

5.03 BIMEKIZUMAB, Solution for injection 160 mg in 1 mL pre-filled pen; Solution for injection 160 mg in 1 mL pre- filled syringe, Bimzelx[®], UCB Australia Pty Ltd.

1 Purpose of submission

- 1.1 The Category 2 submission requested General Schedule, Authority Required (in writing) listing for bimekizumab (BKZ) for the treatment of severe chronic plaque psoriasis (CPP).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis against all PBS-listed biologic disease-modifying anti-rheumatic drugs (bDMARDs) for CPP: adalimumab (ADA), guselkumab (GUS), ixekizumab (IXE), risankizumab (RIS), secukinumab (SEC), ustekinumab (UST), tildrakizumab (TIL), etanercept (ETN) and infliximab (IFX).

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

Component	Description
Population	Adult patients with severe chronic plaque psoriasis (CPP)
Intervention	BKZ 320 mg (given as 2 SC injections of 160 mg each) at Week 0, 4, 8, 12, 16 and every 8 weeks thereafter
Comparator	All currently PBS-listed bDMARDs for CPP.
Outcomes	Primary: PASI 90 Other: PASI 100, PASI 75, safety. The submission's clinical claim was based on three direct randomised controlled trials of BKZ versus ADA, UST, SEC respectively; and a network meta-analysis of BKZ versus all bDMARDs listed on the PBS. Indirect treatment comparison (Bucher method) was also presented as supplementary evidence versus RIS, IXE, GUS and TIL.
Clinical claim	In adults with severe CPP, BKZ is more effective than all currently PBS-listed bDMARDs at achieving PASI 90, PASI 100 and PASI 75. BKZ is similar in safety compared to the currently-PBS listed bDMARDs.

Source: Table 1-1, p26 of the submission.

Abbreviations: ADA=adalimumab; BKZ=bimekizumab; bDMARD=biologic disease-modifying anti-rheumatic drug; CPP=chronic plaque psoriasis; GUS= guselkumab; IXE= ixekizumab; PASI=psoriasis area and severity index; SC=subcutaneous; SEC=secukinumab; TIL= tildrakizumab; UST=ustekinumab

2 Background

Registration status

- 2.1 TGA status at time of PBAC consideration: not registered. The submission was made under the TGA/PBAC Parallel Process. The TGA clinical evaluation report, the TGA Delegate's Overview and the ACM minutes were available at the time of PBAC consideration. The TGA Delegate was supportive of registering bimekizumab for "the

treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy”.

Previous PBAC consideration

- 2.2 This is the first submission for BKZ. If listed, BKZ will be the 10th drug on the PBS for CPP.

3 Requested listing

- 3.1 The submission requested a listing of BKZ consistent with other bDMARD listings for CPP (restriction not produced in full in this section).

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
BIMEKIZUMAB 160 mg in 1mL pre-filled syringe (initial and continuing)	1	2	5 (initial) 2 (cont.)	\$■ published price	Bimzelx®, UCB Australia
Severity:	Severe				
Condition:	Chronic plaque psoriasis (CPP)				
Treatment phase:	Initial and continuing treatment				
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing				
Treatment criteria:	Must be treated by a dermatologist				
Clinical criteria:	Generally similar to that of currently PBS listed bDMARDs for CPP				

Source: Table 1-11, p50; Table 1-12, pp.51-53; Table 1-12, pp.60-61 of the submission.
bDMARDs=biologic disease-modifying anti-rheumatic drugs

- 3.2 The requested restriction was narrower than the proposed TGA indication, but was consistent with the current listings of all bDMARDs listed on the PBS for the treatment of severe CPP.
- 3.3 The submission requested a grandfather restriction; however, did not specify approximately how many patients would be expected to transition to PBS-subsidised BKZ.
- 3.4 The submission stated that the sponsor is seeking a Special Pricing Arrangement (SPA) with the effective price to be determined once confidential comparator prices are known and are used in the economic analysis.
- 3.5 The maximum quantity and number of repeats would be sufficient to complete the proposed 24-week initial treatment course of BKZ (6 doses) and a 24-week continuing treatment course of BKZ (3 doses). There appeared to be an inconsistency in the number of initial scripts and requested number of repeats (sufficient for a total of 6 doses, administered at Weeks 0, 4, 8, 12, 16, and 24 allowing for 32 weeks of treatment), and the maximum duration of initial treatment proposed in the requested restriction (24 weeks). The PBAC agreed with the Secretariat’s proposal to reduce the number of repeats for initial treatment from 5 to 4, allowing initial assessment of response between week 16 and 24.

- 3.6 It was noted that for patients with body weight ≥ 120 kg, more frequent dosing of BKZ after Week 16 may be considered (i.e., dosing every 4 weeks rather than every 8 weeks), requiring 3 additional doses of BKZ during maintenance (i.e., total 6 doses rather than the 3 requested).

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

4 Population and disease

- 4.1 Psoriasis manifests as chronic inflammation of the skin, characterised by disfiguring, scaling and erythematous plaques that may be painful and severely pruritic and may cause significant reductions in quality of life (QoL). The severity of psoriasis can be measured by several indicators, including the Psoriasis Area Severity Index (PASI), the extent of body surface area (BSA) affected and the impact of the condition on patients' quality of life, commonly measured by the Dermatology Life Quality Index (DLQI).
- 4.2 The proposed population for BKZ, severe CPP, is the same as that for other PBS-listed bDMARDs for this condition. The initial treatment criteria for PBS-subsidised biologic therapy for severe CPP requires patients to have a PASI > 15 and have failed to achieve an adequate response, are intolerant or contraindicated to at least two of the four systemic therapies (methotrexate, cyclosporin and acitretin) and/or phototherapy (either PUVA or UVB).
- 4.3 BKZ is proposed as an alternative bDMARD in the treatment of severe CPP. The submission stated that BKZ should be considered interchangeable with any of the listed bDMARDs for CPP.
- 4.4 There are nine bDMARDs currently listed on the PBS for CPP from four drug classes:
- Tumour necrosis factor (TNF) α inhibitor: ETN, ADA, IFX;
 - Interleukin (IL)-12/IL-23 inhibitor: UST;
 - IL-23 inhibitors: GUS, TIL, RIS; and
 - IL-17 inhibitors: SEC and IXE.
- 4.5 BKZ is a humanised monoclonal IgG1 antibody that has dual specificity and high affinity for both IL-17A and IL-17F, with the ability to bind to all three dimers (IL-17A/A, IL-17A/F & IL-17F/F). Directly targeting both IL-17A and IL-17F more completely inhibits the IL-17A pathway than inhibiting IL-17 alone but has greater selectivity than targeting the IL-17A receptor.
- 4.6 The recommended dose of BKZ is 320 mg, given as two subcutaneous injections of 160 mg, at Weeks 0, 4, 8, 12, 16 and every 8 weeks thereafter. The draft product information (PI) stated that for patients with a body weight ≥ 120 kg, 320 mg every 4 weeks after Week 16 may be considered.

5 Comparator

- 5.1 The submission stated the comparators include all currently PBS-listed bDMARDs but only presented clinical comparisons against seven of the nine currently listed bDMARDs, excluding ETN and IFX on the premise that these two bDMARDs are not the most efficacious agents and have a low market share. The ESC noted that while IFX has been available for a longer time it remained a highly effective treatment, despite this its exclusion was unlikely to significantly alter the conclusions of the clinical comparisons. The economic model included ETN and IFX.
- 5.2 The submission noted that, as treatment with BKZ is proposed to be more costly than any of the alternative therapies, the PBAC could only recommend listing BKZ if it is satisfied that BKZ provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapies (Section 101(3B) of the *National Health Act 1953*).

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 reiterated the availability of new treatments with increasing efficacy and stated that as better treatments become available, it is reasonable to improve expectations and treatment goals. The clinician also outlined that total and near-total skin clearance (such as PASI 90) was now a realistic treatment goal for the treatment of plaque psoriasis and this should be considered the new 'gold standard' of treatment.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from a health care professional that supported the notion that PASI 90 should be considered a new standard goal of treatment and with new treatments such as BKZ such goals were becoming realistic for many patients with plaque psoriasis.

Nomination of primary effectiveness outcomes of interest

- 6.3 The submission nominated PASI 90 as the main outcome to assess efficacy of BKZ and nominated comparators. The PBAC had previously based recommendations for the listing of biologics for the treatment of CPP on the proportion of patients achieving and maintaining a PASI 75 response (75% improvement from baseline in PASI score). PASI 75 is also consistent with the PBS eligibility criteria for continued treatment with biologics, including that proposed for BKZ.
- 6.4 The submission argued that with the availability of new treatments, the new 'gold standard' should be PASI 90 and claimed that this has been recommended in recent international guidelines. A review of the quoted references and other published

literature indicated the submission had misrepresented some of the discussion around treatment goals. While there is discussion in the literature on the most appropriate targets for bDMARD treatments, there is so far no consensus on recommendations to change the treatment goals from PASI 75 to PASI 90 or greater.

- 6.5 The Pre-Sub-Committee Response (PSCR) argued there was sufficient discourse in publications and clinical guidelines to justify that the treatment goal of PASI 90 should be the most appropriate measure to determine the clinical effectiveness of these molecules and further argued that it was appropriate for treatment goals to evolve as the treatment landscape changes. In addition, the PSCR also noted that the most recent Cochrane systematic review in CPP¹ nominated clear or almost-clear skin (i.e. PASI 90 or higher) as the primary outcome. The ESC considered that whilst it is appropriate for treatment goals to change over time, also considered PASI 75 remained a relevant outcome, particularly in the context of this outcome being the primary outcome considered for previous bDMARD submissions for CPP. Furthermore, the ESC noted PASI 75 remained a key clinical outcome when considering whether to continue treatment with a bDMARD. The ESC noted the conclusion of the Cochrane Review (using NMA) was that when compared with placebo, the following group of seven biological agents were superior to other agents in reaching PASI 90: IFX, IXE, RIS, BKZ, GUS, SEC and brodalumab. The ESC noted the Cochrane Review stated the clinical effectiveness of these seven drugs was similar, with no one agent superior to all others in this group.
- 6.6 The PSCR also argued that PASI 90 should be considered the most relevant outcome as increasing PASI response is directly related to a patient's quality of life. The ESC considered that while there is some evidence for this association, also noted there is literature suggesting the QoL difference between PASI 75 and PASI 90 may not be clinically significant². The ESC noted in the NICE appraisal of BKZ in the UK, PASI 75 was also considered the key outcome in terms of determining whether or not to continue treatment and considered BKZ was similarly effective compared with brodalumab (not available in Australia), RIS and IXE in terms of PASI 75 responses³.

Clinical trials

- 6.7 The submission was based on:
- Three head-to-head RCTs of BKZ vs active comparators: ADA (BE SURE), UST (BE VIVID), and SEC (BE RADIANT)
 - Three RCTs of BKZ vs. placebo (PBO): BE READY, BE ABLE1, and BE VIVID

¹ <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011535.pub4/full>

² Michael Abrouk, M. Nakamura, T. H. Zhu, B. Farahnik, J. Koo & T. Bhutani (2017) The impact of PASI 75 and PASI 90 on quality of life in moderate to severe psoriasis patients, *Journal of Dermatological Treatment*, 28:6, 488-491, DOI: 10.1080/09546634.2016.1278198

³ <https://www.nice.org.uk/guidance/ta723/chapter/3-Committee-discussion>

- Two open label (OL) extension studies for BKZ: BE ABLE2 (extension of BE ABLE1) and BE BRIGHT (ongoing extension of BE SURE, BE VIVID, BE READY)
- Indirect treatment comparisons (ITCs) of BKZ (BE ABLE 1, BE VIVID and BE READY) vs. RIS (UltIMMa-1, 2), IXE (UNCOVER-1, 2, 3), GUS (VOYAGE-1, 2) and TIL (resurface-1, 2), with PBO as the common reference.
- A network meta-analysis (NMA) including 90 studies, with results focusing on the same comparators included in the ITC. The NMA also included results versus other bDMARDs and DMARDs.

6.8 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
BE READY	Bimekizumab efficacy and safety in moderate to severe plaque psoriasis (BE READY): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial.	September 2020
	Gordon KB, Foley P, Krueger JG, Pinter A, Reich K, Vender R, 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: 475-486
BE SURE	Bimekizumab versus adalimumab efficacy and safety in moderate to severe plaque psoriasis (BE SURE): a multicentre, double-blind, randomised withdrawal phase 3 trial.	September 2020
	Warren, R. B. B., A. Bagel, J. Papp, K. A. Yamauchi, P. Armstrong, A. Langley, et al. Bimekizumab versus Adalimumab in Plaque Psoriasis.	NEJM 2021; 385: 130-141
BE VIVID	Bimekizumab versus ustekinumab and placebo efficacy and safety in moderate to severe plaque psoriasis (BE VIVID): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial.	August 2020
	Reich K, Papp KA, Blauvelt A, Langley RG, Armstrong A, Warren RB, 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; 397:487-498
BE RADIANT	Bimekizumab versus secukinumab efficacy and safety in moderate to severe plaque psoriasis (BE RADIANT): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial.	October 2020
	Reich K, Warren RB, Lebwohl M, Gooderham M, Strober B, Langley RG, et al. Bimekizumab versus Secukinumab in Plaque Psoriasis.	NEJM 2021; 385:142-152
BE ABLE 1	Papp KA, Merola JF, Gottlieb AB, Griffiths CEM, Cross N, Peterson L, 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.	J Am Acad Dermatol. 2018;79: 277-286.e10
BE ABLE 2	Blauvelt A, Papp KA, Merola JF, Gottlieb AB, Cross N, Madden C, et al. Bimekizumab for patients with moderate to severe plaque psoriasis: 60-week results from BE ABLE 2, a randomized, double-blinded, placebo-controlled, phase 2b extension study.	Am Acad Dermatol. 2020; 83:1367-1374.
BE BRIGHT	Bimekizumab extension study BE BRIGHT of efficacy and safety in moderate to severe plaque psoriasis	December 2020

Source: Table 2-4, pp75-78 of the submission.

6.9 The key features of the direct randomised trials are summarised in the table below.

Table 3: Key features of the included BKZ evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Primary Outcomes	Use in modelled evaluation
BKZ vs. ADA						
BE SURE	478	R, DB, P3, MC 56 wks	Low	Moderate to severe CPP	PASI 90 IGA0/1	Yes
BKZ vs. UST (and vs. PBO)						
BE VIVID	567	R, DB, P3, MC 52 wks	Low	Moderate to severe CPP	PASI 90 IGA0/1	Yes
BKZ vs. SEC						
BE RADIANT	743	R, DB, P3, MC 48 wks	Low	Moderate to severe CPP	PASI 100	Yes
BKZ vs. PBO						
BE READY	435	R, DB, P3, MC 56 wks	Low	Moderate to severe CPP	PASI 90 IGA0/1	No
BE ABLE1	250	R, DB, P2, MC 12 wks	Low	Moderate to severe CPP	PASI 90 IGA0/1	No
BKZ extension trials						
BE ABLE2	217	OL ext. ^b , MC 48 wks	Low	Moderate to severe CPP	Long-term safety	No
BE BRIGHT	1286	OL ext. ^a , MC 144 wks (ongoing)	Low	Moderate to severe CPP	Long-term safety	No

Source: Compiled during the evaluation

ADA=adalimumab, BKZ=bimekizumab, CPP=chronic plaque psoriasis, DB=double blind; IGA=investigator global assessment, MC=multi-centre; OL=open label; PASI=psoriasis area and severity index, P2=phase 2, P3=phase 3, R=randomised, SEC=secukinumab, UST=ustekinumab

^a extension of P3 trials BE SURE, BE VIVID, BE READY

^b extension of P2 trial BE ABLE1

- 6.10 All trials were Phase 3, multicentre, active comparator or placebo (PBO) controlled, double-blind RCTs, except for the two open-label (OL) extension studies (BE ABLE2 and BE BRIGHT), and the Phase 2 dose-escalation trial (BE ABLE1). Only data from patients receiving the relevant dose of BKZ 320 mg from BE ABLE1 were presented and included in the analysis.
- 6.11 Overall, the risk of bias in the controlled phase of the trials was considered low.
- 6.12 As most of the trials allowed patients to switch treatment beyond the initial active comparator/placebo-controlled phase (12/16 weeks), outcomes from subsequent periods would be subject to bias. However, appropriately, trial outcomes were assessed at the end of the placebo-controlled periods.
- 6.13 Only the three head-to-head RCTs of BKZ versus active comparators (BE SURE, BE VIVID, BE RADIANT) were fully presented in the submission. Data from BE READY, BE ABLE1 and BE VIVID, used in the ITC where placebo was the common reference were included as supplementary evidence even though these placebo-controlled trials were key evidence for the ITC versus the remaining comparators.
- 6.14 In the BKZ trials, patients had to be candidates for systemic CPP therapy and/or phototherapy, but they were not required to have failed any of these treatments. This differed to the proposed PBS population where patients must have severe CPP (PASI >15) and had to have failed at least 2 of 4 systemic therapies (i.e., methotrexate,

cyclosporin or acitretin) or phototherapy. Therefore, the proposed PBS population is likely to have more severe disease and more treatment exposure compared to the BKZ trial population.

- 6.15 Baseline disease characteristics were generally well balanced across the BKZ trials and reflective of a population with moderate to severe CPP. However, the submission noted differences across the trials for prior anti-tumour necrosis factor (TNF) therapy, and prior chemotherapy or phototherapy (CT/PT) use. A lower proportion of patients had received previous anti-TNF therapy in BE SURE compared to the other BKZ RCTs ($\approx 8\%$ vs. $\approx 15\text{-}19\%$); while BE VIVID included a higher proportion of patients with prior chemo/phototherapy ($\approx 45\%$ vs. $\approx 35\text{-}37\%$).
- 6.16 Data for the bDMARDs included in the ITC (i.e., RIS, IXE, GUS and TIL) were extracted from PBAC Public Summary Documents (PSDs); no independent searches were conducted for these comparators. The PBAC noted the PSDs for these medicines were published between 2016 and 2019 and there may be additional, informative clinical data that was published after this time period.
- 6.17 Most of the 90 trials in the NMA were considered as low risk, but five of the included trials were identified to be at high risk of bias. The NMA report indicated there was a high degree of heterogeneity across the included trials, particularly with respect to disease duration, exposure to prior biologic treatment, phototherapy, or non-biologic treatments.

Comparative effectiveness

- 6.18 The submission nominated a non-inferiority margin of minus (-) 10% for PASI 75 and PASI 90 using the risk difference (RD). This was sourced from the VOYAGE trials of GUS, which nominated a non-inferiority margin of - 10% (lower bound of the 95% CI for the difference in proportions in guselkumab minus adalimumab for PASI 90 or PASI 75 > - 10%) (paragraph 6.20, guselkumab PSD, March 2018 PBAC meeting).
- 6.19 The submission presented results prior to crossover or where the originally assigned treatment was maintained; this was appropriate as crossover would introduce significant bias to the trial results. Nevertheless, the initial treatment periods in the trials varied from 12 to 16 weeks, and this may have favoured drugs with outcome measurement at 16 weeks compared to those with data over a 12-week period.
- 6.20 The submission inappropriately pooled data from the included studies for the ITC instead of conducting a meta-analysis. During the evaluation, these results were updated using the appropriate meta-analysis methodology. The BKZ trials calculated odds ratios (OR) using the Mantel-Haenszel method adjusted by region and prior biologic use. The OR for BKZ trials were recalculated during the evaluation using the Mantel-Haenszel method without adjustment to be consistent with data from the comparator trials included in the ITC.

Direct evidence and ITCs (Bucher method)

- 6.21 Table 4, Table 5, and Table 6 summarise the direct evidence and ITCs for the outcomes of PASI 75, PASI 90 and PASI 100 responses, respectively, for BKZ versus the nominated comparators, based on the results for the ITT population at either 12 or 16 weeks:

Table 4: PASI 75 response at Weeks 12/16 across the trials – ITT population

Trial	Drug n/N (%)	Control n/N (%)	OR (95% CI)	RD (95% CI)
Active-controlled trials				
BKZ vs. ADA*				
BE SURE	295/319 (92.5)	110/159 (69.2)	5.48 (3.21, 9.35)	0.23 (0.16, 0.31)
BKZ vs. UST*				
BE VIVID	296/321 (92.2)	119/163 (73.0)	4.38 (2.56, 7.47)	0.19 (0.12, 0.27)
BKZ vs. SEC*				
BE RADIANT	348/373 (93.3)	337/370 (91.1)	1.36 (0.79, 2.34)	0.02 (-0.02, 0.06)
Placebo-controlled trials				
BKZ vs. PBO				
BE ABLE-1 ^b	40/43 (93.0)	2/42 (4.8)	266.67 (42.26, 1682.59)	0.88 (0.78, 0.98)
BE VIVID	296/321 (92.2)	6/83 (7.2)	151.95 (60.21, 383.43)	0.85 (0.79, 0.91)
BE READY	333/349 (95.4)	2/86 (2.3)	874.13 (197.14, 3875.96)	0.93 (0.89, 0.97)
MA ^a	669/713 (93.8)	10/211 (4.7)	295.29 (97.92, 890.52)	0.89 (0.83, 0.96)
RIS vs. PBO				
UltiMMA-1	264/304 (86.8)	10/102 (9.8)	60.72 (29.19, 126.31)	0.77 (0.70, 0.84)
UltiMMA-2	261/294 (88.8)	8/98 (8.2)	88.98 (39.63, 199.76)	0.81 (0.74, 0.87)
MA ^a	525/598 (87.8)	18/200 (9.0)	72.13 (41.91, 124.13)	0.79 (0.74, 0.84)
IXE vs. PBO				
UNCOVER-1 ^b	386/433 (89.1)	17/431 (3.9)	200.01 (112.91, 354.30)	0.85 (0.82, 0.89)
UNCOVER-2 ^b	315/351 (89.7)	4/168 (2.4)	358.75 (125.53, 1025.30)	0.87 (0.83, 0.91)
UNCOVER-3 ^b	336/385 (87.3)	14/193 (7.3)	87.67 (47.11, 163.15)	0.80 (0.75, 0.85)
MA ^a	1037/1169 (88.7)	35/792 (4.4)	170.85 (81.04, 360.18)	0.84 (0.81, 0.88)
GUS vs. PBO				
VOYAGE-1	300/329 (91.2)	10/174 (5.7)	169.66 (80.66, 356.85)	0.85 (0.81, 0.90)
VOYAGE-2	428/496 (86.3)	20/248 (8.1)	71.75 (42.50, 121.15)	0.78 (0.74, 0.83)
MA ^a	728/825 (88.2)	30/422 (7.1)	105.78 (45.70, 244.85)	0.82 (0.75, 0.89)
TIL vs. PBO				
reSURFACE1 ^b	197/309 (63.8)	9/155 ^c (5.8)	28.53 (14.00, 58.15)	0.58 (0.51, 0.64)
reSURFACE2 ^b	188/307 (61.2)	9/156 (5.8)	25.80 (12.67, 52.54)	0.55 (0.49, 0.62)
Papp 2015	59/89 (66.3)	2/46 (4.3)	43.27 (9.81, 190.77)	0.62 (0.50, 0.73)
MA ^a	444/705 (63.0)	20/356 (5.6)	28.47 (17.68, 45.85)	0.57 (0.53, 0.62)
Indirect treatment comparisons				
		BKZ vs. RIS	4.09 (1.20, 14.01)	0.10 (0.02, 0.18)
		BKZ vs. IXE	1.73 (0.46, 6.55)	0.05 (-0.02, 0.12)
		BKZ vs. GUS	2.79 (0.70, 11.17)	0.07 (-0.03, 0.17)
		BKZ vs. TIL	10.37 (3.12, 34.51)	0.32 (0.24, 0.40)

Bold=statistically significant.

Source: Table 2.33, p118; Table 2.48, p137; Table 2.61, p155; Tables A0-5-8, pp315-316 of the submission.

ADA=adalimumab, BKZ=bimekizumab, CI=confidence interval, GUS=guselkumab, ITT=intention to treat, IXE=ixekizumab, MA=meta-analysis, NNT=number needed to treat, OR=odds ratio, PASI=psoriasis area and severity index, PBO=placebo, RD=risk difference, RIS=risankinumab, SEC=secukinumab, TIL=tildrakizumab, UST=ustekinumab.

* OR and RD calculated during the evaluation using ReviewManager 5.4.1

^a MA (Mantel-Haenszel random effects) conducted during the evaluation using Review Manager 5.4.1 as submission used pooled data.

^b Outcomes calculated at Wk12

^c analysis in the ITT population (using NRI) One patient in the PBO arm was randomised but never treated in reSURFACE

Table 5: PASI 90 response at Weeks 12/16 across the trials – ITT populations

Trial	Drug n/N (%)	Control n/N (%)	OR (95% CI)	RD (95% CI)	
Active-controlled trials					
BKZ vs. ADA					
BE SURE	275/319 (86.2)	75/159 (47.2)	7.00 (4.48, 10.93)	0.39 (0.31, 0.48)	+
BKZ vs. UST					
BE VIVID	273/321 (85.0)	81/163 (49.7)	5.76 (3.73, 8.89)	0.35 (0.27, 0.43)	+
BKZ vs. SEC					
BE RADIANT	319/373 (85.5)	275/370 (74.3)	2.04 (1.41, 2.96)	0.11 (0.05, 0.17)	+
Placebo-controlled trials					
BKZ vs. PBO					
BE ABLE-1 ^b	34/43 (79.1)	0/42 (0)	308.68 (17.34, 5493.85)	0.79 (0.66, 0.92)	+
BE VIVID	273/321 (85.0)	4/83 (4.8)	112.33 (39.30, 321.09)	0.80 (0.74, 0.86)	+
BE READY	317/349 (90.8)	1/86 (1.2)	842.0 (113.4, 6251.35)	0.90 (0.86, 0.93)	+
MA ^a	624/713 (87.5)	5/211 (2.4)	240.31 (61.73, 935.58)	0.84 (0.75, 0.92)	+
RIS vs. PBO					
UltiMMA-1	229/304 (75.3)	5/102 (4.9)	59.23 (23.23, 151.02)	0.70 (0.64, 0.77)	+
UltiMMA-2	220/294 (74.8)	2/98 (2.0)	142.70 (34.33, 593.25)	0.73 (0.67, 0.78)	+
MA ^a	449/598 (75.1)	7/200 (3.5)	77.98 (34.56, 175.91)	0.72 (0.67, 0.76)	+
IXE vs. PBO					
UNCOVER-1 ^b	307/433 (70.9)	2/431 (0.5)	522.63 (128.30, 2128.98)	0.70 (0.66, 0.75)	+
UNCOVER-2 ^b	248/351 (70.7)	1/168 (0.6)	402.10 (55.56, 2910.07)	0.70 (0.65, 0.75)	+
UNCOVER-3 ^b	262/385 (68.1)	6/193 (3.1)	66.39 (28.64, 153.88)	0.65 (0.60, 0.70)	+
MA ^a	817/1169 (69.9)	9/792 (1.1)	213.31 (43.41, 1048.15)	0.69 (0.65, 0.72)	+
GUS vs. PBO					
VOYAGE-1	241/329 (73.3)	5/174 (2.9)	92.57 (36.80, 232.81)	0.70 (0.65, 0.76)	+
VOYAGE-2	347/496 (70.0)	6/248 (2.4)	93.93 (40.86, 215.94)	0.68 (0.63, 0.72)	+
MA ^a	588/825 (71.3)	11/422 (2.6)	93.32 (50.30, 173.11)	0.69 (0.65, 0.72)	+
TIL vs. PBO^c					
reSURFACE1 ^b	107/309 (34.6)	4/155 ^c (2.6)	20.00 (7.21, 55.46)	0.32 (0.26, 0.38)	+
reSURFACE2 ^b	119/307 (38.8)	2/156 (1.3)	48.74 (11.86, 200.37)	0.37 (0.32, 0.43)	+
Papp 2015	34/89 (38.2)	1/46 (2.2)	27.82 (3.66, 211.23)	0.36 (0.25, 0.47)	+
MA ^a	260/705 (36.9)	7/357 (2.0)	27.23 (12.66, 58.57)	0.35 (0.31, 0.39)	+
Indirect treatment comparisons					
		BKZ vs. RIS	3.08 (0.63, 15.02)	0.12 (0.02, 0.22)	+
		BKZ vs. IXE	1.13 (0.14, 9.14)	0.15 (0.06, 0.24)	+
		BKZ vs. GUS	2.58 (0.58, 11.46)	0.15 (0.06, 0.24)	+
		BKZ vs. TIL	8.83 (1.85, 42.00)	0.49 (0.40, 0.58)	+

Bold=statistically significant.

Source: Table 2.26, p112; Table 2.42, p132; Table 2.60, p154; Tables A0.1-4, pp313-315 of the submission.

ADA=adalimumab, BKZ=bimekizumab, CI=confidence interval, GUS=guselkumab, ITT=intention to treat, IXE=ixekizumab, MA=meta-analysis, NNT=number needed to treat, OR=odds ratio, PASI=psoriasis area and severity index, PBO=placebo, RD=risk difference, RIS=risankizumab, SEC=secukinumab, TIL=tildrakizumab, UST=ustekinumab.

^a MA (Mantel-Haenszel random effects) conducted during the evaluation using Review Manager 5.4.1 as submission used pooled data.

^b Outcomes calculated at Wk12

^c analysis in the ITT population (using NRI) One patient in the PBO arm was randomised but never treated in reSURFACE 1

Table 6: PASI 100 response at Weeks 12/16 across the trials – ITT populations

Trial	Drug n/N (%)	Control n/N (%)	OR (95% CI)	RD (95% CI)
BKZ vs. ADA				
BE SURE	194/319 (60.8)	38/159 (23.9)	4.94 (3.22, 7.58)	0.37 (0.28, 0.45)
BKZ vs. UST				
BE VIVID	188/321 (58.6)	34/163 (20.9)	5.36 (3.46, 8.31)	0.38 (0.29, 0.46)
BKZ vs. SEC				
BE RADIANT	230/373 (61.7)	181/370 (48.9)	1.68 (1.25, 2.25)	0.13 (0.06, 0.20)
BKZ vs. PBO				
BE ABLE-1 ^a	24/43 (55.8)	0/42 (0)	106.79 (6.17, 1847.74)	0.56 (0.41, 0.71)
BE VIVID	188/321 (58.6)	0/83 (0)	235.80 (14.50, 3834.95)	0.59 (0.53, 0.64)
BE READY	238/349 (68.2)	1/86 (1.2)	182.25 (25.06, 1325.68)	0.67 (0.62, 0.72)
MA ^a	450/713 (63.1)	1/211 (0.5)	170.86 (41.86, 697.29)	0.62 (0.55, 0.69)

Bold=statistically significant.

Source: Table 2.30, p116; Table 2.46, p135-136; Table 2.57, p151 of the submission; Papp et al. 2018; Gordon et al. 2021; Reich et al. 2021.

ADA=adalimumab, BKZ=bimekizumab, CI=confidence interval, ITT=intention to treat, MA=meta-analysis, NNT=number needed to treat, OR=odds ratio, PASI=psoriasis area and severity index, PBO=placebo, RD=risk difference, RIS=risankinumab, SEC=secukinumab, TIL=tildrakizumab, UST=ustekinumab.

^a Outcomes calculated at Wk12

6.22 In terms of initial PASI 75 response at 12/16 weeks, head-to-head trials showed statistically superior effectiveness of BKZ against ADA and UST, but non-significant differences against SEC (using both the OR and RD statistics). Based on ITCs using placebo as common reference (assessed at the end of trial placebo-controlled periods), BKZ was statistically superior to RIS and TIL, but non-significant differences were observed against IXE and GUS. The OR and RD statistics were consistent across the analyses. All results met the non-inferiority margin of minus (-) 10% on the RD. In summary, based on PASI 75 response, BKZ appeared to be:

- superior to ADA, UST, RIS and TIL;
- non-inferior to SEC, IXE and GUS.

6.23 In terms of initial PASI 90 response at 12/16 weeks, head-to-head trials showed statistically superior effectiveness of BKZ against ADA, UST, and SEC. Based on ITCs, although BKZ was statistically superior to RIS, IXE, GUS and TIL using the RD statistic, the differences versus RIS, IXE and GUS were small and just reached statistical significance, and there were no longer statistically significant when compared using the OR statistic. In summary, based on PASI 90 response, BKZ appeared to be:

- superior to ADA, UST, TIL, SEC, RIS, IXE and GUS. However, the benefit versus RIS, IXE, GUS was small, raising uncertainty about whether these differences would be seen in clinical practice given heterogeneity across trials and noted differences versus the PBS population.

6.24 In terms of initial PASI 100 response at 12/16 weeks, head-to-head trials showed statistically superior effectiveness of BKZ against ADA, UST, and SEC. The submission did not present any ITCs against RIS, IXE, GUS or TIL for this outcome.

Network meta-analysis (NMA)

6.25 The submission presented Bayesian NMAs to support the comparison of BKZ versus RIS, IXE, GUS and TIL, and provided a report as an attachment. Two types of statistical analyses were conducted:

- Multinomial (probit) base-case model evaluating PASI as an ordered categorical outcome in categories of 75%, 90%, and 100% PASI responses (Table 7).
- Binomial (logit) model evaluating PASI as a dichotomous outcome in terms of attainment of 75%, 90%, and 100% PASI responses (Table 8).

Table 7: RE-adjusted, REZ, Multinomial NMA; Probit Probabilities for PASI Outcomes at 10–16 Weeks and Probit differences between BKZ and comparators

Treatment	PASI 75			PASI 90			PASI 100		
	rank	Probit Prob (Crl)	Probit Diff (Crl)	rank	Probit Prob (Crl)	Probit Diff (Crl)	rank	Probit Prob (Crl)	Probit Diff (Crl)
BKZ 320mg	1	0.923 (0.893, 0.945)	Reference	1	0.840 (0.796, 0.877)	Reference	1	0.578 (0.514, 0.637)	Reference
RIS 150mg	2	0.899 (0.869, 0.923)	0.15 (-0.08, 0.37)	2	0.732 (0.684, 0.777)	0.38 (0.16, 0.59)	2	0.445 (0.389, 0.500)	0.34 (0.13, 0.54)
IXE 80mg	3	0.891 (0.855, 0.918)	0.20 (-0.04, 0.43)	4	0.708 (0.651, 0.759)	0.45 (0.23, 0.67)	4	0.381 (0.323, 0.441)	0.50 (0.28, 0.71)
GUS 100mg	5	0.865 (0.829, 0.896)	0.32 (0.09, 0.54)	5	0.674 (0.618, 0.724)	0.55 (0.33, 0.76)	5	0.328 (0.275, 0.383)	0.64 (0.43, 0.85)
TIL 200mg	14	0.668 (0.598, 0.734)	0.99 (0.73, 1.24)	14	0.398 (0.328, 0.472)	1.26 (1.00, 1.50)	12	0.147 (0.105, 0.199)	1.24 (0.98, 1.50)
TIL 100mg ^a	15	0.630 (0.557, 0.698)	1.09 (0.83, 1.34)	15	0.375 (0.306, 0.448)	1.31 (1.06, 1.56)	15	0.135 (0.096, 0.183)	1.30 (1.04, 1.56)

Source: Table 2 112, p237 of the submission. **BOLD=statistically significant**
 BKZ= Bimekizumab, Crl=credibility interval, GUS=Guselkumab, IXE=Ixekizumab, OR=odds ratio, RE=random effects, RIS=Risankizumab, REZ=model modification added a random effects component to parameter z, TIL=Tildrakizumab PASI=Psoriasis Area and Severity Index
^a Only TIL 100mg was presented in the ITC, as current PBS listing and recommended dosing in the PI is 100mg.
 Note: Treatments are sorted by the highest to lowest probabilities of reaching PASI90.

Table 8: RE-unadjusted Binomial NMA: OR for PASI outcomes at 10–16 Weeks

Treatment	PASI 75 OR (95% Crl)	PASI 90 OR (95% Crl)	PASI 100 OR (95% Crl)
BKZ 320mg vs. comparators:			
IXE 80 mg	1.53 (1.03, 2.26)	1.57 (1.06, 2.34)	1.32 (0.76, 2.29)
RIS 150 mg	1.42 (0.96, 2.09)	1.83 (1.30, 2.61)	1.31 (0.84, 2.02)
GUS 100mg	2.09 (1.42, 3.07)	2.68 (1.89, 3.76)	1.89 (1.12, 3.44)
TIL 200mg	6.61 (4.40, 9.88)	6.42 (3.76, 11.16)	5.73 (2.39, 12.68)
TIL 100mg ^a	7.65 (5.08, 11.44)	6.85 (3.87, 12.00)	5.61 (2.34, 12.42)

Source: Table 2-115, p238 of the submission. **BOLD=statistically significant**
 BKZ= Bimekizumab, Crl=credibility interval, GUS=Guselkumab, IXE=Ixekizumab, OR=odds ratio, RE=random effects, RIS=Risankizumab, TIL=Tildrakizumab PASI=Psoriasis Area and Severity Index
^a Only TIL 100mg was presented in the ITC, as current PBS listing and recommended dosing in the PI is 100mg.
 Note: Treatments are sorted by the highest to lowest

6.26 The multinomial NMA found BKZ to be associated with a higher probability of achieving a PASI 75 response versus GUS and TIL, but not compared to RIS and IXE. For PASI 90 and PASI 100 responses, BKZ was associated with statistically significantly higher probability of response versus all comparators.

- 6.27 In the binomial NMA, BKZ was associated with significantly higher odds of achieving a PASI 75 outcome compared to comparators, except for RIS (non-significant difference). The comparison against IXE resulted in significantly higher ORs favouring BKZ, whereas in the multinomial model the probit difference against IXE did not reach statistical significance. The odds of achieving PASI 90 were significantly higher for BKZ compared to all comparators, but only significantly higher versus GUS and TIL for PASI 100.
- 6.28 Overall, the NMA appeared to be properly conducted. However, there was not enough information provided to fully validate the multinomial NMA (base case model) or binomial NMA analysis during the evaluation. In the data files provided by the sponsor during the evaluation, there were some apparent data entry errors, and results need to be interpreted with caution as some uncertainty remained due to the following issues:
- The NMA identified five trials at high risk of bias but did not conduct any sensitivity analyses to assess the impact of including/excluding these trials from the NMA.
 - The NMA included pilot studies, phase 2 and phase 3 trials, with sample sizes ranging from 20 patients to 1306 patients across the studies, bringing additional heterogeneity to the results.
 - The NMA included comparator doses that are not licensed in Australia and that were excluded from the ITC, such as TIL 200 mg and SEC 150 mg. The NMA also included brodalumab (BRO), which is not available in Australia.
 - The NMA was adjusted for variation in placebo-response rates, which was appropriate as response rates for PASI 75 in the placebo group of the included trials ranged from less than 2% to almost 20%. However, the submission did not provide any data to demonstrate lack of heterogeneity following baseline adjustments.
 - Prior exposure to biologic treatment varied widely across trials; 14 studies were conducted in patients naïve to biologic treatment, and among studies with a mixed population with previous biologic exposure and biologic-naïve, the proportion previously treated with biologic treatments ranged from 7.9% to 60%. Prior biologic treatment is a known effect modifier, but no analyses were conducted in trials with a higher proportion of patients exposed to prior biologic treatment. The NMA presented a subgroup analysis in trials with 100% and 90% biologic-naïve patients, but impact of other sources of heterogeneity were not properly explored.

Comparative harms

- 6.29 A summary of treatment emergent adverse events (TEAEs) from the BKZ trials during the double-blind controlled phase is presented in Table 9.

Table 9: Summary of key adverse events in the BKZ trials (controlled phase)

Trials		Any TEAE n (%)	Serious TEAEs n (%)	Discontinuation due to TEAEs n (%)	Drug-related TEAEs n (%)	Severe TEAEs n (%)	Deaths n (%)
BE SURE (Wk 0-24)	BKZ (N=319)	228 (71.5)	5 (1.6)	9 (2.8)	87 (27.3)	5 (1.5)	0
	ADA (N=159)	111 (69.8)	5 (3.1)	5 (3.1)	38 (23.9)	5 (3.1)	1 (0.6)
BE VIVID (Wk 0-16)	BKZ (N=321)	181 (56.4)	5 (1.6)	6 (1.9)	79 (24.6)	5 (1.6)	1 (0.3)
	UST (N=163)	83 (50.9)	5 (3.1)	3 (1.8)	19 (11.7)	3 (1.8)	1 (0.6)
	PBO (N=83)	39 (47.0)	2 (2.4)	6 (7.2)	8 (9.6)	3 (3.6)	1 (1.2)
BE RADIANT (Wk 0-16)	BKZ (N=373)	243 (65.1)	9 (2.4)	9 (2.4)	102 (27.3)	12 (3.2)	0 (0)
	SEC (N=370)	219 (59.2)	7 (1.9)	4 (1.1)	68 (18.4)	4 (1.1)	0 (0)
BE READY (Wk 0-16)	BKZ (N=349)	213 (61.0)	6 (1.7)	3 (0.8)	65 (18.6)	3 (0.9)	0 (0)
	PBO (N=86)	35 (40.7)	2 (2.3)	0 (0)	7 (8.1)	1 (1.2)	0 (0)
BE ABLE1 (Wk 0-12)	BKZ (N=43)	26 (60.5)	0 (0)	1 (2.3)	10 (23.3)	0 (0)	0 (0)
	PBO (N=42)	15 (35.7)	1 (2.4)	1 (2.4)	3 (7.1)	0 (0)	0 (0)

Source: Table 2.27, p172; Table 2.81, p183; Table 2.88, p195 of the submission; and trial publications. Table 8.1.1.1, BE RADIANT, BE READY, BE VIVID CSRs

Abbreviations: n=number of subjects who reported at least 1 TEAE in the category; NR=not reported; PBO=placebo; TEAE=treatment-emergent adverse event

- 6.30 The overall rates of serious and severe treatment emergent adverse events (TEAEs), and discontinuation rates due to TEAEs were low across trials and treatments, with no significant differences observed.
- 6.31 The submission also included ITCs of BKZ versus RIS, IXE, GUS and TIL, with placebo as a common reference for the safety outcomes of serious adverse events (AEs), severe AEs, and discontinuation due to AEs. These ITCs showed no significant differences between BKZ and these comparators regarding these outcomes. The NMA for safety outcomes comparing BKZ versus RIS, IXE, GUS and TIL showed similar results.

Benefits/harms

- 6.32 A summary of the comparative benefits for BKZ versus ADA, UST, SEC (direct comparison) and RIS, IXE, GUS, TIL (indirect comparison) is presented in Table 10, based on the key outcome of PASI 75 and the proposed clinical measure of PASI 90. The OR statistic was presented as it was the main statistic alongside the RD in the trials, which was the main focus as the non-inferiority margin (–10%) for both PASI 75 and PASI 100 was calculated using the RD statistic.
- 6.33 A summary of comparative harms of BKZ versus comparators is not presented given the results support the claim of non-inferior safety.

Table 10: Summary of comparative benefits (PASI 75, PASI 90) for BKZ versus proposed comparators

Comparison (Trial)	BKZ n/N	Comparator n/N	OR (95% CI)	Event rate/100 patients		RD (95% CI)
				BKZ	Comparator	
PASI 75 at 16 weeks – direct comparisons						
BKZ v ADA (BE SURE)	295/319	110/159	5.48 (3.21, 9.35)	92.5	69.2	0.23 (0.16, 0.31)
BKZ v UST (BE VIVID)	296/321	119/163	4.38 (2.56, 7.47)	92.2	73.0	0.19 (0.12, 0.27)
BKZ v SEC (BE RADIANT)	348/373	337/370	1.36 (0.79, 2.34)	93.3	91.1	0.02 (-0.02, 0.06)
PASI 75 at 12-16* weeks – indirect comparisons (Bucher method)						
BKZ v RIS ^(a)	669/713	525/598	4.09 (1.20, 14.01)	93.8	87.8	0.10 (0.02, 0.18)
BKZ v IXE ^(b)	669/713	1037/1169	1.73 (0.46, 6.55)	93.8	88.7	0.05 (-0.02, 0.12)
BKZ v GUS ^(c)	669/713	728/825	2.79 (0.70, 11.17)	93.8	88.2	0.07 (-0.03, 0.17)
BKZ v TIL ^(d)	669/713	444/705	10.37 (3.12, 34.51)	93.8	63.0	0.32 (0.24, 0.40)
PASI 90 at 16 weeks – direct comparisons						
BKZ v ADA (BE SURE)	275/319	75/159	7.00 (4.48, 10.93)	86.2	47.2	0.39 (0.31, 0.48)
BKZ v UST (BE VIVID)	273/321	81/163	5.76 (3.73, 8.89)	85.0	49.7	0.35 (0.27, 0.43)
BKZ v SEC (BE RADIANT)	319/373	275/370	2.04 (1.41, 2.96)	85.5	74.3	0.11 (0.05, 0.17)
PASI 90 at 12-16* weeks – indirect comparisons (Bucher method)						
BKZ v RIS ^(a)	624/713	449/598	3.08 (0.63, 15.02)	87.5	75.1	0.12 (0.02, 0.22)
BKZ v IXE ^(b)	624/713	817/1169	1.13 (0.14, 9.14)	87.5	69.9	0.15 (0.06, 0.24)
BKZ v GUS ^(c)	624/713	588/825	2.58 (0.58, 11.46)	87.5	71.3	0.15 (0.06, 0.24)
BKZ v TIL ^(d)	624/713	260/705	8.83 (1.85, 42.00)	87.5	36.9	0.49 (0.40, 0.58)

Bold=statistically significant.

Source: Table 2.33, p118; Table 2.48, p137; Table 2.61, p155; Tables A0-5-8, pp315-316 of the submission. Table 2.26, p112; Table 2.42, p132; Table 2.60, p154; Tables A0.1-4, pp313-315 of the submission.

See Table 4 and Table 5 for further details.

ADA=adalimumab, BKZ=bimekizumab, CI=confidence interval, GUS=guselkumab, IXE=ixekizumab, MA=meta-analysis, OR=odds ratio, PASI=psoriasis area and severity index, PBO=placebo; RD=risk difference; RIS=risankinumab, SEC=secukinumab, TIL=tildrakizumab, UST=ustekinumab.

* Outcomes from BE ABLE-1, UNCOVER trials, and reSURFACE trials were assessed at Week 12

^a ITC using MA data from BE ABLE-1, BE VIVID, BE READY (BKZ) versus UltIMMa-1-2 (RIS) via placebo

^b ITC using MA data from BE ABLE-1, BE VIVID, BE READY (BKZ) versus UNCOVER-1-2-3 (IXE) via placebo

^c ITC using MA data from BE ABLE-1, BE VIVID, BE READY (BKZ) versus VOYAGE-1-2 (GUS) via placebo

^d ITC using MA data from BE ABLE-1, BE VIVID, BE READY (BKZ) versus reSURFACE-1-2 (GUS) via placebo

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

- **ADA** – Approximately 23 additional patients would achieve PASI 75, and 39 additional patients would achieve PASI 90.
- **UST** – Approximately 19 additional patients would achieve PASI 75, and 35 additional patients would achieve PASI 90.
- **SEC** – There were no significant differences in the number of patients achieving PASI 75, and approximately 11 additional patients would achieve PASI 90

6.35 On the basis of indirect evidence presented by the submission, for every 100 patients treated with BKZ over the initial 12/16 weeks of treatment in comparison with:

- **RIS** – Approximately 10 additional patients would achieve PASI 75, and 12 additional patients would achieve PASI 90.

- IXE – There were no significant differences in the number of patients achieving PASI 75, and approximately 15 additional patients would achieve PASI 90.
 - GUS – There were no significant differences in the number of patients achieving PASI 75, and approximately 15 additional patients would achieve PASI 90.
 - TIL – Approximately 32 additional patients would achieve PASI 75, and 49 additional patients would achieve PASI 90.
- 6.36 The PBAC noted that either no additional patients or a relatively small number of additional patients achieved a PASI 75 or PASI 90 response at 12/16 weeks for IXE, GUS, SEC and RIS.

Clinical claim

- 6.37 The submission described BKZ as superior in terms of effectiveness and non-inferior in terms of safety compared to all currently PBS-listed bDMARDs. The non-inferior safety claim was reasonable; however, the evaluation considered the claim of superior effectiveness may not be adequately supported by the evidence presented.
- 6.38 The ESC noted BKZ showed superior efficacy in terms of PASI 90 to all the relevant comparators during the initial treatment period; however, while the benefit versus RIS, IXE, GUS resulting from the ITCs was statistically significant, the difference was small with uncertainty these differences would be seen in clinical practice, and not consistent across statistical approaches, raising uncertainty around the true effect size. The ESC noted that whilst the direct evidence indicated BKZ may be superior to SEC, it also noted the risk difference was small and it was uncertain if this represented a clinically important difference in clinical practice. Furthermore, the ESC noted that in the only presented sensitivity analysis for the NMA (subgroup analysis by percentage of biological naïve patients), superiority was not sustained versus RIS and GUS, and that an independent NMA (Cochrane review) concluded that no one of these biological agents was superior to all others. Overall, the ESC considered a claim of superior comparative efficacy versus ADA, UST and SEC (based on the direct evidence) and versus TIL (based on the indirect comparisons) for the outcome of PASI 90 may be reasonable. However, for the claim of superiority over SEC, RIS, GUS and IXE, the ESC considered the evidence presented did not strongly support such a claim due to the small magnitude of difference for some of the comparisons (despite reaching statistical significance), and was uncertain whether these differences would be clinically meaningful in practice.
- 6.39 Results for PASI 75 during the initial treatment period were not conclusive:
- Head-to-head trials showed BKZ was statistically superior against ADA and UST for PASI 75, but was non-inferior to SEC.
 - Indirect evidence from the ITCs showed no statistically significant differences for BKZ versus IXE and GUS, and numerically close to RIS despite reaching statistical significance suggesting non-inferiority may be a more appropriate conclusion.

Furthermore, non-inferiority against RIS was also supported by the NMA results, which showed non-significant differences between BKZ and RIS in its analysis using the probit model.

- ITC and NMA results were also inconsistent for the comparisons of BKZ versus GUS; which showed statistically significant differences in the NMA but non-significant difference in the ITC. Overall, these inconsistencies result in further uncertainty around the indirect evidence, in particular where efficacy conclusions were based on small statistical differences.

- 6.40 In summary, the evaluation considered that while BKZ may be superior to ADA, UST and TIL for achieving PASI 75 at 16 weeks, it appeared to be non-inferior to SEC, RIS, IXE and GUS.
- 6.41 For the outcome of PASI 75 response, the ESC noted the direct evidence did not support a claim of superior comparative efficacy versus SEC and further noted the results of the indirect comparisons yielded mixed results, with statistically non-significant differences for the comparisons versus IXE, GUS and RIS by at least one statistical approach.
- 6.42 With regards to the clinical claim more broadly, the ESC reiterated its uncertainty as to whether there was a clinically significant difference in QoL outcomes between PASI 75 and PASI 90 (paragraphs 6.5 and 6.6 refer).
- 6.43 The PBAC considered the claim of superior comparative effectiveness compared to ADA, UST and TIL was adequately supported but the data did not adequately support a superiority claim for IXE, RIS, GUS and SEC. The PBAC noted no comparison to IFX, one of the more effective treatments for severe CPP, was provided.
- 6.44 The PBAC considered the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.45 The submission presented a cost-utility analysis using individual patient level simulation (or microsimulation), which the submission considered a more efficient approach than Markov cohort analysis at handling: i) treatment sequencing and memory of prior treatments, ii) variable induction lengths, and iii) dealing with the 5-year bDMARD-free period, which are all features of bDMARD treatment on PBS. The analysis was informed by data from the BKZ trials (BE VIVID, BE SURE and BE RADIANT) as well as the NMA.
- 6.46 Adequate information was not provided in the submission (or upon request during evaluation) to verify a number of data sources used in the economic model, including the PASI response for the subgroup of patients with baseline DLQI ≥ 10 .

6.47 Table 11 summarises the key components of the economic evaluation.

Table 11: Summary of model structure, key inputs and rationale

Component	Summary	
Treatments	Scenario with PBS listing of BKZ vs scenario without PBS listing of BKZ	
Time horizon	7 years in the model base case versus 16 weeks of comparative data in the initial treatment period in the key trials	
Outcomes	Quality-adjusted life years (QALYs)	
Methods used to generate results	Microsimulation model (simulating individual patient outcomes) which enabled the model to: <ul style="list-style-type: none"> (i) remember the number of bDMARDs a patient had used in the treatment cycle; (ii) memory of prior treatments, which bDMARD had been used (to avoid re-use of same bDMARD); and (iii) count the 5-year bDMARD free period mandated in the PBS criteria. 	
Health states	6 states based on PASI response: <ul style="list-style-type: none"> - Baseline - < PASI 50 - 50 ≤ PASI < 75 - 75 ≤ PASI < 90 - 90 ≤ PASI < 100 - PASI 100. Patients can also move to the death state during any cycle based on background mortality. Some models in the literature (e.g., NICE appraisal of SEC) combined the two highest PASI health states (i.e., PASI 90 and PASI 100) which may also be reasonable if costs and outcomes are expected to be similar.	
Cycle length	2 weeks	
Transition probabilities	<u>PASI Response</u> <ul style="list-style-type: none"> • BKZ based on BE VIVID (base case), BE SURE, BE RADIANT and NMA in sensitivity. • ADA (BE SURE), SEC (BE RADIANT) and UST (BE VIVID) in base case, and NMA in sensitivity analyses. • Other bDMARDs: NMA for both base case and sensitivity analyses. Source data for BKZ were from trial subgroups with baseline DLQI ≥ 10. PASI response rates for this subgroup could not be adequately verified during the evaluation.	
	Discontinuation during maintenance therapy: NostraData 2021. While data were provided by the sponsor during evaluation, there were no explanations accompanying the data so it remained unclear how discontinuation rates were derived and why it was preferred over PBS data.	
	Time to response: 8-24 weeks; based on the direct RCTs (BKZ, ADA, UST, SEC), trials for other bDMARDs, and NMA for BSC. The assumption that BKZ patients would achieve a response at 8 weeks before all nominated comparators favoured BKZ.	
Extrapolation method	The model assumed no waning of response to any bDMARDs in second or third-line use. In the base case, it was assumed that half of the discontinuations in maintenance were due to treatment failure (the rest were assumed to due to intolerance, no data was provided to support this).	
Health related quality of life	Health state utility was based on EQ-5D-3L values from pooled BKZ and certolizumab trial data calculated for PASI responder and non-responders using regression equation.	
	Baseline	0.7235
	PASI < 50	0.7486
	50 ≤ PASI < 75	0.8436
	75 ≤ PASI < 90	0.872
	90 ≤ PASI < 100	0.8996
PASI 100	0.9192	

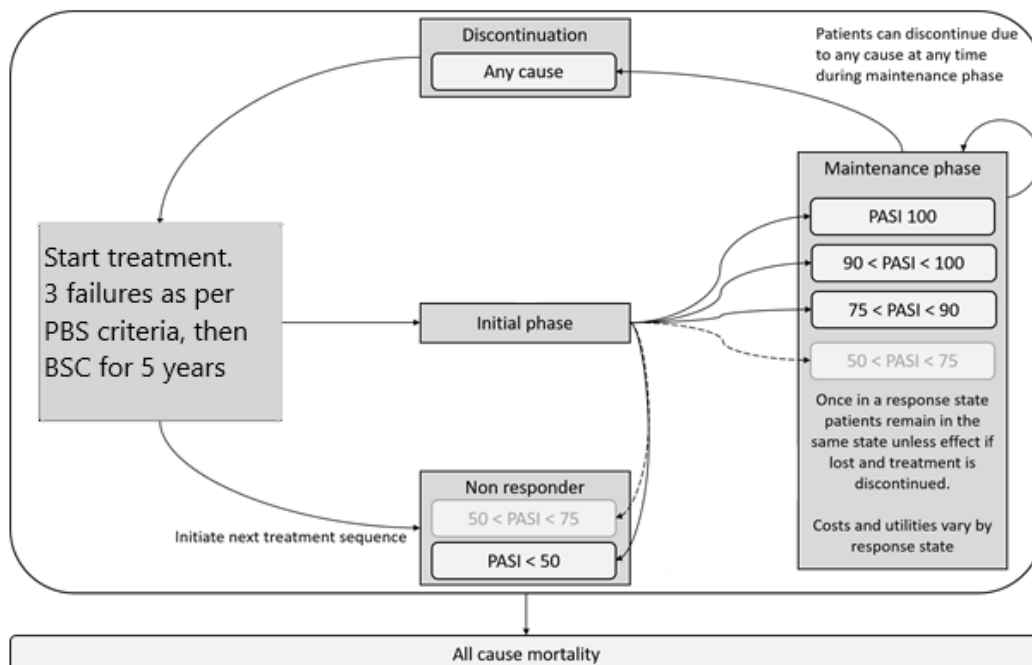
Source: Table 3-1, pp266-267 of the submission.

ADA = adalimumab; BKZ = bimekizumab; SEC = secukinumab; UST = ustekinumab; bDMARD = biologic disease-modifying anti-rheumatic drug; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; NMA = network meta-analysis; PASI=psoriasis area and severity index.

Model structure

- 6.48 The model followed a cohort of patients through two scenarios comparing a world with and a world without BKZ (see Figure 1). Patients in the world with BKZ were assumed to start treatment with BKZ (either as their 1st, 2nd or 3rd line treatment, assumed to be of equal split in the base case). In the world without BKZ, the starting bDMARD was randomly selected from currently PBS-listed bDMARDs for CPP.
- 6.49 Following the initial treatment period, patient response against PBS continuation criteria was assessed. Responders would move to a maintenance period, where they continued to receive the same bDMARD until discontinuation or death. Non-responders would move to the next randomly selected biologic. The model was programmed so that previously selected bDMARDs could not be reselected within the model time horizon. Non-responders to the third bDMARD in the treatment cycle would have a five-year break from bDMARD treatment and would be treated instead with best supportive care (BSC), assumed to be either methotrexate, ciclosporin, apremilast or acitretin. Patients stayed on BSC until death, end of model horizon, or the 5-year bDMARD free period expired. If the bDMARD-free period expired, patients would begin treatment with a new bDMARD.
- 6.50 The base-case scenario assumed patients who attained a PASI 75 response or higher were responders, those with less than a PASI 75 response were considered non-responders.

Figure 1 Model structure



Source: Figure 3-1, p270 of the submission.

- 6.51 The modelled time horizon was seven years in the base case. The submission considered this necessary, arguing that patients who respond to BKZ and continue to maintain that response will likely remain on treatment long term. The duration of follow up in the BKZ trials was up to 56 weeks. While a shorter five-year time horizon was used in models previously considered by the PBAC, for example in the cost effectiveness review of biologic agents for CPP (paragraph 3.14, PMR PSD, July 2020 PBAC meeting) and the UST model for CPP (ustekinumab, PSD, November 2009 PBAC meeting), the submission's model was not overly sensitive to time horizon, with similar ICERs estimated at five and seven years.

PASI response

- 6.52 PASI response rates for BKZ were based on subgroup results for patients with DLQI ≥ 10 from the BKZ trials BE VIVID (base case), BE SURE and BE RADIANT (in sensitivity analyses). Patients with DLQI ≥ 10 were used as proxies for those with severe CPP. On the PBS, severe CPP and eligibility for bDMARDs is determined by baseline PASI score ≥ 15 . While the DLQI is a measure of QoL, it does not perfectly correlate with the PASI. DLQI results may also be confounded by the presence of other conditions, such as anxiety or depression. For these reasons, trial patients with baseline PASI ≥ 15 are considered better representatives of patients with severe CPP and more likely to access BKZ on the PBS than patients with DLQI ≥ 10 .
- 6.53 In the base case, BKZ patients were assumed to follow response rates from BE VIVID, on the basis that the comparator in BE VIVID (UST) was the most used bDMARD on the PBS, based on an IQVIA market share analysis (see below). BKZ response rates from the other two direct RCTs (BE SURE and BE RADIANT) were used in sensitivity analyses.
- 6.54 For the comparators, in the base case, PASI response rates for ADA, UST and SEC were derived from the relevant treatment arms of the respective direct RCTs versus BKZ (i.e., BE SURE, BE VIVID and BE RADIANT). In sensitivity analyses, results from the submission's NMA were used. BSC response rates were derived from an average of NMA results for cyclosporin, methotrexate, apremilast and acitretin. The submission's NMA were conducted using trials of patients with moderate to severe CPP, which was inconsistent with the intended modelled population of patients with severe CPP.
- 6.55 The model assumed bDMARD treatments to be equally efficacious regardless of the order administered or a patient's prior biologic experience. This was based on post-hoc subgroup analyses (of BKZ versus ADA, UST and SEC) by prior treatment showing patients previously treated with a bDMARD had similar response to BKZ compared to treatment-naïve patients. In the NMA, smaller treatment effect differences were noted for BKZ versus comparators in the biologic-naïve population, and statistically significant Probit differences against SEC and GUS in the ITT population were no longer significant in the subgroup of biologic naïve patients. Overall, the impact of prior biologic treatment remains uncertain and appeared to be dependent on the comparator used.

- 6.56 The ESC noted the effect estimates used in the economic model were the most favourable to BKZ across all of the available data sources and considered this was likely to bias in favour of BKZ. Overall, the ESC considered it would be appropriate to use the results from the NMA as the primary source of PASI response estimates for the model, as it was likely to provide the most consistent effect estimates across all bDMARDs.

Time to PASI response and QoL benefit

- 6.57 The model assumed a different time to onset of QoL benefit for each bDMARD, based on when the maximum proportion of PASI 75 responders were reported in the trials. Based on this, patients treated with BKZ were assumed to experience a QoL benefit earlier (at Week 8) than those treated with all other bDMARDs. However, this was also assumed to apply to other PASI responses, including PASI 90 or PASI 100, which were generally slower to attain. Data from the BKZ trials indicated that while maximum PASI 75 response was generally achieved by Week 8 across the trials for BKZ, maximum PASI 90 and PASI 100 were obtained later, at approximately 12 and 24 weeks, respectively. Given BKZ was generally associated with a greater proportion of PASI 90 and PASI 100 responders versus other bDMARDs, this assumption likely favoured BKZ.
- 6.58 Removing the difference in time to QoL benefit (e.g., by assuming all benefits were experienced at 16 weeks) increased the ICER by 35% from the base case. Allowing more time to response (factoring in that a longer time may be needed to obtain a PASI 90 or PASI 100 response) by using PBS initial treatment duration as proxy increased the ICER by 47% from the base case.
- 6.59 The PSCR acknowledged that PASI 90 and PASI 100 accrue later than PASI 75, which therefore assumed patients on BKZ received a QoL benefit earlier than other bDMARDs. The PSCR also argued that this was an effect of the demonstrated superiority of BKZ and stated that a large QoL benefit is accrued in the model between PASI <50 up to PASI 75 and, given other bDMARDs also accrue this benefit (albeit later), little to no bias was expected. The ESC agreed with the evaluation and considered the modelling methodology for time to response was problematic with respect to the application of a constant time to PASI response for PASI 75, PASI 90 and PASI 100, based on the PASI 75 response.
- 6.60 The ESC also noted that the assumed step change in PASI for the whole population did not reflect the data showing a gradual improvement in PASI across the patient population over time. The ESC considered an area under the curve approach capturing time to QoL benefit may have more appropriately captured the gradual PASI improvement associated with a longer time to PASI 90 and PASI 100 health states. The ESC considered that, in the absence of an appropriate methodology, it was appropriate to assume no difference in time to response in the base case.

bDMARD sequence

- 6.61 The submission stated that the selection of PBS listed bDMARDs in the model (except for initial treatment in the BKZ arm, which was set to BKZ) was 'randomly allocated

per patient based on PBS market share of each bDMARD'. This was misleading, while cumulative market share proportions were used as a way to code PBS-listed bDMARDs for selection, treatment selection was based on a random number between 0 and 1 and did not consider market share.

- 6.62 The model did, however, allow users to specify a particular treatment sequence and to support this functionality the submission provided estimates of market share of listed bDMARDs.
- 6.63 The submission's market share estimates were obtained from IQVIA data based on treatment days for PBS-listed bDMARDs. The submission argued it was necessary to use IQVIA data given PBS dispensing data do not capture differences in pack durations of the listed bDMARDs. Although this was a reasonable justification for use of IQVIA data, some differences versus PBS data could not be reconciled, generating uncertainty.
- 6.64 Furthermore, current market share is unlikely to remain as is because listed bDMARDs are experiencing different rates of growth (or decline). PBS data extracted during the evaluation found increasing utilisation of newer biologics such as IXE and RIS, especially RIS, whose utilisation doubled between 2020 and 2021. Declining utilisations were observed for older biologics such as ADA, ETN, IFX and UST, suggesting UST may not be the market leader for much longer.
- 6.65 The ESC noted sensitivity analyses found the ICER to be sensitive to the assumed market share and the resulting order in which bDMARDs are used on the PBS.

Discontinuations

- 6.66 The submission assumed a per-cycle discontinuation rate from bDMARD treatment in the maintenance phase of 15% per annum or 0.62% per 2-weekly cycle, based on NostraData (12 months to September 2021). Minimal detail was provided in the submission on the NostraData analysis. It appeared the analysis may have been based on retail pharmacy sales data, with discontinuation defined as patients who have not taken any drug in the last therapy time period. It was uncertain why NostraData was preferred over PBS data for discontinuation estimates, particularly as NostraData, unlike PBS data, does not completely capture the number of scripts dispensed and appeared to be based on cross-sectional rather than longitudinal estimates. The discontinuation rate was assumed to be the same for BKZ and for all other bDMARDs. The submission did not provide justification for this assumption.
- 6.67 The submission stated that NostraData could not determine the proportion of patients who discontinued due to a reduction in efficacy, which would then contribute to the number of failed bDMARDs each patient is permitted under the PBS criteria. In the model base case, it was assumed that half (50%) of the discontinuations were treatment failures and half (50%) were due to tolerability / general switching. Sensitivity analyses performed during the evaluation found the model was not sensitive to variations in proportion of patients discontinuing due to treatment failure.

Utilities

- 6.68 Health state utilities were based on EQ-5D-3L values from pooled BKZ and certolizumab trials. The submission also reported alternate values from just the BKZ or certolizumab trials, as well as values estimated using two regression equations from the sponsor's clinical trials for certolizumab and values identified in recent NICE evaluations. The ESC noted the ICER was sensitive to alternative utility values. For example, using values from the BKZ trials, the ICER increased by 20% from a base case of \$155,000 to <\$255,000/QALY (corrected base case) to \$155,000 to <\$255,000/QALY.
- 6.69 The ESC noted the utility values in the PASI 90 and PASI 100 health states appeared to be higher than that of the general population and was therefore unsure if the values in these health states were plausible.

Drug Costs

- 6.70 An error was made in the calculation of price per pack for IXE, ADA and ETN which resulted in costs of \$6,842.44, \$1,770.99 and \$4,200.56 being used in the calculation of drug cost per cycle for IXE, ADA and ETN, rather than \$3,421.22, \$885.50 and \$1,050.14, respectively. This was corrected during the evaluation.⁴ With this correction, the ICER increased to \$155,000 to <\$255,000 from the original base case of \$55,000 to <\$75,000 per QALY gained.
- 6.71 The key drivers are summarised in the table below.

⁴ by correctly referencing the DPMQs - setting Row 57 of both 'BKZ Model' and 'No BKZ Model' worksheets to reference Row 80 of 'Inputs AU Pricing' Worksheet

Table 12: Key drivers of the model

Description	Method/Value	Impact Corrected base case: \$■■■■ ¹ /QALY gained.
Source of treatment effectiveness	The model assumed different sources for treatment effects with the most favourable source used for BKZ.	High, favoured BKZ. Using NMA for all treatment effects, increased the ICER to \$■■■■ ¹ /QALY.
Time to PASI response	The model assumed a different time to onset of QoL benefit for each bDMARD, based on time to maximum PASI 75 response in the trials. The model assumed patients treated with BKZ would receive QoL benefit before all other bDMARDs at 8 weeks. In sensitivity analyses, the submission assumed maximum PASI response was achieved at 16 weeks for every bDMARD.	High, favoured BKZ. Assuming maximum PASI response was achieved at 16 weeks for all bDMARDs, increased the ICER to \$■■■■ ¹ /QALY.
Market shares	In the base case of the model, the selection of PBS listed bDMARDs (beyond initial BKZ in the BKZ arm) was randomly allocated. The model did however allow users to specify a particular treatment sequence and to support this functionality, the submission provided estimates of market share of listed bDMARDs. Sensitivity analyses performed during the evaluation found the ICER to be very sensitive to the assumed market share and the resulting order in which bDMARDs are used on the PBS.	High, may or may not favour BKZ. Assuming an alternate order (GUS, SEC, UST, IXE) decreased the ICER to \$■■■■ ² /QALY, whereas assuming earlier use of RIS (given its high growth on PBS) and assuming alternate mechanism of action of subsequent treatments (RIS, UST, SEC and ADA) increased the ICER to \$■■■■ ¹ /QALY.
Utilities	Health state utility was based on EQ-5D-3L values from pooled BKZ and certolizumab trial data. The ICER was sensitive to alternative utility values.	High, may or may not favour BKZ. Assuming utility values identified from the NICE appraisals of IXE, increased the ICER to \$■■■■ ¹ /QALY. While assuming utility values from the NICE appraisal of brodalumab, decreased the ICER to \$■■■■ ³ /QALY.

Source: constructed during the evaluation.

Abbreviations: ADA = adalimumab; BKZ = bimekizumab; ETN = etanercept; GUS = guselkumab; IXE = ixekizumab; RIS = risankizumab; SEC =secukinumab; UST = ustekinumab; bDMARD = biologic disease-modifying anti-rheumatic drug; PASI=psoriasis area and severity index.

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$115,000 to < \$135,000

³ \$95,000 to <\$115,000

Results

- 6.72 Table 13 presents the results of the economic evaluation, including the corrected base case results. However, as all prices used were published prices, these are not a true representation of the cost-effectiveness of BKZ listing on PBS versus status quo.
- 6.73 The ESC noted the PBAC had previously accepted an ICER in the range of \$15,000 - \$45,000 / QALY gained for UST in CPP (ustekinumab PSD, November 2009 PBAC meeting).

Table 13: Results of the economic evaluation (10,000 iterations)

Component	Cost in PBS scenario with BKZ	Cost in PBS scenario without BKZ	Increment
Base Case in Submission			
Costs	\$█	\$173,234	\$█
QALYs	5.388	5.248	0.140
Incremental cost/QALY			\$ ¹
Corrected Base Case			
Costs ^{a, b, c}	\$█	\$150,708	\$█
QALYs	5.388	5.248	0.140
Incremental cost/QALY			\$ ²

Source: Table 3-15, p288 of the submission; constructed during the evaluation.

BKZ = bimekizumab; QALY = quality adjusted life year.

^a IXE DPMQ corrected from \$6,842.22 to \$3,421.22.

^b ADA DPMQ corrected from \$1,770.99 to \$885.50.

^c ETN DPMQ corrected from \$4,200.56 to \$1,050.14.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$155,000 to < \$255,000

6.74 Table 14 presents disaggregated QALYs by health state. Most time in the model was spent in the PASI 100 health state in the scenario with BKZ, and in the PASI 90-100 health state in the scenario without BKZ. The incremental QALYs were driven largely by QALY gain in the PASI 100 health state.

Table 14: Disaggregated summary of QALYs (discounted) included in the economic evaluation (10,000 iterations)

Health state	PBS scenario with BKZ	PBS scenario without BKZ	Incremental QALYs (discounted)	% of total incremental
Baseline	0.356	0.545	-0.189	-135.0%
PASI < 50	0.355	0.611	-0.256	-182.89%
PASI ≥ 50 & < 75	0.086	0.097	-0.011	-7.9%
PASI ≥ 75 & < 90	0.704	1.196	-0.492	-351.4%
PASI ≥ 90 & < 100	1.310	1.448	-0.139	-99.3%
PASI 100	2.578	1.352	1.226	875.7%
Total	5.388	5.248	0.140	100.0%

Source: Table 3-14, p288 of the submission.

6.75 The results of key sensitivity analyses are summarised below.

Table 15: Sensitivity analyses – Corrected Base Case

Analyses	Incremental cost (\$)	Incremental QALY	ICER
Corrected base case ^{a,b,c} – 10,000 iterations		0.140	1
PASI response rates			
Use NMA efficacy data for all bDMARDs including BKZ (#1)		0.126	1
Time to QoL benefit the same for all bDMARDs at 16 weeks (base case: based on time to max PASI 75 response for each bDMARD) (#2)		0.110	1
Time to QoL benefit based on duration of initial PBS treatment for each bDMARD		0.102	2
bDMARDs sequencing			
User-defined order of treatment; according to IQVIA analysis but assuming higher market share for GUS, (GUS, UST, SEC, RIS)		0.129	3
User-defined order of treatment; assuming RIS will be used first (fast growth on PBS) then then trying a different mechanism of action when treatment fails (RIS, UST, SEC, ADA) (#3)		0.101	1
Utilities / QALYs			
BKZ trials as source for utilities (base case BKZ + CTZ) (#4)		0.113	1
SEC NICE evaluation for utilities (base case BKZ + CTZ)		0.144	1
Brodalumab NICE evaluation for utilities (base case BKZ + CTZ)		0.239	3
IXE NICE evaluation for utilities (base case BKZ + CTZ)		0.103	1
Costs			
Health care resource use – 50% reduction in costs (#5)		0.140	1
PASI 100 zero health care resource use		0.140	4
No health care resource costs		0.140	1
Multivariate analysis			
#1 and #2 and #3 and #4		0.051	5
#1 and #2 and #3 and #4 and #5		0.051	5

Source: constructed during the evaluation.

Abbreviations: ADA = adalimumab; BSC = best supportive care; BKZ = bimekizumab; CTZ = certolizumab pegol; ETN = etanercept; GUS = guselkumab; IFX = infliximab; IXE = ixekizumab; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; UST = ustekinumab.

^a IXE DPMQ corrected from \$6,842.22 to \$3,421.22.

^b ADA DPMQ corrected from \$1,770.99 to \$885.50.

^c ETN DPMQ corrected from \$4,200.56 to \$1,050.14.

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$255,000 to < \$355,000

³ \$115,000 to < \$135,000

⁴ \$135,000 to < \$155,000

⁵ \$355,000 to < \$455,000

6.76 The key drivers in the model were: i) the timing of maximum PASI 75 response assumed for each bDMARDs (assumption of different times to QoL benefit in the base case, based on time to maximum proportion of PASI 75 responder in the trials); ii) using user-defined and varying order of bDMARD treatments in the treatment sequence; and iii) utilities.

6.77 In the base case, the model assumed an annual cost of \$ [redacted] for PASI 75 responders and \$ [redacted] for non-responders, based on a previous consideration of dupilumab for atopic dermatitis (Table 13, dupilumab PSD, March 2020 PBAC meeting). The ESC recalled it had considered some elements of this cost may not be plausible (paragraph 6.45, dupilumab PSD, March 2020) and, in particular, the magnitude of phototherapy costs was not reasonable (paragraph 7.15, dupilumab PSD, March 2020 PBAC meeting).

Additionally, the ESC considered it was highly uncertain whether health care resource use and costs would be the same for CPP as for atopic dermatitis and noted that while the same range of services are likely to be needed for both sets of patients, the frequency of use may differ. The ESC noted reducing health care resource costs by 50% increased the ICER to \$155,000 to < \$255,000/ QALY.

- 6.78 The ESC advised the multivariate sensitivity analysis assuming (i) effect estimates from the NMA (ii) the time to QoL benefit was the same for all bDMARDs at 16 weeks (in the absence of a more appropriate methodology, as discussed in 6.59) (iii) BKZ trials as source of utilities and (iv) user-defined order of treatment (RIS, UST, SEC, ADA), should be considered the respecified base case. The ESC noted the revised ICER (based on published prices) was \$355,000 to < \$455,000 / QALY.
- 6.79 The ESC noted a sensitivity analysis using the multivariate analysis outlined in paragraph 6.78 and assuming a 50% reduction in health care resource costs further increased the ICER to \$355,000 to < \$455,000/ QALY.
- 6.80 The PBAC considered that, given the claim of superior effectiveness was not accepted, the economic model was largely uninformative for decision-making. However, in principle, the PBAC agreed with the ESC that numerous assumptions and inputs to the base case model favoured BKZ and the resulting ICER was very high and uncertain.

Drug cost/patient/year: \$ [REDACTED] (maintenance)

- 6.81 Using the requested DPMQ of \$ [REDACTED] per pack of two 160 mg injections, and assuming 15 BKZ packs per patient over the first two years (including both induction and the maintenance treatment phases), the drug cost of BKZ was estimated to be \$ [REDACTED] (over the first two years of treatment). The drug cost of BKZ was estimated to be \$ [REDACTED] for the second year (i.e., during maintenance treatment).

- 6.82 Table 16 summarises drug costs (using published prices) over the first 2 years of treatment comparing BKZ to PBS listed bDMARDs.

Table 16: Two-year costs of BKZ versus comparators (published prices)

Drug	Published DPMQs	Dosing Regimen	Y1 Cost	Y2 Cost	Total 2-year cost
BKZ	\$■	320 mg SC injections (2 injections of 160 mg each) at Weeks 0, 4, 8, 12, 16 and Q8W thereafter	\$■	\$■	\$■
UST	\$3,943.23	45 mg (weight ≤ 100 kg) or 90 mg (weight > 100 kg) SC injection at Weeks 0, 4 and Q12W thereafter	\$19,716 [#]	\$17,087 [#]	\$36,803
SEC	\$1,403.68	300 mg SC injection (2 injections of 150 mg) at Weeks 0,1,2,3,4 then 300 mg monthly	\$22,459	\$18,248	\$40,707
RIS	\$5,400.51	150 mg SC injection (2 injections of 75 mg) at Weeks 0, 4 and Q12W thereafter	\$27,003	\$23,402	\$50,405
GUS	\$3,795.84	100 mg SC injection at Weeks 0, 4 and Q8W thereafter	\$26,571	\$24,673	\$51,244
IXE	\$3,421.22	160 mg SC injection (2 injections of 80 mg) at Week 0, then 80 mg Q2W from Weeks 2 to 12 and Q4W thereafter	\$29,080	\$22,238	\$51,318
TIL	\$3,271.27	100 mg SC injection at Weeks 0, 4 and Q12W thereafter ^l	\$16,356	\$14,176	\$30,532
ADA	\$885.50	80 mg SC injection (2 injections of 40 mg) at Week 0, then 40 mg Q2W starting at Week 1	\$12,176	\$11,512	\$23,687
ETN	\$1,050.14	50 mg SC injection once weekly~	\$13,652~	\$13,652~	\$27,304
IFX	\$320.71	5 mg/kg IV infusion at Weeks 0,2,6, then Q8W thereafter	\$11,133 [^]	\$9,338 [^]	\$20,471

Source: constructed during the evaluation.

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

[#] This costing follows the UST dosing regimen assumed in the Section 3 and Section 4 models in the submission, which assumed all patients are on UST 45 mg.

[^] Excluding wastage, 4.48 vials per dose (7.75 doses Year 1, 6.5 doses Year 2); assumed average weight per patient of 89.587 kg.

~The ETN costing in the Section 3 model followed the higher dosing regimen of 50 mg twice weekly for the first 12 weeks, but the calculation here assumed the standard recommended dose of 50 mg weekly is costed.

Estimated PBS usage & financial implications

6.83 This submission was not considered by DUSC.

6.84 A market share approach was used to estimate the financial implications of the proposed listing. PBS data (September 2020 to August 2021) was used to estimate the number of scripts for listed biologics for severe CPP and to extrapolate future utilisations. The key assumptions in the submission's estimates were:

- ETN, ADA, UST are declining in usage over time,
- SEC, IXE, GUS, TIL, RIS are increasing in usage over time, assuming the same market growth rate;
- BKZ will take market share at the same rate from all included comparators.

It may not be reasonable to assume the same market growth rate for SEC, IXE, GUS, TIL and RIS. For example, TIL had a much lower uptake compared to GUS when coming onto the market. The most recent PBS data also illustrated a difference in rate of growth of different bDMARDs. BKZ may also differentially substitute other listed treatments; for example, it may substitute products with a similar mechanism of action (i.e., other IL-17 inhibitors) more than drugs with a different mechanism of action.

6.85 The submission incorrectly cross-referenced the number of initial and continuing packs for ADA continuing and ETN initial. The errors resulted in an overestimate of

patients treated with BKZ, and increased net cost to the PBS/RPBS. These errors were corrected during the evaluation.

6.86 Table 17 summarises the key inputs in the financial estimates. Table 18 summarises the estimated used and financial implications of BKZ listing.

Table 17: Key inputs for financial estimates

Parameter	Value applied and source	Comment																														
Split of initial and continuing packs for GUS	Initial: 60% in Year 1 decreasing to 10% in Year 6	No explanation for these proportions were provided and the financial estimates were found to be sensitive to this assumption.																														
Market growth (per annum)	<p>ETN, ADA, UST: assumption of declining use: negative 1%</p> <p>SEC, IXE, GUS, TIL, RIS: assumptions based on PBS data. Same market growth assumed to apply to all of SEC, IXE, GUS, TIL, RIS.</p> <table border="1"> <thead> <tr> <th>Year</th> <th>Market Growth</th> </tr> </thead> <tbody> <tr> <td>2021</td> <td>10%</td> </tr> <tr> <td>2022</td> <td>7%</td> </tr> <tr> <td>2023</td> <td>6%</td> </tr> <tr> <td>2024</td> <td>5%</td> </tr> <tr> <td>2025</td> <td>4%</td> </tr> <tr> <td>2026</td> <td>3.5%</td> </tr> </tbody> </table>	Year	Market Growth	2021	10%	2022	7%	2023	6%	2024	5%	2025	4%	2026	3.5%	Assuming identical growth rates for all recently listed bDMARDs (i.e., SEC, IXE, GUS, TIL and RIS) may not be appropriate.																
Year	Market Growth																															
2021	10%																															
2022	7%																															
2023	6%																															
2024	5%																															
2025	4%																															
2026	3.5%																															
BKZ market share (uptake)	<table border="1"> <thead> <tr> <th>Y1</th> <th>Y2</th> <th>Y3</th> <th>Y4</th> <th>Y5</th> <th>Y6</th> </tr> </thead> <tbody> <tr> <td>7.5%</td> <td>15%</td> <td>20%</td> <td>25%</td> <td>30%</td> <td>35%</td> </tr> </tbody> </table>	Y1	Y2	Y3	Y4	Y5	Y6	7.5%	15%	20%	25%	30%	35%	BKZ was assumed to take market share from listed bDMARDs at the same rate. This was in contrast to Section 3 where market share was based instead on IQVIA data on the justification that it takes into account differences in bDMARD pack durations whereas PBS dispensing data do not.																		
Y1	Y2	Y3	Y4	Y5	Y6																											
7.5%	15%	20%	25%	30%	35%																											
Grandfathered patients	Not included	The submission did not specify approximately how many patients would be expected to transition to PBS-subsidised BKZ under the grandfathering clause.																														
Packs (initial per 16 week period, continuing per year)	<table border="1"> <thead> <tr> <th>Drug</th> <th>Initial</th> <th>Continuing</th> </tr> </thead> <tbody> <tr> <td>BKZ</td> <td>5</td> <td>6.5</td> </tr> <tr> <td>UST</td> <td>3</td> <td>4.3</td> </tr> <tr> <td>SEC</td> <td>3.27</td> <td>13</td> </tr> <tr> <td>IXE</td> <td>4.5</td> <td>6.5</td> </tr> <tr> <td>GUS</td> <td>3</td> <td>6.5</td> </tr> <tr> <td>TIL</td> <td>3</td> <td>4.3</td> </tr> <tr> <td>RIS</td> <td>3</td> <td>4.3</td> </tr> <tr> <td>ADA</td> <td>5</td> <td>13</td> </tr> <tr> <td>ETN</td> <td>4</td> <td>13</td> </tr> </tbody> </table> <p>Based on dosing in Product Information leaflets.</p>	Drug	Initial	Continuing	BKZ	5	6.5	UST	3	4.3	SEC	3.27	13	IXE	4.5	6.5	GUS	3	6.5	TIL	3	4.3	RIS	3	4.3	ADA	5	13	ETN	4	13	Some issues identified with the number of initial packs for SEC and ETN which appear to be underestimated.
Drug	Initial	Continuing																														
BKZ	5	6.5																														
UST	3	4.3																														
SEC	3.27	13																														
IXE	4.5	6.5																														
GUS	3	6.5																														
TIL	3	4.3																														
RIS	3	4.3																														
ADA	5	13																														
ETN	4	13																														

Source: constructed during the evaluation.

ADA = adalimumab; BSC = best supportive care; BKZ = bimekizumab; ETN = etanercept; GUS = guselkumab; IFX = infliximab; IXE = ixekizumab; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; UST = ustekinumab.

Table 18: Estimated use and financial implications (using published prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Biologic scripts displaced by BKZ (substitution rate^a to BKZ scripts: initial/continuing)						
UST	-1	-1	-1	-1	-1	-1
SEC	-1	-1	-1	-3	-3	-3
IXE	-1	-1	-1	-1	-1	-1
GUS	-1	-1	-1	-3	-3	-3
TIL	-2	-1	-1	-1	-1	-1
RIS	-2	-1	-1	-1	-1	-1
ADA	-1	-1	-1	-1	-1	-1
ETN	-2	-1	-1	-1	-1	-1
Total net change in scripts	-3	-4	-4	-5	-5	-6
Estimated extent of use (BKZ)						
Number of BKZ scripts dispensed ^b	3	4	4	5	5	6
Estimated financial implications of BKZ						
Cost to PBS/RPBS less copayments (\$)	7	11	13	15	16	16
Estimated financial implications for UST, SEC, IXE, GUS, TIL, RIS, ADA, ETN						
Cost to PBS/RPBS less copayments (\$)	-10	-3	-11	-12	-14	-15
Net financial implications						
Net cost to PBS/RPBS/MBS (\$)	9	10	7	7	7	8

Source: Tables 4-4, 4-11; pp.295-300 of the submission; '3a. Scripts – proposed' and '5. Impact – net' worksheet.

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

^a BKZ substitution rates (initial, continuing) assumed were: UST 1.67, 1.5; SEC 1.53, 0.5; IXE 1.11, 1.0, GUS 1.67, 1.0; TIL 1.67, 1.5; RIS 1.67, 1.5; ADA 1.0 0.5; ETN 1.25, 0.5.

^b Cross-referencing errors were corrected. In the '3a. Scripts – proposed' worksheet, cells J157:K157 the script equivalence numbers for ADA (continuing) incorrectly referred to the numbers for ADA (initial). Similarly, cells J158:K158 the script equivalence numbers for ETN (initial) incorrectly referred to the numbers for ADA (continuing).

The redacted values correspond to the following ranges:

- ¹ 500 to < 5,000
- ² < 500
- ³ 5,000 to < 10,000
- ⁴ 10,000 to < 20,000
- ⁵ 20,000 to < 30,000
- ⁶ 30,000 to < 60,000
- ⁷ \$20 million to < \$30 million
- ⁸ \$30 million to < \$40 million
- ⁹ \$0 to < \$10 million
- ¹⁰ \$10 million to < \$20 million
- ¹¹ \$50 million to < \$60 million
- ¹² \$60 million to < \$70 million
- ¹³ \$70 million to < \$80 million
- ¹⁴ \$80 million to < \$90 million
- ¹⁵ \$90 million to < \$100 million
- ¹⁶ \$100 million to < \$200 million

6.87 The total net cost to the PBS/RPBS of listing BKZ was estimated to be \$30 million to < \$40 million in Year 6, and a total of \$100 million to < \$200 million in the first 6 years of listing, based on published prices.

6.88 The BKZ market may be higher or lower, depending on its uptake within the biologic market. The scripts for BKZ may be higher if BKZ increases the size of the overall BKZ

market. The PSCR and pre-PBAC response acknowledged the listing of BKZ had the potential to grow the market and indicated a willingness to work with the Department to refine the financial estimates.

Financial Management – Risk Sharing Arrangements

- 6.89 The sponsor acknowledged the likelihood of a RSA and stated that they will engage with the Department of Health following a positive recommendation by the PBAC.

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 bimekizumab (BKZ) for the treatment of severe chronic plaque psoriasis (CPP). The PBAC considered that, based on the evidence presented in the submission, BKZ was likely to be superior to adalimumab (ADA), tildrakizumab (TIL) and ustekinumab (UST) and non-inferior to guselkumab (GUS), ixekizumab (IXE), secukinumab (SEC) and risankizumab (RIS) in terms of achieving PASI 75 and PASI 90 responses at 12/16 weeks. The PBAC noted comparisons versus infliximab (INF), one of the more effective treatments for severe CPP, were not presented in the submission. The PBAC further noted the long-term impact of the differences observed in PASI 75 and 90 at 12/16 weeks is unknown. The PBAC recalled that GUS, IXE and RIS were listed for CPP on the basis of cost-minimisation to the least costly alternative bDMARD and, given the PBAC considered BKZ was likely to be non-inferior to these medicines, it was appropriate to list BKZ on the same basis.
- 7.2 The PBAC considered that while the clinical need for an additional treatment for severe CPP was low, the addition of another option which may offer a higher chance of achieving a PASI 90 response compared with some of the alternative bDMARDs, may be useful in particular patients.
- 7.3 The PBAC noted the submission nominated all currently PBS-listed bDMARDs as comparators. The PBAC considered BKZ was more likely to substitute for the recently listed bDMARDs that tended to be the more effective treatment options (i.e., IXE and RIS). However, the PBAC considered all currently PBS-subsidised bDMARDs for CPP were relevant alternative therapies.
- 7.4 The PBAC noted the clinical evidence presented in the submission to support the clinical claim included three direct randomised controlled trials (RCTs) of BKZ versus ADA, UST and SEC and an indirect treatment comparison (ITC) versus RIS, IXE, GUS and TIL with placebo as a common reference. The ITC was further supported in the submission by a network meta-analysis (NMA), however, the PBAC noted there were concerns raised regarding this analysis during the evaluation (refer to paragraph 6.28).
- 7.5 The PBAC noted that there was evidence to suggest BKZ is associated with a statistically significant higher proportion of patients achieving a 75% improvement in psoriasis area and severity index (PASI 75) score at 12/16 weeks compared to ADA,

UST and TIL. However, the PBAC noted there was no statistically significant difference versus SEC based on the direct comparison or versus IXE and GUS based on the ITC. The PBAC noted the ITC resulted in a statistically significant difference versus RIS but noted the difference was relatively small (risk difference 10% with lower 95% confidence interval of 2%).

- 7.6 The PBAC noted there was evidence to suggest BKZ is associated with a statistically significant higher proportion of patients achieving a 90% improvement in psoriasis area and severity index (PASI 90) score at 12/16 weeks compared to ADA, UST and TIL. The PBAC considered that, whilst there was some evidence to suggest BKZ is associated with a statistically significant higher proportion of patients achieving a PASI 90 score compared to SEC, RIS, IXE and GUS at 12/16 weeks, the differences were relatively small (risk difference of 11% for the direct comparison versus SEC and 12 to 15% for the ITC versus RIS, IXE, GUS with lower 95% confidence intervals of 2% to 6%). Further, the PBAC noted that using the odds ratio measure rather than risk difference, BKZ was not statistically significantly superior to RIS, IXE and GUS.
- 7.7 The PBAC noted there was direct evidence to suggest BKZ is associated with a statistically significant higher proportion of patients achieving a 100% improvement in psoriasis area and severity index (PASI 100) score at 12/16 weeks compared to ADA, UST and SEC. The PBAC noted no ITC for the PASI 100 outcome versus GUS, IXE, RIS, and TIL was presented in the submission.
- 7.8 The PBAC considered that, overall, based on the direct and indirect evidence presented in the submission, the claim that BKZ was of superior effectiveness versus ADA, UST and TIL (as measured by PASI 75 and PASI 90) was reasonable but was not supported for IXE, GUS, SEC and RIS. However, the PBAC considered a claim of non-inferior effectiveness for BKZ vs IXE, GUS, SEC and RIS was reasonably supported. The PBAC considered a claim of non-inferior safety compared to all currently PBS-listed bDMARDs was reasonable.
- 7.9 The PBAC noted that based on the post market review undertaken in 2018, the efficacy of the individual agents vary, with IXE and INF generally being more effective (paragraphs 3.26 and 3.27, PMR PSD, April 2018 PBAC meeting). The PBAC noted RIS (the most recently PBS listed bDMARD) was not included in the post market review but it had previously considered that RIS was non-inferior to GUS and IXE and may be superior to ADA, ETA, INF, SEC and TIL (paragraphs 6.33 and 6.34, RIS PSD, July 2019 PBAC meeting). The PBAC noted the data included in this submission did not support a claim of superior effectiveness for BKZ versus GUS, IXE and RIS and no comparison with IFX was presented. The PBAC recalled GUS, IXE and RIS were recommended for CPP on the basis of cost-minimisation to the least costly alternative bDMARD and considered it was appropriate to list BKZ on the same basis. In this regard, the PBAC considered that the economic model presented was largely uninformative for decision-making. Notwithstanding this, the PBAC noted the ICER for the respecified base case was very high at \$355,000 to < \$455,000/ QALY using the published price of comparators and was even higher using effective prices.

- 7.10 The PBAC considered a standard cost minimisation approach with costs over two years was appropriate, consistent with previous approach for bDMARDs. The PBAC considered the equi-effective doses of BKZ and alternative bDMARDs could be derived with reference to the relevant Product Information documents.
- 7.11 The PBAC considered the listing should align with other bDMARD listings for the treatment of CPP, with flow-on changes to the other bDMARD listings to include BKZ in the list of eligible treatments as part of a treatment cycle. The PBAC considered the number of initial repeats should be reduced from 5 to 4, such that the first continuing dose is given in week 24, after the response to treatment has been assessed following the dose in week 16. The PBAC considered it was reasonable to apply a grandfather restriction for the listing of BKZ, which should be reviewed after 12 months, as per standard practice.
- 7.12 The PBAC considered that, given its recommendation was on a cost minimisation basis to the least costly alternative bDMARD, the listing of BKZ on this basis was likely to be cost neutral or modestly cost saving to the PBS, as it may also substitute for more costly bDMARDs. The PBAC considered that, as BKZ would be the tenth bDMARD available on the PBS, the listing was unlikely to accelerate growth in the market.
- 7.13 The PBAC recommended that BKZ should be treated as interchangeable on an individual patient basis with all other bDMARDs currently listed for the treatment of CPP.
- 7.14 The PBAC advised that BKZ is not suitable for prescribing by nurse practitioners, consistent with other bDMARD listings for CPP.
- 7.15 The PBAC recommended that the Early Supply Rule should apply.
- 7.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because bimekizumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over all the PBS-listed bDMARDs, 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.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item/s as follows:

Public Summary Document – March 2022 PBAC Meeting

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Manufacturer	Name and
BIMEKIZUMAB						
160mg/mL injection, 2 x 1 mL syringe	NEW	1	2	4	Bimelx®	UCB Australia Proprietary Limited
160mg/mL injection, 2 x 1 mL pen device	NEW	1	2	4		

Minor amendments based on Benefit Type (guselkumab)

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – In Writing
Administrative Advice: <i>Advices 7606, 7607 and 7608 (standard ‘no increases’ and special pricing arrangement) clauses should apply. Minor amendments to Administrative Advice 27644 should apply (noted at end) and flowed on to other bDMARD listings for severe chronic plaque psoriasis.</i>
Episodicity:
Severity: Severe
Condition: Chronic plaque psoriasis
Indication: Severe chronic plaque psoriasis
Same as RS /ToC with the following differences
Treatment Phase: Initial treatment - Initial 1, Whole body (new patient)
Clinical criteria: <i>Patient must not receive more than 24 weeks of treatment under this restriction.</i>
Prescribing Instructions: Items 26651, 26652, 26653, 26386, 23217, 25769, 23934 and 23935 should apply
Administrative Advice: 26654 and 25744 should apply.
Same as RS 10856/ToC 10742 with the following differences
Treatment Phase: Initial treatment - Initial 2, Whole body (change or re-commencement of treatment after a break in biological medicine of less than 5 years)
Clinical criteria: <i>Patient must not receive more than 24 weeks of treatment under this restriction.</i>
Prescribing Instructions: Items 24057, 22873, 25769, 23934, 23954, 23935 and 23943 should apply
Administrative Advice: 25744 should apply.
Same as RS /ToC with the following differences
Treatment Phase: Initial treatment - Initial 3, Whole body (re-commencement of treatment after a break in biological medicine of more than 5 years)
Clinical criteria: <i>Patient must not receive more than 24 weeks of treatment under this restriction.</i>
Prescribing Instructions: Items 26387, 23957, 25769, 23934 and 23935 should apply
Administrative Advice: 25744 should apply.

Public Summary Document – March 2022 PBAC Meeting

Same as RS /ToC with the following differences						
Treatment Phase: Initial treatment - Initial 1, Face, hand, foot (new patient)						
Clinical criteria:						
<i>Patient must not receive more than 24 weeks of treatment under this restriction.</i>						
Prescribing Instructions: Items 26651, 26652, 26653, 26388, 16804, 24055, 25769, 23934 and 23935 should apply						
Administrative Advice: Items 26654 and 25744 should apply.						
Same as RS /ToC with the following differences						
Treatment Phase: Initial treatment - Initial 2, Face, hand, foot (change or re-commencement of treatment after a break in biological medicine of less than 5 years)						
Clinical criteria:						
<i>Patient must not receive more than 24 weeks of treatment under this restriction.</i>						
Prescribing Instructions: Items 23226, 16804, 22873, 25769, 23934, 23942, 23935 and 23943 should apply						
Administrative Advice: 25744 should apply.						
Same as RS /ToC with the following differences						
Treatment Phase: Initial treatment - Initial 3, Face, hand, foot (re-commencement of treatment after a break in biological medicine of more than 5 years)						
Clinical criteria:						
<i>Patient must not receive more than 24 weeks of treatment under this restriction.</i>						
Prescribing Instructions: Items 26387, 16804, 23948, 25769, 23934, and 23935 should apply						
Administrative Advice: 25744 should apply.						
Same as RS /ToC with the following differences						
Treatment Phase: Initial treatment - Initial 1, Whole body or Face, hand, foot (new patient) or Initial 2, Whole body or Face, hand, foot (change or re-commencement of treatment after a break in biological medicine of less than 5 years) or Initial 3, Whole body or Face, hand, foot (re-commencement of treatment after a break in biological medicine of more than 5 years) - balance of supply						
Clinical criteria:						
<i>The treatment must provide no more than the balance of up to 24 weeks treatment available under the above restrictions.</i>						
Administrative Advice: 25745 should apply.						
Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Manufacturer	Name and
BIMEKIZUMAB						
160mg/mL injection, 2 x 1 mL syringe	NEW	1	2	2	Bimelx®	UCB Australia Proprietary Limited
160mg/mL injection, 2 x 1 mL pen device	NEW	1	2	2		

Notes on continuing restrictions under Benefit Type 49345 (Separate listing required due to difference in proposed repeats)

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Level / Method:

Public Summary Document – March 2022 PBAC Meeting

<input checked="" type="checkbox"/> Authority Required – In Writing
Administrative Advice: Advices 7606, 7607 and 7608 (standard 'no increases' and special pricing arrangement) clauses should apply. Minor amendments to Administrative Advice 27644 should apply (noted at end) and flowed on to other bDMARD listings for severe chronic plaque psoriasis.
Episodicity:
Severity: Severe
Condition: Chronic plaque psoriasis
Indication: Severe chronic plaque psoriasis
Same as RS/ToC
Treatment Phase: Continuing treatment, Whole body
Nil changes to continuing restriction.
Prescribing Instructions: Items 24057, 26389, 26394, 23934, 23935 and 23943 should apply
Administrative Advice: 25744 should apply.
Same as RS /ToC
Treatment Phase: Continuing treatment, Face, hand, foot
Nil changes to continuing restriction.
Prescribing Instructions: Items 23226, 23240, 26387, 23239, 16804, 26394, 23934, 23935 and 23943 should apply
Administrative Advice: 25744 should apply.
Same as RS /ToC
Treatment Phase: Continuing treatment, Whole body or Continuing treatment, Face, hand, foot - balance of supply
Nil changes to continuing balance of supply restriction
Administrative Advice: 25744 should apply.

Grandfather restriction:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Manufacturer	Name and
BIMEKIZUMAB						
160mg/mL injection, 2 x 1 mL syringe	NEW	1	2	2	Bimelx®	UCB Australia Proprietary Limited
160mg/mL injection, 2 x 1 mL pen device	NEW	1	2	2		

Notes on continuing restrictions under Benefit Type 49345 (Separate listing required due to difference in proposed repeats)

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – In Writing
Administrative Advice:

Public Summary Document – March 2022 PBAC Meeting

Advices 7606, 7607 and 7608 (standard 'no increases' and special pricing arrangement) clauses should apply. Minor amendments to Administrative Advice 27644 should apply (noted at end) and flowed on to other bDMARD listings for severe chronic plaque psoriasis.
Episodicity:
Severity: Severe
Condition: Chronic plaque psoriasis
Indication: Severe chronic plaque psoriasis
Same as RS/ToC
Treatment Phase: Initial treatment, Whole body – Grandfather patients
Clinical criteria:
Patient must have a <i>documented</i> severe chronic plaque psoriasis where lesions have been present for at least 6 months from the time of initial diagnosis prior to commencing non-PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have received non-PBS subsidised therapy with this drug for this condition prior to [list date]
AND
Clinical criteria:
Patient must have a <i>documented failure to achieve an adequate response, as demonstrated by a Psoriasis Area and Severity Index (PASI) assessment, to at least 2 of the following 5 treatments prior to commencing non-PBS-subsidised treatment with this drug for this condition:</i> <i>(i) phototherapy (UVB or PUVA) for 3 treatments per week for at least 6 weeks;</i> <i>(ii) methotrexate at a dose of at least 10 mg weekly for at least 6 weeks;</i> <i>(iii) cyclosporin at a dose of at least 2 mg per kg per day for at least 6 weeks;</i> <i>(iv) acitretin at a dose of at least 0.4 mg per kg per day for at least 6 weeks,</i> <i>(v) apremilast at a dose of 30 mg twice a day for at least 6 weeks</i>
AND
Clinical criteria:
Patient must have a <i>documented</i> had a Psoriasis Area and Severity Index (PASI) score of greater than 15 prior to commencing non-PBS subsidised treatment with this drug for this condition
AND
Clinical criteria:
The treatment must be as systemic monotherapy (other than methotrexate)
AND
Clinical criteria:
Patient must not receive more than 24 weeks of treatment under this restriction
AND
Population criteria:
Patient must be aged 18 years or older
Prescribing Instructions: Items 24057, 26389, 26394 should apply.
Insert also: The most recent PASI assessment must be no more than 1 month old at the time of application. A Grandfather patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria. <i>This restriction is only valid for 12 months following [list date].</i>

Public Summary Document – March 2022 PBAC Meeting

	Administrative Advice: 25744 should apply.
	Same as RS /ToC
	Treatment Phase: Initial treatment, Face, hand, foot – Grandfather patients
	Clinical criteria:
	Patient must have a <i>documented</i> severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot where lesions have been present for at least 6 months from the time of initial diagnosis prior to commencing non-PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have received non-PBS subsidised therapy with this drug for this condition prior to [list date]
	AND
	Clinical criteria:
	Patient must have a documented failure to achieve an adequate response, as demonstrated by a Psoriasis Area and Severity Index (PASI) assessment, to at least 2 of the following 5 treatments prior to commencing non-PBS-subsidised treatment with this drug for this condition: (i) phototherapy (UVB or PUVA) for 3 treatments per week for at least 6 weeks; (ii) methotrexate at a dose of at least 10 mg weekly for at least 6 weeks; (iii) cyclosporin at a dose of at least 2 mg per kg per day for at least 6 weeks; (iv) acitretin at a dose of at least 0.4 mg per kg per day for at least 6 weeks, (v) apremilast at a dose of 30 mg twice a day for at least 6 weeks
	AND
	Clinical criteria:
	The treatment must be as systemic monotherapy (other than methotrexate)
	AND
	Clinical criteria:
	Patient must not receive more than 24 weeks of treatment under this restriction
	AND
	Population criteria:
	Patient must be aged 18 years or older
	Prescribing Instructions: Items 24057, 26389, 26394 should apply The most recent PASI assessment must be no more than 1 month old at the time of application. A Grandfather patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria. <i>This restriction is only valid for 12 months following [list date].</i>
	Administrative Advice: Items 25744 should apply.

	Amend the following paragraphs as outlined: [Paragraph 1]: The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological medicines adalimumab, <i>bimekizumab</i> , etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab and ustekinumab for adult patients with severe chronic plaque psoriasis. Therefore, where the term 'biological medicines' appears in notes and restrictions, it refers to
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<p>adalimumab, bimekizumab, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab only.</p> <p>[Paragraph 3]: A patient who received PBS-subsidised adalimumab, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab treatment prior to 1 February 2019 is considered to start their first cycle as of 1 February 2019.</p> <p>[Paragraph 16]: An application for initial treatment will be limited to provide for a maximum of 16 weeks of therapy for adalimumab, etanercept, ixekizumab, and secukinumab, 20 weeks of therapy for guselkumab, 22 weeks of therapy for infliximab, 24 weeks for <i>bimekizumab</i> and 28 weeks of therapy for risankizumab, tildrakizumab and ustekinumab.</p> <p>[Paragraph 17]: It is recommended that a patient is reviewed for response following a minimum of 12 weeks of therapy; or a <i>minimum of 16 weeks for bimekizumab</i>.</p> <p>(4) Swapping therapy., Once initial treatment with the first PBS-subsidised biological medicine is approved, a patient may swap to an alternate biological medicine without having to requalify with respect to the indices of disease severity (i.e. a PASI score of greater than 15), or the prior non-biological therapy requirements, except if the patient has had a break in therapy of more than 5 years who would need to requalify with respect to the indices of disease severity. A patient who is not able to complete a minimum of 12 weeks, or a <i>minimum of 16 weeks for bimekizumab</i>, of an initial treatment course will be deemed to have failed treatment with that biological medicine unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment...</p>

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.