Patients with Non-radiographic Axial Spondyloarthritis: Results from a Randomized Controlled Phase III Study Stratified by Baseline Objective Signs of Inflammation [conference abstract] <i>Poddubnyy D, Deodhar A, Baraliakos X, et al. POS0900 Secukinumab 150 mg provides sustained improvement in signs and symptoms of non-radiographic axial spondyloarthritis: 2-year results from the PREVENT study</i>	Arthritis and Rheumatology 2020; 72(SUPPL 10):2764-2765 <i>Annals of the Rheumatic Diseases 2021;80:707.</i>

Source: Table 2.2-2, p51 of the submission; Table 2(i).2 1, pp7-8 in Appendix 2 of the submission  
Texts in *italics* indicate publications identified during the evaluation.

- 6.7 The key features of the randomised trials included in indirect comparisons are summarised in Table 3.
- 6.8 All trials were multicentre, double-blind, randomised placebo-controlled trials. The duration of the double-blind phases ranged from 16 to 52 weeks. The blinded treatment dosing period in the COAST-X trial was 52 weeks. From week 16 to week 44, inadequate responders were allowed to have changes in background therapy (e.g. NSAIDs, nonbiological DMARDs) or switch to rescue treatment (IXE 80 mg Q2W) while remaining blinded to the original treatment allocation. The blinded treatment phase in the GO-AHEAD trial was 16 weeks, followed by 36 weeks of open-label GLM treatment. Participants in the PREVENT trial had 52 weeks of double-blind treatment, followed by 52 weeks of open-label SEC treatment. All trials reported key clinical response outcomes at Week 16. The trials had a low risk of bias.
- 6.9 There were key differences in study design and patient characteristics across the trials, including:
- All three trials recruited patients aged  $\geq 18$  years, but the GO-AHEAD trial further limited the participants to age  $\leq 45$  years. Patients in the GO-AHEAD trial were

younger than patients in the COAST-X or PREVENT trials (mean age 31 years vs. 39/40 years). The difference in ages across the trials may impact the results of the indirect comparison as age is a treatment modifier: in the COAST-X trial, aged <40 years vs. ≥40 years was a statistically significant treatment effect modifier for ASAS40 at week 16, with greater treatment benefit of IXE among those aged <40 years, but not at week 52.

- Objective signs of inflammation (MRI+ and/or CRP+) was an inclusion criterion in the COAST-X and the PREVENT trials but not in the GO-AHEAD trial. The PREVENT trial also required the CRP to be greater than the upper limit of normal to be counted as elevated.
  - Both the COAST-X and the GO-AHEAD trials excluded patients previously treated with biologic agents. In contrast, the PREVENT trial allowed patients intolerant or inadequate response to previous treatment with a TNF inhibitor (not more than one) to participate after wash-out period.
- 6.10 The submission presented results on the intention-to-treat (ITT) population (MRI+ and/or CRP+) in the COAST-X and the PREVENT trials, which was in line with the TGA indication ('TGA population'); and the PBS population (MRI+ and CRP+), which was in line with the PBS indication ('PBS population'). Results from the 'TGA population' in the GO-AHEAD trial were prespecified subgroup analyses (around 20% of the trial participants did not have objective signs of inflammation).
- 6.11 The PBS population subgroups in the trials represented small proportions of the total patients across the trials.
- 6.12 Despite presenting results for this PBS subgroup, there were still differences across the trials that may violate the assumption of transitivity/exchangeability of the common reference arm and bias results of the indirect comparison. As the submission did not present the baseline patient characteristics for the PBS population subgroups across the trials, it was unknown whether the comparison groups included in the indirect comparisons were balanced and sufficiently similar. It was also unclear what proportion of the PBS subgroup also met other PBS eligibility criteria, and whether such differences (between the trial and Australian settings) may have impacted the estimated treatment effects. The Pre-Sub-Committee Response (PSCR) stated that it was not possible to compare baseline characteristics for the subgroup comparisons as this data was not published for the comparator therapies.

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
COAST-X	IXEQ4W: 96 IXEQ2W: 102 PBO: 105	R, DB, MC, 52 wks	Low	Active nr-axSpA, aged ≥18 yrs, OSI (MRI and/or CRP>5 mg/L), inadequate response/ intolerant to ≥2 NSAIDs, bDMARD-naive	Primary: ASAS40 at wks 16 and 52 Secondary: ASAS20, BASDAI50
GO-AHEAD	GLMQ4W: 98 PBO: 100	R, DB (to 16 wks), MC, 52 wks	Low	Active nr-axSpA, aged ≥18 to ≤45 yrs, inadequate response/ intolerant to ≥1 NSAID	Primary: ASAS20 at wks 16 Secondary: ASAS 40, BASDAI50
PREVENT	SEC LD: 185 SEC NL: 184 PBO: 186	R, DB, MC, 2 yrs	Low	Active nr-axSpA, aged ≥18 yrs, OSI (MRI and/or CRP >ULN), ≥2 different NSAIDs at the highest recommended dose for ≥4 wks or intolerant	Primary: ASAS40 at wks 16 and 52 Secondary: ASAS20, BASDAI50
Indirect comparison (IXEQ4W vs. GLMQ4W)		Included COAST-X and GO-AHEAD; sub-group analysis; placebo as the reference comparator; assessed ASAS40, ASAS20 and BASDAI50 at week 16			
Indirect comparison (IXEQ4W vs. SEC LD; IXEQ4W vs. SEC NL)		Included COAST-X and PREVENT; sub-group analysis; placebo as the reference comparator; assessed ASAS20, ASAS40 and BASDAI50 at week 16			

Source: Compiled during the evaluation based on Deodhar 2020, Sieper 2015 and Deodhar 2021a

ASAS=Assessment of SpondyloArthritis International Society; ASAS20=20% or more improvement in ASAS; ASAS40=40% or more improvement in ASAS; ASDAS= Ankylosing Spondylitis Disease Activity Score; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50=50% improvement in BASDAI; bDMARD=biologic disease-modifying antirheumatic drugs; CRP=C-reactive protein; DB=double blind; GLM=golimumab; IXE=ixekizumab; LD=loading dose; MC=multi-centre; MRI=magnetic resonance imaging; NL=no loading dose; NSAID=non-steroidal anti-inflammatory drugs; OL=open label; OSI=objective signs of inflammation; PBO=placebo; Q4W=every 4 weeks; R=randomised; SEC=secukinumab; SF-36 PCS= Medical Outcome Short Form-36 Physical Component Summary (SF-36 PCS); SPARCC=Spondyloarthritis Research Consortium of Canada; ULN=upper limit of normal; vs.=versus; wks=weeks  
ASAS40 response: defined as an improvement of ≥40% and an absolute improvement from baseline of ≥2 units (range 0–10) in ≥3 of the four domains (patient global, spinal pain, function, and inflammation) without worsening remaining one domain.

## Comparative effectiveness

- 6.13 All the trials measured treatment response as the proportion of patients achieving ≥40% improvement in Assessment of SpondyloArthritis International Society (ASAS40), ≥20% improvement in ASAS (ASAS20) and ≥50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50). These outcomes were either primary, secondary or other outcomes in the trials. As all trials enrolled patients with a BASDAI score of ≥4 at baseline, a 50% improvement in the BASDAI (i.e. BASDAI50) corresponded to a reduction from baseline in the BASDAI score of ≥2. The proposed restrictions defined an adequate response to therapy as a reduction in the BASDAI score of ≥2 units (on a scale of 0-10) from baseline and either CRP <10 mg/L or reduction of CRP by ≥20% from baseline. The proposed criteria for adequate response are the same as the current PBS listings of other bDMARDs for nr-axSpA.
- 6.14 In November 2017, “the ESC considered BASDAI50 was a clinically relevant outcome ... and has been recommended by ASAS [guidelines] as the response criteria used to determine treatment success” (para. 6.24, Golimumab Public Summary Document (PSD), November 2017 PBAC meeting). “The ESC noted while the ASAS20 was the primary outcome measure used in GO-AHEAD, and the basis upon which the MCID was stated, the use of the BASDAI50 (a secondary endpoint in the trial) better reflects

the preferred clinical measure for the assessment of response to treatment in nr-axSpA. It was agreed that this was the appropriate basis for the assessment of response and cost-effectiveness in this condition” (para. 6.14, Golimumab PSD, November 2017 PBAC meeting).

- 6.15 The submission did not nominate a non-inferiority margin. At its November 2019 meeting, the PBAC stated that “...non-inferiority was demonstrated based on ASAS20 for all the populations, because the 95%CI of RR estimates all crossed 1 and the lower bounds were larger than 0.43 (which is the non-inferiority margin accepted for ankylosing spondylitis).” (para. 6.18, Certolizumab Pegol PSD, November 2019 PBAC meeting). The PBAC also noted the lack of non-inferiority margin for BASDAI50, but considered the overall claim of non-inferiority (based on ASAS20 and BASDAI50) was reasonable (para. 6.24 and 7.3, Certolizumab Pegol PSD, November 2019 PBAC meeting).
- 6.16 Tables 4-6 present indirect comparisons of IXE versus GLM and SEC for ASAS40, ASAS20 and BASDAI50 respectively in the TGA and PBS populations. PBO was the reference comparator.

Table 4: ASAS40 response in patients with nr-axSpA plus OSI defined according to the TGA population (MRI+ and/or CRP+) and PBS population (MRI+ and CRP+) at week 16

Trial	Drug n/N (%)	Control n/N (%)	RR (95%CI)	RD (95%CI)	NNT (95%CI)
<b>TGA population: nr-axSpA (MRI+ AND/OR CRP+)</b>					
<b>IXE 80 mg Q4W vs. PBO</b>					
COAST-X, ITT (N=201) <sup>a</sup>	34/96 (35.4)	20/105 (19.0)	<b>1.86 (1.15, 3.00)</b>	<b>0.16 (0.04, 0.29)</b>	6 (4, 24)
<b>GLM vs. PBO</b>					
GO-AHEAD, PSS (N=158) <sup>b</sup>	47/78 (60.3)	18/80 (22.5)	<b>2.68 (1.72, 4.18)</b>	<b>0.38 (0.24, 0.52)</b>	3 (2, 4)
<b>SEC 150 mg LD vs. PBO</b>					
PREVENT, ITT (N=555) <sup>a</sup>	74/185 (40.0)	52/186 (28.0)	<b>1.43 (1.07, 1.91)</b>	<b>0.12 (0.02, 0.22)</b>	8 (5, 40)
PREVENT, PSS <sup>^</sup> (N=501) <sup>a</sup>	68/164 (41.5)	50/171 (29.2)	<b>1.42 (1.06, 1.91)</b>	<b>0.12 (0.02, 0.22)</b>	8 (5, 49)
<b>SEC 150 mg NL vs. PBO</b>					
PREVENT, ITT (N=555) <sup>a</sup>	75/184 (40.8)	52/186 (28.0)	<b>1.46 (1.09, 1.95)</b>	<b>0.13 (0.03, 0.22)</b>	8 (4, 31)
PREVENT, PSS <sup>^</sup> (N=501) <sup>a</sup>	70/166 (42.2)	50/171 (29.2)	<b>1.44 (1.08, 1.93)</b>	<b>0.13 (0.03, 0.23)</b>	8 (4, 36)
<b>PBS population: nr-axSpA (MRI+ AND CRP+)</b>					
<b>IXE 80 mg Q4W vs. PBO</b>					
COAST-X, PHS (N=51) <sup>b</sup>	10/20 (50.0)	5/31 (16.1)	<b>3.10 (1.24, 7.74)</b>	<b>0.34 (0.08, 0.59)</b>	3 (2, 12)
COAST-X, PHS (N=68) <sup>a</sup>	13/30 (43.3)	8/38 (21.1)	2.06 (0.98, 4.31)	<b>0.22 (0.00, 0.44)</b>	4 (2, 317)
<b>GLM vs. PBO</b>					
GO-AHEAD, PHS (N=53) <sup>b</sup>	18/26 (69.2)	7/27 (25.9)	<b>2.67 (1.34, 5.31)</b>	<b>0.43 (0.19, 0.68)</b>	2 (1, 5)
<b>SEC 150 mg LD vs. PBO</b>					
PREVENT, PSS <sup>^</sup> (N=151) <sup>a</sup>	26/49 (53.1)	11/50 (22.0)	<b>2.41 (1.34, 4.33)</b>	<b>0.31 (0.13, 0.49)</b>	2 (2, 8)
<b>SEC 150 mg NL vs. PBO</b>					
PREVENT, PSS <sup>^</sup> (N=151) <sup>a</sup>	28/52 (53.8)	11/50 (22.0)	<b>2.45 (1.37, 4.37)</b>	<b>0.32 (0.14, 0.50)</b>	2 (2, 7)
<b>Indirect comparisons</b>					
<b>TGA population: nr-axSpA (MRI+ AND/OR CRP+)</b>					
IXE <sup>a</sup> vs. GLM <sup>b</sup>			0.69 (0.36, 1.33)	<b>-0.21 (-0.40, -0.03)</b>	-
IXE <sup>a</sup> vs. SEC LD <sup>a</sup>			1.30 (0.74, 2.27)	0.04 (-0.11, 0.2)	-
IXE <sup>a</sup> vs. SEC NL <sup>a</sup>			1.28 (0.73, 2.23)	0.04 (-0.12, 0.19)	-
IXE <sup>a</sup> vs. SEC LD <sup>a</sup> <sup>a</sup>			1.31 (0.75, 2.30)	0.04 (-0.12, 0.2)	-
IXE <sup>a</sup> vs. SEC NL <sup>a</sup> <sup>a</sup>			1.29 (0.74, 2.26)	0.03 (-0.12, 0.19)	-
<b>PBS population: nr-axSpA (MRI+ AND CRP+)</b>					
IXE <sup>b</sup> vs. GLM <sup>b</sup>			1.16 (0.37, 3.64)	-0.09 (-0.45, 0.26)	-
IXE <sup>a</sup> vs. SEC LD <sup>a</sup> <sup>a</sup>			0.85 (0.33, 2.19)	-0.09 (-0.37, 0.2)	-
IXE <sup>a</sup> vs. SEC NL <sup>a</sup> <sup>a</sup>			0.84 (0.33, 2.15)	-0.1 (-0.38, 0.19)	-

Source: Table 2.6-7, p106 of the submission; Table 2(i).6-6, pp52-53, Appendix 2 of the submission

ASAS=Assessment of SpondyloArthritis international Society; ASAS40=40% improvement in ASAS; CI=confidence interval; CRP=C-reactive protein; GLM=golimumab; ITT=intention-to-treat; IXE=ixekizumab; LD=loading dose; MRI=magnetic resonance imaging; NL=no loading dose; NNT=number needed to treat; nr-axSpA=non-radiographic axial spondyloarthritis; OSI=objective signs of inflammation; PBO=placebo; PBS=Pharmaceutical Benefits Scheme; PHS=post-hoc subgroup; PSS=pre-specified subgroup; Q4W=once every 4 weeks; RD=risk difference; RR=relative risk; SEC=secukinumab; TGA=Therapeutic Goods Administration; TNFi=tumour necrosis factor inhibitor; vs.=versus

<sup>a</sup> CRP threshold >5 mg/L

<sup>b</sup> CRP threshold >9 mg/L

<sup>c</sup> CRP threshold >9.99 mg/L

<sup>d</sup> CRP threshold >10 mg/L

<sup>^</sup> TNFi-naïve

Data in **bold** indicate statistically significant results.

Table 5: ASAS20 response in patients with nr-axSpA plus OSI defined according to the TGA population (MRI+ and/or CRP+) and PBS population (MRI+ and CRP+) at week 16

Trial	Drug n/N (%)	Control n/N (%)	RR (95%CI)	RD (95%CI)	NNT (95%CI)
<b>TGA population: nr-axSpA (MRI+ AND/OR CRP+)</b>					
<b>IXE 80 mg Q4W vs. PBO</b>					
COAST-X, ITT (N=201) <sup>a</sup>	52/96 (54.2)	41/105 (39.0)	<b>1.39 (1.03, 1.88)</b>	<b>0.15 (0.01, 0.29)</b>	7 (3, 68)
<b>GLM vs. PBO</b>					
GO-AHEAD, PSS (N=158) <sup>b</sup>	60/78 (76.9)	30/80 (37.5)	<b>2.05 (1.51, 2.79)</b>	<b>0.39 (0.25, 0.54)</b>	3 (2, 4)
<b>SEC 150 mg LD vs. PBO</b>					
PREVENT, ITT (N=555) <sup>a</sup>	105/185 (56.8)	85/186 (45.7)	<b>1.24 (1.02, 1.52)</b>	<b>0.11 (0.01, 0.21)</b>	9 (5, 106)
<b>SEC 150 mg NL vs. PBO</b>					
PREVENT, ITT (N=555) <sup>a</sup>	107/184 (58.2)	85/186 (45.7)	<b>1.27 (1.04, 1.55)</b>	<b>0.12 (0.02, 0.23)</b>	8 (4, 43)
<b>PBS population: nr-axSpA (MRI+ AND CRP+)</b>					
<b>IXE 80 mg Q4W vs. PBO</b>					
COAST-X, PHS (N=51) <sup>b</sup>	14/20 (70.0)	10/31 (32.3)	<b>2.17 (1.21, 3.90)</b>	<b>0.38 (0.12, 0.64)</b>	3 (2, 8)
COAST-X, PHS (N=45) <sup>c</sup>	14/19 (73.7)	9/26 (34.6)	<b>2.13 (1.18, 3.85)</b>	<b>0.39 (0.12, 0.66)</b>	3 (2, 8)
<b>GLM vs. PBO</b>					
GO-AHEAD, PHS (N=53) <sup>b</sup>	22/26 (84.6)	10/27 (37.0)	<b>2.28 (1.36, 3.84)</b>	<b>0.48 (0.25, 0.70)</b>	2 (1, 4)
<b>SEC 150 mg LD vs. PBO</b>					
PREVENT, PHS (N=88) <sup>d</sup>	21/30 (70.0)	7/25 (28.0)	<b>2.50 (1.28, 4.89)</b>	<b>0.42 (0.18, 0.66)</b>	2 (2, 6)
<b>SEC 150 mg NL vs. PBO</b>					
PREVENT, PHS (N=88) <sup>d</sup>	23/33 (48.5)	7/25 (28.0)	<b>2.49 (1.28, 4.85)</b>	<b>0.42 (0.18, 0.65)</b>	2 (2, 6)
<b>Indirect comparisons</b>					
<b>TGA population: nr-axSpA (MRI+ AND/OR CRP+)</b>					
IXE <sup>a</sup> vs. GLM <sup>b</sup>			0.68 (0.44, 1.04)	<b>-0.24 (-0.44, -0.05)</b>	-
IXE <sup>a</sup> vs. SEC LD <sup>a</sup>			1.12 (0.78, 1.6)	0.04 (-0.13, 0.21)	-
IXE <sup>a</sup> vs. SEC NL <sup>a</sup>			1.09 (0.76, 1.56)	0.03 (-0.14, 0.2)	-
<b>PBS population: nr-axSpA (MRI+ AND CRP+)</b>					
IXE <sup>b</sup> vs. GLM <sup>b</sup>			0.95 (0.43, 2.08)	-0.1 (-0.44, 0.25)	-
IXE <sup>c</sup> vs. SEC LD <sup>d</sup>			0.85 (0.35, 2.08)	-0.03 (-0.39, 0.33)	-
IXE <sup>c</sup> vs. SEC NL <sup>d</sup>			0.86 (0.35, 2.09)	-0.03 (-0.38, 0.33)	-

Source: Table 2.6-6, p103 of the submission; Table 2(i).6-5, p50, Appendix 2 of the submission

ASAS=Assessment of SpondyloArthritis international Society; ASAS20=20% improvement in ASAS; CI=confidence interval; CRP=C-reactive protein; GLM=golimumab; ITT=intention-to-treat; IXE=ixekizumab; LD=loading dose; MRI=magnetic resonance imaging; NL=no loading dose; NNT=number needed to treat; nr-axSpA=non-radiographic axial spondyloarthritis; OSI=objective signs of inflammation; PBO=placebo; PBS=Pharmaceutical Benefits Scheme; PHS=post-hoc subgroup; PSS=pre-specified subgroup; Q4W=once every 4 weeks; RD=risk difference; RR=relative risk; SEC=secukinumab; TGA=Therapeutic Goods Administration; vs.=versus

<sup>a</sup> CRP threshold >5 mg/L<sup>b</sup> CRP threshold >9 mg/L<sup>c</sup> CRP threshold >9.99 mg/L<sup>d</sup> CRP threshold >10 mg/LData in **bold** indicate statistically significant results.

Table 6: BASDAI50 response in patients with nr-axSpA plus OSI defined according to the TGA population (MRI+ and/or CRP+) and PBS population (MRI+ and CRP+) at week 16

Trial	Drug n/N (%)	Control n/N (%)	RR (95%CI)	RD (95%CI)	NNT (95%CI)
<b>TGA population: nr-axSpA (MRI+ AND/OR CRP+)</b>					
<b>IXE 80 mg Q4W vs. PBO</b>					
COAST-X, ITT (N=201) <sup>a</sup>	30/96 (31.3)	15/105 (14.3)	<b>2.19 (1.26, 3.81)</b>	<b>0.17 (0.06, 0.28)</b>	6 (4, 18)
<b>GLM vs. PBO</b>					
GO-AHEAD, PSS (N=158) <sup>b</sup>	46/78 (59.0)	23/80 (28.7)	<b>2.05 (1.39, 3.03)</b>	<b>0.30 (0.15, 0.45)</b>	3 (2, 6)
<b>SEC 150 mg LD vs. PBO</b>					
PREVENT, ITT (N=555) <sup>a</sup>	69/185 (37.3)	39/186 (21.0)	<b>1.78 (1.27, 2.49)</b>	<b>0.16 (0.07, 0.25)</b>	6 (4, 14)
<b>SEC 150 mg NL vs. PBO</b>					
PREVENT, ITT (N=555) <sup>a</sup>	69/184 (37.5)	39/186 (21.0)	<b>1.79 (1.28, 2.50)</b>	<b>0.17 (0.07, 0.26)</b>	6 (4, 14)
<b>PBS population: nr-axSpA (MRI+ AND CRP+)</b>					
<b>IXE 80 mg Q4W vs. PBO</b>					
COAST-X, PHS (N=56) <sup>b</sup>	9/20 (45.0)	4/31 (12.9)	<b>3.49 (1.24, 9.82)</b>	<b>0.32 (0.07, 0.57)</b>	3 (2, 14)
COAST-X, PHS (N=45) <sup>c</sup>	9/19 (47.4)	3/26 (11.5)	<b>4.11 (1.28, 13.16)</b>	<b>0.36 (0.10, 0.61)</b>	3 (2, 10)
<b>GLM vs. PBO</b>					
GO-AHEAD, PHS (N=53) <sup>b</sup>	18/26 (69.2)	10/27 (37.0)	<b>1.87 (1.07, 3.25)</b>	<b>0.32 (0.07, 0.58)</b>	3 (2, 15)
<b>SEC 150 mg LD vs. PBO</b>					
PREVENT, PHS (N=88) <sup>d</sup>	15/30 (50.0)	3/25 (12.0)	<b>4.17 (1.36, 12.77)</b>	<b>0.38 (0.16, 0.60)</b>	3 (2, 6)
<b>SEC 150 mg NL vs. PBO</b>					
PREVENT, PHS (N=88) <sup>d</sup>	16/33 (48.5)	3/25 (12.0)	<b>4.04 (1.32, 12.36)</b>	<b>0.36 (0.15, 0.58)</b>	3 (2, 7)
<b>Indirect comparisons</b>					
<b>TGA population: nr-axSpA (MRI+ AND/OR CRP+)</b>					
IXE <sup>a</sup> vs. GLM <sup>b</sup>			1.07 (0.54, 2.1)	-0.13 (-0.32, 0.05)	-
IXE <sup>a</sup> vs. SEC LD <sup>a</sup>			1.23 (0.64, 2.35)	0.01 (-0.14, 0.15)	-
IXE <sup>a</sup> vs. SEC NL <sup>a</sup>			1.22 (0.64, 2.34)	0.00 (-0.14, 0.15)	-
<b>PBS population: nr-axSpA (MRI+ AND CRP+)</b>					
IXE <sup>b</sup> vs. GLM <sup>b</sup>			1.87 (0.58, 6.04)	-0.001 (-0.36, 0.35)	-
IXE <sup>c</sup> vs. SEC LD <sup>d</sup>			0.99 (0.2, 4.96)	-0.02 (-0.36, 0.32)	-
IXE <sup>c</sup> vs. SEC NL <sup>d</sup>			1.02 (0.2, 5.11)	-0.01 (-0.34, 0.33)	-

Source: Table 2.6-8, p108 of the submission; Table 2(i).6-9, pp65-67, Appendix 2 of the submission

BASDAI50=50% improvement in Bath Ankylosing Spondylitis Disease Activity Index; CI=confidence interval; CRP=C-reactive protein; GLM=golimumab; ITT=intention-to-treat; IXE=ixekizumab; LD=loading dose; MRI=magnetic resonance imaging; NL=no loading dose; NNT=number needed to treat; nr-axSpA=non-radiographic axial spondyloarthritis; OSI=objective signs of inflammation; PBO=placebo; PBS=Pharmaceutical Benefits Scheme; PHS=post-hoc subgroup; PSS=pre-specified subgroup; Q4W=once every 4 weeks; RD=risk difference; RR=relative risk; SEC=secukinumab; TGA=Therapeutic Goods Administration; vs.=versus

<sup>a</sup> CRP threshold >5 mg/L

<sup>b</sup> CRP threshold >9 mg/L

<sup>c</sup> CRP threshold >9.99 mg/L

<sup>d</sup> CRP threshold >10 mg/L

Data in **bold** indicate statistically significant results.

6.17 The results for BASDAI50 and ASAS20/40 demonstrated that the three bDMARDs (IXE, SEC, and GLM) were more effective than placebo at producing a response to treatment across all three trials. Treatment benefit was greater in the PBS population subgroup than in the TGA population across all trials for all three outcomes. These subgroups represented a small proportion of the total patients across the trials (e.g., 21% in the IXE once every four weeks (IXE Q4W) and 30% in the PBO group in the COAST-X trial). The 95% confidence interval (CI) was wider as the PBS population subgroup was smaller. The PBAC had previously noted the indirect comparisons of SEC

versus CZP and GLM were based on the PBS population subgroups of small patient numbers (para. 7.4, secukinumab PSD, November 2020 PBAC meeting).

- 6.18 The indirect comparisons in the TGA populations found results generally favoured: GLM over IXE for all three outcomes; and IXE over SEC for all three outcomes. The indirect comparisons in the PBS populations found results generally favoured: GLM over IXE for ASAS20/40 and IXE over GLM for BASDAI50; and SEC over IXE for all three outcomes. However, the differences were not statistically significant.
- 6.19 Based on the non-inferiority margin nominated by the submission for ASAS 20 (0.43 for the relative risk (RR) statistic), non-inferiority was just satisfied between IXE and GLM (the lower 95%CI = 0.43) but not IXE and SEC (the lower 95%CI was = 0.35) in the PBS populations.
- 6.20 In the comparison of the PBS populations between IXE and GLM, the event rates in the common reference arm (placebo) varied between the trials, particularly for BASDAI50 (12.9% to 37.0%) and ASAS40 (16.1% to 25.9%), suggesting poor transitivity/exchangeability of the COAST-X and GO-AHEAD trials included in the analysis. The uncertainty in the indirect comparisons was further complicated by the use of subgroups to inform the analyses, where no baseline characteristics were available for the comparator trials.
- 6.21 No indirect comparisons beyond 16 weeks' treatment were presented. The PSCR stated that while longer-term data was available for both IXE and the comparator(s), differences in the design of the COAST-X (IXE) and GO-AHEAD (GLM) studies would make these comparisons likely uninformative and reiterated the results of the COAST-X trial demonstrated the effectiveness and safety of IXE up to week 52.

### ***Comparative harms***

- 6.22 In the COAST-X trial, around half of the patients on IXE treatment had one or more treatment-emergent adverse event (TEAE), most of which were mild or moderate in severity. The most frequently reported adverse events were infections and injection site reactions. Nasopharyngitis and diarrhoea were also common.
- 6.23 Tables 7 and 8 present the indirect comparison of the safety outcomes of IXE versus GLM and SEC, at week 16, respectively in the Safety Population. Safety Population was defined as patients who received at least one dose of study medications.

Table 7: Indirect comparison – IXE vs. GLM – safety outcomes at week 16 (Safety Population\*)

Trial	Proposed medicine n/N (%)	Common reference n/N (%)	Comparator n/N (%)	Treatment effect (95% CI), p-value		
<b>SAEs</b>						
	IXE	PBO	GLM	RD	RR	OR
COAST-X† <sup>a</sup>	0/96 (0.0)	1/104 (1.0)	-	-0.01 (-0.04, 0.02); p=0.480	0.4 (0.0, 8.8); p=0.530	0.4 (0.0, 8.9); p=0.530
GO-AHEAD <sup>b</sup>	-	2/100 (2.0)	1/97 (1.0)	-0.01 (-0.04, 0.02); p=0.580	0.5 (0.1, 5.6); p=0.590	0.5 (0.1, 5.7); p=0.590
<b>Indirect estimate (RE) (95% CI)</b>				0 (-0.04, 0.04); p=0.997	0.7 (0.01, 37.53); p=0.861	0.7 (0.01, 39.02); p=0.862
<b>TEAEs</b>						
	IXE	PBO	GLM	RD	RR	OR
COAST-X <sup>a</sup>	52/96 (54.2)	51/104 (49.0)	-	0.05 (-0.09, 0.19); p=0.470	1.1 (0.8, 1.4); p=0.470	1.2 (0.7, 2.1); p=0.470
GO-AHEAD <sup>b</sup>	-	47/100 (47.0)	40/97 (41.2)	-0.06 (-0.2, 0.08); p=0.410	0.9 (0.6, 1.2); p=0.420	0.8 (0.5, 1.4); p=0.420
<b>Indirect estimate (RE) (95% CI)</b>				0.11 (-0.09, 0.3); p=0.276	1.26 (0.83, 1.91); p=0.276	1.55 (0.7, 3.43); p=0.276
<b>Discontinuation due to AEs</b>						
	IXE	PBO	GLM	RD	RR	OR
COAST-X† <sup>a</sup>	0/96 (0.0)	2/104 (1.9)	-	-0.02 (-0.05, 0.01); p=0.250	0.2 (0.0, 4.5); p=0.320	0.2 (0.0, 4.5); p=0.320
GO-AHEAD <sup>b</sup>	-	1/100 (1.0)	2/97 (2.1)	0.01 (-0.02, 0.04); p=0.540	2.1 (0.2, 22.4); p=0.550	2.1 (0.2, 23.4); p=0.550
<b>Indirect estimate (RE) (95% CI)</b>				-0.03 (-0.08, 0.02); p=0.216	0.11 (0, 4.94); p=0.251	0.1 (0, 4.99); p=0.250

Source: Tables 2.6-9, p110 of the submission.

AE=adverse events; CI=confidence interval; GLM=golimumab; IXE=ixekizumab; n=number of participants with event; N=total participants in group; OR=odds ratio; PBO=placebo; RD=risk difference; RE=random effects; SAE=serious adverse event; TEAE=Treatment-emergent adverse event; vs.=versus

\* Safety Population – defined as patients who received at least one dose of study medications.

<sup>a</sup> CRP threshold >5 mg/L

<sup>b</sup> CRP threshold >9 mg/L

† 0.5 added to the test and control cells.

Data in **bold** indicate statistically significant results.

**Table 8: Indirect comparison – IXE vs. SEC – safety outcomes (IXE at week 16, SEC at week 20) (Safety Population\*)**

Trial	Proposed medicine n/N (%)	Common reference n/N (%)	Comparator n/N (%)	Treatment effect (95% CI), p-value		
<b>SAEs</b>						
	IXE	PBO	SEC	RD	RR	OR
COAST-X† <sup>a</sup>	0/96 (0.0)	1/104 (1.0)	-	-0.01 (-0.04, 0.02), p=0.480	0.36 (0.01, 8.76), p=0.530	0.36 (0.01, 8.88), p=0.530
PREVENT LD <sup>a</sup>	-	5/186 (2.7)	2/185 (1.1)	-0.02 (-0.04, 0.01), p=0.250	0.4 (0.08, 2.05), p=0.270	0.4 (0.08, 2.07), p=0.270
PREVENT NL <sup>a</sup>	-	5/186 (2.7)	4/184 (2.2)	-0.01 (-0.04, 0.03), p=0.750	0.8 (0.2, 3.0), p=0.750	0.8 (0.2, 3.0), p=0.750
Indirect estimate (RE), IXE vs. SEC LD, (95% CI)				0.01 (-0.03, 0.04), p=0.742	0.9 (0.03, 32.19), p=0.953	0.9 (0.02, 33.5), p=0.956
Indirect estimate (RE), IXE vs. SEC NL, (95% CI)				0 (-0.05, 0.04), p=0.832	0.45 (0.01, 13.96), p=0.646	0.44 (0.01, 14.39), p=0.648
<b>TEAEs</b>						
	IXE	PBO	SEC	RD	RR	OR
COAST-X <sup>a</sup>	52/96 (54.2)	51/104 (49.0)	-	0.05 (-0.09, 0.19), p=0.470	1.1 (0.84, 1.45), p=0.470	1.23 (0.7, 2.14), p=0.470
PREVENT LD <sup>a</sup>	-	101/186 (54.3)	119/185 (64.3)	0.1 (0, 0.2), p=0.050	1.18 (1, 1.4), p=0.050	1.52 (1, 2.3), p=0.050
PREVENT NL <sup>a</sup>	-	101/186 (54.3)	107/184 (58.2)	0.04 (-0.06, 0.14), p=0.450	1.1 (0.9, 1.3), p=0.460	1.2 (0.8, 1.8), p=0.460
Indirect estimate (RE), IXE vs. SEC LD, (95% CI)				-0.05 (-0.22, 0.12), p=0.574	0.93 (0.68, 1.28), p=0.666	0.81 (0.4, 1.62), p=0.551
Indirect estimate (RE), IXE vs. SEC NL, (95% CI)				0.01 (-0.16, 0.18), p=0.884	1.03 (0.75, 1.43), p=0.851	1.05 (0.53, 2.1), p=0.890
<b>Discontinuation due to AEs</b>						
	IXE	PBO	SEC	RD	RR	OR
COAST-X† <sup>a</sup>	0/96 (0)	2/104 (1.9)	-	-0.02 (-0.05, 0.01), p=0.250	0.22 (0.01, 4.45), p=0.320	0.21 (0.01, 4.48), p=0.320
PREVENT LD <sup>a</sup>	-	3/186 (1.6)	0/185 (0.0)	-0.02 (-0.04, 0), p=0.130	0.14 (0.01, 2.76), p=0.200	0.14 (0.01, 2.76), p=0.200
PREVENT NL <sup>a</sup>	-	3/186 (1.6)	3/184 (1.6)	0.00 (-0.03, 0.03), p=0.990	1.0 (0.2, 4.9), p=0.990	1.0 (0.2, 5.1), p=0.990
Indirect estimate (RE), IXE vs. SEC LD, (95% CI)				0 (-0.04, 0.04), p=0.875	1.51 (0.02, 103.49), p=0.849	1.5 (0.02, 106.09), p=0.851
Indirect estimate (RE), IXE vs. SEC NL, (95% CI)				-0.02 (-0.06, 0.02), p=0.359	0.21 (0.01, 6.52), p=0.377	0.21 (0.01, 6.62), p=0.375

Source: Tables 2(i).6-10, pp60-61, Appendix 2 of the submission.

AE=adverse events; CI=confidence interval; IXE=ixekizumab; n=number of participants with event; N=total participants in group; PBO=placebo; RD=risk difference; RE=random effects; SEC=secukinumab; SAE=Serious adverse event; TEAE=Treatment-emergent adverse event; vs.=versus

\* Safety Population – defined as patients who received at least one dose of study medications.

<sup>a</sup> CRP threshold >5 mg/L

† 0.5 added to the test and control cells.

Data in **bold** indicate statistically significant results.

6.24 There was no statistically significant difference in any of the AE comparisons between IXE and GLM and SEC.

6.25 The comparative safety of IXE versus GLM or SEC beyond week 16 weeks was unclear.

### **Clinical claim**

- 6.26 The submission described IXE as non-inferior to GLM or SEC with regard to comparative efficacy and safety. The clinical claim was based on the indirect comparisons between IXE and GLM/SEC for ASAS20, ASAS40 and BASDAI50 in the PBS population at Week 16.
- 6.27 The evaluation considered the clinical claim of non-inferior efficacy and safety may be reasonable, however, the following key issues were noted:
- As the patient population in all the trials was broader than the PBS population, the submission used subgroups in the indirect comparisons. These subgroups represented a small proportion of the total patients across the trials (e.g., 21% in the IXE once every four weeks (IXE Q4W) and 30% in the PBO group in the COAST-X trial). This substantially increases the uncertainty in the indirect estimates, with wider 95% CIs. The PSCR acknowledged that indirect comparisons based on subgroups reduces the precision of the estimates due to smaller sample sizes. However, the PSCR stated the comparisons showed no statistically significant differences in any of the outcomes compared between IXE and GLM or SEC and thus conclusions of non-inferiority are reasonable. The PSCR noted a similar observation was made when the PBAC evaluated SEC in the same indication of nr-axSpa, whereby they noted that the indirect comparisons of SEC versus CZP and GLM were based on the PBS population subgroups of small patient numbers (para. 7.4, Secukinumab, PSD November 2020 PBAC meeting).
  - There is potential poor transitivity/exchangeability across the trials, including differences in the study design and patient characteristics (e.g., age, previous treatments, duration of treatment), and differences in the event rates in the PBO arms (e.g. 12.0-37.0% achieved BASDAI50, 16.1-25.9% achieved ASAS40 and 28.0-37.0% achieved ASAS20 responses). The PSCR agreed with the evaluation that there were potential limitations in the transitivity/exchangeability across the trials presented; however, on balance, the similarities outweigh the differences. The PSCR noted similar limitations were noted by the PBAC when reviewing the comparison of SEC versus CZP and GLM in this indication (Secukinumab PSD of November 2020 PBAC Meeting).
- 6.28 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.29 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

### **Economic analysis**

- 6.30 The submission presented a CMA comparing IXE 80 mg Q4W versus GLM 50 mg Q4W over two years.
- 6.31 The equi-effective doses were estimated as:
- IXE 80 mg by subcutaneous injection once every four weeks; and
  - GLM 50 mg by subcutaneous injection once every four weeks.
- 6.32 No equi-effective doses were nominated for SEC. The PBAC advised the following equi-effective doses at the November 2020 PBAC meeting:
- SEC: 150 mg at Week 0, 1, 2, 3 and 4, then SEC 150 mg every 4 weeks; or SEC 150 mg every 4 weeks
  - GLM: 50 mg every 4 weeks
  - CZP: 400 mg at Week 0, 2, 4, then 200 mg every 2 weeks; or CZP 400 mg every 4 weeks (para. 7.2, PSD, Secukinumab, November 2020 PBAC meeting).
- 6.33 The dosing regimen for IXE was not the same as the regimen in the COAST-X trial with 50% of patients receiving a loading dose of 160 mg, however it aligns with the dose regimen for IXE for nr-axSpA in the approved TGA Product Information (PI).
- 6.34 The dosing regimen of GLM in the GO-AHEAD trial (50 mg Q4W) differed from the TGA PI (50 mg once a month, on the same date each month), however aligns with the PBAC's previously-recommendations with regards to considering equi-effective doses that "the 4-weekly dosing was the most appropriate frame of reference for considering equi-effective doses" (para. 7.2, Secukinumab PSD, March 2016 PBAC meeting).
- 6.35 The submission did not apply any additional costs or use any cost offsets in the CMA comparing IXE and GLM. This was reasonable.
- 6.36 Table 9 presents the results of the CMA as presented in the submission (based on published prices).

**Table 9: Results of the CMA as presented in the submission (published prices)**

	IXE 80 mg Q4W	GLM 50 mg Q4W
Total administrations	26	26
Injections per pack	2	1
Injections per prescription	2	1
Prescriptions	13 [26 / 2]	26 [26 / 1]
AEMP per prescription [published]	\$3,260.00	\$1,044.43
Total cost over 2 years	\$42,380.00	\$27,155.18
Difference in cost of treatment	\$15,224.82	

Source: Table 3.3-2, p128 of the submission.

AEMP=Approved ex-manufacturer price; GLM=golimumab; IXE=ixekizumab; Q4W=once every four weeks

6.37 The submission did not explicitly propose any indication-specific price for IXE in adults with nr-axSpA. Instead, the CMA used the published approved ex-manufacturer prices (AEMPs) of IXE and GLM.

6.38 The ESC considered the approach to the CMA was reasonable.

### **Drug cost/patient/course/year**

6.39 Based on the requested published DPMQ of \$3,421.22 and 6.5 prescriptions per patient per year, the drug cost is \$22,237.93 per patient per year.

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

6.40 This submission was not considered by DUSC. The submission used a market share approach to predict the utilisation and financial implications of the proposed listing of IXE in nr-axSpA, based on the substitution of GLM and CZP (Table 10).

**Table 10: Key inputs for financial estimates**

Data	Value	Source	Comment
<b>Treatment utilisation</b>			
IXE market share (% initiation periods)	Yr 1: █ % Yr 2: █ % Yr 3: █ % Yr 4: █ % Yr 5: █ % Yr 6: █ %	Eli Lilly. Assumed both CZP and GLM each lost █ % market share to IXE in Yr 1	No further details were provided. The accuracy of these estimates is unclear.
Maintenance scripts required per 52 weeks	IXE: 6.5 GLM: 13 CZP: 13	IXE: 6.5 = 52/4/2 GLM: 13=52/4 CZP: 13=52/4	This is reasonable.

Source: Table 4.1-1, p131 of the submission.

CMA=Cost-minimisation analysis; CZP=Certolizumab pegol; GLM=Golimumab; IXE=ixekizumab; PBS=Pharmaceutical Benefits Scheme; RPBS=Repatriation Pharmaceutical Benefits Scheme; Yr=Year

6.41 Table 11 presents the estimated net cost of IXE to the PBS/ RPBS presented in the submission using published prices.

**Table 11: Summary of the estimated net cost of IXE to the PBS/RPBS (published prices)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Market share (% of initiation periods)	%	%	%	%	%	%
Number of IXE scripts dispensed	1	1	1	2	2	2
<b>Estimated financial implications of IXE</b>						
Cost to the PBS/RPBS less co-payments	3	3	3	3	3	3
<b>Estimated financial implications for other biological medicines (GLM, CZP)</b>						
Number of scripts substituted	1	1	2	2	2	2
Cost to the PBS/RPBS less co-payments	3	3	3	3	3	3
<b>Net financial implications to the PBS/RPBS</b>						
Net cost to PBS/RPBS	3	3	3	3	3	3
Net cost to MBS	3	3	3	3	3	3
Net cost to PBS/RPBS/MBS	3	3	3	3	3	3

Source: Tables 4.2-2 to 4.2-6, pp133-136 of the submission.

CZP=certolizumab pegol; GLM=golimumab; IXE=ixekizumab; PBS=Pharmaceutical Benefits Scheme; RPBS=Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

<sup>3</sup> \$0 to < \$10 million

6.42 The submission claimed that SEC was only PBS listed on 1 April 2021 and consequently there were insufficient data to inform the analysis and was therefore not included in the utilisation estimates but this is unlikely to impact the analysis given that it was listed on a cost-minimisation basis to the lowest cost alternative.

6.43 The submission claimed that IXE is proposed to be listed on a cost-minimisation basis to alternative biological medicines. Consequently, the net financial implications for the PBS/ RPBS when estimated using the indication-specific effective prices for all medicines are likely to be marginal. The PBAC noted these costs were based on the published price of the comparator. The net cost to the PBS will reduce once the effective price of the comparator is applied.

### Quality Use of Medicines

6.44 The submission did not present any quality use of medicines factors.

### Financial Management – Risk Sharing Arrangements

6.45 The submission did not propose any risk-sharing agreement.

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

## 7 PBAC Outcome

7.1 The PBAC recommended the Authority Required listing of ixekizumab (IXE) for the treatment of non-radiographic axial spondyloarthritis (nr-axSpA). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of IXE would be acceptable if it were cost-minimised to the least costly biologic disease-modifying anti-rheumatic drug (bDMARD) for this indication.

- 7.2 The PBAC considered the nominated comparators of golimumab (GLM) and secukinumab (SEC) were appropriate; however, considered (CZP) was also a relevant alternative therapy. On that basis, the PBAC advised the equi-effective doses were:
- IXE 80 mg once every four weeks;
  - GLM 50 mg once every four weeks;
  - SEC: 150 mg at Week 0, 1, 2, 3 and 4, then SEC 150 mg every 4 weeks; or SEC 150 mg every 4 weeks, at a 70:30 weighting for loading dose versus no loading dose (as outlined in paragraph 7.7 of the SEC November 2020 PSD); and
  - CZP: 400 mg at Week 0, 2, 4, then 200 mg every 2 weeks; or CZP 400 mg every 4 weeks.
- 7.3 The PBAC recommended listing IXE under the same circumstances as that of the other bDMARDs for nr-axSpA. In providing this advice, the PBAC considered the number of treatment failures in a treatment cycle in the listings for nr-axSpA should not increase maintaining consistency with other bDMARD listings. The PBAC also noted the flow-on restriction changes necessary to other bDMARD listings for nr-axSpA as a result of listing ixekizumab.
- 7.4 The PBAC noted the requested listing was for a maximum quantity of two injections which would provide two months of treatment per script dispensing. The PBAC noted the listings for GLM, SEC and CZP provide for one month of treatment per script dispensing and considered it was appropriate for the IXE listing provide the same duration of treatment per script dispensing. The PBAC considered it was appropriate to list IXE with a medicinal product pack containing 1 injection per contained product with a maximum quantity of one injection unit/pack plus 3 repeats for the initial restriction treatment and one injection plus 5 repeats for the continuing restriction treatment, which would provide thereby ensuring one month of treatment per script dispensing without need for broken packs. The PBAC recalled it had previously expressed a preference for a pack with one injection be made available to facilitate listing a maximum quantity of one injection on the PBS. The pre-PBAC response stated the sponsor was progressing with a pack of one injection, but raised concerns regarding any potential delay in patient access. The PBAC noted the initial request for a pack with one injection to amend the maximum quantity in the context of chronic plaque psoriasis to a quantity of 1 unit was made some time ago (July 2017), but the sponsor had not acted to supply a 1-unit presentation to enable practical supply of this quantity. The PBAC considered that, because IXE would be the fourth bDMARD for nr-AxSpA, there was no urgent clinical need for an additional bDMARD to be listed for this indication.
- 7.5 The PBAC noted the maximum treatment duration allowed under initial treatment was different: 16 weeks for IXE and GLM, 20 weeks for SEC and 18-20 weeks for CZP. However, the PBAC advised that the requested duration of initial treatment of 16

weeks was clinically appropriate and consistent with the initial treatment duration of IXE for other listed indications.

- 7.6 The PBAC considered there were uncertainties with the results of the indirect comparisons of IXE versus GLM and SEC given the transitivity issues between the trials (see paragraph 6.10), the lack of non-inferiority margin for BASDAI50 (the primary outcome measure) and ASAS 40, and inconsistent results for the ASAS20 comparison (see paragraph 6.17). However, the PBAC noted the indirect comparisons based on the PBS population subgroup demonstrated there were no statistically significant differences between IXE and SEC or GLM for BASDAI50, ASAS20 or ASAS40, although the comparisons were based on small patient numbers. The PBAC recalled it has previously considered IXE to be non-inferior to SEC and GLM in other indications including AS. The PBAC considered that, on balance, a claim of non-inferior comparative efficacy to both these bDMARDs was likely to be reasonable.
- 7.7 The PBAC noted the most commonly reported adverse events (AEs) in the COAST-X trial were infections, injection site reactions, nasopharyngitis and diarrhoea, however also noted there were no serious AEs or discontinuations due to adverse events observed in the pivotal trial. The PBAC noted the indirect comparisons of safety showed no statistically significant difference in SAEs, treatment-emergent adverse events (TEAEs) or discontinuations due to AEs. Overall, the PBAC considered that the claim of non-inferior comparative safety to other bDMARDs for nr-axSpA was reasonable.
- 7.8 The PBAC considered the cost minimisation approach should be based on the effective price of the least costly alternative bDMARD over 2 years, consistent with its previously accepted approach for listing bDMARDs. If listed under the parameters of its recommended listing on a cost minimisation basis with the least costly alternative bDMARD for nr-axSpA, the PBAC considered the listing of IXE should not result in any additional cost to the PBS.
- 7.9 The PBAC recommended the IXE be included within the current risk sharing arrangements (RSA) for GLM, CZP and SEC with no increase to the expenditure cap levels.
- 7.10 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because IXE is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over GLM, 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.
- 7.11 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 indication (22964 – non radiographic axial spondyloarthritis) as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
IXEKIZUMAB					
ixekizumab 80 mg/mL injection, 2 x 1 mL pen device	NEW	1	1	1	Taltz
<b>Restriction Summary 11484 / ToC: 11431 (as per golimumab, PBS item code 11538G as at 1 November 2021)</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in-writing only via post/HPOS upload)					
Prescribing rule level	<p><b>Administrative Advice:</b></p> <p><b>TREATMENT OF ADULT PATIENTS WITH NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS</b></p> <p>The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of biological medicines listed specifically for the indication of: 'non-radiographic axial spondyloarthritis'. A patient is eligible for PBS-subsidised treatment with only 1 biological medicine at any one time.</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.</p> <p>A serious adverse reaction requiring permanent withdrawal of treatment, including serious infusion or injection related reactions, Steven's Johnson Syndrome, development of a demyelinating lesion, progressive multifocal leukoencephalopathy and malignancy related to treatment with the biological medicine, is not considered as a treatment failure.</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>Once a patient has either failed or ceased to respond to treatment 3 times (once with any biological medicine) within the same treatment cycle, they are deemed to have completed a treatment cycle and they must have, at a minimum, a 5-year break in PBS-subsidised biological medicine therapy before they are eligible to commence the next cycle. The 5-year break is measured from the date of the last prescription for PBS-subsidised biological medicine treatment in the most recent cycle to the date of the first application for initial treatment with a biological medicine under the new treatment cycle.</p> <p>A patient who has failed fewer than 3 trials of biological medicine therapy in a treatment cycle and who has a break in therapy of less than 5 years may commence a further course of treatment within the same treatment cycle.</p> <p>A patient who has failed 3 trials or fewer of biological medicine therapy in a treatment cycle and who has a break in therapy of more than 5 years may commence a new treatment cycle.</p> <p>There is no limit to the number of treatment cycles a patient may undertake in their lifetime.</p> <p>How to prescribe PBS-subsidised biological medicine through the various 'treatment phase' listings:</p> <p>(1) Initiating treatment:</p> <p>Apply through an 'Initial treatment' phase where:</p> <p>(i) the patient has never been treated with biological medicine – the patient is considered 'new' to biological medicine (Initial 1 - New patient); or</p> <p>(ii) the patient has received prior PBS-subsidised (initial or continuing) biological medicine, but is changing to an alternate biological medicine (Initial 2 - Change) [further details are under 'Changing biological medicine' below]; or</p>				

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	<p><i>(iii) the patient is recommencing biological medicine following a break in PBS-subsidised therapy of less than 5 years (Initial 2 - Recommencement of treatment after a break in therapy of less than 5 years); or</i></p> <p><i>(iv) the patient is recommencing biological medicine following a break in PBS-subsidised therapy of more than 5 years (Initial 3 - Recommencement of treatment after a break in biological medicine of more than 5 years).</i></p> <p><i>A patient must be assessed for response to a course of initial PBS-subsidised treatment following a minimum of 12 weeks of therapy.</i></p> <p><i>(2) Continuing treatment with the same biological medicine:</i></p> <p><i>Apply through the 'Continuing treatment' phase – do not initiate a treatment-naïve patient through this phase or where the biological medicine of choice is changing.</i></p> <p><i>For continuing courses of PBS-subsidised biological medicine it is recommended that a patient be reviewed the month prior to completing their current course of treatment to ensure uninterrupted biological medicine supply.</i></p> <p><i>Following the completion of an initial treatment course with a specific biological medicine, a patient may qualify to receive up to 24 weeks of continuing treatment with that biological medicine provided they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing biological medicine treatment in courses of up to 24 weeks provided they continue to sustain an adequate response.</i></p> <p><i>A patient must be assessed for response to a course of continuing therapy, and the assessment must be conducted no later than 4 weeks from the cessation of that treatment course. Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with that biological medicine, unless the patient has experienced a serious adverse reaction requiring permanent treatment withdrawal.</i></p> <p><i>(3) Changing biological medicine:</i></p> <p><i>Once initial treatment with the first PBS-subsidised biological medicine is approved, treatment may change to an alternate biological medicine within the same treatment cycle without having to requalify with respect to the indices of disease severity (i.e. the C-reactive protein (CRP) level and the BASDAI score), or the prior NSAID therapy and exercise program requirements. Apply through the 'Initial 2' treatment phase. Do not apply under 'Continuing treatment' to change the biological medicine.</i></p> <p><i>To ensure a patient receives the maximum treatment opportunities allowed under these arrangements, it is important that they are assessed for response to every course of treatment.</i></p> <p><i>A patient who is not able to complete a minimum of 12 weeks of an initial treatment course will be deemed to have failed treatment with that biological medicine unless the patient has experienced a serious adverse reaction requiring permanent treatment withdrawal.</i></p> <p><i>(4) Baseline measurements to determine response:</i></p> <p><i>A response to treatment is based on improvement in (or maintaining any such improvement) of the baseline BASDAI score and CRP level documented in the patient's medical records.</i></p> <p><i>For a new patient, the BASDAI score used to determine baseline disease severity must be measured while the patient is receiving NSAID therapy and completing their exercise program.</i></p> <p><i>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.</i></p> <p><i>Prescribers may provide new baseline measurements with any new 'Initial treatment' authority application, but eligibility for continuing treatment must be assessed according to these revised baseline measurements.</i></p> <p><i>(5) Recommencement of treatment after a 5-year break in PBS-subsidised therapy:</i></p> <p><i>Apply under the 'Initial 3 treatment' phase where there has been an absence of PBS-subsidy for at least 5 years, but the patient has previously qualified for PBS-subsidised treatment. The same clinical criteria and indices of disease</i></p>
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	severity (i.e. the C-reactive protein (CRP) levels and the BASDAI) as for the Initial 1 (New patient) restriction will need to be met, but a re-trial of NSAID therapy and exercise therapy is not required.
	<b>Administrative Advice:</b> Where the term 'biological medicine' appears in these restrictions, it refers to: golimumab, certolizumab pegol, ixekizumab, secukinumab.
	<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>Indication:</b> Non-radiographic axial spondylarthritis
	<b>Treatment Phase:</b> Initial treatment - Initial 1 (New patient)
	<b>Clinical criteria:</b> Patient must not have received PBS-subsidised treatment with a biological medicine for this condition
	<b>AND</b>
	<b>Clinical criteria:</b> Patient must have had chronic lower back pain and stiffness for 3 or more months that is relieved by exercise but not rest
	<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
	<b>AND</b>
	<b>Clinical criteria:</b> Patient must have one or more of the following: (a) enthesitis (heel); (b) uveitis; (c) dactylitis; (d) psoriasis; (e) inflammatory bowel disease; or (f) positive for Human Leukocyte Antigen B27 (HLA-B27)
	<b>AND</b>
	<b>Clinical criteria:</b> The condition must not be radiographically evidenced on plain x-ray of Grade II bilateral sacroiliitis or Grade III or IV unilateral sacroiliitis
	<b>AND</b>
	<b>Clinical criteria:</b> The condition must be non-radiographic axial spondyloarthritis, as defined by Assessment of Spondyloarthritis International Society (ASAS) criteria
	<b>AND</b>
	<b>Clinical criteria:</b> The condition must be sacroiliitis with active inflammation and/or oedema on non-contrast Magnetic Resonance Imaging (MRI)
	<b>AND</b>
	<b>Clinical criteria:</b> The condition must have presence of Bone Marrow Oedema (BMO) depicted as a hyperintense signal on a Short Tau Inversion Recovery (STIR) image (or equivalent)
	<b>AND</b>
	<b>Clinical criteria:</b> The condition must have BMO depicted as a hypointense signal on a T1 weighted image (without gadolinium)
	<b>AND</b>
	<b>Clinical criteria:</b> The treatment must not exceed a maximum of 16 weeks with this drug under this restriction
	<b>AND</b>
	<b>Population criteria:</b> Patient must be aged 18 years or older
	<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 non-radiographic axial spondyloarthritis

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	<p><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.</p> <p>If treatment with NSAIDs is contraindicated according to the relevant TGA-approved Product Information, the application must provide details of the contraindication.</p> <p>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:</p> <p>(a) a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of at least 4 on a 0-10 scale; and (b) C-reactive protein (CRP) level greater than 10 mg per L.</p> <p>The baseline BASDAI score and CRP level must be determined at the completion of the 3-month NSAID and exercise trial, but prior to ceasing NSAID treatment. All measures must be no more than 4 weeks old at the time of initial application.</p>
	<p><b>Prescribing Instructions:</b> If the requirement to demonstrate an elevated CRP level could not be met, the reason must be stated in the application. Treatment with prednisolone dosed at 7.5 mg or higher daily (or equivalent) or a parenteral steroid within the past month (intramuscular or intravenous methylprednisolone or equivalent) is an acceptable reason.</p>
	<p><b>Prescribing Instructions:</b> The assessment of the patient's response to the initial course of treatment must be conducted following a minimum of 12 weeks of treatment and no later than 4 weeks from the cessation of that treatment course. If the response assessment is not conducted within these timeframes, the patient will be deemed to have failed this course of treatment in this treatment cycle.</p>
	<p><b>Prescribing Instructions:</b> The authority application must be made in writing and must include: (a) a completed authority prescription form(s); and (b) a completed PBS authority application form relevant to the indication and treatment phase (the latest version located at the website specified in the Administrative Advice).</p>
	<p><b>Prescribing Instructions:</b> The baseline BASDAI score and CRP level must also be documented in the patient's medical records.</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. EST 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</p>
<p><b>Restriction Summary 11483 edited / ToC: 11387 (as per golimumab, PBS item code 11538G as at 1 November 2021)</b></p>	
<p><b>Category / Program:</b> GENERAL – General Schedule (Code GE)</p>	
<p><b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners</p>	
<p><b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS authorities system)</p>	
	<p><b>Indication:</b> Non-radiographic axial spondyloarthritis</p>
	<p><b>Treatment Phase:</b> Initial treatment - Initial 2 (Change or re-commencement of treatment after a break of less than 5 years)</p>

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	<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>
	<del>Patient must not have failed, or ceased to respond to, PBS-subsidised treatment with biological medicines more than three times for this PBS indication during the current treatment cycle</del>
	The condition must not have failed to adequately respond to biological medicine on 3 occasions within the current treatment cycle
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have failed PBS-subsidised therapy with this biological medicine for this PBS indication more than once in the current treatment cycle
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not exceed a maximum of 16 weeks with this drug under this restriction
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<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 non-radiographic axial spondyloarthritis
	<b>Prescribing Instructions:</b>
	An application for Initial 2 treatment must indicate whether the patient has demonstrated an adequate response (an absence of treatment failure), failed or experienced an intolerance to the most recent supply of biological medicine treatment. A new baseline Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score and C-reactive protein (CRP) level may be provided at the time of this application.
	<b>Prescribing Instructions:</b>
	An adequate response to therapy with this biological medicine is defined as a reduction from baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score by 2 or more units (on a scale of 0-10) and 1 of the following: (a) a CRP measurement no greater than 10 mg per L; or (b) a CRP measurement reduced by at least 20% from baseline.
	<b>Prescribing Instructions:</b>
	The assessment of the patient's response to the most recent supply of biological medicine must be conducted following a minimum of 12 weeks of treatment.
	<b>Prescribing Instructions:</b>
	BASDAI scores and CRP levels must be documented in the patient's medical records.
	<b>Prescribing Instructions:</b>
	The assessment of the patient's response to the initial course of treatment must be conducted following a minimum of 12 weeks of treatment and no later than 4 weeks from the cessation of that treatment course. If the response assessment is not conducted within these timeframes, the patient will be deemed to have failed this course of treatment in this treatment cycle.
	<b>Prescribing Instructions:</b>
	The following must be provided at the time of application and documented in the patient's medical records: (a) the BASDAI score; and (b) the C-reactive protein (CRP) level.
	<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. EST Monday to Friday).

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<b>Restriction Summary 10525 / ToC: 10515</b>	
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)	
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners	
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS authorities system)	
	<b>Indication:</b> Non-radiographic axial spondyloarthritis
	<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 had chronic lower back pain and stiffness for 3 or more months that is relieved by exercise but not rest
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have had 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>
	Patient must have one or more of the following: (a) enthesitis (heel); (b) uveitis; (c) dactylitis; (d) psoriasis; (e) inflammatory bowel disease; or (f) positive for Human Leukocyte Antigen B27 (HLA-B27)
	<b>AND</b>
	<b>Clinical criteria:</b>
	The condition must not be radiographically evidenced on plain x-ray of Grade II bilateral sacroiliitis or Grade III or IV unilateral sacroiliitis
	<b>AND</b>
	<b>Clinical criteria:</b>
	The condition must be non-radiographic axial spondyloarthritis, as defined by Assessment of Spondyloarthritis International Society (ASAS) criteria
	<b>AND</b>
	<b>Clinical criteria:</b>
	The condition must be sacroiliitis with active inflammation and/or oedema on non-contrast Magnetic Resonance Imaging (MRI)
	<b>AND</b>
	<b>Clinical criteria:</b>
	The condition must have presence of Bone Marrow Oedema (BMO) depicted as a hyperintense signal on a Short Tau Inversion Recovery (STIR) image (or equivalent)
	<b>AND</b>
	<b>Clinical criteria:</b>
	The condition must have BMO depicted as a hypointense signal on a T1 weighted image (without gadolinium)
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not exceed a maximum of 16 weeks duration under this restriction
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<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 non-radiographic axial spondyloarthritis
	<b>Prescribing Instructions:</b>
	The following must be provided at the time of application and documented in the patient's medical records: (a) a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of at least 4 on a 0-10 scale; and (b) C-reactive protein (CRP) level greater than 10 mg per L.
	<b>Prescribing Instructions:</b>
	The BASDAI score and CRP level must be no more than 4 weeks old at the time of this application.

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	<b>Prescribing Instructions:</b> If the requirement to demonstrate an elevated CRP level could not be met, the reason must be stated in the application. Treatment with prednisolone dosed at 7.5 mg or higher daily (or equivalent) or a parenteral steroid within the past month (intramuscular or intravenous methylprednisolone or equivalent) is an acceptable reason.
	<b>Prescribing Instructions:</b> The assessment of the patient's response to the initial course of treatment must be conducted following a minimum of 12 weeks of treatment and no later than 4 weeks from the cessation of that treatment course. If the response assessment is not conducted within these timeframes, the patient will be deemed to have failed this course of treatment in this treatment cycle.
	<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. EST Monday to Friday).
<b>Restriction Summary 10511 / ToC: 10436</b>	
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)	
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners	
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS authorities system)	
	<b>Indication:</b> Non-radiographic axial spondyloarthritis
	<b>Treatment Phase:</b> Initial 1 (New patient), Initial 2 (Change or re-commencement 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
	<b>Clinical criteria:</b> 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
	<b>AND</b>
	<b>Clinical criteria:</b> The treatment must provide no more than the balance of up to 16 weeks treatment
	<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 non-radiographic axial spondyloarthritis
	<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. EST Monday to Friday).

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
IXEKIZUMAB ixekizumab 80 mg/mL injection, 2 x 1 mL pen device	NEW	1	1	2	Taltz
<b>Restriction Summary 10603 / ToC: 10461 (as per golimumab, PBS item code 11521J as at 1 November 2021)</b>					
	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				

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	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS authorities system)
Prescribing rule level	<b>Administrative Advice:</b> <b>TREATMENT OF ADULT PATIENTS WITH NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS</b> <i>See above administrative advice at the start of Initial 1.</i>
	<b>Administrative Advice:</b> <i>For the purposes of interpreting these restrictions for this PBS-indication, the term 'biological medicine' currently refers to: golimumab, certolizumab pegol, ixekizumab, secukinumab.</i>
	<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>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. EST Monday to Friday).
	<b>Indication:</b> Non-radiographic axial spondyloarthritis
	<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 for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not exceed a maximum of 24 weeks with this drug per authorised course under this restriction
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<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 non-radiographic axial spondyloarthritis
	<b>Prescribing Instructions:</b> An adequate response to therapy with this biological medicine is defined as a reduction from baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score by 2 or more units (on a scale of 0-10) and 1 of the following: (a) a CRP measurement no greater than 10 mg per L; or (b) a CRP measurement reduced by at least 20% from baseline.
	<b>Prescribing Instructions:</b> If the requirement to demonstrate an elevated CRP level could not be met under an initial treatment restriction, a reduction in the BASDAI score from baseline will suffice for the purposes of administering this continuing treatment restriction.
	<b>Prescribing Instructions:</b> The patient remains eligible to receive continuing treatment with the same biological medicine in courses of up to 24 weeks providing they continue to sustain an adequate response. It is recommended that a patient be reviewed in the month prior to completing their current course of treatment.
	<b>Restriction Summary 10604 / ToC: 10434</b>
	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS authorities system)
	<b>Indication:</b> Non-radiographic axial spondyloarthritis
	<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 of treatment
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must provide no more than the balance of up to 24 weeks treatment
	<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 non-radiographic axial spondyloarthritis

8.2 Flow-on changes to certolizumab pegol, golimumab and secukinumab in non-radiographic axial spondyloarthritis indications are as follows:

Concept / Action / Reason	Lineage
<p>27999 Administrative Advice: <b>Treatment of Adult Patients With Non-Radiographic Axial Spondyloarthritis</b> (<i>long, common explanatory note</i>)</p> <p>Remove &amp; Retire</p> <p>Replace with: New AA1 + AA2 as above</p> <p>Reason: To add 'ixekizumab' to the existing 3 drugs</p>	<p>11538G / golimumab 50 mg/0.5 mL injection, 0.5 mL pen device 11521J / golimumab 50 mg/0.5 mL injection, 0.5 mL pen device 11560K / golimumab 50 mg/0.5 mL injection, 0.5 mL syringe 11516D / golimumab 50 mg/0.5 mL injection, 0.5 mL syringe</p> <p>12027B / certolizumab pegol 200 mg/mL injection, 2 x 1 mL pen device 12063X / certolizumab pegol 200 mg/mL injection, 2 x 1 mL syringes 12013G / certolizumab pegol 200 mg/mL injection, 2 x 1 mL pen devices 12040Q / certolizumab pegol 200 mg/mL injection, 2 x 1 mL syringes 12028C / certolizumab pegol 200 mg/mL injection, 2 x 1 mL pen devices 12005W / certolizumab pegol 200 mg/mL injection, 2 x 1 mL syringes</p> <p>2321L / secukinumab 150 mg/mL injection, 1 mL pen device 2297F / secukinumab 150 mg/mL injection, 1 mL pen device 12307R / secukinumab 150 mg/mL injection, 1 mL pen device</p>
<p>25960 – in Initial 2 treatment phase <b>Clinical criterion:</b> Patient must not have failed, or ceased to respond to, PBS-subsidised treatment with biological medicines more than three times for this PBS-indication during the current treatment cycle.</p> <p>Remove &amp; Retire</p> <p>Replace with New CC1 <b>Clinical criterion:</b> The condition must not have failed to adequately respond to biological medicine on 3 occasions within the current treatment cycle</p> <p>Reason: editorial correction</p>	<p>11538G / golimumab 50 mg/0.5 mL injection, 0.5 mL pen device 11560K / golimumab 50 mg/0.5 mL injection, 0.5 mL syringe</p> <p>12027B / certolizumab pegol 200 mg/mL injection, 2 x 1 mL pen devices 12063X / certolizumab pegol 200 mg/mL injection, 2 x 1 mL syringes</p> <p>12321L / secukinumab 150 mg/mL injection, 1 mL pen device</p>

## 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.