

**6.07 SECUKINUMAB,
150 mg/1 mL pre-filled pen,
Cosentyx[®],
Novartis Pharmaceuticals Australia Pty Ltd.**

1 Purpose of Application

1.1 To request an Authority Required listing for secukinumab for treatment of ankylosing spondylitis.

2 Requested listing

2.1 The requested listing was similar to that of anti-TNF α bDMARDs adalimumab, etanercept, golimumab, infliximab and certolizumab, currently listed for treatment of ankylosing spondylitis.

Initial treatment

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max Qty (units)	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SECUKINUMAB Injections, 150 mg in 1 mL pre-filled pen, 1	5	1	0	\$ [REDACTED]	Cosentyx Novartis Pharmaceuticals
SECUKINUMAB Injections, 150 mg in 1 mL pre-filled pen, 1	1	1	1	\$ [REDACTED]	Cosentyx Novartis Pharmaceuticals

Continuing treatment

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max Qty (units)	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SECUKINUMAB Injections, 150 mg in 1 mL pre-filled pen, 1	1	1	5	\$ [REDACTED]	Cosentyx Novartis Pharmaceuticals

2.2 The requested basis for listing was a cost-minimisation analysis versus adalimumab.

2.3 The PSCR confirmed that the submission was only seeking the listing of 1 x 150mg pack for ankylosing spondylitis.

2.4 The PSCR confirmed that the patient would get 8 weeks of treatment (equivalent to 5 units) under the initial 1 or 2 treatment restrictions and the remaining two doses were under the initial 1 or 2 “balance of supply” restriction. The PSCR also agreed with the Secretariat’s suggestion of telephone Authority for the balance of supply.

- 2.5 The PSCR specified that the patient must be treated by a rheumatologist.
- 2.6 The PSCR requested a grandfather restriction for secukinumab with the same wording as that for adalimumab, etanercept, infliximab and certolizumab.

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

3 Background

- 3.1 TGA status at time of PBAC consideration: The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Delegate's Overview was available.
- 3.2 Secukinumab has not been considered by PBAC previously for this indication. A submission seeking listing of secukinumab for use in psoriatic arthritis will also be considered at the March 2016 PBAC meeting (Item 6.08 refers).
- 3.3 Secukinumab was considered and recommended for listing on a cost-minimisation basis with adalimumab at the March 2015 PBAC meeting for the treatment of severe chronic plaque psoriasis.

4 Clinical place for the proposed therapy

- 4.1 Ankylosing spondylitis is a form of progressive axial spondyloarthritis caused by chronic inflammation and enthesitis (inflammation of soft tissues like muscles, tendons or ligaments where these enter into the bones) involving the spine and the peripheral joints.
- 4.2 Secukinumab is proposed to be an alternative to the currently PBS-listed bDMARDs (adalimumab, etanercept, golimumab, infliximab and certolizumab) for ankylosing spondylitis.

5 Comparator

- 5.1 Adalimumab (main comparator); etanercept, golimumab, infliximab, certolizumab (secondary comparators). The PBAC considered that these were appropriate comparators.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on five indirect comparisons constructed from 12 placebo-controlled trials including one placebo-controlled trial of secukinumab (n=253) and;

- adalimumab – 2 trials comparing adalimumab and placebo (n=659);
- etanercept – 4 trials comparing etanercept and placebo (n=799);
- golimumab – 2 trials comparing golimumab and placebo (n=569);
- infliximab – 2 trials comparing infliximab and placebo (n=349);
- certolizumab – 1 trial comparing certolizumab and placebo (n=325).
- in addition a sixth indirect comparison was constructed between secukinumab and a meta-analysed pooled group of all bDMARDs

The exclusion of two trials (Canadian-AS (adalimumab versus placebo); Barkham 2010 (etanercept versus placebo)) was deemed inappropriate during the evaluation and has been included in the Commentary.

6.4 Details of the trials presented in the submission are provided in Table 1.

Table 1: Trials and associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Secukinumab versus placebo		
MEASURE 2	CSR 2310. A randomized, double-blind, placebo-controlled phase III multicentre study of subcutaneous secukinumab in prefilled syringes to demonstrate the efficacy at 16 weeks and to assess the long-term efficacy, safety and tolerability up to 5 years in patients with active ankylosing spondylitis.	Clinical Study Report CSR 2310. November 2014.
Adalimumab versus placebo		
Huang 2014	Huang F, et al. Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: results of a randomised, controlled trial.	Annals of the Rheumatic Diseases, 2014; 73: 587-594.
Van der Heijde 2006a (ATLAS)	Van der Heijde D, Kivitz A, Schiff M, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: Results of a multicenter, randomized, double-blind, placebo-controlled trial.	Arthritis & Rheumatism, 2006; 54(7):2136-2146.
Lambert 2007 (Canadian-AS)	Lambert R, Salonen D, Rahman P, et al. Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis.	Arthritis & Rheumatism, 2007; 56(12):4005-4014.
Maksymowych 2008 (Canadian-AS)	Maksymowych WP, Rahman P, Shojania K, et al. Beneficial effects of adalimumab on biomarkers reflecting structural damage in patients with ankylosing spondylitis	Journal of Rheumatology, 2008; 35(10):2030-2037.
Etanercept versus placebo		
Calin 2004	Calin A, Dijkmans B, Emery P, et al. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis.	Annals of the Rheumatic Diseases, 2004; 63(12):1594-1600.
Davis 2003	Davis Jr JC, van der Heijde D, Braun J, Dougados M, Cush J, Clegg DO et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: A	Arthritis & Rheumatism, 2003; 48(11): 3230-6.

Public Summary Document – March 2016 PBAC Meeting

Trial	Protocol title/ Publication title	Publication citation
	randomised, controlled trial.	
Dougados 2011 (SPINE)	Dougados M, et al. Efficacy of etanercept on rheumatic signs and pulmonary function tests in advanced ankylosing spondylitis: results of a randomised double-blind placebo-controlled study (SPINE)	Annals of the Rheumatic Diseases, 2011; 70:799–804.
Van der Heijde 2006b	Van der Heijde D, Da Silva J, Dougados M, et al. Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis.	Annals of the Rheumatic Diseases, 2006; 65:1572-1577.
Barkham 2010	Barkham N, Coates LC, Keen H, Hensor E, Fraser A, Redmond A, Cawkwell L, Emery P. Double-blind placebo-controlled trial of etanercept in the prevention of work disability in ankylosing spondylitis.	Annals of the Rheumatic Diseases 2010; 69(11):1926-1928.
Golimumab versus placebo		
Bao 2014	Bao C, et al. Safety and efficacy of golimumab in Chinese Patients with Active Ankylosing Spondylitis: 1-year results from a multicentre, randomized, double-blind, placebo-controlled Phase III trial. Bao C, et al. Golimumab Administered Subcutaneously Every 4 Weeks in Chinese Patients with Active Ankylosing Spondylitis: Week 24 Safety and Efficacy Results From a Randomized, Placebo-Controlled Study	Rheumatology, 2014; 53(9): 1654-1663. Arthritis and Rheumatism 2012; 64 SUPPL. 10 (S589)
Inman 2008 (GO-RAISE)	Inman RD, Davis J, Van Der Heijde D, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: Results of a randomised, double-blind, placebo-controlled, phase III trial.	Arthritis and Rheumatism, 2008; 58(11):3402-3412.
Infliximab versus placebo		
Braun 2002	Braun J, Brandt J, Listing J, Zink A, Alten R, Golder W et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multi-centre trial.	Lancet, 2002; 359(9313): 1187-93.
Van der Heijde 2005 (ASSERT)	Van Der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: Results of a randomized, placebo-controlled trial (ASSERT).	Arthritis and Rheumatism, 2005; 52:582-591.
Certolizumab versus placebo		
Landewe 2014	Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled phase 3 study.	Annals of Rheumatic Disease, 2014; 73: 39-47.

Source: Tables 8-9, pp31-36 of the submission.

6.5 The key features of the randomised trials are summarised in Table 2.

Table 2: Key features of the included evidence – indirect comparison

Trial	N	Design / duration	Bias risk	Patient population	Outcome(s)	Previously considered by PBAC
SEC v PBO						
MEASURE 2	253	R, DB, 3A, 52wk ^a	Low	AS; TNF α naïve and experienced	1°: ASAS20 wk16 2°: BASDAI50 wk16	No
ADA v PBO						
Canadian-AS	82	R, DB, 2A ESC, 24wk	Low	AS; TNF α naïve	1°: ASAS20 wk12	ADA (Nov 06) GOL (Mar 10)

Public Summary Document – March 2016 PBAC Meeting

Van der Heijde 2006a (ATLAS)	315	R, DB, 2A ESC, 24wk	Low	AS; TNFα naïve	1°: ASAS20 wk12 2°: BASDAI50 wk12	CZP (Mar 14)
Huang 2014	344	R, DB, 2A, 24wk	Low	AS; TNFα naïve	1°: ASAS20 wk12 2°: BASDAI50 wk12	CZP (Mar14)
ETC v PBO						
Davis 2003	277	R, DB, 2A, 24wk	Low	AS; TNFα naïve	1°: ASAS20 wk12	ETC (Jul 04) ADA (Nov 06)
Calin 2004	84	R, DB, 2A, 12wk	Low	AS; TNFα naïve	1°: ASAS20 wk12	GOL (Mar 10) CZP (Mar 14)
Van der Heijde 2006b (Wyeth study)	356	R, DB, 3A, 12wk	Low	AS; TNFα naïve	1°: ASAS20 wk12 2°: BASDAI50 wk12	GOL (Mar 10) CZP (Mar 14)
Barkham 2010	40	R, DB, 2A, 12wk	Low	AS; TNFα naïve	1°: AS-WIS wk 12 2°: BASDAI50 wk12	CZP (Mar 14)
Dougados 2011 (SPINE)	82	R, DB, 2A, 12wk	Low	AS; TNFα naïve	1°: BASDAI ^e wk12 2°: ASAS20 wk12	CZP (Mar 14)
GOL v PBO						
Inman 2008 (GO RAISE)	356	R, DB, 3A ESC, 24wk	Low	AS; TNFα naïve	1°: ASAS20 wk14 2°: BASDAI50 wk14	GOL (Mar 10) CZP (Mar 14)
Bao 2014	213	R, DB, 2A ESC, 48wk	Low	AS; TNFα naïve	1°: ASAS20 wk14	No ^b
INF v PBO						
Braun 2002	70	R, DB, 2A, 12wk	Low	AS; TNFα naïve	1°: BASDAI50 wk12	INF (Dec 03) ETC (Jul 04) GOL (Mar 10) CZP (Mar 14)
Van der Heijde 2005 (ASSERT)	279	R, DB, 2A, 24wk	Low	AS; TNFα naïve	1°: ASAS20 wk24 2°: BASDAI50 wk24	GOL (Mar 10) CZP (Mar 14)
CZP v PBO						
Landewe 2014	325 ^c	R, DB, 3A ESC, 204wk ^d	Low/ Unclear	axSpA; TNFα naïve and experienced	1°: ASAS20 wk12 2°: BASDAI50 wk12	CZP (Mar 14)

Abbreviations: ADA=adalimumab; ETC=etanercept; CZP=certolizumab; GOL=golimumab; INF=infliximab; PBO=placebo; SEC=secukinumab; DB=double blind; R=randomised; A=arm; ESC=escape regimen (for placebo); AS=ankylosing spondylitis; axSpA=axial spondyloarthritis; TNFα=tumour necrosis factor alpha (inhibitor); AS-WIS = Ankylosing Spondylitis Work Instability Scale.

- ^a At Week 16, placebo patients were re-randomised to receive active treatment. This trial is still continuing, but safety data for 52 weeks are included. 52 weeks of blinded treatment and 4 years of additional long-term treatment.
- ^b The abstract of this study (Bao 2012) was considered by the PBAC at the March 2014 meeting (certolizumab March 2014 PSD).
- ^c n=178 for AS subgroup.
- ^d The trial was placebo-controlled to week 24, dose-blind to week 48 and is open label to week 204.
- ^e Primary outcome was normalised net incremental AUC for the BASDAI.

Source: compiled during the evaluation.

Comparative effectiveness

6.6 The results for ASAS20 response (Ankylosing Spondylitis Assessment Study group minimum 20% improvement) in the controlled, double-blind phase of the randomised trials at week 12 (week 14 for golimumab trials) are presented in Table 3.

Table 3: Results of the indirect comparisons - ASAS20 response at Week 12 (Week 14 for golimumab trials) – FAS (or the AS sub-group in Landewe 2014) and the αTNF-naïve population in MEASURE 2

Tx	Trial	Drug n/N (%)	PBO n/N (%)	RR (95% CI)	Indirect comparison RR (95% CI) ^a	
					All	αTNF-naïve
SEC	MEASURE 2 (all)	████ (██)	████ (██)	████ (██, ███)	-	-
	MEASURE 2 (αTNF-naïve)	████ (██)	████ (██)	████ (██, ███)	-	-
ADA	Canadian-AS	18/38 (47.4)	12/44 (27.3)	1.74 (0.97, 3.13)	0.91 (0.57, 1.47)	1.04 (0.58, 1.84)
	Van der Heijde 2006a (ATLAS)	154/229 (67.2)	35/115 (30.4)	2.21 (1.65, 2.96)		
	Huang 2014	121/208 (58.2)	22/107 (20.6)	2.83 (1.92, 4.18)		
	Meta-analysis ^d			2.31 (1.85, 2.88)		
ETC25	Davis 2003	82/138 (59.4)	39/139 (28.1)	2.12 (1.57, 2.86)	1.01 (0.63, 1.63)	1.14 (0.64, 2.04)
	Calin 2004	26/45 (57.8)	9/39 (23.1)	2.50 (1.34, 4.68)		
	Van der Heijde 2006b	107/150 (71.3)	19/51 (37.3)	1.91 (1.32, 2.77)		
	Meta-analysis ^d			2.09 (1.68, 2.60)		
ETC50	Van der Heijde 2006b	115/155 (74.2)	19/51 (37.3)	1.99 (1.38, 2.88)	1.07 (0.64, 1.78)	1.21 (0.66, 2.22)
	Dougados 2011 (SPINE)	25/39 (64.1)	14/43 (32.6)	1.97 (1.21, 3.21)		
	Meta-analysis ^d			1.98 (1.48, 2.66)		
GOL ^b	Inman 2008 (GO RAISE)	82/138 (59.4)	17/78 (21.8)	2.73 (1.75, 4.24)	0.93 (0.55, 1.57)	1.05 (0.57, 1.95)
	Bao 2014	53/108 (49.1)	26/105 (24.8)	1.98 (1.35, 2.91)		
	Meta-analysis ^d			2.28 (1.67, 3.12)		
CZP	Landewe 2014 ^c (AS sub-group)	73/121 (60.3)	21/57 (36.8)	1.64 (1.13, 2.37)	1.29 (0.73, 2.26)	1.46 (0.76, 2.79)
Meta-analysis of all comparator bDMARDs ^d				2.11 (1.88, 2.37)	1.00 (0.65, 1.55)	1.13 (0.66, 1.96)

Source: constructed during the evaluation.

^a secukinumab versus the meta-analysis (where relevant) for the comparators

^b measured at week 14

^c includes 200 mg Q2W and 400 mg Q4W

^d using a random effects model

6.7 The ESC noted that the sponsor-nominated a priori non-inferiority limit of 0.43 on the RR for the ASAS20 was based on the March 2014 certolizumab Public Summary Document, which quantified the effect of certolizumab on a 20% improvement in ASAS20 relative to placebo. The ESC also states that as per the report, CZP would be considered non-inferior to other treatments if the 95% CI of the RR in the ASAS20 response included 1.00 and lower CI margin was > 0.43.

- 6.8 The results indicated that a statistically significantly greater proportion of patients achieve ASAS20 response when treated with secukinumab, adalimumab, etanercept, golimumab and certolizumab, compared with placebo. The only exception was the Canadian-AS study (adalimumab versus placebo).
- 6.9 The results of the indirect comparisons indicated no statistically significant differences in the proportion of patients achieving ASAS20 when treated with secukinumab 150 mg at 12 weeks compared with:
- adalimumab, etanercept and certolizumab at 12 weeks when using placebo as the common reference; and
 - golimumab at 14 weeks
- when using placebo as the common reference. The infliximab trials were excluded as the included publications did not report ASAS20 response at 12 weeks. The differences in the placebo response rates between the trials (ranging from 20.6% to 37.3%) raised concerns regarding the exchangeability of the trials and validity of the indirect comparisons.
- 6.10 Table 4 presents the results for the BASDAI50 outcome, measured at 12 weeks in all trials with the exception of the golimumab trial (Inman 2008 / GO-RAISE), which was measured at 14 weeks. Table B.6.2 presents the results for the total and α TNF-naïve populations in MEASURE 2 and the indirect comparisons of secukinumab and other PBS-listed bDMARDs for the total and treatment naïve sub-group.

Table 4: Summary of results of the indirect comparisons – BASDAI50 response at Week 12 (Week 14 for golimumab trials) – FAS (or the AS sub-group in Landewe 2014) and the αTNF-naïve population in MEASURE 2

Tx	Trial	Drug n/N (%)	PBO n/N (%)	RR (95% CI)	Indirect comparison RR (95% CI) ^a	
					All	αTNF-naïve
SEC	MEASURE 2 (all)	████ (████)	████ (████)	████ (████, █████)	-	-
	MEASURE 2 (αTNF-naïve)	████ (████)	████ (████)	████ (████, █████)	-	-
ADA	Van der Heijde 2006a (ATLAS)	94/208 (45.2)	17/107 (15.9)	2.84 (1.79, 4.51)	1.61 (0.62, 4.24)	1.86 (0.56, 6.19)
	Huang 2014	114/229 (49.8)	19/115 (16.5)	3.01 (1.96, 4.64)		
	Meta-analysis (ADA) ^d				2.93 (2.14, 4.02)	
ETC25	Barkham 2010	7/20 (35.0)	1/20 (5.0)	7.00 (0.95, 51.80)	1.50 (0.52, 4.34)	1.73 (0.48, 6.23)
	Van der Heijde 2006b	87/150 (58.0)	10/51 (19.6)	2.96 (1.67, 5.24)		
	Meta-analysis (ETC25) ^d				3.16 (1.82, 5.47)	
ETC50	Van der Heijde 2006b	93/155 (60.0)	10/51 (19.6)	3.06 (1.73, 5.41)	1.88 (0.69, 5.14)	2.16 (0.63, 7.46)
	Dougados 2011 (SPINE)	18/39 (46.2)	10/43 (23.3)	1.98 (1.05, 3.76)		
	Meta-analysis (ETC50) ^d				2.52 (1.64, 3.88)	
GOL ^b	Inman 2008 (GO RAISE)	61/138 (44.2)	12/78 (15.4)	2.87 (1.65, 5.00)	1.65 (0.57, 4.79)	1.90 (0.53, 6.87)
INF	Braun 2002	18/34 (52.9)	3/35 (8.6)	6.18 (2.00, 19.07)	0.77 (0.18, 3.26)	0.88 (0.18, 4.45)
CZP	Landewe 2014 ^c (AS sub-group)	50/121 (41.3)	6/57 (10.5)	3.93 (1.79, 8.62)	1.20 (0.36, 4.01)	1.39 (0.34, 5.63)
Meta-analysis of all comparator bDMARDs ^d				2.98 (2.44, 3.65)	1.59 (0.62, 4.04)	1.83 (0.56, 5.94)

^a secukinumab versus the meta-analysis (where relevant) for the comparators

^b measured at week 14

^c includes 200 mg Q2W and 400 mg Q4W

^d using a random effects model

- 6.11 All trials (Table B.6.2) demonstrated that the active treatments resulted in a statistically significantly greater proportion of patients achieving a 50% improvement in the BASDAI score (BASDAI50) compared with placebo at week 12 or 14, with the exception of Barkham 2010 (an etanercept versus placebo study of 40 patients) using the relative risk statistic. The indirect comparisons indicated there was no statistically significant difference between secukinumab and any of the bDMARDs or the combined bDMARDs. However, these results require consideration as the placebo (common reference) response rates are different between the secukinumab and comparator trials and may indicate exchangeability issues. The placebo rate of the MEASURE 2 trial is lower compared to the placebo arms of all the comparator trials.
- 6.12 The submission presents the results for the BASDAI50 response outcome, measured at 16 weeks for the pivotal MEASURE 2 trial for the ITT (pp86-88) and anti-TNFα naïve patients (pp98-99), and measured at 12 weeks in all comparator trials with the exception of the golimumab trial (measured at 14 weeks) (pp93-94).

The results of the indirect comparisons are consistent with the results of BASDAI50 response measured at 12 weeks in the MEASURE 2 trial. The indirect comparisons indicated there was no statistically significant difference between secukinumab and any of the bDMARDs or the combined bDMARDs.

- 6.13 The ESC considered that the issue of different placebo response rates was in part offset by use of the Bucher method which explicitly adjusted the indirect comparison for event rate differences in the common reference placebo arm of trials included in the indirect comparison.
- 6.14 However, the ESC noted that whilst such approach may provide broad adjustment for differences in baseline risk secondary to imbalance between trials with regards to key prognostic correlates of end-point, this adjustment did not directly adjust for differences in the distribution of baseline confounders between trials, nor address systematic differences across several other exchangeability domains:
- Trial methods - concealment of randomisation, blinding, follow-up duration, loss to follow up, cross-over, differences in trial duration and sample size
 - Setting confounders (health systems, geography, in- vs out-patient, mixture of trial dates)
 - Treatment arms (dose, duration, timing)
- 6.15 The ESC noted that even with a standard indirect (Bucher) comparison for different event rates in the various placebo arms, “placebo response rate”, the results were likely to be subject to significant, residual confounding and bias. This was because the transitivity assumption, that was, that a reliable comparison could be made through a common “anchor” treatment (i.e. placebo), may not be maintained where there are genuine differences across the results for the placebo. Such differences would likely reflect the effect of other differences across the trials and be associated with time (such as co-interventions, baseline disease severity, patient comorbidities), rather than true variations in a “placebo response”. Adjustment for these differences was not possible as the true effect modifiers were unknown and as such, any adjusted analysis would not provide a confident estimate of comparative effectiveness.
- 6.16 The results for ASAS20 measured at 16 weeks (primary outcome) for both the FAS and α TNF-naïve population for the pivotal MEASURE 2 trial, and measured at 12 weeks in all comparator trials with the exception of the golimumab trials (measured at 14 weeks), are consistent with the results using ASAS20 at 12 weeks in the MEASURE 2 trial. The results indicated there was no statistically significant difference between secukinumab and any of the bDMARDs or the combined bDMARDs.
- 6.17 The submission nominated a non-inferiority criterion of 0.43 for the relative risk of ASAS20 at week 12 based on the PSD for certolizumab and golimumab in AS (March 2014 and March 2010, respectively). This nominated non-inferiority criterion of 0.43 was satisfied in all indirect comparisons.
- 6.18 Overall, the ESC considered that the clinical data regarding the comparative effectiveness of secukinumab should be interpreted with caution, secondary to

several systematic differences between included trials, particularly with respect to trial methods, setting confounders and differences in end- and time-points.

Comparative harms

6.19 The safety profile of secukinumab showed no new or unexpected safety signals.

Table 5: Summary of key adverse events in MEASURE 2 trial up to Week 16

Trial ID	Secukinumab 150 mg n/N (%)	Placebo n/N (%)	RD (95% CI)	RR (95% CI)
Any AEs	(%)	(%)	(- ,)	(,)
Treatment-related AEs	(%)	(%)	(- ,)	(,)
Severe AEs	(%)	(%)	(- ,)	(,)
Serious AEs ^a	(%)	(%)	(- ,)	(,)
Discontinued due to any AEs	(%)	(%)	(- ,)	(,)
Any AE resulting in hospitalisation ^b	(%)	(%)	(- ,)	(,)
Death			-	-
Infections and infestations	(%)	(%)	(- ,)	(,)

Source: pp.155, 163, 164, 166 of the trial report.

^a secukinumab: hepatic enzyme increased, NMR imaging brain abnormal, costochondritis and malignant melanoma. The event of hepatic enzyme increase was suspected to be related to the study medication by the investigator. Placebo: concussion, arthritis & intervertebral disc protrusion, and depression.

^b No relationship between the event and study medication was suspected.

6.20 An indirect comparison of secukinumab and any of the bDMARDs or the combined bDMARDs (using placebo as the common reference) indicated no statistically significant differences in the proportion of patients experiencing at least one adverse event between the treatments.

Clinical claim

6.21 The submission claimed that secukinumab was non-inferior to adalimumab, etanercept, golimumab, infliximab and certolizumab in comparative effectiveness and equivalent in comparative safety. This claim was adequately supported by the data presented in the submission, if the trials were considered to be sufficiently comparable and/or had been appropriately adjusted in the indirect comparison for differences in baseline risk and other systematic differences in design or setting to inform a valid indirect comparison and that a non-stringent non-inferiority margin of 0.43 on the relative risk statistic for the ASAS20 outcome is considered reasonable.

6.22 The PBAC considered that the claim of non-inferior comparative effectiveness and safety were reasonably supported.

Economic analysis

6.23 The submission presented a cost minimisation analysis versus adalimumab over 2 years of treatment.

6.24 The equi-effective doses were estimated as secukinumab 150 mg for Weeks 0, 1, 2, 3, and 4 followed by 150 mg every month over 2 years of therapy and adalimumab 40 mg once every 2 weeks over 2 years of therapy. The submission claimed that this

was based on clinical trials. However, the secukinumab dosing appeared to be based on the proposed PI as the maintenance dosing in the pivotal secukinumab trial was 150 mg every 4 weeks from Week 4.

- 6.25 The results of the cost minimisation presented by the submission are presented in Table 5. The submission's analysis and proposed price of secukinumab was based on cost neutrality with adalimumab assuming 12 scripts per patient per year for maintenance therapy for secukinumab (monthly dosing) based on the proposed PI. The submission also incorrectly assumes 9.5, instead of 9 packs of adalimumab in the 36-week period following the initial 16 weeks.
- 6.26 The PSCR stated that for the 36-week continuing treatment period in year 1, 9 scripts of adalimumab should be assumed because the last script in this period should be counted in year 2 therefore; the year 2 scripts should be increased from 13 to 13.5. When this adjustment was made to both year 1 and 2 figures the net effect on the cost minimisation analysis was nil. The ESC considered that this was reasonable
- 6.27 An ex-manufacturer price for secukinumab was estimated during the evaluation assuming 9 scripts for adalimumab for continuing treatment for 36 weeks in Year 1 and 13 scripts for secukinumab in Year 2, both with and without the application of discounting in year 2. The PSCR stated that 12 scripts of secukinumab per calendar year was appropriate given Australian prescribers will be influenced by the TGA-approved PI recommending dosing be done monthly, not four-weekly which is consistent with that for psoriasis indication. Thus 12 injections per year in the maintenance phase are used in cost-minimisation analysis.

Table 6: Cost-minimisation analysis of secukinumab versus adalimumab – 2 years of treatment – ex-manufacturer prices - provided by the submission and two alternative cost analyses performed during the evaluation

	Unit cost (ex-man)	Mg/ pack	Year 1 (52 weeks)						Year 2 (52 weeks)			Total cost over 2 years
			Initial			Continuing			Packs	Weeks	Cost	
			Packs	Weeks	Cost	Packs	Weeks	Cost				
Submission's assumptions (Table 45, p124 of the submission)												
SEC	\$ [REDACTED]	150	7	16	\$ [REDACTED]	9	36	\$ [REDACTED]	12	52	\$ [REDACTED]	\$ [REDACTED]
ADA	\$1,630.00	80	4	16	\$6,520.00	9.5	36	\$15,485.00	13	52	\$21,190.00	\$43,195.00
Difference			\$ [REDACTED]			-\$ [REDACTED]			\$ [REDACTED]			
Alternative assumption – 9 continuing scripts of adalimumab in Year 1 and 13 scripts of secukinumab in Year 2 (undiscounted)												
SEC	\$ [REDACTED]	150	7	16	\$ [REDACTED]	9	36	\$ [REDACTED]	13	52	\$ [REDACTED]	\$ [REDACTED]
ADA	\$1,630.00	80	4	16	\$6,520.00	9	36	\$14,670.00	13	52	\$21,190.00	\$42,380.00
Difference			\$ [REDACTED]			-\$ [REDACTED]			\$ [REDACTED]			
Alternative assumption – 9 continuing scripts of adalimumab in Year 1 and 13 scripts of secukinumab in Year 2 (second year discounted at 5%)												
SEC	\$ [REDACTED]	150	7	16	\$ [REDACTED]	9	36	\$ [REDACTED]	13	52	\$ [REDACTED]	\$ [REDACTED]
ADA	\$1,630.00	80	4	16	\$6,520.00	9	36	\$14,670.00	13	52	\$20,180.95	\$41,370.95
Difference			\$ [REDACTED]			-\$ [REDACTED]			-\$ [REDACTED]			

Drug cost/patient/year:

6.28 At the requested DPMQ of secukinumab and using the current adalimumab price:

	Initiation (16 weeks)	12 months of maintenance
Secukinumab	\$ [REDACTED] (1 pack at \$ [REDACTED]/pack + 2 packs at \$ [REDACTED]/pack)	\$ [REDACTED] (13 packs# at \$ [REDACTED]/pack)
Adalimumab	\$7,054.23 (4 packs at \$1,763.56/pack)	\$22,926.25 (13 packs at \$1,763.56/pack)

based on maintenance dosing once every 4 weeks from Week 4 in the pivotal trial

Estimated PBS usage & financial implications

6.29 The submission was not considered by DUSC. The submission used a market share approach to estimate PBS usage and financial implications, relying primarily on PBS data. Although secukinumab will substitute for the currently PBS-listed bDMARDs for the treatment of AS, the submission assumed no market growth which may not be reasonable as secukinumab offers an alternate mechanism of action (selectively binds to interleukin-17A or IL-17A) to the currently listed bDMARDs (all anti-TNF-α treatments). As such, secukinumab has a different adverse event profile to other bDMARDs currently listed for AS. The size of this additional population was unknown. The PSCR stated that the estimates presented in the submission assumed no additional growth beyond that already in the market (estimated at around 20% annually).

Table 7: Estimated use and financial implications

Year ^b	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number treated - initiation						
Market share	5%	9%	11%	13%	14%	15%
Scripts ^a						
Estimated net cost to PBS/RPBS/MBS						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	-\$
Net cost to MBS	-\$	-\$	-\$	-\$	-\$	-\$
Estimated total net cost						
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$	-\$

^a Assuming 7 initiation scripts (initial 16-week treatment period) and 12 continuation scripts per year in maintenance as estimated by the submission.

^b The submission inappropriately assumes Year 1 corresponds to 2015/2016, and estimates 6 years of financial implications. The actual first year of PBS listing roughly aligns to “Year 2” in the submission.

Source: pp137-147 of the submission; Excel workbook Usage and financial estimates Ankylosing Spondylitis Final, Market Share Model worksheet

The redacted table above shows that at year 6, the estimated number of scripts was 10,000 – 50,000 and the net savings to PBS would be less than \$10 million per year.

- 6.30 The submission’s estimate of the financial impact may not have been reasonable as:
- the cost per patient year of secukinumab was likely to be an underestimate since the submission assumed only 12 scripts per patient per year (monthly dosing according to the proposed PI) for continuation instead of 13 scripts per patient per year (maintenance dosing once every 4 weeks according to the pivotal secukinumab trial vs monthly dosing as per PI); and
 - the assumption of no market growth.

7 PBAC Outcome

- 7.1 The PBAC recommended General Schedule Authority Required listing of secukinumab for the treatment of ankylosing spondylitis on a cost minimisation basis with infliximab. The PBAC considered that any biological disease modifying antirheumatic drug (bDMARD) on the PBS for ankylosing spondylitis could be an appropriate comparator and noted that infliximab had the lowest cost of these comparators. Based on the evidence presented in the submission, the PBAC was not satisfied that secukinumab provides a significant improvement in efficacy or reduction of toxicity over infliximab for some patients. Therefore, there was no basis for secukinumab to have a price advantage over infliximab for an equivalent treatment period.
- 7.2 The PBAC noted the submission’s arguments favouring monthly dosing over four-weekly dosing. The PBAC considered that in practice patients would likely find four-weekly less confusing, noting that monthly use would lead to dosing on different days of the week. The PBAC therefore considered four-weekly dosing was the most appropriate frame of reference for considering equi-effective doses.
- 7.3 The equi-effective doses were considered to be secukinumab 150 mg administered at weeks 0, 1, 2, 3, and 4 and followed by 150 mg every four weeks over 2 years,

and infliximab 5mg/kg at weeks 0, 2 and 6 followed by 5mg/kg every six weeks.

- 7.4 The PBAC noted the clinical claim of non-inferior comparative effectiveness and safety compared with adalimumab, etanercept, golimumab, infliximab and certolizumab. The PBAC also noted the issues raised by the ESC about differences in placebo response rates and potential systematic differences between the included trials, particularly trial methods, setting confounders and differences in end- and time-points. The PBAC considered that the differences in the placebo response rates between the trials were reasonably offset by use of the Bucher method to adjust the indirect comparison for event rate differences in the common reference placebo arm of included trials. Overall, the PBAC considered that a conclusion of non-inferior comparative effectiveness was reasonable.
- 7.5 The PBAC noted that in light of secukinumab's different mechanism of action compared to the other bDMARDs, it would be reasonable to expect a different adverse event profile. The PBAC considered that the claim of non-inferior comparative safety was adequately supported.
- 7.6 The PBAC noted the ESC's advice regarding market growth for bDMARDs for AS. The PBAC considered that the submission's estimates of market growth were reasonable.
- 7.7 The PBAC recommended the same restriction for secukinumab as for the other bDMARDs for ankylosing spondylitis, noting that the availability of this will allow clinicians to choose from a range of bDMARDs depending on the circumstances of individual patients. The PBAC noted the submission's request for a grandfather restriction for secukinumab for AS. The PBAC considered this to be reasonable.
- 7.8 The PBAC advised, under Section 101(3BA) of the *National Act 1953*, secukinumab for the treatment of ankylosing spondylitis should be treated as interchangeable on an individual patient basis with adalimumab, etanercept, golimumab, infliximab and certolizumab.
- 7.9 The PBAC advised that there was no reason to exempt secukinumab for AS from the Early Supply Rule.
- 7.10 The PBAC advised that secukinumab is not suitable for prescribing by nurse practitioners.
- 7.11 The PBAC noted that this submission is not eligible for an Independent Review, because the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new indication:

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.