

**5.10 IXEKIZUMAB
INJECTION 80 MG IN 1 ML PRE-FILLED SYRINGE, INJECTION
80 MG IN 1 ML PRE-FILLED PEN,
TALTZ® ELI LILLY**

1 Purpose of Application

- 1.1 Authority Required listing for ixekizumab for treatment of severe chronic plaque psoriasis that is refractory to treatment with non-biological DMARDs.

2 Requested listing

- 2.1 The requested listing was similar to that of ustekinumab (and other bDMARDs including secukinumab, adalimumab, etanercept and infliximab), currently listed for treatment of severe chronic plaque psoriasis. The restriction will be aligned with other bDMARDs for severe chronic plaque psoriasis.
- 2.2 The requested basis for listing in the submission was cost minimisation versus ustekinumab. This was despite the claim of superiority in comparative effectiveness versus ustekinumab. In the pre-PBAC response, the requested basis for listing was changed to cost minimisation versus secukinumab.

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

3 Background

- 3.1 TGA status at time of PBAC meeting: the submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the Request for ACPM's Advice (previously known as the TGA Delegate's Overview) was available.
- 3.2 Ixekizumab has not been considered by the PBAC previously.

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

4 Clinical place for the proposed therapy

- 4.1 Psoriasis is a chronic inflammatory skin disease, with plaque psoriasis being the most common form. The major manifestation is chronic inflammation of the skin characterised by disfiguring, scaling and erythematous plaques that may be painful or pruritic.
- 4.2 Ixekizumab is expected to be used as an alternative to other existing bDMARDs (ustekinumab, secukinumab, adalimumab, etanercept and infliximab). The ESC considered that the high unmet clinical need for treatment in this condition stated by the sponsor (Executive Summary of major submission, p2) was questionable given there are five bDMARDs currently available on the PBS for use in this indication, including secukinumab, which targets the same interleukin cytokine pathway (IL-17A) as ixekizumab. The PBAC agreed with ESC noting the availability of five other bDMARDs listed on the PBS.

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

5 Comparator

- 5.1 In the submission, the nominated comparators were ustekinumab (main comparator) and secukinumab and adalimumab (supplementary comparators). The evaluation considered the nominated comparators were reasonable, however all bDMARDs that are currently PBS-listed for the treatment of psoriasis are relevant alternative therapies. In the PSCR, the sponsor contested that while secukinumab may be an appropriate comparator, the choice of ustekinumab is justified on the basis of ustekinumab being the current market leader as demonstrated in an analysis of the 10% PBS sample [REDACTED]. As the assumptions and methods underpinning this analysis were not provided, the ESC could not verify the conclusions. In the pre-PBAC response, the nominated comparator for the basis of cost-minimisation was changed to secukinumab.
- 5.2 The ESC noted that in the clinician hearing for the secukinumab submission (March 2015 Public Summary Document, 6.2), the clinician presenting at the hearing acknowledged that etanercept's efficacy in the condition appeared to be inferior to other existing bDMARDs. This view was reiterated by the clinician providing expert opinion in Attachment 01 of this submission. Given that ustekinumab was listed on a cost-effectiveness basis versus etanercept, it is not clear that ustekinumab is superior to other bDMARDs. In the absence of demonstrated superior comparative effectiveness or comparative safety of ixekizumab over alternative therapies, there is no basis for ixekizumab to have a cost advantage over the lowest priced bDMARD for an equivalent treatment period.

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 sponsor addressed the choice of comparator and therapeutic relativities of currently listed bDMARDs, and the clinician discussed the burden of disease, unmet clinical need and other matters in response to the Committee's questions. The PBAC considered that the hearing did not add substantively to the evidence presented in the submission, and in the pre-PBAC response.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from one individual via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ixekizumab including reduction in inflammation, pain and mental and physical deterioration, which may enable patients to be a more productive member of the community.

Clinical trials

- 6.3 The submission was based on an indirect comparison of ixekizumab compared with ustekinumab (primary comparison), secukinumab and adalimumab using placebo and/or etanercept as the common reference. Further analyses of ixekizumab compared with infliximab and etanercept were conducted during the evaluation for completeness. The comparisons were based on the trials listed in Table 1.

Table 1: Trials used for the indirect comparison of ixekizumab and comparators

Comparator	Ixekizumab N=3,866	Ustekinumab N=7,212	Secukinumab N=2,403	Adalimumab N=2,291	Infliximab ^a N=1,678	Etanercept ^b N=971
Placebo	UNCOVER-1, UNCOVER-2 UNCOVER-3	PHOENIX 1, PHOENIX 2, PEARL, Igarashi 2012, LOTUS, AMAGINE-2, AMAGINE-3	ERASURE, FEATURE, JUNCTURE, FIXTURE	CHAMPION, REVEAL, Gordon 2006, Asahina 2010, M13-606	SPIRIT, EXPRESS, EXPRESS2, Torii 2010, Yang 2012, Chaudhari 2001	Leonardi 2003, Papp 2005, Gottlieb 2003, van de Kerkhof 2008
Etanercept	UNCOVER-2 UNCOVER-3	ACCEPT	FIXTURE	-	-	-

^a derived from secukinumab Mar 2015 submission (PSD Mar 2015)

^b derived from ustekinumab Nov 2009 submission (PSD Nov 2009)

- 6.4 Details of the trials presented in the submission are provided in Table 2. Only the primary publications for each trial are represented below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Ixekizumab versus placebo		
UNCOVER-1 (IXE ₁)	RHAZ CSR. A multicentre study with a randomized, double-blind, placebo-controlled induction dosing period followed by a randomized maintenance dosing period and a long term extension period to evaluate the efficacy and safety of LY2439821 in patients with moderate-to-severe plaque psoriasis.	RHAZ Clinical Study Report February 2015.

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	Gordon KB, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis.	N Engl J Med 2016;375:345-356
Ixekizumab versus placebo / etanercept		
UNCOVER-2 (IXE ₂)	RHBA CSR. A multicentre, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of LY2439821 to etanercept and placebo in patients with moderate-to-severe plaque psoriasis. Griffiths CE, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): Results from two phase 3 randomised trials. Gordon KB, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis.	RHBA Clinical Study Report February 2015. Lancet 2015;386: 541-551. N Engl J Med 2016;375:345-356.
UNCOVER-3 (IXE ₃)	RHBC CSR. A 12-week multicentre, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of LY2439821 to etanercept and placebo in patients with moderate-to-severe plaque psoriasis with a long-term extension period. Griffiths CE, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): Results from two phase 3 randomised trials. Gordon KB, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis.	RHBC Clinical Study Report January 2015. Lancet 2015;386: 541-551. N Engl J Med 2016;375:345-356.
Ustekinumab versus placebo		
PHOENIX 1 (UST ₂)	Leonardi CL, et al. Efficacy and safety of ustekinumab, human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double blind, placebo-controlled trial (PHOENIX 1).	Lancet 2008;371: 1665-1674.
PHOENIX 2 (UST ₃)	Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double blind, placebo-controlled trial (PHOENIX 2).	Lancet 2008;371: 1675-1684.
PEARL (UST ₄)	Tsai TF, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: A phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL).	J Dermatol Sci 2011; 63: 154-163.
Igarashi 2012 (UST ₅)	Igarashi A, et al. The Japanese Ustekinumab Study Group. Efficacy and safety of ustekinumab in Japanese patients with moderate- to severe plaque-type psoriasis: Long-term results from a phase 2/3 clinical trial.	J Dermatol. 2012; 39: 242-252.
LOTUS (UST ₆)	Zhu X, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS).	J Drugs Dermatol. 2013; 12(2): 166-174.
AMAGINE-2 (UST ₇)	Lebwohl M, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis.	N Engl J Med 2015; 373: 1318-1328.
AMAGINE-3 (UST ₈)		
Ustekinumab versus etanercept		
ACCEPT (UST ₁)	Griffith CE, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis (ACCEPT).	N Engl J Med 2010; 362: 118-128.

Secukinumab versus placebo		
ERASURE (SEC ₁)	Langley RG, et al. Secukinumab in plaque psoriasis: results of two phase three trials. Ohtsuki M, et al. Secukinumab efficacy and safety in Japanese patients with moderate-to-severe plaque psoriasis: Subanalysis from ERASURE, a randomized, placebo-controlled, phase 3 study.	N Engl J Med 2014; 371(4): 326-338. J Dermatol. 2014; 41(12): 1039-1046.
FEATURE (SEC ₃)	Blauvelt A, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE).	Br J Dermatol. 2015; 172: 484-493.
JUNCTURE (SEC ₄)	Paul C, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE).	J Eur Acad Dermatol Venereol 2015; 29: 1082-1090.
Secukinumab versus placebo and etanercept		
FIXTURE (SEC ₂)	Langley RG, et al. Secukinumab in plaque psoriasis: results of two phase three trials.	N Engl J Med 2014; 371(4): 326-338.
Adalimumab versus placebo		
CHAMPION (ADA ₁)	Saurat JH, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION).	Br J Dermatol. 2008; 158(3): 558-566.
REVEAL (ADA ₂)	Menter A, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial.	J Am Acad Dermatol. 2008; 58(1): 106-115.
Gordon 2006 (ADA ₃)	Gordon KB, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study.	J Am Acad Dermatol. 2006; 55(4): 598-606.
Asahina 2010 (ADA ₄)	Asahina A, et al. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a Phase II/III randomized controlled study.	J Dermatol. 2010; 37(4): 299-310.
M13-606 (ADA ₅)	Zhang J, et al. Efficacy and safety of adalimumab in Chinese patients with moderate to severe plaque psoriasis: Results from a phase 3, randomized, placebo-controlled, double-blind study. Zhang J, et al. Efficacy and safety of adalimumab in Chinese patients with moderate to severe plaque psoriasis: Results from a phase 3, randomized, placebo-controlled, double-blind study.	J Am Acad Dermatol. 2015; 72(5): AB 232 (abstract). Poster presented at 73 rd Annual Meeting of the American Academy of Dermatology, San Francisco, CA, 2015.

Source: Table B.2-4, pp 51-53 of the submission.

- 6.5 The submission identified an ongoing head-to-head trial comparing ixekizumab 300 mg and ustekinumab 45 and 90 mg (RHBS, NCT02561806). The primary completion date is July 2016. The submission stated (p48) that “The full clinical study report for Study RHBS will be provided to PBAC upon availability.” The ESC considered that the results of this trial will add to the evidence base, which may assist interpretation of the clinical evidence provided in this submission. In its pre-PBAC response, the sponsor provided the week 12 results of trial RHBS [REDACTED]. The PBAC noted that these data could not be used to inform its current deliberations, however, the sponsor could choose to make a further submission based on the results of this trial.
- 6.6 The key features of the direct randomised trials during the induction phase are summarised in Table 3.

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Ixekizumab versus placebo/etanercept					
IXE ₁ (UNCOVER-1)	1296	R, DB, 2A ^a , 12wks	Low	Moderate to severe; PASI score _≥ 12 AND sPGA _≥ 3 AND BSA _≥ 10%	PASI 75 sPGA (0,1) at 12 weeks
IXE ₂ (UNCOVER-2)	1224	R, DB, 3A ^a , 12wks	Low		
IXE ₃ (UNCOVER-3)	1346	R, DB, 3A ^a , 12 wks	Low		
Meta-analysis	2,701	Included all trials – relevant treatment arms only			
Ustekinumab versus placebo					
UST ₂ (PHOENIX 1)	766	R, DB, 2A ^b , 12 wks	Low	Moderate to severe; PASI score _≥ 12 AND BSA _≥ 10%	PASI 75 at 12 weeks
UST ₃ (PHOENIX 2)	1230	R, DB, 2A ^b , 12 wks	Low		
UST ₄ (PEARL)	121	R, DB, 2 ^{ac} , 12 wks	Low	Moderate to severe; PASI score _≥ 12 AND BSA _≥ 10%; Korean or Taiwanese pts	
UST ₅ (Igarashi 2012)	158	R, DB, 2A ^b , 12 wks	Low	Moderate to severe; PASI score _≥ 12 AND BSA _≥ 10%; Japanese pts	
UST ₆ (LOTUS)	322	R, DB, 2A ^c , 12 wks	Low	Moderate to severe; PASI score _≥ 12 AND BSA _≥ 10%; Chinese pts	
UST ₇ (AMAGINE-2)	1831	R, DB, 3A ^d , 12 wks	Low	Moderate to severe; PASI score _≥ 12 AND sPGA _≥ 3 AND BSA _≥ 10%	PASI 75 sPGA (0,1) at 12 weeks
UST ₈ (AMAGINE-3)	1881	R, DB, 3A ^d , 12 wks	Low		
Meta-analysis	3,834	Included all trials – relevant treatment arms only			
Ustekinumab versus etanercept					
UST ₁ (ACCEPT)	903	R, SB, 2A ^b , 12wks	Low	Moderate to severe; PASI score _≥ 12 AND PGA _≥ 3 AND BSA _≥ 10%	PASI 75 at 12 weeks
Secukinumab versus placebo					
SEC ₁ (ERASURE)	738	R, DB, 2A ^e , 12wks	Low	Moderate to severe; PASI score _≥ 12 AND IGA mod 2011 score _≥ 3 AND BSA _≥ 10%	PASI 75 IGA (0,1) at 12 weeks
SEC ₃ (FEATURE)	177	R, DB, 2A ^e , 12wks	Low		
SEC ₃ (JUNCTURE)	182	R, DB, 2A ^e , 12wks	Low		
Meta-analysis	732	Included all trials – relevant treatment arms only			
Secukinumab versus placebo/etanercept					
SEC ₄ (FIXTURE)	1306	R, DB, 3A ^e , 12wks	Low	Moderate to severe; PASI score _≥ 12 AND IGA mod 2011 score _≥ 3 AND BSA _≥ 10%	PASI 75 IGA (0,1) at 12 weeks
Adalimumab versus placebo					
ADA ₁ (CHAMPION)	271	R, DB, 3A ^f , 16wks	Low	Moderate to severe; PASI score _≥ 10 AND BSA _≥ 10%	PASI 75 at 16 weeks
ADA ₂ (REVEAL)	1,212	R, DB, 2A, 16wks	Low	Moderate to severe; PASI score _≥ 12 AND PGA _≥ 3 AND BSA _≥ 10%	
ADA ₃ (Gordon 2006)	148	R, DB, 2A ^g , 12wks	Low	Moderate to severe; BSA _≥ 5%	PASI 75 at 12 weeks
ADA ₄ (Asahina 2010)	235	R, DB, 2A, 16wks	Low	Moderate to severe; PASI score _≥ 12 AND BSA _≥ 10%; Japanese pts	PASI 75 at 16 weeks
ADA ₅ (M13-606)	425	R, DB, 2A, 12wks	Low	Moderate to severe; PASI score _≥ 10 AND PGA _≥ 3 AND BSA _≥ 10%; Chinese pts	PASI 75 at 12 weeks

Meta-analysis	2,131	Included all trials – relevant treatment arms only
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ADA=adalimumab; A=arm; BSA=body surface area; DB=double blind; IFX=infliximab; IGA=investigator's global assessment; IGA mod 2011=2011 modified investigator's global assessment; IXE=ixekizumab; PASI=psoriasis area and severity index; PGA= physician global assessment; PBO=placebo; ETN=etanercept; R=randomised; SEC=secukinumab, sPGA=static physician global assessment; UST=ustekinumab.

Source: compiled during the evaluation.

- a Two ixekizumab induction dose regimens: 80 mg Q2W and (excluded) 80 mg Q4W
- b Two ustekinumab doses of 45 mg and 90 mg.
- c Ustekinumab 45 mg dose only.
- d Three treatment regimens: (excluded) brodalumab, ustekinumab and placebo.
- e Two secukinumab dose regimens: (excluded) 150 mg and 300 mg.
- f Three treatment regimens: adalimumab, (excluded) methotrexate and placebo.
- g Two adalimumab dose regimens: 40 mg every other week and (excluded) 40 mg per week.

Comparative effectiveness

6.7 The results for PASI 75 response in the controlled, double-blind phase of the direct randomised trials (weeks 10-16) are presented in Table 4.

Table 4: Results of PASI 75 response at the end of the controlled, double-blind phase of the direct randomised trials

Trial ID	Comparison	Test n/N (%)	Control n/N (%)	RD (95% CI)	NNT (95% CI)	RR (95% CI)	OR (95% CI)
Ixekizumab 80 mg# - 12 weeks							
IXE ₁	IXE v PBO	386/433 (89.1)	17/431 (3.9)	0.85 (0.82, 0.89)	1.2 (1.1, 1.2)	22.6 (14.2, 36.1)	200.0 (112.9, 354)
IXE ₂		315/351 (89.7)	4/168 (2.4)	0.87 (0.83, 0.91)	1.1 (1.1, 1.2)	37.7 (14.3, 99.3)	358.8 (125.5, 1025)
IXE ₃		336/385 (87.3)	14/193 (7.3)	0.80 (0.75, 0.85)	1.3 (1.2, 1.3)	12.0 (7.3, 20.0)	87.7 (47.1, 163.2)
Meta-analysis – IXE v PBO				0.84 (0.81, 0.88)	1.2 (1.1, 1.2)	19.9 (11.0, 35.9)	170.9 (81.0, 360.2)
IXE ₂	IXE v	315/351 (89.7)	149/358 (41.6)	0.48 (0.42, 0.54)	2.1 (1.9, 2.4)	2.2 (1.9, 2.5)	12.3 (8.2, 18.4)
IXE ₃	ETN	336/385 (87.3)	204/382 (53.4)	0.34 (0.28, 0.40)	2.9 (2.5, 3.6)	1.6 (1.5, 1.8)	6.0 (4.2, 8.6)
Meta-analysis – IXE v ETN				0.41 (0.27, 0.55)	2.4 (1.8, 3.7)	1.9 (1.4, 2.5)	8.5 (4.2, 17.2)
Ustekinumab 45 mg – 12 weeks							
UST ₂	UST v PBO	171/255 (67.1)	8/255 (3.1)	0.64 (0.57, 0.70)	1.6 (1.4, 1.8)	21.4 (11.0, 42.2)	62.9 (29.7, 133.2)
UST ₃		273/409 (66.7)	15/410 (3.7)	0.63 (0.58, 0.68)	1.6 (1.5, 1.7)	18.2 (11.2, 30.1)	52.9 (30.3, 92.1)
UST ₄		41/61 (67.2)	3/60 (5.0)	0.62 (0.48, 0.74)	1.6 (1.4, 2.1)	13.4 (4.8, 39.6)	39.0 (10.9, 139.8)
UST ₅		38/64 (59.4)	2/31 (6.5)	0.53 (0.35, 0.66)	1.9 (1.5, 2.9)	9.2 (2.8, 33.6)	21.2 (4.7, 96.6)
UST ₆		132/160 (82.5)	18/162 (11.1)	0.71 (0.63, 0.78)	1.4 (1.3, 1.6)	7.4 (4.9, 11.6)	37.7 (19.9, 71.3)
Meta-analysis – UST45 v PBO				0.64 (0.60, 0.69)	1.6 (1.4, 1.7)	13.1 (7.8, 22.0)	46.4 (33.0, 65.4)
UST ₁	UST v ETN	141/209 (67.5)	197/347 (56.8)	0.11 (0.02, 0.19)	9 (5, 50)	1.2 (1.0, 1.4)	1.6 (1.1, 2.3)
Ustekinumab 90 mg – 12 weeks							
UST ₂	UST v PBO	170/256 (66.4)	8/255 (3.1)	0.63 (0.57, 0.69)	1.6 (1.4, 1.8)	21.2 (10.9, 41.8)	61.0 (28.8, 129.3)
UST ₃		311/411 (75.7)	15/410 (3.7)	0.72 (0.67, 0.76)	1.4 (1.3, 1.5)	20.7 (12.7, 34.0)	81.9 (46.7, 143.8)
UST ₅		42/62 (67.7)	2/31 (6.5)	0.61 (0.43, 0.74)	1.6 (1.4, 2.3)	10.5 (3.2, 38.2)	30.5 (6.6, 140.4)
Meta-analysis – UST90 v PBO				0.67 (0.60, 0.74)	1.5 (1.4, 1.7)	19.7 (13.4, 29.0)	68.7 (44.6, 105.7)
UST ₁	UST v ETN	256/347 (73.8)	197/347 (56.8)	0.17 (0.10, 0.24)	5.9 (4.2, 10)	1.3 (1.1, 1.4)	2.1 (1.6, 3.0)
Ustekinumab 45&90 mg (pooled) – 12 weeks							
UST ₂	UST v PBO	341/511 (66.7)	8/255 (3.1)	0.64 (0.59, 0.68)	1.6 (1.5, 1.7)	21.3 (10.7, 42.2)	61.9 (30.0, 128.2)
UST ₃		584/820 (71.2)	15/410 (3.7)	0.68 (0.64, 0.71)	1.5 (1.4, 1.6)	19.5 (11.8, 32.1)	65.2 (38.1, 111.5)
UST ₄		41/61 (67.2)	3/60 (5.0)	0.62 (0.49, 0.75)	1.6 (1.4, 2.1)	13.4 (4.4, 41.1)	39.0 (10.9, 139.8)
UST ₅		80/126 (63.5)	2/31 (6.5)	0.57 (0.45, 0.69)	1.8 (1.5, 2.4)	9.8 (2.6, 37.9)	25.2 (5.8, 110.6)
UST ₆		132/160 (82.5)	18/162 (11.1)	0.71 (0.64, 0.79)	1.4 (1.3, 1.6)	7.4 (4.8, 11.5)	37.7 (19.9, 71.3)
Meta-analysis – UST45&90 v PBO				0.66 (0.62, 0.69)	1.5 (1.4, 1.6)	13.5 (7.7, 23.4)	50.9 (36.4, 71.2)
UST ₁	UST v ETN	397/556 (71.4)	197/347 (56.8)	0.15 (0.08, 0.21)	7 (5, 13)	1.3 (1.1, 1.4)	1.9 (1.4, 2.5)
Ustekinumab Label – 12 weeks							
UST ₇	UST v	210/300 (70.0)	25/309 (8.1)	0.62 (0.56, 0.68)	1.6 (1.5, 1.8)	8.7 (5.9, 12.7)	26.5 (16.4, 42.7)
UST ₈	PBO	217/313 (69.3)	19/315 (6.0)	0.63 (0.58, 0.69)	1.6 (1.4, 1.7)	11.5 (7.4, 17.9)	35.2 (20.9, 59.4)

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Meta-analysis – Ustekinumab Label v PBO			0.63 (0.58, 0.67)	1.6 (1.5, 1.7)	9.8 (7.3, 13.1)	30.2 (21.2, 42.9)	
Secukinumab 300 mg – 12 weeks							
SEC ₁	SEC v PBO	200/245 (81.6)	11/246 (4.5)	0.77 (0.72, 0.83)	1.3 (1.2, 1.4)	18.3 (10.2, 32.6)	95.0 (47.8, 188.5)
SEC ₂		249/323 (77.1)	16/324 (4.9)	0.72 (0.67, 0.77)	1.4 (1.3, 1.5)	15.6 (9.7, 25.3)	64.8 (36.8, 114.0)
SEC ₃		44/59 (74.6)	0/59 (0.0)	0.75 (0.63, 0.86)	1.3 (1.1, 1.5)	89.0 (5.6, ∞)	341.7 (19.9, ∞)
SEC ₄		52/60 (86.7)	2/61 (3.3)	0.83 (0.74, 0.93)	1.2 (1.1, 1.4)	26.4 (6.7, 103.7)	191.8 (39.0, 943.8)
Meta-analysis – SEC v PBO			0.76 (0.72, 0.80)	1.3 (1.3, 1.4)	17.7 (12.4, 25.2)	83.2 (54.9, 126.2)	
SEC ₂	SEC v ETN	249/323 (77.1)	142/323 (44.0)	0.33 (0.26, 0.40)	3 (2, 4)	1.8 (1.5, 2.0)	4.3 (3.1, 6.0)
Adalimumab – 12 (ADA₃, ADA₅) or 16 weeks (ADA₁, ADA₂, ADA₄)							
ADA ₁	ADA v PBO	86/108 (79.6)	10/53 (18.9)	0.61 (0.48, 0.74)	1.6 (1.4, 2.2)	4.2 (2.4, 7.4)	16.8 (7.3, 38.6)
ADA ₂		578/814 (71.0)	26/398 (6.5)	0.64 (0.61, 0.68)	1.6 (1.5, 1.7)	10.9 (7.5, 15.8)	35.0 (22.9, 53.6)
ADA ₃		24/46 (52.2)	2/52 (3.9)	0.48 (0.33, 0.64)	2.1 (1.6, 3.0)	13.6 (3.4, 54.3)	27.3 (5.9, 125.6)
ADA ₄		27/43 (62.8)	2/46 (4.3)	0.58 (0.43, 0.74)	1.4 (1.4, 2.4)	14.4 (3.7, 57.1)	37.1 (7.9, 174.2)
ADA ₅		263/338 (77.8)	10/87 (11.5)	0.66 (0.58, 0.74)	1.5 (1.4, 1.7)	6.8 (3.8, 12.2)	27.0 (13.3, 54.8)
Meta-analysis – ADA v PBO			0.63 (0.58, 0.67)	1.6 (1.5, 1.7)	8.0 (5.0, 12.8)	29.6 (21.5, 40.7)	
Infliximab – 10 weeks							
IFX ₁	IFX v PBO	87/99 (87.9)	3/51 (5.9)	0.82 (0.70, 0.89)	1.2 (1.1, 1.4)	14.9 (5.5, 43.6)	116.0 (31.2, 431.3)
IFX ₂		242/301 (80.4)	2/77 (2.6)	0.78 (0.70, 0.83)	1.3 (1.2, 1.4)	31.0 (8.9, 112.5)	141.5 (33.7, 593.9)
IFX ₃		237/314 (75.5)	4/208 (1.9)	0.74 (0.68, 0.78)	1.4 (1.3, 1.5)	39.5 (15.6, 101)	157.0 (56.5, 436.4)
IFX ₄		24/35 (68.6)	0/19 (0.0)	0.69 (0.49, 0.82)	1.4 (1.2, 2.0)	27.2 (4.0, ∞)	83.1 (4.6, 1500.0)
IFX ₅		68/84 (81.0)	1/45 (2.2)	0.79 (0.67, 0.86)	1.3 (1.2, 1.5)	36.4 (7.0, 206.2)	187.0 (23.9, 1461)
IFX ₆		9/11 (81.8)	2/11 (18.2)	0.64 (0.22, 0.86)	1.6 (1.2, 4.5)	4.5 (1.6, 16.3)	20.3 (1.7, 293.5)
Meta-analysis – IFX v PBO			0.76 (0.73, 0.79)	1.3 (1.3, 1.4)	19.7 (9.1, 42.7)	121.9 (65.5, 266.8)	
Etanercept 50 mg/wk – 12 weeks							
ETN ₁	ETN v PBO	55/162 (34.0)	6/166 (3.6)	0.30 (0.23, 0.38)	3 (3, 4)	9.4 (4.2, 21.2)	13.7 (5.7, 33.0)
ETN ₂		67/196 (34.2)	6/193 (3.1)	0.31 (0.24, 0.38)	3 (3, 4)	11.0 (4.9, 24.8)	16.2 (6.8, 38.4)
ETN ₃		17/57 (29.8)	1/55 (1.8)	0.28 (0.16, 0.40)	4 (3, 6)	16.4 (2.3, 119.1)	23.0 (2.9, 179.7)
ETN ₄		36/96 (37.5)	1/46 (2.2)	0.35 (0.25, 0.46)	3 (2, 3)	17.3 (2.4, 121.9)	27.0 (3.6, 204.4)
Meta-analysis – ETN v PBO			0.31 (0.27, 0.36)	3 (3, 4)	10.9 (6.4, 18.6)	16.1 (9.2, 28.4)	

IXE=ixekizumab, UST=ustekinumab, SEC=secukinumab, ADA=adalimumab, IFX=infliximab; ETN=etanercept; PBO=placebo; RD=risk difference, NNT=number needed to treat, RR=relative risk, OR=odds ratio.

Source: Table B.6-1, pp106-107 of the submission; Table B(i)-1 of Appendix 1, Table B(ii).6-1, p61 of Appendix 2 of the submission; Secukinumab PSD March 2015; Ustekinumab PSD November 2009.

Bold typography indicates statistically significant differences

Risk statistics estimated during the evaluation using RevMan 5.1, NNT calculated during the evaluation as 1/RD. It is acknowledged that NNT should be whole numbers, however given the high response rates there was no delineation between the point estimates and 95% CIs.

This refers to the dosing regimen in the proposed PI (ixekizumab 80 mg Q2W in induction). Results for the additional dosing regimens investigated in the UNCOVER trials (Q4W induction, Q12W maintenance) have not been reported in the submission.

- 6.8 The PSCR stated that the non-significant differences between ixekizumab and ustekinumab in the indirect comparisons using the risk ratio statistic were due to the low placebo response rates which resulted in small variations across trials leading to wide confidence intervals. The ESC considered that the placebo response rates were not uniformly low.
- 6.9 The results indicated that a statistically significantly greater proportion of patients achieved PASI 75 when treated with all bDMARDs at the TGA-approved doses compared with placebo and that a statistically significantly greater proportion of patients achieved PASI 75 when treated with ixekizumab, ustekinumab and secukinumab compared with etanercept 100 mg weekly.
- 6.10 The results of the indirect comparisons, conducted using the Bucher method, are presented in Table 5.

Table 5: Indirect comparisons of ixekizumab versus ustekinumab, secukinumab, adalimumab, infliximab and etanercept using placebo and etanercept (where relevant) as the common reference – PASI 75 response at 12 weeks (or 12/16 weeks for adalimumab and 10 weeks for infliximab)

	Ixekizumab versus					
	PBO as common reference			ETN as common reference		
	RD (95% CI)	RR (95% CI)	OR (95% CI)	RD (95% CI)	RR (95% CI)	OR (95% CI)
Ustekinumab 45 mg	0.20 (0.14, 0.26)	1.5 (0.7, 3.3)	3.7 (1.6, 8.4)	0.30 (0.14, 0.46)	1.6 (1.2, 2.1)	5.4 (2.4, 11.9)
Ustekinumab 90 mg	0.17 (0.09, 0.25)	1.0 (0.5, 2.0)	2.5 (1.1, 5.9)	0.24 (0.08, 0.40)	1.4 (1.1, 1.9)	4.0 (1.8, 8.6)
Ustekinumab 45&90 mg	0.18 (0.13, 0.23)	1.5 (0.7, 3.3)	3.4 (1.5, 7.6)	0.26 (0.11, 0.41)	1.5 (1.1, 2.0)	4.5 (2.1, 9.6)
Ustekinumab Label	0.21 (0.15, 0.27)	2.0 (1.1, 3.9)	5.7 (2.5, 12.9)	-	-	-
Ustekinumab 45 mg (≤100kg) ^a						
Ustekinumab 90 mg (>100kg) ^a						
Secukinumab	0.08 (0.03, 0.13)	1.1 (0.6, 2.2)	2.1 (0.9, 4.8)	0.08 (-0.08, 0.24)	1.1 (0.8, 1.5)	2.0 (0.9, 4.3)
Adalimumab	0.21 (0.15, 0.27)	2.5 (1.2, 5.3)	5.8 (2.6, 13.0)	-	-	-
Infliximab	0.08 (0.03, 0.13)	1.0 (0.4, 2.7)	1.4 (0.5, 3.9)	-	-	-
Etanercept	0.53 (0.47, 0.59)	1.8 (0.8, 4.0)	10.6 (4.2, 27.0)	-	-	-

Source: Table B.6-1, pp.106-107 of the submission; Table B(i)-1 of Appendix 1 of the submission, Table B(ii).6-1, p61 of Appendix 2 of the submission

Abbreviations: PBO=placebo; ETN=etanercept

Bold typography indicates statistically significant differences

^a compared with those ≤ and >100kg treated with ixekizumab, see Table B.6-7 and Table B.6-8, pp. 131-132 of the submission for trial results by weight for ixekizumab and ustekinumab

6.11 The results of the indirect comparisons were inconsistent, depending on whether placebo or etanercept was used as the common reference in the indirect comparison, and depending on which risk statistic was used. The results indicated that:

- A statistically significantly greater proportion of patients in the overall trial populations achieved a PASI 75 response at 12 weeks when treated with ixekizumab compared with:
 - Ustekinumab (45 mg, 90 mg and pooled 45/90 mg) when using etanercept as the common reference for the OR, RR and RD statistics;
 - Ustekinumab (45 mg, 90 mg and pooled 45/90 mg) when using placebo as the common reference for the OR and RD statistics (but not the RR statistic);
 - Ustekinumab Label (dosed according to weight, 45 mg for those ≤100 kg and 90 mg for those >100 kg) when using placebo as the common reference for the OR, RR and RD statistics;
 - Adalimumab for the OR, RR and RD statistics;
 - Infliximab for the RD statistic (but not the OR or RR statistics);
 - Etanercept for the OR and RD statistics (but not the RR statistic). However, a statistically significant difference in all three risk statistics was observed for the head-to-head comparison based on the UNCOVER-2 and -3 trials.
- No statistically significant differences in the proportion of patients achieving PASI 75 at 12 weeks were found between ixekizumab and secukinumab, using etanercept as the common reference, and based on the RR and OR statistics when placebo is used as the common reference. The difference was significant only when placebo is used as the common reference and the RD statistic was used.

- 6.12 The interpretation of these results required consideration that:
- they were derived from indirect comparisons;
 - the etanercept response rates were lower in the ixekizumab trials (47.7%) compared to the ustekinumab trials (56.8%) and may be indicative of exchangeability issues;
 - the placebo response rate in the ustekinumab LOTUS study (UST₆; 11.1%), adalimumab M13-606 (ADA₅; 11.5%) and CHAMPION (ADA₁; 18.9%) studies, and infliximab Chaudhari 2001 study (18.2%), were comparatively higher than the placebo response rates in the other trials (0.0 to 8.1%), and may be indicative of exchangeability issues;
 - the inconsistencies in the results reported for the comparison of ixekizumab versus ustekinumab, and the comparison of ixekizumab versus secukinumab, based on the risk statistic reported and the common reference used;
 - the response rates for ustekinumab were reported at 12 weeks when initial treatment on the PBS is for a maximum of 28 weeks; and
 - the PI for ustekinumab recommends weight based dosing such that those weighing ≤ 100 kg are treated with 45 mg and those >100 kg are treated with 90 mg, dosing which was not represented in six of the eight ustekinumab trials.
- 6.13 Noting potential exchangeability issues and that only short-term comparative outcomes data were available, the PBAC considered that there was no clear evidence that demonstrated that ixekizumab provided a significant improvement in efficacy or reduction of toxicity compared to the alternative bDMARDs.

Comparative harms

- 6.14 There were no significant differences in proportion of patients with infections with ixekizumab compared to placebo in UNCOVER-1 and UNCOVER-2, but a significantly higher proportion with ixekizumab versus placebo in UNCOVER-3. In the UNCOVER trials, significantly more patients had injection site reactions with ixekizumab versus placebo. There were no significant differences in injection site reactions between ixekizumab and etanercept in the UNCOVER trials.
- 6.15 Considering differences across trials in terms of how adverse event data were collected and the definition of “treatment-emergent” adverse events, an indirect comparison of the proportion of patients with at least one treatment emergent adverse event (TEAE), indicated that there were no statistically significant differences between ixekizumab versus ustekinumab (doses pooled), secukinumab and adalimumab, with the exception of ixekizumab compared with ustekinumab 45 mg and ustekinumab 90 mg, where a statistically significantly greater number of events was associated with ixekizumab.
- 6.16 An indirect comparison of injection site reactions (including only three ustekinumab studies reporting proportion of patients with injection site reactions) showed that ixekizumab was associated with statistically significantly more patients with at least one injection site reaction, compared to ustekinumab, secukinumab and adalimumab.
- 6.17 The PSCR presented additional indirect comparisons of ixekizumab versus ustekinumab, secukinumab and adalimumab, for patients reporting at least one TEAE. It showed that when ixekizumab data on TEAEs excluding injection site

reactions were used, only the difference between ixekizumab and ustekinumab 90 mg remained statistically significant. However, the data used for ustekinumab, secukinumab and adalimumab on the proportion of patients with TEAEs included injection site reactions, whereas data used for ixekizumab excluded injection site reactions. Hence, these comparisons may favour ixekizumab over the comparators.

- 6.18 The second round TGA CER recommended that the adverse effects section of the Product Information include a statement relating to the risk of elevated creatine kinase levels in patients being treated with ixekizumab. The TGA evaluator considered that this information will be of particular relevance to patients taking statins.

Benefits/harms

- 6.19 A summary of the comparative benefits and harms for ixekizumab versus ustekinumab, secukinumab and adalimumab, using placebo as the common reference, is presented in Table 6.

Table 6: Summary of comparative benefits and harms for ixekizumab compared with ustekinumab, secukinumab and adalimumab

Trial	IXE	PBO/Comparator	RR (95% CI)	Event rate/100 patients*			RD (95% CI)	
				IXE	PBO/Comparator			
Benefits								
PASI 75: Indirect comparison - results of meta-analyses								
	IXE	PBO	Comp	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					IXE	PBO	Comp	
IXE (All)	1037/1169	35/792	-	19.9 (11.0, 35.9)	89	4	-	0.84 (0.81, 0.88)
UST45 (All)	-	46/918	655/949	13.1 (7.8, 22.0)	-	5	69	0.64 (0.60, 0.69)
UST90 (All)	-	25/696	523/729	19.7 (13.4, 29.0)	-	4	72	0.67 (0.60, 0.74)
UST45/90 pooled (All)	-	46/918	1178/1678	13.5 (7.7, 23.4)	-	5	70	0.66 (0.62, 0.69)
UST Label (All)	-	44/624	427/613	9.8 (7.3, 13.1)	-	7	70	0.63 (0.58, 0.67)
SEC	-	29/690	545/687	17.7 (12.4, 25.2)	-	4	79	0.76 (0.72, 0.80)
ADA	-	50/636	978/1349	8.0 (5.0, 12.8)	-	8	72	0.63 (0.58, 0.67)
Indirect comparisons (placebo as common reference)								
IXE v UST45				1.5 (0.7, 3.3)				0.20 (0.14, 0.26)
IXE v UST90				1.0 (0.5, 2.0)				0.17 (0.09, 0.25)
IXE vs UST 45/90 pooled				1.5 (0.7, 3.3)				0.18 (0.13, 0.23)
IXE vs UST Label				2.0 (1.1, 3.9)				0.21 (0.15, 0.27)
IXE v SEC				1.1 (0.6, 2.2)				0.08 (0.03, 0.13)
IXE v ADA				2.5 (1.2, 5.3)				0.21 (0.15, 0.27)
Proportion patients with ≥1 TEAE: indirect comparison - results of meta-analyses								
	IXE	PBO	Comp	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					IXE	PBO	Comp	
IXE	678/1167	369/791	-	1.25 (1.11, 1.42)	58	47	-	0.12 (0.07, 0.17)
UST45	-	452/918	514/949	1.08 (0.99, 1.18)	-	49	54	0.04 (-0.0, 0.09)
UST90	-	348/697	365/728	0.99 (0.89, 1.10)	-	50	50	-0.0 (-0.06, 0.05)
UST Label	-	317/622	345/613	1.11 (1.00, 1.23)	-	51	56	0.05 (-0.0, 0.11)
SEC	-	340/694	388/690	1.15 (1.04, 1.27)	-	49	56	0.07 (0.02, 0.13)
ADA	-	372/636	810/1347	1.04 (0.95, 1.15)	-	58	60	0.04 (-0.01, 0.09)
Indirect comparisons								
IXE v UST45				1.16 (1.00, 1.35)				0.08 (0.01, 0.15)
IXE v UST90				1.26 (1.07, 1.49)				0.12 (0.05, 0.19)
IXE v UST Label				1.13 (0.96, 1.32)				0.07 (-0.00, 0.14)
IXE v SEC				1.09 (0.93, 1.27)				0.05 (-0.02, 0.12)
IXE v ADA				1.20 (1.03, 1.41)				0.08 (0.01, 0.15)

Abbreviations: PBO = placebo; RD = risk difference; RR = risk ratio

Bold typography indicates statistically significant differences

Source: Compiled during the evaluation.

Clinical claim

6.20 The submission claimed that ixekizumab:

- Was superior to ustekinumab in comparative effectiveness and equivalent in comparative safety. The claim was possibly supported by the indirect comparison at 12 weeks (however the claim was not supported by all analyses with inconsistent results depending on the common reference used and the risk statistic considered). Moreover, given ustekinumab effectiveness at 12 weeks was primarily assessed, it is unclear whether the incremental difference estimated will be maintained over the long-term. The PBAC has previously expressed (adalimumab March 2009 PSD) that in the absence of long term data there is no reason to assume superiority would be maintained in the long term. There were limited comparative safety data presented in the submission to support a claim of

equivalent safety. The data presented indicate that the incidence of treatment-emergent adverse events may be greater with ixekizumab.

- Was at least non-inferior in terms of comparative efficacy and equivalent in terms of comparative safety over secukinumab. The efficacy claim may be reasonably supported by the data presented over 12 weeks. There was limited comparative safety data in the submission to support a claim of equivalent safety.
- Was superior to adalimumab in comparative effectiveness and equivalent in comparative safety. The claim was possibly supported by the indirect comparison at 12 (or 16) weeks but the PBAC has previously expressed (adalimumab March 2009 PSD) that in the absence of long term data there is no reason to assume superiority would be maintained in the long term. The ESC considered that there were limited comparative safety data presented in the submission to support a claim of equivalent safety. Only the indirect comparison with adalimumab produced consistently statistically significant results across the RD, RR and OR statistics. It may be the only indirect comparison upon which a conclusion on comparative clinical efficacy can be drawn.

- 6.21 The PBAC considered that there was limited evidence that any one bDMARD is superior to another bDMARD. The PBAC considered that based on the results of indirect comparisons presented by the submission it is reasonable to conclude that ixekizumab is of non-inferior comparative effectiveness and safety to the currently listed bDMARDs.

Economic analysis

- 6.22 A cost minimisation analysis versus ustekinumab over 48 weeks of maintenance treatment was presented in the submission. Ustekinumab was listed on the basis of acceptable cost-effectiveness versus etanercept, whereas all other bDMARDs have been cost-minimised to each other, with the exception of infliximab (listed on the basis of acceptable cost-effectiveness versus etanercept [and efalizumab]), and are associated with lower drug costs. Cost minimisation analyses versus secukinumab, adalimumab, etanercept and infliximab were also conducted during the evaluation. The ESC noted that ustekinumab is not the least expensive alternative therapy. The ESC further noted that the PBAC could only recommend a higher price for ixekizumab if it is satisfied that it provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapies. The alternative therapies in this case include adalimumab, secukinumab, etanercept and infliximab. The ESC considered that given inconsistent results from the indirect comparisons, cost minimisation with the highest priced comparator (ustekinumab) was not justified.

- 6.23 In the pre-PBAC response, the nominated comparator for the basis of cost-minimisation was changed to secukinumab.

Drug cost/patient

- 6.24 At the requested DPMQ for ixekizumab and using the current (April 2016) ustekinumab, secukinumab and adalimumab prices, the drug cost per patient is presented in Table 7.

Table 7: Drug cost per patient

	Initiation	12 months of maintenance
Ixekizumab	\$ [redacted] (4 scripts at \$ [redacted] ^a /script)	\$ [redacted] (6.5 scripts at \$ [redacted] ^a /script)
Ustekinumab 45 mg	\$ [redacted] (3 scripts at \$ [redacted] ^b /script)	\$ [redacted] (4 scripts at \$ [redacted] ^b /script)
Secukinumab	\$12,344.92 (7 scripts at \$1,763.56/script)	\$22,926 (13 scripts at \$1,763.56/script)
Adalimumab	\$8,396.05 (5 scripts at \$1,679.21/script)	\$21,830 (13 scripts at \$1,679.21/script)

^a DPMQ requested by the submission of \$ [redacted] was based on a cost-minimisation versus the ustekinumab DPMQ prior to 1 April 2016. As of 1 April 2016, a 5% price reduction was applied to ustekinumab; based on the current ustekinumab DPMQ, the DPMQ for ixekizumab is \$ [redacted].

^b The weighted average price (DPMQ) per dose for ustekinumab ($\blacksquare\% \leq 100 \text{ kg} : \blacksquare\% > 100 \text{ kg}$) is estimated as $(\blacksquare\% \times \$ [redacted]) + (\blacksquare\% \times \$ [redacted]) = \$ [redacted]$.

Estimated PBS usage & financial implications

6.25 This submission was not considered by DUSC. The submission used a market share approach to estimate PBS usage and the overall financial impact as presented in Table 8, relying primarily on PBS data. The submission requested grandfathering of patients in the ongoing ixekizumab trial (estimate of up to [redacted] patients over the first two years of PBS listing). The estimated financial implications do not take into account the grandfathered patients.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Market share	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Scripts ^a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost to MBS	-\$ [redacted]	-\$ [redacted]	-\$ [redacted]	-\$ [redacted]	-\$ [redacted]
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

^a Assuming 4 scripts in initiation and 6.5 scripts per year in maintenance as estimated by the submission. Source: Table E.2-1, pp246-247; Table E.2-3, p249; Table E.3-1, p250 of the submission.

The redacted table shows that at year 5, the estimated number of scripts would be less than 10,000 per year, and the net cost to the PBS/RPBS/MBS would be less than \$10 million per year.

6.26 The submission's estimates of the financial impact may not be reasonable as:

- ABS data on weight for the Australian population suggest a much lower proportion of patients weighing >100 kg, and hence a lower proportion would be treated with ustekinumab 90 mg. The PSCR argued that based on the observation of [redacted] vials of ustekinumab per prescription dispensed, [redacted]% of patients prescribed ustekinumab weighed >100 kg. Given the uncertainty in the methods underpinning the [redacted] analysis, the potential for increasing ustekinumab dosing to every eight weeks, and the distribution of BMI from the Australian psoriasis registry provided in the sponsors response the second round CER report (Table 3.2 CER pp 183), the ESC considered that the proportion of psoriasis patients weighing >100 kg was likely to be less than [redacted]%.

Financial Management – Risk Sharing Arrangements

- 6.27 The sponsor indicated it is willing to enter into a special pricing arrangement as exists for the comparators. No further information was provided.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

7 PBAC Outcome

- 7.1 The PBAC recommended an Authority Required listing of ixekizumab for the treatment of severe chronic plaque psoriasis that is refractory to treatment with non-biological DMARDs.
- 7.2 The PBAC accepted that the clinical place for therapy of ixekizumab would be as an alternative treatment option to the currently PBS listed bDMARDs. The PBAC noted the availability of five alternative bDMARDs listed on the PBS for the treatment of severe chronic plaque psoriasis and concluded that it was uncertain how ixekizumab addressed a clinical need that was not provided by another bDMARD.
- 7.3 The PBAC noted that in the sponsor’s pre-PBAC response, the nominated comparator was changed (from ustekinumab in the submission) to secukinumab. The PBAC considered that any of the currently PBS listed bDMARDs could be an appropriate comparator, and that in the absence of demonstrated superior comparative effectiveness or safety over the alternative bDMARDs, ixekizumab should be cost-minimised to the least costly bDMARD.
- 7.4 The equi-effective doses of ixekizumab (initial dose 160 mg, then 80 mg fortnightly from weeks 2 to 12, then 80 mg every 4 weeks) and each of the less costly bDMARDs (i.e. excluding infliximab and ustekinumab) are presented in Table 9.

Table 9: Equi-effective doses of less costly bDMARDs (based on PBS prices at 1 July 2016)

Drug	Dosage (subcutaneous)
Adalimumab	Initial dose 80 mg, then 40 mg fortnightly, starting one week after the initial dose.
Etanercept	50 mg per week, once weekly (single 50 mg injection) or twice weekly (single 25 mg injections three to four days apart).
Secukinumab	300 mg with initial dosing at weeks 0, 1, 2, and 3, then maintenance dosing of 300 mg every 4 weeks starting at week 4.

- 7.5 The PBAC did not accept the submission’s claim that ixekizumab was superior in terms of comparative effectiveness and equivalent in comparative safety over ustekinumab and adalimumab. Noting potential exchangeability issues, and that only short-term comparative outcomes were available, the PBAC considered that there was no clear evidence that demonstrated that ixekizumab provided a significant improvement in efficacy or reduction of toxicity compared to the alternative bDMARDs.

- 7.6 The PBAC noted that the number of prescriptions for chronic plaque psoriasis was highest for adalimumab, and that the number of prescriptions of secukinumab was rapidly increasing. The PBAC also noted that the total number of patients being treated with bDMARDs for chronic plaque psoriasis was higher than anticipated.
- 7.7 The PBAC recommended that ixekizumab should be treated as interchangeable on an individual patient basis with adalimumab, etanercept and secukinumab, according to s101(3BA) advice.
- 7.8 The PBAC advised that ixekizumab is not suitable for prescribing by nurse practitioners.
- 7.9 The PBAC recommended that the Early Supply Rule should apply for continuing therapy only.
- 7.10 The PBAC noted that this submission is not eligible for an Independent Review, as the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item:
Restriction to be finalised

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.