

**6.12 RISANKIZUMAB,  
Injection 150 mg in 1 mL pre-filled syringe,  
Injection 150 mg in 1 mL pre-filled pen,  
Skyrizi<sup>®</sup>,  
AbbVie Pty Ltd.**

**1 Purpose of submission**

- 1.1 The Category 2 submission requested an Authority Required listing for two new presentations of risankizumab subcutaneous injection, a 150 mg/1 mL pre-filled pen (PFP) and a 150 mg/1 mL pre-filled syringe (PFS), under similar circumstances as the currently listed 75 mg/0.83 mL PFS for severe chronic plaque psoriasis (CPP).
- 1.2 Listing of risankizumab 150 mg PFP and 150 mg PFS was requested on a cost-minimisation basis versus the currently listed risankizumab 75 mg PFS, or alternatively, on a cost-minimisation basis to the least costly non-inferior biologic comparator of ixekizumab, guselkumab and bimekizumab (if PBS listed). The ESC noted bimekizumab was listed on the PBS on the 1 October 2023.

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

Component	Description
Population	Adult patients with severe CPP
Intervention	RIS is an IL-23 inhibitor. RIS 150 mg (1x 150 mg injection) subcutaneously at Week 0, 4, then every 12 weeks.
Comparator	Current form: RIS 150 mg (2x 75 mg injections) subcutaneously at Week 0, 4, then every 12 weeks Other listed / near-market biologics: <ul style="list-style-type: none"> <li>• <u>TNF<math>\alpha</math> inhibitors</u> <ul style="list-style-type: none"> <li>○ ADA 80 mg subcutaneously at Week 0, 40 mg Week 1, then every 2 weeks</li> <li>○ ETN 50 mg subcutaneously once weekly, or 25 mg twice weekly</li> <li>○ IFX (excluded as a comparator)</li> </ul> </li> <li>• <u>IL-23 inhibitors</u> <ul style="list-style-type: none"> <li>○ GUS 100 mg subcutaneously at Week 0, 4, then every 8 weeks</li> <li>○ TIL 100 mg subcutaneously at Week 0, 2, then every 12 weeks</li> </ul> </li> <li>• <u>IL-17A inhibitors</u> <ul style="list-style-type: none"> <li>○ BKZ 320 mg subcutaneously at Week 0, 4, 8, 12, 16, then every 8 weeks (near-market)</li> <li>○ IXE 160 mg subcutaneously at Week 0, 80 mg Week 2, 4, 6, 8, 10, 12, then every 4 weeks</li> <li>○ SEC 300 mg subcutaneously at Week 0, 1, 2, 3, 4, then monthly</li> </ul> </li> <li>• <u>IL-12/23 inhibitors</u> <ul style="list-style-type: none"> <li>○ UST 45 mg or 90 mg (&gt;100 kg) subcutaneously at Week 0, 4, then every 12 weeks</li> </ul> </li> </ul>
Outcomes	PASI 75, PASI 90, PASI 100, sPGA(0,1), DLQI(0,1)
Clinical claim	In patients with severe CPP, RIS 150 mg (1x 150 mg injection) is equivalent to RIS 150 mg (2x 75 mg injection) in efficacy and safety. Compared to other listed biologics (excluding IFX): <ul style="list-style-type: none"> <li>• In terms of efficacy, RIS is superior to ADA, ETN, SEC, TIL, UST and non-inferior to BKZ, GUS, IXE.</li> <li>• In terms of safety, RIS is non-inferior to ADA, ETN, SEC, TIL, UST, BKZ, GUZ, IXE.</li> </ul>

Source: Table 1.1, p14 of the submission.

CPP=chronic plaque psoriasis, RIS=Risankizumab, IFX=Infliximab, ADA=Adalimumab, BKZ=Bimekizumab, ETN=Etanercept, GUS=Guselkumab, IXE=Ixekizumab, SEC=Secukinumab, TIL=Tildrakizumab, UST=Ustekinumab, PASI x=psoriasis area and severity index x response criteria, sPGA=static Physician's Global Assessment, DLQI=Dermatology Life Quality Index, IL=interleukin, TNF $\alpha$ =tumour necrosis factor alpha

## 2 Background

### Registration status

- 2.1 Risankizumab was TGA registered on 16 July 2019 for the treatment of moderate to severe plaque psoriasis in adults (18 years or older) who are candidates for phototherapy or systemic therapy. The recommended dose is 150 mg by subcutaneous injection at Week 0, Week 4 and every 12 weeks thereafter.
- 2.2 The risankizumab 75 mg PFS was listed on the Australian Register of Therapeutic Goods (ARTG) on 16 July 2019; the 150 mg PFP and 150 mg PFS were listed on the ARTG on 19 August 2021. The product information (PI) states bioequivalence was demonstrated between a single 150 mg injection and two 75 mg injections, with the recommended 150 mg dose administered either as two 75 mg injections or one 150 mg injection.

### **Previous PBAC consideration**

- 2.3 At its July 2019 meeting, the PBAC recommended listing risankizumab for severe CPP on a cost-minimisation basis with the least costly biologic currently listed on the PBS. Risankizumab 75 mg PFS (two pack) was subsequently PBS-listed on 1 December 2019, with patients required to administer two 75 mg injections per dose.
- 2.4 At its November 2021 meeting, the PBAC recommended listing risankizumab 150 mg PFP and 150 mg PFS for severe CPP under the same circumstances as risankizumab 75 mg PFS on a cost-minimisation basis with the least costly biologic available. The sponsor had requested the same published and effective prices for the 150 mg presentations as the 75 mg PFS (two pack). The PBAC considered that the 150 mg presentations were likely to be equivalent in efficacy and safety compared to the 75 mg PFS (i.e. 2 x 75 mg), but advised that the 150 mg presentations should be cost-minimised to the lowest cost biologic under Section 101(3B) of *the National Health Act 1953* (herein referred to as 'the Act'). No comparative clinical data versus other biologics were presented in the November 2021 Category 4 submission.
- 2.5 In this current submission, the sponsor stated that adalimumab is currently the least costly biologic and priced  $\frac{1}{2}$ % below risankizumab. Hence, the decision to replace the current presentation with a new presentation would require the sponsor to accept a  $\frac{1}{2}$ % price reduction. Therefore, the purpose of the submission was to request that the PBAC reconsider its decision to recommend listing of the 150 mg preparations on a cost-minimisation basis to the least costly PBS-listed biologic. The current submission approached this issue in two ways:
- The submission argued that the 150 mg PFP and 150 mg PFS are an equivalent intervention to the 75 mg PFS (two pack), and bioequivalence was accepted by the TGA and noted by the PBAC. Given the 150 mg preparations will directly substitute for the 75 mg PFS, the submission requested the same list price in line with the November 2021 submission.
  - The submission argued listing on a cost-minimisation basis versus adalimumab does not reflect the incremental value of risankizumab. Direct and indirect evidence presented in the submission showed that risankizumab has superior efficacy versus some biologics (adalimumab, etanercept, secukinumab, tildrakizumab, ustekinumab) and non-inferior efficacy versus others (bimekizumab, ixekizumab, guselkumab). Given this, the submission alternatively requested listing on a cost-minimisation basis versus the least costly alternative therapy of ixekizumab, guselkumab and bimekizumab (if PBS listed). The submission argued that infliximab should not be considered a relevant comparator given low utilisation.
- 2.6 Prior to its March 2023 meeting, the PBAC had recommended listing the most recent biologics (ixekizumab, guselkumab, tildrakizumab, certolizumab, risankizumab) on a cost-minimisation basis versus the lowest cost biologic. At its March 2023 meeting,

the PBAC recommended listing of bimekizumab on a cost-minimisation basis of the least costly alternative therapy of infliximab, guselkumab, ixekizumab, risankizumab, tildrakizumab and secukinumab (excluding adalimumab, etanercept and ustekinumab). The PBAC considered there was sufficient evidence to conclude bimekizumab provides, for some patients, a significant improvement in efficacy compared to adalimumab, etanercept and ustekinumab.

### 3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
RISANKIZUMAB 150 mg/1 mL injection, 1 mL syringe	\$5,400.57 published \$ effective	1	1	Init: 2 Cont: 1	Skyrizi
RISANKIZUMAB 150 mg/1 mL injection, 1 mL pen device	\$5,400.57 published \$ effective	1	1	Init: 2 Cont: 1	Skyrizi
<b>Severity:</b> Severe					
<b>Condition:</b> Chronic plaque psoriasis					
<b>Treatment Phase:</b> Initial treatment					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required - in writing					
<b>Treatment criteria:</b> As per current risankizumab listing					
<b>Clinical criteria:</b> As per current risankizumab listing, but with removal of the '3-strike rule': Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with 3 biological medicines for this condition within this treatment cycle					
<b>Treatment Phase:</b> Continuing treatment					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)					
<b>Treatment criteria:</b> As per current risankizumab listing					
<b>Clinical criteria:</b> As per current risankizumab listing					

- 3.1 The submission requested listing of risankizumab 150 mg PFP and 150 mg PFS under similar circumstances as the currently listed risankizumab 75 mg PFS. The sponsor requested the same published and effective prices as the 75 mg PFS (two pack), but proposed changes to the Restriction Authority level and treatment cycle criteria.
- 3.2 The sponsor requested that the Authority Required level is lowered from a written authority to a streamlined authority application for continuing treatment. The submission argued there is no clinical, economic or administrative basis to continue to stipulate a written authority for continuing treatment. Clinicians are familiar with the treatment options and the likelihood of patients continuing to access treatment despite not achieving the continuation criteria is low given a reasonably high proportion of patients would meet the criteria across the available treatments. To mitigate the risk of use beyond the restriction, the submission proposed to maintain the written authority for all initial applications.
- 3.3 At its March 2022 meeting, the PBAC reviewed the written authority level of biologics for CPP (Adult) as part of the Tranche 6 medicines. The Committee acknowledged the administrative burden of written authority applications for prescribers but did not recommend an amendment to the authority requirements of any medicine for CPP (Adult) due to market instability, growth in utilisation / expenditure of the new

biologic medicines, the risk of use beyond the restriction and the financial risk to government (Tranche 6 Review of Written Authority PBS listings, PBAC Outcomes March 2022). The Pre-Sub-Committee Response (PSCR) reiterated there is no clinical, economic or administrative basis to continue to stipulate a written authority for continuing prescriptions in severe CPP which compounds existing challenges faced by the dermatology workforce to meet demand, and the change would remove an administrative burden for these specialists.

- 3.4 The submission requested removal of the current ‘three-strike’ rule from the restriction and implementation of a more ‘patient-centric’ approach to optimising treatment outcomes. Currently, patients must undergo a five year break from treatment after failing or ceasing to respond to three biologics for this condition. The submission stated specifying a maximum number of failed therapies (or strikes) causes clinician reticence around switching treatments in patients achieving suboptimal outcomes and leads to over prescribing of topical treatments. The submission stated neither of these therapeutic strategies is in the best interests of patients.
- 3.5 The submission did not propose any wording for the proposed restriction to achieve a more patient-centric approach to prescribing biologics, nor any economic evidence to support removal of the current three-strike criteria. At its November 2022, the PBAC noted a request to amend the three-strike rule to a four-strike rule when considering listing of upadacitinib for the treatment of radiographic axial spondyloarthritis. The PBAC considered it may be reasonable to review the design of treatment cycle requirements for biologics broadly given the range of available treatments with different mechanisms of action since these requirements were originally devised. The PBAC noted such a review was broader than the scope of its consideration of upadacitinib (paragraph 7.3, upadacitinib Public Summary Document (PSD), November 2022). The PSCR agreed a broader review of strike rules for biologics was a reasonable approach and argued that specifying a maximum number of failed therapies which does not take into consideration the number of available mechanisms of action, followed by a punitive measure of losing subsidised access to treatment for 5 years is not in the best interest of patients and is misaligned with a treatment paradigm of optimal patient care.
- 3.6 The submission also requested that all preparations of risankizumab (150 mg PFP, 150 mg PFS and 75 mg PFS) be considered equivalent for the purposes of substitution (i.e. ‘a’ flagged in the Schedule) under Section 101(4AACD) of the *National Health Act 1953*. The submission stated any training in the use of each preparation could be adequately managed by prescribers and pharmacists, and the sponsor will continue to provide tailored patient education and administration training via the existing Patient Support Program.
- 3.7 The submission stated that the sponsor intends to remove the 75 mg PFS from the PBS after the 150 mg presentations are PBS-listed.

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

## 4 Population and disease

- 4.1 Plaque psoriasis is a chronic immune-mediated, painful, and disabling disease of the skin, characterised by disfiguring, scaling and erythematous plaques that may cause significant reductions in quality of life. The target population proposed for the new presentations of risankizumab (150 mg PFP and 150 mg PFS) is the same as for the currently listed presentation of risankizumab (75 mg PFS): patients with severe CPP who have failed to achieve an adequate response with at least two therapies including methotrexate, cyclosporin, acitretin, apremilast, deucravacitinib (as of 1 October 2023) or phototherapy (either UVB or PUVA). On the PBS, disease severity and response to treatment on the PBS is measured by the Psoriasis Area Severity Index (PASI).
- For whole body disease, patients must have a PASI score > 15 for an initial course of treatment. Continuing treatment is conditional on patients achieving and maintaining a 75% reduction in the PASI score at baseline (i.e., PASI 75 response).
  - For disease affecting the face, hand or foot, patients must have 2 of 3 PASI symptom sub-scores for erythema, thickness or scaling rated as ‘severe’ or ‘very severe’, or the skin affected is more than 30% of the face, palm of hand or sole of foot. Continuing treatment is conditional on patients achieving and maintaining an adequate response, defined as all 3 PASI sub-scores for erythema, thickness or scaling rated as ‘slight’ or ‘better’, or a 75% reduction in the skin area affected compared to baseline.

## 5 Comparator

- 5.1 The submission stated that the new presentations of risankizumab (150 mg PFP and 150 mg PFS) will directly substitute for the currently listed presentation of risankizumab (75 mg PFS, two pack). Given the demonstrated bioequivalence across the presentations, the submission stated that the 150 mg PFP and 150 mg PFS are an equivalent intervention to the 75 mg PFS (two pack) rather than a comparator as defined by the PBAC guidelines.
- 5.2 At its November 2021 meeting, the PBAC considered the current presentation of risankizumab (75 mg PFS, two pack) was the appropriate comparator. However, the PBAC also considered relevant alternative therapies under Section 101(3B) of the Act included other PBS-listed biologics: adalimumab, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab and ustekinumab (paragraphs 4.1 and 6.3, risankizumab PSD, November 2021). The current submission identified bimekizumab as a near-market comparator, which the PBAC recommended for CPP in March 2023 but was not currently listed at the time of the submission (paragraph 7.1, bimekizumab PSD, March 2023). Bimekizumab was listed on the PBS on 1 October 2023.

- 5.3 The sponsor stated that other PBS-listed biologics can be considered alternative therapies to risankizumab in general, with the exception of infliximab due to limited use. The submission stated that an analysis of PBS data indicated that infliximab was virtually never initiated (approximately 10 patients initiated treatment with infliximab from May 2022 to April 2023, representing 0.2% of all patients initiating a biologic treatment for CPP). The submission attributed the low use to the burdensome intravenous administration for initial treatment and a preference for prescribing newer biologics with better evidence of achieving clear skin. Prospection data presented in the submission showed an average of 80 patients per month were treated with infliximab (initial and continuing) in the 2022 calendar year. This compares to an average of 189 patients per month treated with etanercept (the next least used treatment) and an average of 1,211 patients per month treated with secukinumab (the most commonly used treatment) in the 2022 calendar year.
- 5.4 The relatively low utilisation of infliximab compared to other biologics does not preclude it from being an alternative treatment. The PBAC had consistently considered infliximab an alternative therapy when deciding to list other biologics for CPP, including for risankizumab in July 2019 and November 2021. It was noted that a subcutaneous version of infliximab was PBS-listed in August 2022 for maintenance treatment (following intravenous induction).
- 5.5 The PSCR argued infliximab should not be considered a comparator in this submission, on the basis the PBAC Guidelines (version 5.0) state a comparator should be selected in the context of the therapies most likely to be replaced in clinical practice. The Response reiterated current utilisation suggests it is the least utilised therapy in CPP and argued the majority of current treatments being used target the IL-17/23 pathways. Therefore, the PSCR argued infliximab should be considered of historical relevance only and not be considered a comparator. The ESC considered that while the use of infliximab in CPP was very low, it may still be reasonably considered an alternative therapy. The pre-PBAC response stated that expert opinion attributed the lack of infliximab use to the excessive administrative and patient burden in arranging and attending an infusion centre which may not be readily accessible. The pre-PBAC response stated that newer, more convenient subcutaneous (SC) therapies are also widely accepted as providing greater efficacy, improved durability of response, and being better tolerated than infliximab. The pre-PBAC response stated that with nine SC alternatives currently reimbursed, the majority of which target the IL-17/23 axis, the treatment paradigm in CPP has changed with there now being essentially no clinical reason for dermatologists to prescribe infliximab for CPP.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician noted in the years

following the introduction of the first biologics for CPP (TNF $\alpha$  inhibitors, IL-12/23 inhibitor), the newer IL-17 and IL-23 inhibitors have emerged as highly effective treatment options and there is a clinical view that these newer agents are superior to the older options and highly favoured in practice. The clinician noted the most recent review of treatment goals in psoriasis included a consensus statement from clinicians that, with the availability of these newer therapies, an absolute PASI score  $\leq 3$ , a physician global assessment (PGA) score of 0 or 1 ('clear/ almost clear') or a PASI90 response should be the goal of treatment.<sup>1</sup> The clinician noted safety concerns for TNF $\alpha$  inhibitors including tuberculosis reactivation (infliximab), increased infections, paradoxical autoimmune reactions that, though rare, can lead to the development of autoimmune conditions and the development of neutralising antibodies that can result in decreased efficacy. The clinician noted infliximab infusions can be inconvenient and time consuming. The clinician noted risankizumab is one of the more effective treatments and stated the availability of a 150 mg form was unlikely to change prescribing patterns significantly. The clinician noted the ability to give the recommended dose (150 mg) as a single injection, rather than two injections, would provide significant benefit for patients and noted some patients experience anxiety with the second injection.

### **Consumer comments**

- 6.2 The PBAC noted the advice received from the Australasian College of Dermatologists, which supported the listing and noted the availability of a single 150 mg injection to replace the 2 x 75 mg form reduces injection burden and will likely improve patient compliance to treatment.

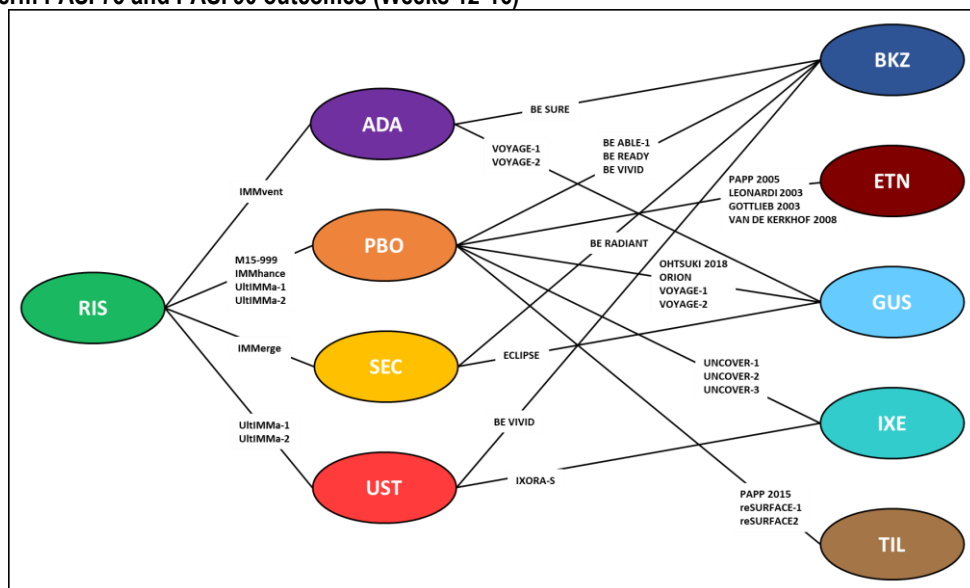
### **Clinical trials**

- 6.3 The submission was based on: i) four direct randomised controlled trials (RCTs) comparing risankizumab to adalimumab (IMMvent), secukinumab (IMMerge) and ustekinumab (UltIMMa-1 and UltIMMa-2), and ii) an indirect treatment comparison (ITC) comparing risankizumab to etanercept, guselkumab, ixekizumab and tildrakizumab. The ITC included data from a total of 27 RCTs (the four direct RCTs plus a further 23 RCTs) and presented comparisons using placebo and/or active common comparators. Figure 1 presents the network diagram of RCTs included in the direct comparisons and ITC.

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<sup>1</sup> Foley P; Gebauer K, Sullivan J et al. Australian consensus: Treatment goals for moderate to severe psoriasis in the era of targeted therapies – adult patients. *Australas J Dermatol.* 2023; 64(4): 476 – 487.

Figure 1: Network diagram of trials included in the direct and indirect comparisons of risankizumab vs comparators for short-term PASI 75 and PASI 90 outcomes (Weeks 12-16)



Source: Figure 2.3, p 54 of the submission

RIS=Risankizumab, IFX=Infliximab, ADA=Adalimumab, BKZ=Bimekizumab, ETN=Etanercept, GUS=Guselkumab, IXE=Ixekizumab, SEC=Secukinumab, TIL=Tildrakizumab, UST=Ustekinumab

6.4 The submission conducted a pragmatic literature search to identify all relevant trials that were not identified in the risankizumab July 2019 submission; the bioequivalence study (M15-990) presented in the risankizumab November 2021 submission was excluded in this submission. The PBAC had (directly) considered evidence from 21 of the 27 included RCTs in past submissions of biologics for severe CPP, including three of the six risankizumab trials across the risankizumab July 2019 and November 2021 submissions. New trials included IMMhance (risankizumab versus placebo), IMMvent (risankizumab versus adalimumab), IMMerge (risankizumab versus secukinumab), ORION (guselkumab versus placebo), Ohtsuki 2018 (guselkumab versus placebo) and ECLIPSE (guselkumab versus secukinumab). However, the PBAC had also considered evidence from published network meta-analyses (NMAs) by Armstrong et al 2022<sup>2</sup> and Sbidian et al 2022<sup>3</sup> that included data from all 27 RCTs (paragraph 6.2, bimekizumab PSD, March 2023).

6.5 Details of the trials included in the submission are provided in Table 2.

<sup>2</sup> Armstrong, A. W., et al. (2020). Comparison of Biologics and Oral Treatments for Plaque Psoriasis: A Meta-analysis. *JAMA Dermatology* 156(3): 258-269

<sup>3</sup> Sbidian E, et al. (2022) Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database of Systematic Reviews*; 5: Cd011535.

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

Trial ID	Protocol title/ Publication title	Publication citation
<b>Risankizumab trials</b>		
M15-999 NCT03875482	M15-999 CSR. A multicentre, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of risankizumab using a new formulation for the treatment of adult subjects with moderate to severe plaque psoriasis	October 2020
	Blauvelt A, Gordon KB, Lee P et al. Efficacy, safety, usability, and acceptability of risankizumab 150 mg formulation administered by prefilled syringe or by an autoinjector for moderate to severe plaque psoriasis.	The Journal of dermatological treatment 2022;33(4):2085-2093
IMMhance M15-992 NCT02672852	M15-992 CSR. Risankizumab versus placebo in a multicenter randomized double-blind study in patients with moderate to severe chronic plaque psoriasis evaluating the efficacy and safety with randomized withdrawal and re-treatment	January 2018
	Blauvelt A, Leonardi CL, Gooderham M et al. Efficacy and safety of continuous risankizumab therapy vs treatment withdrawal in patients with moderate to severe plaque psoriasis: a phase 3 randomized clinical trial.	JAMA Dermatology 2020;156(6):649-658
IMMvent M16-010 NCT02694523	M16-010 CSR. Risankizumab versus adalimumab in a randomised, double-blind, parallel group trial in moderate to severe plaque psoriasis to assess safety and efficacy after 16 weeks of treatment and after incomplete adalimumab response	September 2017
	Reich K, Gooderham M, Thaci D et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial.	Lancet 2019;394(10198):576-586
IMMerge M16-766 NCT03478787	M16-766 CSR. A multicenter, randomized, open label, efficacy assessor-blinded study of risankizumab compared to secukinumab for the treatment of adult subjects with moderate to severe plaque psoriasis who are candidates for systemic therapy	July 2020
	Warren RB, Blauvelt A, Poulin Y et al. Efficacy and safety of risankizumab vs. secukinumab in patients with moderate-to-severe plaque psoriasis (IMMerge): results from a phase III, randomized, open-label, efficacy-assessor-blinded clinical trial	British Journal of Dermatology 2021;184(1):50-59
UltIMMa-1 M16-008 NCT02684370 / UltIMMa-2 M15-995 NCT02684357	M16-008 CSR. Risankizumab versus and placebo comparators in a randomised double- blind trial for maintenance use in moderate to severe plaque type psoriasis (trial 1)	December 2017
	M15-995 CSR. Risankizumab versus and placebo comparators in a randomised double- blind trial for maintenance use in moderate to severe plaque type psoriasis (trial 2)	December 2017
	Gordon KB, Strober B, Lebwohl M et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials.	Lancet 2018;392(10148):650-661
<b>Bimekizumab trials</b>		
BE ABLE 1 PS0010 NCT02905006	Papp KA, Merola JF, Gottlieb AB et al. Dual neutralization of both interleukin 17A and interleukin 17F with bimekizumab in patients with psoriasis: Results from BE ABLE 1, a 12-week randomized, double-blinded, placebo-controlled phase 2b trial.	Journal of the American Academy of Dermatology 2018;79(2):277-286.e10
BE READY PS0013 NCT03410992	Gordon KB, Foley P, Krueger JG et al. Bimekizumab efficacy and safety in moderate to severe plaque psoriasis (BE READY): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial.	Lancet 2021;397(10273):475-486
BE SURE PS0008 NCT03412747	Warren RB, Blauvelt A, Bagel J et al. Bimekizumab versus Adalimumab in Plaque Psoriasis.	N Engl J Med 2021;385(2):130-141

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<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
BE RADIANT PS0015 NCT03536884	Reich K, Papp KA, Blauvelt A et al. Bimekizumab versus ustekinumab for the treatment of moderate to severe plaque psoriasis (BE VIVID): efficacy and safety from a 52-week, multicentre, double-blind, active comparator and placebo controlled phase 3 trial.	Lancet 2021;397(10273):487-498
BE VIVID PS0009 NCT03370133	Reich K, Warren RB, Lebwohl M et al. Bimekizumab versus Secukinumab in Plaque Psoriasis.	N Engl J Med 2021;385(2):142-152
<b>Etanercept trials</b>		
Leonardi 2003	Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis	N Engl J Med 2003;349(21):2014-22
Papp 2005	Papp KA, Tying S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction.	Br J Dermatol 2005;152(6):1304-12
Van De Kerkof 2008	van de Kerkhof PC, Segaert S, Lahfa M, et al. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension.	Br J Dermatol 2008;159(5):1177-85
Gottlieb 2003	Gottlieb AB, Matheson RT, Lowe N, et al. A randomized trial of etanercept as monotherapy for psoriasis.	Arch Dermatol 2003;139(12):1627-32
<b>Guselkumab trials</b>		
ORION NCT02905331	Ferris LK, Ott E, Jiang J, et al. Efficacy and safety of guselkumab, administered with a novel patient-controlled injector (One-Press), for moderate-to-severe psoriasis: results from the phase 3 ORION study	J Dermatolog Treat 2020;31(2):152-159
Ohtsuki 2018 NCT02325219	Ohtsuki M, Kubo H, Morishima H, Goto R, Zheng R, Nakagawa H. Guselkumab, an anti-interleukin-23 monoclonal antibody, for the treatment of moderate to severe plaque-type psoriasis in Japanese patients: Efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study.	J Dermatol 2018;45(9):1053-1062
VOYAGE-1 NCT02207231	Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial.	J Am Acad Dermatol 2017;76(3):405-417
VOYAGE-2 NCT02207244	Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial.	J Am Acad Dermatol 2017;76(3):418-431
ECLIPSE NCT03090100	Reich K, Armstrong AW, Langley RG, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial.	Lancet 2019;394(10201):831-839
<b>Ixekizumab trials</b>		
UNCOVER-1 NCT01474512	Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis.	New England Journal of Medicine 2016;375(4):345-356
UNCOVER-2 NCT01597245	Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis	New England Journal of Medicine 2016;375(4):345-356
UNCOVER-3 NCT01646177	Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials.	Lancet 2015;386(9993):541-51
IXORA-S NCT02561806	Reich K, Pinter A, Lacour JP, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study.	Br J Dermatol 2017;177(4):1014-1023

Trial ID	Protocol title/ Publication title	Publication citation
<b>Tildrakizumab trials</b>		
PAPP NCT01225731	Papp K, Thaçi D, Reich K, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial.	Br J Dermatol 2015;173(4):930-9
reSURFACE-1 NCT01722331 / reSURFACE-2 NCT01729754	Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials.	Lancet 2017;390(10091):276-288

Source: Table2-3 and Table 2-4, p 35-52

CSR=clinical study report; RCT=randomised control trial

6.6 The key features of the direct randomised trials are summarised in Table 3. The table does not present irrelevant treatment arms which were excluded from the ITC. Treatment arms excluded from the ITC were for non-registered doses/regimens (e.g. four different doses of bimekizumab in BE ABLE 1, three different doses of tildrakizumab in Papp 2015, 25 mg once-weekly etanercept in Leonardi 2003, ixekizumab every 4 weeks in the UNCOVER trials), or a comparator that was not used in the ITC (e.g. adalimumab in the VOYAGE trials, ustekinumab in the UltIMMa trials).

**Table 3: Key features of the included evidence**

Trial	N (N in ITC)	Design / follow-up duration	Risk of bias	Patient population	Key Outcomes
<b>Risankizumab trials (comparator)</b>					
M15-999 (PBO)	157 (157)	P3, R, DB, MC, 48 wks	Low	Moderate to severe CPP; BSA ≥10%; PASI ≥12; sPGA ≥3	PASI 75 (16, 52 wks); PASI 90 (16, 44 wks); PASI 100 (16, 44/52 wks); sPGA 0/1 (16, 52 wks)
IMMhance (PBO)	507 (507)	P3, R, DB, MC, 104 wks	Low		
IMMvent (ADA)	605 (605)	P3, R, DB, MC, 48 wks	Low		
IMMerge (SEC)	327 (327)	P3, R, OL, MC, 84 wks	Moderate		
UltIMMa-1 (PBO, UST)	506 (406)	P3, R, DB, MC, 56 wks	Low		
UltIMMa-2 (PBO, UST)	491 (392)		Low		
<b>Bimekizumab trials (comparator)</b>					
BE ABLE 1 (PBO)	250 (85)	P2B, R, DB, MC, 12 wks	Low	Moderate to severe CPP; BSA ≥10%; PASI ≥12; IGA ≥3	PASI 75 (12 wks); PASI 90 (12 wks)
BE READY (PBO)	435 (435)	P3, R, DB, MC, 76 wks	Low		
BE SURE (ADA)	478 (478)	P3, R, DB, MC, 76 wks	Low		
BE RADIANT (SEC)	743 (743)	P3, R, DB, MC, 48 wks	Low		
BE VIVID (PBO, UST)	567 (484)	P3, R, DB, MC, 72 wks	Low		
<b>Etanercept trials (comparator)</b>					
Leonardi 2003 (PBO)	672 (328)	P3, R, DB, MC, 24 wks	Low	Moderate to severe CPP; BSA ≥10%; PASI ≥10	PASI 75 (12 wks); PASI 90 (12 wks)
Papp 2005 (PBO)	611 (389)	P3, R, DB, MC, 24 wks	Low		
Van De Kerkhof 2008 (PBO)	142 (142)	P3, R, DB (12 wks then OL), MC, 24 wks	Low		
Gottlieb 2003 (PBO)	112 (112)	P2, R, DB, MC, 24 wks	Low		
<b>Guselkumab trials (comparator)</b>					
VOYAGE-1 (PBO, ADA)	837 (503)	P3, R, DB, MC, 48 wks	Low	Moderate to severe CPP; BSA ≥10%; PASI ≥12; IGA ≥3	PASI 75 (16 wks); PASI 90 (16 wks); IGA 0/1 (16 wks)
VOYAGE-2 (PBO, ADA)	992 (744)	P3, R, DB (72 wks then OL), MC, 264 wks	Low		
ORION (PBO)	78 (78)	P3, R, DB, MC, 40 wks	Low		
Ohtsuki 2018 (PBO)	192 (127)	P3, R, DB, MC, 52 wks	Low		

Trial	N (N in ITC)	Design / follow-up duration	Risk of bias	Patient population	Key Outcomes
ECLIPSE (SEC)	1048 (1048)	P3, R, DB, MC, 56 wks	Low		PASI 75 (12, 48 wks); PASI 90 (12, 48 wks), PASI 100 (48 wks), IGA 0/1 (48 wks)
<b>Ixekizumab trials (comparator)</b>					
UNCOVER-1 (PBO)	1296 (864)	P3, R, DB, MC, 60 wks	Low	Moderate to severe CPP; BSA ≥10%; PASI ≥12; IGA ≥3	PASI 75 (12 wks); PASI 90 (12 wks); PASI 100 (12 wks); sPGA 0/1 (12 wks)
UNCOVER-2 (PBO, ETN)	1224 (519)		Low		
UNCOVER-3 (PBO, ETN)	1346 (578)		Low		
IXORA-S (UST)	302 (302)	P3, R, DB, MC, 52 wks	Low	Moderate to severe CPP; PASI ≥10	
<b>Tildrakizumab trials (comparator)</b>					
Papp 2015 (PBO)	355 (134)	P2B, R, DB, MC, 72 wks	Low	Moderate to severe CPP; BSA ≥10%; PASI ≥12; PGA ≥3	PASI 75 (12, 16 wks); PASI 90 (16 wks); PGA 0/1 (12, 16 wks)
reSURFACE-1 (PBO)	772 (463)	P3, R, DB, MC, 64 wks	Low		
reSURFACE-2 (PBO, ETN)	1090 (463)	P3, R, DB, MC, 52 wks	Low		

Source: Table 2-7, p 65-67 of the submission and Table 1-2, 19-30 of Appendix 1; M15-999 CSR; IMMhance CSR; IMMvent CSR; IMMerge CSR; Gordon et al. 2021 (BE READY); Warren et al. 2021 (BE SURE); Reich et al. 2021 (BE VIVID); van de Kerkhof et al. 2008; <https://clinicaltrials.gov/study/NCT02207244> (VOYAGE-2)

ADA=adalimumab; BKZ=bimekizumab; BSA=body surface area; CPP = chronic plaque psoriasis; DB=double-blind; DLQI=Dermatology Life Quality Index; ETN=etanercept; IGA= Investigator's Global Assessment; ITC=indirect treatment comparison; IXE=ixekizumab; MC=multicentre; OL=open-label; P2=phase II; P2B=phase IIB; P3=phase III; PASI=Psoriasis Activity and Severity Index; PGA=Physician Global Assessment; PBO=placebo; RCT=randomised controlled trial; RIS=risankizumab; SEC=secukinumab; sPGA=Static Physician Global Assessment; TIL=tildrakizumab; UST=ustekinumab; wks=weeks.

- 6.7 The included RCTs were Phase 2 or Phase 3, randomised, active and/or placebo-controlled trials in patients with moderate to severe CPP. The trials generally had a double-blind treatment phase of at least 12 to 16 weeks (up to 52 weeks), with the exception of one open-label trial to 52 weeks (IMMerge). Most trials generally included treatment switching after the double-blind phase, but the submission excluded data after any switching from the ITC. The submission also excluded data from treatment arms using unapproved doses from the ITC.
- 6.8 The inclusion criteria across the RCTs were broadly similar, designed to enrol patients with moderate to severe psoriasis who were candidates for systemic therapy. Across the trials included in the ITC, the most notable difference was use of prior biologics (e.g. 41% in risankizumab trials, 35% in bimekizumab trials, 24% in ixekizumab trials, 22% in guselkumab trials, 20% in tildrakizumab trials, 0% in etanercept trials). The increased rate of prior biologic exposure may be attributable to the risankizumab clinical trial program being conducted more recently than some comparators, or the geographic availability of biologic treatments.
- 6.9 The primary and secondary endpoints reported across the RCTs were again broadly similar, with most trials reporting PASI 90, PASI 100 and/or static physician's global assessment (sPGA) score 0/1 at Week 16 as primary or co-primary endpoint, and PASI 75 at Week 16 as a secondary outcome. Most trials also analysed outcomes on an intention-to-treat basis and used conservative imputation methods where data were

missing, predominantly last observation carried forward and non-responder imputation.

- 6.10 Overall, the included trials had a low risk of bias for key endpoints. The trials were also generally comparable in terms of design, patient population, outcome definitions and assessment time points. Aside from the notable differences in use of prior biologics, the submission argued that the trials met the transitivity assumption of the ITC. Event rates across the common reference arms were generally comparable with a few exceptions (e.g. in relative terms for placebo, with 8.8% PASI 75 response / 3.1% PASI 90 response in the risankizumab trials compared to 3.0% PASI 75 response / 0.7 % PASI 90 response in the etanercept trials). The submission also argued that, as the PBAC had relied on similar direct and indirect evidence to inform past decisions, the included RCTs are sufficiently applicable for patients with severe disease and sufficiently exchangeable to inform decision-making.

### ***Comparative effectiveness***

- 6.11 The PBAC had previously based recommendations for listing of biologics for the treatment of severe CPP on the proportion of patients achieving and maintaining a PASI 75 response ( $\geq 75\%$  improvement from baseline in the Psoriasis Area and Severity Index score). This is also consistent with the PBS eligibility criteria for continued treatment with biologics. Although a higher response rate (e.g. PASI 90 or PASI 100) may be useful in particular patients, the PBAC had considered that PASI 75 remained a relevant outcome for severe CPP (paragraphs 7.5 and 7.9, bimekizumab PSD, March 2023).
- 6.12 The submission presented both direct evidence and an ITC (using the Bucher method) comparing risankizumab to the nominated comparators across several outcomes (including PASI 75, PASI 90, PASI 100, sPGA and DLQI) following short-term (Week 12-16) and long-term (Week 48-52) treatment. To interpret the results, the submission nominated a non-inferiority margin of -10% (i.e. non-inferior if lower bound of risk difference no less than -0.10) for PASI 75 and PASI 90 to demonstrate non-inferiority and statistical significance to demonstrate superiority. The nominated non-inferiority margin was consistent with past PBAC decisions. For brevity, the evaluation focused on results for PASI 75 and PASI 90. The PSCR argued the outcomes of PASI100 and sPGA were also highly clinically relevant and stated these results further support the clinical claims made in the submission.
- 6.13 The submission stated that a random effects model was used for meta-analysis across trials with common interventions (e.g. prior to conducting the ITC), in-line with recommendations in the PBAC guidelines. The results presented in the submission, however, actually corresponded to meta-analysis assuming a fixed effects model. This did not appear to influence the overall conclusion of results, and results were not updated during the evaluation given the large number of estimates affected.

Short term response

6.14 Table 4 summarises the results of the direct evidence and ITC, comparing risankizumab to the nominated comparators in terms of short-term PASI 75 and PASI 90 response (Week 12 to 16). The PASI 75 results for reSURFACE-2 trials reported in the submission differed by one responder compared to the trial publication, and there were several rounding errors in the estimated treatment effects, but neither changed the overall interpretation of the results.

**Table 4: Summary of PASI 75 and PASI 90 response in the short-term (12-16 weeks) based on the direct randomised trials and indirect treatment comparisons presented by the submission for risankizumab versus other biologics.**

Risankizumab versus comparator	PASI 75			PASI 90		
	OR (95% CI)	RR (95% CI)	RD (95% CI)	OR (95% CI)	RR (95% CI)	RD (95% CI)
<b>Direct evidence (week 16)</b>						
Adalimumab <sup>1</sup>	<b>3.85 (2.42, 6.11)</b>	<b>1.26 (1.17, 1.37)</b>	<b>0.19 (0.13, 0.25)</b>	<b>2.92 (2.08, 4.09)</b>	<b>1.53 (1.33, 1.75)</b>	<b>0.25 (0.18, 0.33)</b>
Secukinumab <sup>1</sup>	<b>2.72 (1.39, 5.30)</b>	<b>1.15 (1.05, 1.26)</b>	<b>0.12 (0.04, 0.19)</b>	1.47 (0.92, 2.37)	1.12 (0.97, 1.30)	0.08 (-0.02, 0.18)
Ustekinumab <sup>1</sup>	<b>3.33 (2.21, 5.02)</b>	<b>1.23 (1.13, 1.35)</b>	<b>0.17 (0.10, 0.24)</b>	<b>3.72 (2.66, 5.21)</b>	<b>1.68 (1.43, 1.97)</b>	<b>0.30 (0.23, 0.38)</b>
<b>Indirect treatment comparison (week 12-16), [common reference]</b>						
Bimekizumab <sup>2</sup>	[P] <b>0.27 (0.12, 0.63)</b>	[P] <b>0.46 (0.22, 0.96)</b>	[P] <b>-0.09(-0.14,-0.04)</b>	[P] 0.38 (0.13, 1.11)	[P] 0.74 (0.16, 3.47)	[P] <b>-0.14(-0.19,-0.09)</b>
	[A] 0.72 (0.36, 1.47)	[A] 0.95 (0.83, 1.10)	[A] -0.04(-0.14, 0.06)	[A] <b>0.42 (0.24, 0.73)</b>	[A] 0.84 (0.67, 1.04)	[A] <b>-0.14(-0.26,-0.02)</b>
	[S] 2.00 (0.84, 4.73)	[S] <b>1.13 (1.02, 1.25)</b>	[S] <b>0.10 (0.02, 0.19)</b>	[S] 0.72 (0.40, 1.31)	[S] 0.97 (0.83, 1.15)	[S] -0.03(-0.15, 0.09)
	[U] 0.79 (0.41, 1.55)	[U] 0.98 (0.85, 1.12)	[U] -0.02(-0.12, 0.08)	[U] 0.65 (0.37, 1.12)	[U] 0.98 (0.78, 1.23)	[U] -0.05(-0.16, 0.06)
Etanercept <sup>1</sup>	[P] <b>4.63 (2.29, 9.35)</b>	[P] 0.90 (0.48, 1.70)	[P] <b>0.49 (0.44, 0.54)</b>	[P] <b>5.24(1.51,18.20)</b>	[P] 1.66 (0.50, 5.50)	[P] <b>0.59 (0.55, 0.63)</b>
Guselkumab <sup>2</sup>	[P] 0.80 (0.45, 1.43)	[P] 0.80 (0.50, 1.28)	[P] -0.01(-0.06, 0.04)	[P] 0.84 (0.36, 1.96)	[P] 0.81 (0.36, 1.81)	[P] 0.01(-0.03, 0.05)
	[A] 1.18 (0.68, 2.03)	[A] 1.01 (0.91, 1.11)	[A] 0.01(-0.06, 0.08)	[A] 1.08 (0.72, 1.62)	[A] 1.03 (0.88, 1.22)	[A] 0.02(-0.07, 0.11)
	[S] <b>3.58 (1.62, 7.89)</b>	[S] <b>1.19 (1.07, 1.31)</b>	[S] <b>0.14 (0.06, 0.22)</b>	[S] <b>2.10 (1.22, 3.61)</b>	[S] <b>1.23 (1.04, 1.45)</b>	[S] <b>0.15 (0.04, 0.26)</b>
Ixekizumab <sup>2</sup>	[P] <b>0.47 (0.27, 0.84)</b>	[P] <b>0.52 (0.32, 0.83)</b>	[P] -0.04(-0.08, 0.00)	[P] 0.47 (0.19, 1.16)	[P] <b>0.42 (0.18, 0.99)</b>	[P] 0.01(-0.03, 0.05)
	[U] 0.97 (0.47, 2.04)	[U] 0.96 (0.83, 1.12)	[U] -0.03(-0.14, 0.08)	[U] 1.01 (0.56, 1.83)	[U] 0.97 (0.75, 1.26)	[U] -0.01(-0.14, 0.12)
Tildrakizumab <sup>1</sup>	[P] <b>2.71 (1.44, 5.10)</b>	[P] 0.91 (0.53, 1.58)	[P] <b>0.23 (0.17, 0.29)</b>	[P] 2.92 (1.09, 7.79)	[P] 1.26 (0.49, 3.25)	[P] <b>0.35 (0.30, 0.40)</b>

Source: Tables 1-22 and 1-23, pp 107-112 of Appendix 1 and Attachment 5.2 of the submission

. **Bold**=statistically significant.

A=adalimumab; CI=confidence intervals; RD=risk difference; OR=odds ratio; PASI=Psoriasis Area Severity Index; P=placebo; S=secukinumab; RR=relative risk; U=ustekinumab.

Note: Meta-analyses conducted using fixed effects in RevMan 5.

<sup>1</sup> The submission made the clinical claim that risankizumab has superior efficacy versus comparator

<sup>2</sup> The submission made the clinical claim that risankizumab has non-inferior efficacy versus comparator.

6.15 The results of the short-term direct comparisons found more patients achieved PASI 75 at Week 16 with risankizumab compared to adalimumab, secukinumab and ustekinumab, and PASI 90 at Week 16 with risankizumab compared to adalimumab and ustekinumab. Numerically more patients achieved PASI 90 at Week 16 with risankizumab compared to secukinumab, but the result did not reach statistical significance.

6.16 The results and interpretation of the short-term ITC (Week 12-16), however, varied considerably depending on the outcome, risk statistic and/or common reference used:

- For comparison versus bimekizumab, there was no clear pattern of results. For PASI 75, results using placebo as the common reference favoured bimekizumab, results using secukinumab as the common reference generally favoured risankizumab, and results using adalimumab or ustekinumab as the common reference showed no significant difference. For PASI 90, results either favoured bimekizumab or showed no significant difference.

- For comparison versus etanercept, PASI 75 and PASI 90 results using the risk difference and odds ratio favoured risankizumab but there was no significant difference using the relative risk statistic.
  - For comparison versus guselkumab, PASI 75 and PASI 90 results using secukinumab as the common reference favoured risankizumab but results using placebo or adalimumab showed no significant difference.
  - For comparison versus ixekizumab, PASI 75 results using placebo as the common reference favoured ixekizumab but results using ustekinumab as common reference showed no difference. The results generally showed no difference in terms of PASI 90.
  - For comparison versus tildrakizumab, PASI 75 and PASI 90 results using the risk difference and odds ratio favoured risankizumab but there was no significant difference using the relative risk statistic.
- 6.17 For completeness, Table 5 presents comparative results from published NMAs comparing risankizumab to other biologics for CPP. These results include data from the NMA presented in the risankizumab July 2019 submission (subsequently published as Armstrong et al 2020<sup>4</sup>), and NMAs presented in the bimekizumab March 2023 submission (Armstrong et al 2022 and Sbidian et al 2022) extracted and included during the evaluation. Overall, the published NMAs concluded that risankizumab was one of several biologics found to be more effective than other biologics in terms of short-term PASI response. For example, Armstrong found the most effective biologics included risankizumab, bimekizumab and guselkumab, whereas Sbidian et al 2022 found the most effective biologics included risankizumab, bimekizumab, guselkumab and infliximab.

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<sup>4</sup> Armstrong AW, Puig L, Joshi A, et al. Comparison of Biologics and Oral Treatments for Plaque Psoriasis: A Meta-analysis. *JAMA Dermatol.* 2020;156(3):258–269. doi:10.1001/jamadermatol.2019.4029

**Table 5: Short-term (weeks 10-16) PASI 75 and PASI 90 responses from published network meta-analyses**

Risankizumab versus comparator	PASI 75 - Relative Risk (95% CI)			PASI 90 - Relative Risk (95% CI)		
	Armstrong 2020 (Bayesian NMA)	Armstrong 2022 (Bayesian NMA)	Sbidian 2022 (Frequentist NMA)	Armstrong 2020 (Bayesian NMA)	Armstrong 2022 (Bayesian NMA)	Sbidian 2022 (Frequentist NMA)
Bimekizumab	NR	0.97 (0.93,1.02)	1.00 (0.90,1.12) <sup>^</sup>	NR	<b>0.87 (0.80,0.94)</b>	0.95 (0.85,1.05) <sup>^</sup>
Ixekizumab	1.00 (0.97,1.04)	1.01 (0.96, 1.06)	0.99 (0.87,1.12) <sup>^</sup>	<b>1.01 (0.93, 1.09)</b>	1.03 (0.94,1.14)	0.95 (0.85,1.06) <sup>^</sup>
Guselkumab	1.03 (0.99,1.07)	1.04 (0.99,1.09)	1.09 (0.98,1.21) <sup>^</sup>	<b>1.06 (0.98, 1.16)</b>	1.09 (0.98,1.20)	<b>1.19 (1.08,1.32)<sup>^</sup></b>
Infliximab	<b>1.11 (1.05,1.17)</b>	<b>1.13 (1.06,1.21)</b>	0.76 (0.50,1.16) <sup>^</sup>	<b>1.25 (1.12, 1.40)</b>	<b>1.35 (1.19,1.53)</b>	0.57 (0.24,1.39) <sup>^</sup>
Tildrakizumab	<b>1.42 (1.30,1.56)</b>	<b>1.43 (1.27,1.60)</b>	<b>1.28 (1.05,1.55)<sup>^</sup></b>	<b>1.94 (1.67, 2.29)</b>	<b>1.95 (1.60,2.39)</b>	<b>1.55 (1.19,2.01)<sup>^</sup></b>
Etanercept	<b>2.22 (1.97,2.52)</b>	25*: <b>2.38 (2.02,2.81)</b> 50*: <b>1.76 (1.63,1.91)</b>	<b>1.69 (1.51,1.89)<sup>^</sup></b>	<b>3.99 (3.31, 4.85)</b>	25*: <b>5.27 (3.96,7.00)</b> 50*: <b>3.11 (2.69,3.60)</b>	<b>2.70 (2.35,3.10)<sup>^</sup></b>
Adalimumab	<b>1.28 (1.23,1.35)</b>	<b>1.29 (1.21,1.37)</b>	<b>1.33 (1.21,1.47)<sup>^</sup></b>	<b>1.64 (1.50, 1.79)</b>	<b>1.61 (1.44,1.81)</b>	<b>1.66 (1.50,1.83)<sup>^</sup></b>
Ustekinumab	<b>1.28 (1.22,1.35)</b>	<b>1.26 (1.19,1.34)</b>	<b>1.21 (1.12,1.31)<sup>^</sup></b>	<b>1.63 (1.48, 1.79)</b>	<b>1.62 (1.45,1.81)</b>	<b>1.52 (1.38,1.67)<sup>^</sup></b>
Secukinumab	<b>1.07 (1.03,1.12)</b>	<b>1.31 (1.19,1.45)</b>	1.06 (0.97,1.15) <sup>^</sup>	<b>1.17 (1.07, 1.27)</b>	<b>1.15 (1.04,1.28)</b>	<b>1.09 (1.00,1.20)<sup>^</sup></b>

**Bold**=statistically significant.

Source: Armstrong 2020, Table S9 of Armstrong 2022, Figure 7 of Sbidian 2022

CI=confidence intervals; ITC=indirect treatment comparison; NWM=network meta-analysis; NR=not reported; PASI=Psoriasis Area Severity Index; 25\*=25mg etanercept, 50\*=50mg etanercept

Note: Given Armstrong et al 2022 only reported results comparing bimekizumab versus other biologics, results comparing risankizumab versus other biologics were derived during the evaluation from these estimates.

<sup>^</sup> Different dose arms in the included trials (approved and other doses) were grouped together in one 'arm' for the base case analysis

6.18 The ESC noted the NMA results appeared to have notable differences in results depending on whether Bayesian or frequentist approach was used, however also noted the NMAs included different lists of trials, with Armstrong 2020 including 60 trials, Armstrong 2022 (an update to the 2020 publication) including 86 trials and Sbidian 2022 including 167 studies. The ESC recalled it had been previously noted that the Armstrong 2022 review included a subset of RCTs included in the Sbidian 2022 review due to the narrower selection criteria (e.g., exclusion of unapproved treatments/doses, without PASI response outcomes, unpublished RCTs, non-English publications) and earlier search date (paragraph 6.13, bimekizumab PSD, March 2023 PBAC meeting).

### Longer term response

6.19 Table 6 summarises the results of the direct evidence and ITC, comparing risankizumab versus the nominated comparators in terms of long-term PASI 75 and PASI 90 response (Week 48 to 52). The results showed more patients had PASI 75 response at Week 52 with risankizumab compared to secukinumab and ustekinumab, and PASI 90 at Week 48-52 with risankizumab compared to secukinumab, ustekinumab, bimekizumab, guselkumab and ixekizumab.

**Table 6: Summary of PASI 75 and PASI 90 response in the long-term (48-52 weeks) based on the direct randomised trials and indirect treatment comparisons presented by the submission for risankizumab versus other biologics.**

Risankizumab versus comparator	PASI 75			PASI 90		
	OR (95% CI)	RR (95% CI)	RD (95% CI)	OR (95% CI)	RR (95% CI)	RD (95% CI)
<b>Direct evidence</b>						
Secukinumab <sup>1</sup>	3.98 (2.15, 7.35)	1.29 (1.15, 1.44)	0.20 (0.12, 0.29)	4.86 (2.81, 8.38)	1.52 (1.31, 1.76)	0.30 (0.20, 0.39)
Ustekinumab <sup>1</sup>	3.98 (2.60, 6.10)	1.25 (1.14, 1.36)	0.18 (0.12, 0.25)	4.84 (3.42, 6.84)	1.72 (1.48, 2.00)	0.34 (0.26, 0.42)
<b>Indirect Treatment Comparison [common reference]</b>						
Bimekizumab <sup>2</sup>	[S] 2.19 (0.95, 5.01)	[S] 1.21 (1.06, 1.37)	[S] 0.14 (0.04, 0.24)	[S] 2.12 (1.04, 4.32)	[S] 1.30 (1.10, 1.54)	[S] 0.17 (0.05, 0.29)
Guselkumab <sup>2</sup>	NR	NR	NR	[S] 2.09 (1.12, 3.91)	[S] 1.26 (1.07, 1.48)	[S] 0.16 (0.05, 0.27)
Ixekizumab <sup>2</sup>	[U] 1.67 (0.78, 3.58)	[U] 1.08 (0.94, 1.23)	[U] 0.06(-0.05, 0.17)	[U] 2.14 (1.16, 3.95)	[U] 1.32 (1.06, 1.64)	[U] 0.17 (0.04, 0.30)

Source: Tables 1-26 and 1-27, pp 119-120 of Appendix 1 and Attachment 5.2 of the submission

. **Bold**=statistically significant.

CI=confidence intervals; NR=not reported; OR=odds ratio; PASI=Psoriasis Area Severity Index; RD=risk difference; RR=relative risk; S=secukinumab; U=ustekinumab.

Note: Meta-analyses were conducted using fixed effects in RevMan 5.

<sup>1</sup> The submission made the clinical claim that risankizumab has superior efficacy to adalimumab, etanercept, secukinumab, tildrakizumab, secukinumab, and ustekinumab.

<sup>2</sup> The submission made the clinical claim that risankizumab has non-inferior efficacy to bimekizumab, guselkumab and ixekizumab.

## Comparative harms

6.20 Table 7 summarises adverse events (AEs) reported in the direct risankizumab trials during the treatment period is presented. Overall rates of AEs were similar across active treatment, with low rates of serious AEs and AEs leading to treatment discontinuation. The submission also presented a side by side comparison of short-term safety outcomes across all included RCTs, which showed overall event rates were comparable across different biologic treatments. The safety profile of risankizumab is well established and the PBAC has previously accepted non-inferior safety between risankizumab and other biologics available for CPP (paragraphs 6.32 and 6.34, risankizumab PSD, July 2019).

**Table 7: Summary of key adverse events in the active-controlled risankizumab trials (double-blind phase)**

Trial ID	Txt	N	Any AE, n (%)	Any serious AE, n (%)	Any AE leading to disc., n (%)	Any AE related to txt, n (%)	Any AE leading to death, n (%)	Serious infections, n (%)
<b>Short-term (16-weeks)</b>								
UltIMMa-1	UST	100	50 (50.0)	8 (8.0)	2 (2.0)	11 (11.0)	0 (0.0)	3 (3.0)
	RIS	304	151 (49.7)	7 (2.3)	2 (0.7)	36 (11.8)	0 (0.0)	1 (0.3)
UltIMMa-2	UST	99	53 (53.5)	3 (3.0)	0 (0.0)	18 (18.2)	0 (0.0)	1 (0.3)
	RIS	294	134 (45.6)	6 (2.0)	1 (0.3)	29 (9.9)	0 (0.0)	3 (1.0)
IMMvent	ADA	304	173 (56.9)	9 (3.0)	6 (2.0)	61 (20.1)	2 (0.7)	1 (0.3)
	RIS	301	168 (55.8)	10 (3.3)	4 (1.3)	55 (18.3)	1 (0.3)	1 (0.3)
<b>Long-term (52 weeks)</b>								
UltIMMa-1	UST	100	77 (77.0)	11 (11.0)	2 (2.0)	23 (23.0)	0 (0.0)	3 (3.0)
	RIS	304	221 (72.7)	23 (7.6)	2 (0.7)	60 (19.7)	0 (0.0)	3 (1.0)
UltIMMa-2	UST	99	80 (80.8)	7 (7.1)	2 (2.0)	29 (29.3)	0 (0.0)	1 (1.0)
	RIS	294	198 (67.3)	19 (6.5)	3 (1.0)	59 (20.1)	1 (0.3)	5 (1.7)
IMMmerge <sup>a</sup>	SEC	163	116 (71.2)	6 (3.7)	8 (4.9)	46 (28.2)	0 (0.0)	3 (1.8)
	RIS	164	117 (71.3)	9 (5.5)	2 (1.2)	49 (29.9)	0 (0.0)	0 (0.0)

Source: Table 2-24 and Table 2-25, 100 of the submission

ADA=adalimumab; AE=Adverse Event; CSR=Clinical Study Report; PBO=placebo; RIS=risankizumab; Txt=treatment; SEC=secukinumab; UST=ustekinumab

<sup>a</sup> Safety events for IMMerge were reported at 52 weeks only. Therefore, only the long-term effects are presented (Appendix 1)

## Benefits/harms

6.21 Table 8 presents a summary of the short-term comparative benefits for risankizumab versus adalimumab, ustekinumab and secukinumab, based on direct evidence presented in the submission. The table does not include comparative benefits based on indirect evidence, given variation in the interpretation of results depending on the outcome, the common reference and the risk statistic. The table does not include comparative harms given the results support the claim of non-inferior safety versus the nominated comparators.

**Table 8: Summary of comparative benefits (PASI 75, PASI 90) for risankizumab versus adalimumab, secukinumab and ustekinumab**

Comparison	RIS n/N	Comparator n/N	OR (95% CI)	Event rate/100 patients		RD (95% CI)
				RIS	Comparator	
<b>PASI 75 at 16 weeks – direct comparisons</b>						
RIS vs ADA	273/301	218/304	<b>3.85 (2.42, 6.11)</b>	90.7	71.7	<b>0.19 (0.13, 0.25)</b>
RIS vs SEC	150 <sup>a</sup> /164	130 <sup>a</sup> /163	<b>2.72 (1.39, 5.30)</b>	91.5	79.8	<b>0.12 (0.04, 0.19)</b>
RIS vs UST	538/598	145/199	<b>3.33 (2.21, 5.02)</b>	90.0	72.9	<b>0.17 (0.10, 0.24)</b>
<b>PASI 90 at 16 weeks – direct comparisons</b>						
RIS vs ADA	218/301	144/304	<b>2.92 (2.08, 4.09)</b>	72.4	47.4	<b>0.25 (0.18, 0.33)</b>
RIS vs SEC	121/164	107/163	1.47 (0.92, 2.37)	73.8	65.6	0.08 (-0.02, 0.18)
RIS vs UST	449/598	89/199	<b>3.72 (2.66, 5.21)</b>	75.1	44.7	<b>0.30 (0.23, 0.38)</b>

**Bold**=statistically significant.

Source: Tables 1-22 and 1-23, pp 107-112 of Appendix 1 and Attachment 5.2 of the submission

ADA=adalimumab; BKZ=bimekizumab; CI=confidence interval; OR=odds ratio; PASI=psoriasis area and severity index; PBO=placebo; RD=risk difference; RIS=risankizumab; SEC=secukinumab; UST=ustekinumab.

<sup>a</sup> Submission reported 151/164 for intervention and 132/163 for comparator. Publication (M16-766 IMMerge CSR Table 14.2\_1.4.1, p 385) reported 150/164 for intervention and 130/163 for comparator.

6.22 On the basis of direct evidence presented by the submission, for every 100 patients treated with risankizumab over the initial 16 weeks of treatment in comparison with:

- Adalimumab – Approximately 19 additional patients would achieve PASI 75, and 25 additional patients would achieve PASI 90.
- Secukinumab – Approximately 12 additional patients would achieve PASI 75 and no significant differences in the number of patients achieving PASI 90.
- Ustekinumab – Approximately 17 additional patients would achieve PASI 75, and 30 additional patients would achieve PASI 90.

## Clinical claim

6.23 The submission described risankizumab as:

- superior in terms of effectiveness and non-inferior in terms of safety to adalimumab, etanercept, secukinumab, tildrakizumab, and ustekinumab;
- non-inferior in terms of effectiveness and safety to bimekizumab, guselkumab, and ixekizumab.

6.24 The evaluation considered the claim was generally reasonable (though the submission made no claim versus infliximab). The direct evidence presented in the submission

reasonably supported the claim of superior effectiveness for risankizumab compared to adalimumab, secukinumab and ustekinumab; and the indirect evidence reasonably supported the claim of non-inferior effectiveness versus bimekizumab, guselkumab and ixekizumab. The evaluation considered the claim of superior effectiveness compared to etanercept and tildrakizumab may also be reasonable on the totality of the indirect evidence given the indirect treatment comparisons generally favoured risankizumab versus etanercept and tildrakizumab (using the odds ratio and risk difference statistics) and the published NMAs also found risankizumab was a more effective treatment.

6.25 The PBAC had previously accepted non-inferior safety between all available biologics for CPP (paragraph 7.11, bimekizumab PSD, March 2023), but its' interpretation of the clinical evidence in terms of effectiveness (and corresponding pricing considerations) had varied over time:

- The clinical claim presented in the submission was consistent with the risankizumab July 2019 submission. Based on the evidence presented in July 2019, the PBAC considered a claim of superior effectiveness 'was reasonable' versus ustekinumab and 'may be supported' versus adalimumab, secukinumab, etanercept, infliximab, and tildrakizumab. However, the PBAC also considered that, based on extensive experience with biologics in clinical practice, there was unlikely to be any clinically significant difference in long-term outcomes between any of the biologic medicines. The PBAC subsequently recommended listing of risankizumab on a cost-minimisation basis to the least costly biologic (paragraphs 6.32 and 6.34, risankizumab PSD, July 2019).
- Based on similar evidence for bimekizumab considered at its March 2023 meeting, however, the PBAC only accepted superior effectiveness for bimekizumab versus adalimumab, etanercept and ustekinumab. The submission presented direct evidence comparing bimekizumab versus adalimumab, ustekinumab and secukinumab, and indirect evidence including published NMAs for other comparators. The PBAC noted there was no direct evidence comparing bimekizumab versus etanercept, but accepted the claim of superiority based on previous consideration of the efficacy of etanercept and the conclusion in the published NMAs. For other comparators, the PBAC noted that the interpretation of the results from indirect treatment comparisons and published NMAs was inconsistent and varied based on the risk statistic. The PBAC subsequently recommended listing of bimekizumab on a cost-minimisation basis to the least costly biologic excluding adalimumab, etanercept and ustekinumab (paragraphs 7.1, 7.9, and 7.10, bimekizumab PSD, March 2023).

6.26 The ESC noted additional information was available to assist with considering the clinical claim in the current submission (compared to prior risankizumab submissions for CPP), including NMAs, which it considered were informative. The ESC considered the head to head evidence presented supported a claim that risankizumab is likely to

be of superior comparative effectiveness to adalimumab and ustekinumab, and the indirect evidence supported a claim that risankizumab is likely to be superior to etanercept also. With regards to the claims versus other PBS listed therapies for severe chronic plaque psoriasis, the ESC noted that:

- For secukinumab, the direct evidence indicated no statistically significant difference for the outcome of PASI90, and the results of the NMAs were mixed, with the frequentist NMA (Sbidian 2022) not finding a statistically significant difference between risankizumab and secukinumab for PASI75. Overall, the ESC considered the claim of superior comparative effectiveness over secukinumab to be uncertain and that a claim of non-inferiority may be more appropriate. The Pre-PBAC Response argued the Bayesian NMA (Armstrong 2022) provides a more accurate representation of the relative efficacy of each treatment as unapproved doses were excluded from the base case analysis, whereas the frequentist NMA (Sbidian 2022) included those trials in their analyses. The Response noted the results of the Bayesian NMA found a statistically significant difference in favour of risankizumab over secukinumab for PASI 75 and PASI 90 (see Table 5) and argued the importance of PASI 90 and PASI 100 as attainable treatment goals in current clinical practice emphasise the importance of these outcomes.
  - For tildrakizumab, while the NMA results generally found statistically significant results favouring risankizumab for PASI75 and PASI90, the results of the short-term ITCs generally did not find a statistically significant difference between risankizumab and tildrakizumab. Based on the available analyses, which were short-term only, the ESC considered the claim of superior comparative effectiveness over tildrakizumab to be uncertain and that a claim of non-inferiority may be more appropriate. The Pre-PBAC Response argued the results of the short-term ITCs demonstrated a statistically significant difference favouring risankizumab across PASI 75, PASI 90 and PASI 100 for the odds ratio and risk difference statistics, which supports the claim of superiority made in the submission.
  - For bimekizumab, ixekizumab and guselkumab, the majority of the ITC and NMA results did not find a statistically significant difference for PASI75 or PASI90. Overall, the ESC considered the claim of non-inferior comparative effectiveness was likely to be reasonable.
  - For infliximab, the ESC noted the majority of the NMA results were mixed, with the frequentist NMA (Sbidian 2022) not finding a statistically significant difference between risankizumab for either PASI75 or PASI90.
- 6.27 The ESC considered the claim of non-inferior comparative safety to adalimumab, etanercept, secukinumab, tildrakizumab, ustekinumab, bimekizumab, guselkumab, and ixekizumab was adequately supported.
- 6.28 The PBAC considered that the claim of superior comparative effectiveness to adalimumab, etanercept and ustekinumab was adequately supported by the data;

however, the PBAC considered the claim of superior comparative effectiveness to secukinumab and tildrakizumab was not adequately supported, and a claim of non-inferiority was more reasonable. The PBAC considered the claim of non-inferior comparative effectiveness to bimekizumab, guselkumab and ixekizumab was reasonable. The PBAC provided additional advice regarding its view on infliximab, this is discussed further in Section 7 (PBAC Outcome).

- 6.29 The PBAC considered that the claim of non-inferior comparative safety to other bDMARDs (excluding IFX) for CPP was adequately supported.

### ***Economic analysis***

- 6.30 Consistent with the November 2021 submission, the sponsor requested the same published and effective prices for the 150 mg PFP and 150 mg PFS as the PBS-listed 75 mg PFS (two pack). The submission presented a cost-minimisation approach comparing risankizumab 150 mg PFP and 150 mg PFS with risankizumab 75 mg PFS, assuming the 150 mg presentations are equi-effective with two doses of the 75 mg PFS at the same recommended dosing schedule. The submission requested no changes to the existing Special Pricing Arrangement for risankizumab in severe CPP.
- 6.31 At its November 2021 meeting, the PBAC considered that risankizumab 150 mg PFP and 150 mg PFS are equivalent in efficacy and safety to two doses of risankizumab 75 mg PFS, but recommended listing on a cost-minimisation basis to the lowest cost biologic agent available for severe CPP under Section 101(3B) of the Act (paragraphs 6.2 and 6.3, risankizumab PSD, November 2021).
- 6.32 The submission requested that the PBAC reconsider this prior advice, and argued a new presentation of the same medicine should be listed on a cost-minimisation basis to the existing presentation of that medicine, rather than the lowest cost alternative of different medicines. In addition, the submission argued that inferior treatments should be excluded as relevant comparators under Section 101(3B) of the Act (described as ‘the alternative therapy or therapies’ in the Act). Hence, should the PBAC reject the request to list the new presentations of risankizumab on a cost-minimisation basis to the existing presentation of risankizumab, then the submission alternatively requested listing on a cost-minimisation basis versus bimekizumab (if PBS listed), guselkumab and ixekizumab.
- 6.33 From an economic perspective, the new presentations of risankizumab are likely ‘perfect’ substitutes for the current presentation, and the submission’s request to list the 150 mg presentations at the same published and effective price as the 75 mg PFS (two pack) was unlikely to influence the propensity of doctors to prescribe risankizumab compared to an alternative biologic. The expected economic outcomes (e.g., quality adjusted life years and costs) are therefore unlikely to change. The PSCR argued that recommendations for new presentations should be on a cost minimisation basis with existing presentations, and other approaches are misaligned with policy intent to encourage innovative, user-friendly presentations that provide benefit, with the ultimate outcome being lack of access for Australian patients. The ESC considered

the issue of whether it was reasonable for risankizumab 150 mg PFS to be listed at the same price as the 2 x 75 mg PFS pack was a policy matter for the PBAC to consider.

- 6.34 For completeness, Table 9 summarises the drug costs over the first two years for all current PBS-listed treatments based on the published AEMP, and the corresponding AEMP for risankizumab 150 mg (PFP and PFS) assuming a cost minimisation approach to each treatment. The calculations are based on a similar table considered by the PBAC for bimekizumab, which included drug costs only for subcutaneous treatments as well as administration costs (MBS item 14245, \$107.30 fee) for intravenous treatments (Table 2, bimekizumab PSD, March 2023). It was noted that the parameters assumed in this table may differ to those used for the purposes of pricing determination.

**Table 9: Comparison of treatment costs over the first two years for PBS-listed biologics for severe CPP using the published AEMP, and the corresponding AEMP for risankizumab from a cost-minimisation approach to each treatment.**

Drug	Dosing Regimen	Published AEMP	Doses over two years	Cost over two years	RIS 150 mg AEMP (CMA)
RIS (150 mg)	150 mg SC injection (1 injection of 150 mg) at Weeks 0, 4 and Q12W thereafter	\$5,239.29	9.33	\$48,882.58	\$5,239.29
<b>Other biologics</b>					
GUS	100 mg SC injection at Weeks 0, 4 and Q8W thereafter	\$3,634.62	13.5	\$49,067.37	\$5,259.10
RIS (75 mg)	150 mg SC injection (2 injections of 75 mg) at Weeks 0, 4 and Q12W thereafter	\$5,239.29	9.33	\$48,882.58	\$5,239.29
IXE	160 mg SC injection (2 injections of 80 mg) at Week 0, 80 mg Q2W from Weeks 2 to 12 and Q4W thereafter	\$3097.00 (2 doses)	30	\$46,455.00	\$4,979.10
UST#	45 mg (weight ≤ 100 kg) or 90 mg (weight > 100 kg) SC injection at Weeks 0, 4 and Q12W thereafter	\$3809.09	9.33	\$35,538.72	\$3,809.08#
TIL	100 mg SC injection at Weeks 0, 4 and Q12W thereafter <sup>l</sup>	\$3,110.05	9.33	\$29,016.77	\$3,110.05
ETN	50 mg SC injection once weekly (or 25 mg twice weekly)*	\$743.6 (4 doses)	105	\$19,519.50	\$2,092.12
SEC	300 mg SC injection (2 injections of 150 mg) at Weeks 0,1,2,3,4 then 300 mg monthly	\$658.28	29	\$19,090.12	\$2,046.10
IFX SC	120 mg SC injection Q2W (maintenance dosing assumed to start at Week 6, Week 0 and 2 doses to be IFX IV)	SC: \$332.8 IV: \$253.52	49 SC inj. + 2 IV inf. (8.96 vials)	\$18,578.74*, \$18,793.34 <sup>^</sup>	\$1,991.29*, \$2,014.29 <sup>^</sup>
IFX IV	5 mg/kg IV infusion at Weeks 0,2,6, Q8W thereafter	\$253.52	14.25 IV inf. (63.83 vials)	\$16,182.18*, \$17,711.21 <sup>^</sup>	\$1,734.42*, \$1,898.31 <sup>^</sup>
ADA	80 mg SC injection (2 injections of 40 mg) at Week 0, 40 mg Q2W starting at Week 1	\$618.90 (2 doses)	53.5	\$16,555.58	\$1,774.45

Source: constructed during the evaluation based on Table 2 in the Bimekizumab Public Summary Document March 2023.

ADA=adalimumab; ETN=etanercept; GUS=guselkumab; IFX=infliximab; IXE=ixekizumab; RIS=risankizumab; SEC=secukinumab; TIL=tildrakizumab; UST=ustekinumab.

# UST 45 mg dose; total cost over two years for UST likely reflects some weighted average across the 45 mg and 90 mg doses

\* Drug cost only

<sup>^</sup> Drug cost plus administration cost (IFX IV infusion, MBS item 14245 \$107.30 fee)

- 6.35 The ESC noted the price of IFX SC reduced on 1 October 2023 to \$252.40 per injection (not reflected in the table above).

**Drug cost/patient/year: \$ [REDACTED]**

- 6.36 Using the requested effective DPMQ of \$ [REDACTED] per pack of one 150 mg injection (PFP or PFS), and assuming 9.33 injections (units) per patient over the first two years, the average drug cost per patient per year is \$ [REDACTED] (\$ [REDACTED] over the first two years). At the published DPMQ of \$5,239.29 per pack, the average drug cost per patient per year is \$24,441 (\$48,883 over the first two years).

**Estimated PBS usage & financial implications**

- 6.37 This submission was not considered by DUSC.
- 6.38 The submission stated there will be no net financial impact to the PBS, MBS or overall health budget associated with the listing the new 150 mg presentations of risankizumab. The new 150 mg presentations will directly substitute for the current 75 mg presentations at the same price, with no differences in the mark ups and co-payments, and no expected change to the current utilisation of risankizumab.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Authority Required (in writing) listing of two new forms of risankizumab (RIS, 150 mg pre-filled syringe (PFS) and 150 mg pre-filled pen (PFP)) for the treatment of severe chronic plaque psoriasis (CPP). The Committee noted it had previously recommended the listing of these forms of RIS for CPP in November 2021 and advised the basis of this recommendation differed to that of the previous outcome. The PBAC noted the 150 mg form, and the 75 mg form are bioequivalent, and considered there is sufficient evidence to conclude that the 150 mg forms of RIS provides, for some patients, a significant improvement in efficacy compared to adalimumab (ADA), etanercept (ETN) and ustekinumab (UST). The PBAC was also satisfied that RIS provides, for some patients, a significant improvement in efficacy or reduction of toxicity over infliximab (IFX). The PBAC's recommendation for listing was therefore based on, among other matters, its assessment that the cost effectiveness of the 150 mg presentations of RIS would be acceptable if they were cost minimised to the least costly alternative therapy of RIS (2 x 75 mg presentation), bimekizumab (BKZ), guselkumab (GUS), ixekizumab (IXE), tildrakizumab (TIL) and secukinumab (SEC).
- 7.2 The PBAC recalled that RIS 150 mg PFP and PFS were recommended at the November 2021 meeting on a cost minimisation basis 'to the lowest cost biological agent available for severe CPP, noting that any of the current PBS listed bDMARDs for severe CPP could be an alternative therapy to risankizumab' (paragraph 6.3, risankizumab PSD, November 2021). The PBAC also recalled it had originally recommended the 75 mg form of RIS on a similar basis. The Committee further recalled that in March 2023 it considered BKZ to be of superior comparative effectiveness to ADA, ETN and UST and considered the cost minimisation approach for BKZ should exclude these

- therapies for which superiority had been adequately established.
- 7.3 The PBAC noted RIS was already listed on the PBS (as a 75 mg PFS) for the treatment of CPP, however acknowledged that replacing 2 x 75 mg injections with a single 150 mg injection would reduce the injection burden for patients.
- 7.4 The PBAC considered the nominated comparator of 2 x 75 mg injections of RIS was reasonable and noted that the 1 x 150 mg injection was bioequivalent to 2 x 75 mg injections (as stated in the Product Information). The PBAC considered that all currently PBS listed biologic disease modifying anti-rheumatic drugs (bDMARDs) for severe CPP could be considered alternative therapies for the purposes of Section 101(3B) of the *National Health Act 1953*.
- 7.5 The PBAC noted the arguments in the PSCR, pre-PBAC response and by the clinician in the sponsor hearing regarding IFX no longer being a relevant treatment of severe CPP in the Australian context. The PBAC noted very few new patients initiate treatment with IFX (as discussed in paragraph 5.3) and that this was thought to be related to (i) the IV administration with associated patient burden and lack of access to infusion facilities, (ii) the preference for use of treatments that target the IL-17/23 axis rather than TNF inhibitors given they are generally accepted as being more effective, and (iii) the relative poor tolerability of IFX. Regarding the route of administration, the PBAC noted a SC formulation of IFX is PBS listed, although acknowledged that patients are unable to initiate treatment with the SC formulation. The PBAC noted the relative efficacy of RIS and IFX was unclear. The PBAC noted the Armstrong 2020/2022 network meta-analysis concluded that RIS was statistically significantly superior to IFX for short term PASI 75 and PASI 90 responses (see Table 5). However, the PBAC also noted that a difference in PASI 75 and PASI 90 was not demonstrated in the Sbidian 2022 analysis with the wide 95% confidence limits for the relative risk indicating a high level of uncertainty for this comparison. The PBAC noted the Sbidian 2022 analysis stated at a drug level, RIS and BKZ might be the overall best treatments, considering the outcomes of PASI 90 and serious adverse events jointly, noting other highly effective drugs (including IFX) had serious adverse events. The PBAC did however also note that the safety evidence was considered by the authors to be of low to moderate quality. Overall, based on these factors together, the PBAC was satisfied for the purposes of Section 101(3B) of the *National Health Act 1953* that RIS provides, for some patients, a significant improvement in efficacy or reduction of toxicity over IFX.
- 7.6 The PBAC recalled it had previously considered the claim of superior effectiveness or safety for BKZ compared to IFX was not accepted during its March 2023 consideration of BKZ for severe CPP. However, based on the same rationale as above, the PBAC was now satisfied for the purposes of Section 101(3B) of the *National Health Act 1953* that BKZ provides, for some patients, a significant improvement in efficacy or reduction of toxicity over IFX.
- 7.7 The PBAC noted the key clinical evidence presented to support the clinical claim included 3 direct randomised trials of RIS vs ADA, UST and SEC, pairwise indirect

treatment comparisons (ITCs) versus BKZ, ETN, GUS, IXE and TIL with multiple common reference treatments, and two short-term NMAs (Armstrong 2022 [86 studies, 34,476 patients], Sbidian 2022 [167 studies, 58,912 patients]), and longer-term comparisons based on head-to-head studies versus SEC and UST and ITCs versus BKZ, GUS and IXE. The PBAC noted the short-term NMAs were also considered as part of the March 2023 submission for BKZ, and considered the overall evidence base for RIS was similar to that for BKZ.

- 7.8 The PBAC considered, based on the totality of the evidence, and with consistent results across the direct trials and supported by the short-term NMAs, that RIS provides, for some patients, a significant improvement in efficacy (as measured by PASI 75 and PASI 90) versus ADA and UST. The PBAC recalled that the post market review of biologic medicines for CPP found ETN to have one of the lowest response rates (Figure 1, PMR PSD, April 2018 PBAC meeting). The PBAC noted there was no direct evidence comparing RIS and ETN but considered that, based on previous consideration of the efficacy of ETN, and supported by the conclusion in the NMAs, RIS provides, for some patients, a significant improvement in efficacy (as measured by PASI 75 and PASI 90) compared to ETN.
- 7.9 The PBAC noted for SEC, the direct evidence indicated no statistically significant difference for the outcome of PASI 90, and the results of the NMAs were mixed, with Sbidian 2022 not finding a statistically significant difference between RIS and SEC for PASI 75. Overall, the PBAC agreed with ESC and considered the claim of superior comparative effectiveness over SEC to be uncertain, but that a claim of non-inferiority was reasonable.
- 7.10 The PBAC noted for TIL, while the NMA results generally found statistically significant results favouring RIS for PASI 75 and PASI 90, the results of the short-term ITCs generally did not find a statistically significant difference between RIS and TIL. Overall, the PBAC agreed with ESC and considered the claim of superior comparative effectiveness over TIL to be uncertain, but that a claim of non-inferiority was reasonable.
- 7.11 The PBAC considered the claims of non-inferior comparative effectiveness to BKZ, IXE and GUS were adequately supported by the available data (paragraphs 6.26, 6.28).
- 7.12 The PBAC considered the evidence presented supported a conclusion that RIS is of non-inferior comparative safety to BKZ, GUS, IXE, SEC, TIL, ADA, UST and ETN for CPP.
- 7.13 The PBAC noted the submission requested listing of the RIS 1 x 150 mg forms on a cost minimisation basis versus the currently listed RIS 2 x 75 mg form, or alternatively, on a cost minimisation basis with the least costly non-inferior biologic comparator of GUS, IXE or BKZ. Noting its advice above, the PBAC considered that whilst it is reasonable for presentations of RIS 1 x 150 mg to be listed on a cost minimisation basis with the 2 x 75 mg forms, the listing also should not be more costly than that of BKZ, GUS, IXE, SEC or TIL. The PBAC considered a standard cost minimisation approach with costs over two years was appropriate, consistent with the previous approach for

bDMARDs. The PBAC considered the cost minimisation approach should be based on an equi-effective dose of RIS 150 mg (given as 2 x 75 mg injection or 1 x 150 mg injection) subcutaneously at Week 0, 4, then every 12 weeks, and the doses of alternative bDMARDs (excluding ADA, ETN, UST and IFX) could be derived with reference to the relevant Product Information documents.

- 7.14 The PBAC considered that, given RIS 1 x 150 mg will predominantly replace RIS 2 x 75 mg in practice and its recommendation was on a cost minimisation basis to the least costly alternative therapy (excluding ADA, ETN, UST and IFX), the listing of RIS 1 x 150 mg forms would be cost neutral.
- 7.15 The PBAC considered that it would be timely to review its approach to considering applications for new forms of listed drugs. The PBAC requested the Department prepare a review and discussion paper exploring these issues, potential implications, and options for potential changes to be considered at a future meeting.
- 7.16 The PBAC considered the listing should reflect the current listing for RIS 2 x 75 mg, maintaining the current Authority Required (in writing) listing. The PBAC also reaffirmed its advice expressed in its consideration of upadacitinib in November 2022 that it would be timely to review the design of treatment cycle requirements for biologics broadly given the range of available treatments with different mechanisms of action since these requirements were originally devised (paragraph 3.5 refers).
- 7.17 The PBAC advised, under Section 101 (4AACD) of the *National Health Act*, that RIS 150 mg PFS, 150 mg PFP and 75 mg PFS should be considered equivalent for the purposes of substitution (i.e., 'a' flagged in the Schedule with a NOTE stating PBS of one form and PBS of another form are equivalent for the purposes of substitution).
- 7.18 The PBAC recommended that the Early Supply Rule should apply, similar to the listing of the 75 mg PFS.
- 7.19 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because the RIS 1 x 150 mg forms are not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over 2 x 75 mg form, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were not met.
- 7.20 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.
- 7.21 The PBAC noted the sponsor's intention to delist the 2 x 75 mg form once the 1 x 150 mg forms are listed on the PBS. The PBAC will consider the sponsor's request to delist at an appropriate time.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Add new item:

Restrictions to be the same as current 2 x 75 mg risankizumab forms for severe chronic plaque psoriasis – items 11827L and 11858D, with the addition of a NOTE that the 2 x 75 mg and 1 x 150 mg forms are considered to be substitutable as the pharmacy level (i.e. 'a' flagged).

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## 10 Sponsor's Comment

AbbVie welcomes the PBAC recommendation for a new presentation of risankizumab and the Departmental review for the process of listing applications of new forms of listed drugs.