

**6.08 SECUKINUMAB,  
150 mg/1 mL pre-filled pen,  
Cosentyx<sup>®</sup>,  
Novartis Pharmaceuticals Australia Pty Ltd.**

**1 Purpose of Application**

1.1 To request an Authority Required (in writing) listing for the treatment of severe active psoriatic arthritis in patients meeting certain criteria.

**2 Requested listing**

2.1 The requested listing was generally consistent with the current PBS restrictions of the other biological disease-modifying antirheumatic drugs (bDMARDs) listed for severe active psoriatic arthritis: adalimumab, etanercept, infliximab, golimumab, and certolizumab pegol.

Name, Restriction, Manner of administration and form	Max. Qty	No.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SECUKINUMAB 150 mg in 1 mL pre-filled pen, 1	5	0	\$ [REDACTED]	Cosentyx <sup>®</sup> Novartis Pharmaceuticals
SECUKINUMAB 150 mg in 1 mL pre-filled pen, 1	1	1	\$ [REDACTED]	
SECUKINUMAB 150 mg in 1 mL pre-filled pen, 2	5	0	\$ [REDACTED]	
SECUKINUMAB 150 mg in 1 mL pre-filled pen, 2	1	1	\$ [REDACTED]	
<b>Treatment phase</b>	Initial treatment – Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more)			
<b>Clinical criteria:</b>	Patient must have severe active psoriatic arthritis, <b>AND</b> Patient must have received no prior PBS-subsidised treatment with a biological agent for this condition; <b>OR</b> Patient must have received no PBS-subsidised treatment with a biological agent for at least 5 years if they have previously received PBS-subsidised treatment with a biological agent for this condition, <b>AND</b> Patient must have failed to achieve an adequate response to methotrexate at a dose of at least 20 mg weekly for a minimum period of 3 months, <b>AND</b> Patient must have failed to achieve an adequate response to sulfasalazine at a dose of at least 2 g per day for a minimum period of 3 months; <b>OR</b> Patient must have failed to achieve an adequate response to leflunomide at a dose of up to 20 mg daily for a minimum period of 3 months <b>AND</b> Patient must not receive more than 16 weeks of treatment under this restriction.			
<b>Treatment phase</b>	Initial 2 (change or recommencement of treatment)			
<b>Clinical criteria:</b>	Patient must have a documented history of severe active psoriatic arthritis, <b>AND</b> Patient must have received prior PBS-subsidised treatment with a biological agent for this condition in this Treatment Cycle, <b>AND</b> Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with 3			

Public Summary Document – March 2016 PBAC Meeting

<b>Treatment phase:</b>	Initial treatment – Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more)
	biological agents within this Treatment Cycle, <b>AND</b> Patient must not have failed, or ceased to respond to, PBS-subsidised treatment with this drug during the current Treatment Cycle, <b>AND</b> Patient must not receive more than 16 weeks of treatment under this restriction.
<b>Treatment phase:</b>	Initial treatment – Initial 3 (initial PBS-subsidised supply for continuing treatment in a patient commenced on non-PBS-subsidised therapy)
<b>Clinical criteria:</b>	Patient must have a documented history of severe active psoriatic arthritis, <b>AND</b> Patient must have been receiving treatment with secukinumab for this condition prior to 1 April 2015, <b>AND</b> Patient must be receiving treatment with secukinumab at the time of application, <b>AND</b> Patient must have demonstrated a response to treatment as specified in the criteria for continuing PBS-subsidised treatment with secukinumab, <b>AND</b> Patient must not receive more than 24 weeks of treatment under this restriction.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SECUKINUMAB 150 mg in 1 mL pre-filled pen, 1	1	5	\$ [REDACTED]	Cosentyx® Novartis Pharmaceuticals
SECUKINUMAB 150 mg in 1 mL pre-filled pen, 2	1	5	\$ [REDACTED]	

<b>Treatment phase:</b>	Continuing treatment
<b>Clinical criteria:</b>	Patient must have a documented history of severe active psoriatic arthritis <b>AND</b> Patient must have received this drug as their most recent course of PBS-subsidised treatment with a biological agent for this condition in the current Treatment Cycle <b>AND</b> Patient must demonstrate, at the time of application, an adequate response to treatment with this drug <b>AND</b> Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction.

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

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

### **3 Background**

- 3.1 TGA status at the time of PBAC consideration: The submission was made under TGA/PBAC Parallel Process. The Round 1 and 2 Clinical Evaluation Reports were provided prior to the ESC meeting. The TGA Delegates Overview was available at the time of the PBAC consideration.
- 3.2 Secukinumab has not been considered by PBAC previously for this indication. A concurrent submission seeking listing of secukinumab for the treatment of ankylosing spondylitis was also considered at the March 2016 PBAC meeting (Item 6.07 refers).
- 3.3 Secukinumab was recommended for the treatment of severe chronic plaque psoriasis on a cost-minimisation basis versus adalimumab at the March 2015 PBAC meeting.

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

### **4 Clinical place for the proposed therapy**

- 4.1 The submission proposed secukinumab as an alternative to the currently PBS-listed bDMARDs (adalimumab, etanercept, infliximab, golimumab, and certolizumab pegol).
- 4.2 Secukinumab (interleukin (IL)-17A inhibitor) and ustekinumab (IL12/23 inhibitor) are in a different class of biological treatment to the currently PBS-listed bDMARDs for psoriatic arthritis, which are tumour necrosis factor alpha (TNF $\alpha$ ) inhibitors.

### **5 Comparator**

- 5.1 Adalimumab (main comparator); etanercept, infliximab, golimumab, certolizumab pegol (secondary comparators). These were appropriate comparators.
- 5.2 In addition, the PBAC recommended ustekinumab for the treatment of psoriatic arthritis during its November 2015 meeting, thus ustekinumab may also be an appropriate comparator.
- 5.3 The ESC noted that the PSCR claimed with regard to ustekinumab as a possible comparator that as it was, "...unclear when it will be PBS listed... ustekinumab as a secondary comparator is not supported and as such information regarding the comparison with ustekinumab is of less relevance." The ESC noted that drugs previously recommended by the PBAC but not yet PBS listed may still be relevant 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 No head-to-head trial was available. The submission was based on a series of five indirect comparisons sourced from nine placebo-controlled clinical trials of secukinumab versus adalimumab and its secondary comparators, using placebo as the common reference. A sixth indirect comparison was constructed between secukinumab and a meta-analysed pooled group of all bDMARDs.

6.4 Whilst not nominated by the sponsor as a secondary comparator, additional data for ustekinumab were extracted from two randomised trials during the evaluation given its positive recommendation during the November 2015 PBAC meeting. The results extracted were consistent with the ustekinumab results included in the Public Summary Document (PSD) for the deferred July 2015 re-submission.

6.5 Details of the trials presented in the submission and the additional ustekinumab trials are provided in Table 1 below.

**Table 1: Trials and associated reports presented in the submission**

Trial ID	Protocol title/Publication title	Publication citation
<b>Secukinumab vs placebo</b>		
FUTURE2 (Trial 2312)	A Phase III randomized, double-blind, placebo-controlled multicenter study of subcutaneous secukinumab in prefilled syringes to demonstrate the efficacy at 24 weeks and to assess the long term efficacy, safety and tolerability up to 5 years in patients with Active Psoriatic Arthritis	Interim analyses at Week 24: 22 October 2014. Interim analyses at Week 52: 5 June 2015.
	McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P <i>et al.</i> Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): A randomised, double-blind, placebo-controlled, phase 3 trial.	<i>Lancet</i> 2015; 386(9999): 1137-46.
<b>Adalimumab vs placebo</b>		
ADEPT Mease 2005	Mease PJ, Gladman DD, Ritchlin C, <i>et al.</i> Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomised, placebo controlled trial.	<i>Arthritis &amp; Rheumatism</i> 2005; 52(10):3279-89
	Gladman DD, Mease PJ, Cifaldi MA, <i>et al.</i> Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial.	<i>Annals of the Rheumatic Diseases</i> 2007; 66(2):163-168
	Gladman DD, Mease PJ, Ritchlin C, <i>et al.</i> Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial.	<i>Arthritis &amp; Rheumatism</i> 2007; 56(2):476-88.

Public Summary Document – March 2016 PBAC Meeting

Trial ID	Protocol title/Publication title	Publication citation
	Mease PJ, Ory P, Sharp JT, <i>et al.</i> Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the adalimumab effectiveness in psoriatic arthritis trial (ADEPT).	<i>Annals of Rheumatic Disease</i> 2009; 68: 702-9.
	Mease PJ, Heckaman M, Kary S, <i>et al.</i> Application and modifications of minimal disease activity measures for patients with psoriatic arthritis treated with adalimumab: subanalyses of ADEPT.	<i>Journal of Rheumatology</i> 2013; 40(5); 647-652.
Genovese 2007	Genovese MC, Mease PJ, Thomson GTD, <i>et al.</i> Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy.	<i>Journal of Rheumatology</i> 2007; 34(5):1040-50. [Erratum appears in <i>Journal of Rheumatology</i> 2007; 34(6):1439]
<b>Etanercept vs placebo</b>		
Mease 2004	Mease PJ, Kivitz AJ, Burch FX, <i>et al.</i> Etanercept treatment of psoriatic arthritis; safety, efficacy, and effect on disease progression.	<i>Arthritis and Rheumatism</i> 2004; 50(7):2264–72
	Mease PJ, Kivitz AJ, Burch FX, <i>et al.</i> Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept.	<i>Journal of Rheumatology</i> 2006; 33:712-21.
	Mease PJ, Woolley JM, Singh A, <i>et al.</i> Patient-reported outcomes in a randomised trial of etanercept in psoriatic arthritis.	<i>Journal of Rheumatology</i> , 2010; 37(6):1221-7.
	Mease PJ, Woolley JM, Bitman B, <i>et al.</i> Minimally important difference of Health Assessment Questionnaire in psoriatic arthritis: relating thresholds of improvement in functional ability to patient-rated importance and satisfaction.	<i>Journal of Rheumatology</i> , 2011; 38(11):2461-5.
Mease 2000	Mease PJ, Goffe BS, Metz J, <i>et al.</i> Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial.	<i>Lancet</i> 2000; 356:385–90.
<b>Infliximab vs placebo</b>		
IMPACT Antoni 2005a	Antoni CE, Kavanaugh A, Kirkham B, <i>et al.</i> Sustained Benefits of Infliximab Therapy for Dermatologic and Articular Manifestations of Psoriatic Arthritis: Results From the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT).	<i>Arthritis and Rheumatism</i> 2005a; 52(4):1227–1236
	Kavanaugh A, Antoni CE, Gladman D, <i>et al.</i> The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year.	<i>Annals of the Rheumatic Diseases</i> 2006; 65(8):1038-43.
	Antoni CE, Kavanaugh A, Van Der Heijde D, <i>et al.</i> Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: Findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT).	<i>Journal of Rheumatology</i> 2008; 35:869-76.
IMPACT2 Antoni 2005b	Antoni C, Krueger GG, De VK, <i>et al.</i> Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial.	<i>Annals of the Rheumatic Diseases</i> 2005b;64:1150–1157
	Kavanaugh A, Antoni C, Krueger GG, <i>et al.</i> Infliximab improves health related quality of life and physical function in patients with psoriatic arthritis.	<i>Annals of the Rheumatic Diseases</i> 2006; 65(4):471-7.
	Kavanaugh A, Antoni C, Mease P, <i>et al.</i> Effect of infliximab therapy on employment, time lost from work, and productivity in patients with psoriatic arthritis.	<i>Journal of Rheumatology</i> 2006; 33:2254-9.
	Kavanaugh A, Krueger GG, Beutler A, <i>et al.</i> Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: Results from the IMPACT 2 trial.	<i>Annals of the Rheumatic Diseases</i> 2007; 66:498-505.
	Van Der Heijde D, Kavanaugh A, Gladman DD, <i>et al.</i> Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2.	<i>Arthritis &amp; Rheumatism</i> 2007; 56(8):2698-707.
<b>Golimumab vs placebo</b>		

Public Summary Document – March 2016 PBAC Meeting

<b>Trial ID</b>	<b>Protocol title/Publication title</b>	<b>Publication citation</b>
GO-REVEAL Kavanaugh 2009	Kavanaugh A, McInnes I, Mease P, <i>et al.</i> Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis.	<i>Arthritis &amp; Rheumatism</i> 2009; 60(4):976–986.
	Kavanaugh A, van der Heijde D, McInnes IB, <i>et al.</i> Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomised, placebo-controlled trial.	<i>Arthritis &amp; Rheumatism</i> 2012; 64(8):2504-17.
	Kavanaugh A & Mease P. Treatment of psoriatic arthritis with tumor necrosis factor inhibitors: Longer-term outcomes including enthesitis and dactylitis with golimumab treatment in the long-term extension of a randomized, placebo-controlled study (GO-REVEAL).	<i>Journal of Rheumatology</i> 2012; 39:90-3.
	Kavanaugh A, McInnes IB, Mease PJ, <i>et al.</i> Clinical efficacy, radiographic and safety findings through 2 years of golimumab treatment in patients with active psoriatic arthritis: Results from a long-term extension of the randomised, placebo-controlled GO-REVEAL study.	<i>Annals of the Rheumatic Diseases</i> 2013; 72:1777-85.
	Kavanaugh A, McInnes IB, Krueger GG, <i>et al.</i> Patient-reported outcomes and the association with clinical response in patients with active psoriatic arthritis treated with golimumab: Findings through 2 years of a phase III, multicentre, randomized, double-blind, placebo-controlled trial.	<i>Arthritis Care and Research</i> 2013; 65:1666-73.
	Kavanaugh A, McInnes IB, Mease P, <i>et al.</i> Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: Results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study).	<i>Annals of the Rheumatic Diseases</i> 2014; 73:1689-1694.
<b>Certolizumab pegol vs placebo</b>		
RAPID-PsA Mease 2014	Mease PJ, Fleischmann R, Deodhar AA, <i>et al.</i> Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA).	<i>Annals of the Rheumatic Diseases</i> 2014; 73:48-55.
	Gladman D, Fleischmann R, Coteur G, <i>et al.</i> Effect of certolizumab pegol on multiple facets of psoriatic arthritis as reported by patients: 24-week patient-reported outcome results of a phase III, multicenter study.	<i>Arthritis Care and Research</i> 2014; 66:1085-92.
	van der Heijde D, Fleischmann R, Wollenhaupt J, <i>et al.</i> Effect of different imputation approaches on the evaluation of radiographic progression in patients with psoriatic arthritis: results of the RAPID-PsA 24-week phase III double-blind randomised placebo-controlled study of certolizumab pegol.	<i>Annals of the Rheumatic Diseases</i> 2014; 73(1):233-7.
	Kavanaugh A, Gladman D, van der Heijde D, <i>et al.</i> Improvements in productivity at paid work and within the household, and increased participation in daily activities after 24 weeks of certolizumab pegol treatment of patients with psoriatic arthritis: Results of a phase 3 double-blind randomised placebo-controlled study.	<i>Annals of the Rheumatic Diseases</i> 2015; 74(1):44-51.
	Mease P, Deodhar A, Fleischmann R, <i>et al.</i> Effect of certolizumab pegol over 96 weeks in patients with psoriatic arthritis with and without prior antitumour necrosis factor exposure.	<i>RMD Open</i> 2015; 1(1):e000119.
<b>Ustekinumab vs placebo</b>		
PSUMMIT-1	McInnes IB, Kavanaugh A, Gottlieb AB, <i>et al.</i> Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT-1 trial.	<i>Lancet</i> 2013; 382(9894):780-9.

Trial ID	Protocol title/Publication title	Publication citation
PSUMMIT-2	<i>Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial.</i>	<i>Annals of the Rheumatic Diseases 2014; 73(6):990-9.</i>
PSUMMIT-1 and PSUMMIT-2	<i>Kavanaugh A, Ritchlin C, Rahman P, et al. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials</i>	<i>Annals of the Rheumatic Diseases 2014; 73(6):1000-6.</i>

Source: Table 8, pp28-32 of the submission and Public Summary Document for ustekinumab, November 2014 PBAC meeting. Additional data in italics extracted during the evaluation. Identified abstract were not included in the table unless there is no full publication available.

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

**Table 2: Key features of the included evidence**

Trial	N*	Design / duration	Risk of bias	Patient population	Intervention	Key outcome(s)
<b>Secukinumab vs placebo</b>						
FUTURE2	397	R, DB, MC for 52 wks. PBO arm CO at Wk 16 (non-responders <sup>a</sup> ) or Wk 24 (responders). OL extension up to 256 wks.	Low	Anti-TNFα naïve or experienced	SEC 75mg or SEC 150 mg or SEC 300 mg vs PBO at Wk 0, 1, 2, 3, 4, then every 4 wks. PBO arm re-randomised to SEC 150 mg or SEC 300 mg at Wk 16/24.	ACR20 at Wk 24, ACR50
<i>Anti-TNFα naïve</i>	180		<i>Unclear</i>	<i>Anti-TNFα naïve only</i>		
<b>Main comparator</b>						
<b>Adalimumab vs placebo</b>						
ADEPT	313	R, DB, MC for 24 wks. OL extension additional 120 wks.	Low	Anti-TNFα naïve	ADA 40 mg every 2 wk vs PBO every 2 wks. Rescue meds after Wk 12 <sup>b</sup> .	ACR20 at Wk 12 & change in mTSS at Wk 24, ACR50
Genovese 2007	100	R, DB, MC for 12 wks. OL extension up to 24 wks.	Low	Anti-TNFα naïve	ADA 40 mg every 2 wk vs PBO every 2 wks.	ACR20 at Wk 12, ACR 50
<b>Secondary comparators</b>						
<b>Etanercept vs placebo</b>						
Mease 2000	60	R, DB for 12 wks.	Low	Anti-TNFα naïve	ETC 25mg twice weekly vs PBO twice weekly.	PsARC at Wk 12, ACR20, ACR50
Mease 2004	205	R, DB, MC for 24 wks. OL extension additional 48 wks.	Low	Anti-TNFα naïve	ETC 25mg twice weekly vs PBO twice weekly.	ACR20, ACR50
<b>Infliximab vs placebo</b>						
IMPACT	104	R, DB, MC for 50 wks. PBO-controlled for 16 wks.	Low	Anti-TNFα naïve	INF 5mg/kg at Wk 0, 2, 6 then every 8 wks (with PBO at Wk 16 and 18) vs PBO at Wk 0, 2, 6, 14, then INF at Wk 16, 18, 22, then every 8 wks	ACR20 at Wk 16, ACR50

Trial	N*	Design / duration	Risk of bias	Patient population	Intervention	Key outcome(s)
IMPACT2	200	R, DB, MC for 24 wks. PBO arm CO at Wk 16 (non-responders <sup>c</sup> ).	Low	Anti-TNFα naïve	INF 5mg/kg vs PBO at Wk 0, 2, 6 then every 8 wks. Non-responders also received doses at Wk 16 and 18 <sup>c</sup> .	ACR20 at Wk 14, ACR50
<b>Golimumab vs placebo</b>						
GO-REVEAL	405	R, DB, MC for 24 wks. Dose escalation/ crossover at Wk 16 (non-responders <sup>d</sup> ). PBO crossover at Wk 24 for remainder. OL extension up to 236 wks.	Low	Anti-TNFα naïve	GOL 50 mg or GOL 100 mg vs PBO every 4 wks. Dose escalation/ CO at Wk 16 if non-responder <sup>d</sup> .	ACR20 at Wk 14, ACR50
<b>Certolizumab pegol vs placebo</b>						
RAPID-PsA	409	R, DB, MC for 16/24 wks. PBO arm CO at Wk 16 (non-responders <sup>e</sup> ) or Wk 24 (responders).	Low	Anti-TNFα naïve or experienced	CZP 400 mg at Wk 0, 2 and 4, then CZP 200 mg every 2 wks or CZP 400 mg every 4 wks; vs PBO. PBO arm re-randomised to CZP 200 mg or CZP 400 mg with loading at Wk 16/24 <sup>e</sup> .	ACR20 at Wk 12 & change in mTSS at Wk 24, ACR50
Anti-TNFα naïve	329	Dose-blind to Wk 48. OL extension up to 216 wks.	Unclear	Anti-TNFα naïve only		
<b>Ustekinumab vs placebo</b>						
PSUMMIT-1	615	R, DB, MC for 24wks. Dose escalation/ CO at Wk 16 (non-responders <sup>f</sup> ) or Wk 24 (responders). Up to 106 wks.	Low	Anti-TNFα naïve	UST 45 mg or UST 90 mg vs PBO at Wk 0 and 4, then every 12 wks. Dose escalation/CO at Wk 16 if non-responders <sup>f</sup> . PBO responder CO to UST 45mg at Wk 24 with loading.	ACR20 at Wk 24, ACR50
PSUMMIT-2	312	R, DB, MC for 24wks. Dose escalation/ CO at Wk 16 (non-responders <sup>f</sup> ) or Wk 24 (responders). Up to 60 wks for safety.	Low	Anti-TNFα naïve or experienced	UST 45 mg or UST 90 mg vs PBO at Wk 0 and 4, then every 12 wks. Dose escalation or CO at Wk 16 if non-responders <sup>f</sup> . PBO responder CO to UST 45mg at Wk 24 with loading.	ACR20 at Wk 24, ACR50
Anti-TNFα naïve	132		Unclear	Anti-TNFα naïve only		

Abbreviations: ACR20 = at least 20% improvement in the American College of Rheumatology response criteria; ACR50 = at least 50% improvement in the American College of Rheumatology response criteria; ADA = adalimumab; CO = crossover; CZP = certolizumab pegol; DB = double blind; ETC = etanercept; GOL = golimumab; INF = infliximab; MC = multicentre; mTSS = modified Total Sharp Score; OL = open-label; PBO = placebo; PsARC = Psoriatic Arthritis Response Criteria; R = randomised; SEC = secukinumab; TNFα = tumour necrosis factor alpha; UST = ustekinumab

\* number of patients analysed.

<sup>a</sup> <20% improvement from baseline in tender and swollen joint counts.

<sup>b</sup> <20% decrease in both swollen and tender joint counts on two consecutive visits – rescued with corticosteroids or DMARDs.

<sup>c</sup> <10% improvement from baseline in both swollen and tender joint counts - received INF 5 mg/kg at weeks 16, 18, and 22. Patients randomised to INF who had <10% improvement received additional PBO infusions at weeks 16 and 18.

<sup>d</sup> <10% decrease in swollen and tender joint counts switched to either active treatment (if on PBO) or higher dose (if already receiving active treatment (GOL50 mg to GOL100 mg). GOL 100 mg maintained.

<sup>e</sup> <10% decrease in swollen and tender joint counts at Weeks 14 and 16.

<sup>f</sup> <5% decrease in swollen and tender joint counts switched to either active treatment (if on PBO) or higher dose (if already receiving active treatment (UST 45mg to 90 mg). UST 90 mg maintained.

Source: compiled during the evaluation, pp36-55 of the submission and respective publications.

6.7 The risk of bias for the indirect comparisons was unclear given the potential heterogeneity across the included trials. There were concerns that the included trials were not exchangeable, given the differences across the trials in terms of the trial design (including rescue or early escape), eligibility criteria, baseline characteristics, outcome measures (e.g. timing, joint counts), and period of trial conduct (over a more

than 10 year time period).

- 6.8 The secukinumab trial (FUTURE2), certolizumab pegol trial (RAPID-PsA) and one of the ustekinumab trials (PSUMMIT-2) included both anti-TNF $\alpha$  naïve and experienced patients, and were therefore more consistent with the requested PBS population given the interchangeability of the bDMARDs on the PBS.
- 6.9 The submission considered that the extent of prior anti-TNF $\alpha$  treatment exposure was the main difference between secukinumab and the comparator trials. The submission argued that the secukinumab trial population could be interpreted as representing patients who were more difficult to treat versus the anti-TNF $\alpha$  naïve populations, thus the indirect comparisons were only conducted in the anti-TNF $\alpha$  naïve population. While limiting the analyses to those who are anti-TNF $\alpha$  naïve may reduce the heterogeneity across the included trials, this also limited the applicability of the results to the requested PBS population, whilst increasing the imprecision around the effect size point estimates included in the indirect comparison. The submission did not present indirect comparisons in the entire trial populations to demonstrate that the results were robust to the population used to inform the comparisons.

### **Comparative effectiveness**

- 6.10 The submission presented indirect comparisons of the American College of Rheumatology 50% improvement criteria (ACR50) and 20% improvement criteria (ACR20) response rates using Week 16 secukinumab data from the FUTURE2 trial versus its comparators, via placebo as the common reference based on the odds ratio (OR). The submission noted that the results indicated that there were no statistically significant differences between secukinumab versus its comparators (individually or pooled) in the ACR50 and the ACR20. The submission claimed that this suggested that secukinumab was non-inferior to the comparators, alone or combined. Formal non-inferiority testing was not conducted.
- 6.11 The ESC considered that the influence of observed differences in trial sample sizes and the use of a FUTURE 2 sub-population on the precision of the estimates used in the indirect comparison were difficult to separate from genuine non-inferiority.
- 6.12 Relative risks (RRs) and non-inferiority margins based on RRs had been used in previous PBAC considerations of bDMARDs for the treatment of psoriatic arthritis. The submission's use of ACR50 and ACR20 response rates at Week 16 for secukinumab was not consistent with the requested initial treatment supply of a maximum of 16 weeks, for which response rates at 12 weeks were more applicable. Use of week 16 response rates was likely to favour secukinumab. Therefore, indirect comparisons were performed during the evaluation based on ACR50 and ACR20 response rates at 12 weeks for secukinumab, with the analysis based on the RR statistic. Additional data were extracted during the evaluation for certolizumab pegol and ustekinumab.
- 6.13 The ESC noted that the PSCR maintained the appropriateness of using response rates at week 16, as the last dose would be administered at week 12, thereby allowing sufficient time for the administrative requirement to ensure ongoing supply.

*Public Summary Document – March 2016 PBAC Meeting*

The PSCR further claimed that response rates measured at week 12 would mean that the patient's last dose would have been administered at week 8.

**Table 3: Indirect comparison of ACR50 (secukinumab vs comparators) via placebo as the common reference at the primary time point (Week 12 results for secukinumab) – anti-TNF $\alpha$  naïve patients only**

Tx	Trial	bDMARD n/N (%)	Placebo n/N (%)	RR (95% CI)	Indirect comparison RR (95% CI) <sup>a</sup>	
SEC	FUTURE2 (12 wk, subgp)					
	SEC 150 mg				-	-
	SEC 300 mg		5/63 (7.9)		-	-
	SEC ('lumped')				-	-
ADA	ADEPT (12 wk)	55/151 (36.4)	7/162 (4.3)	<b>8.43 (3.96, 17.93)</b>	SEC 150 mg	0.47 (0.15, 1.50)
	Genovese 2007 (12 wk)	13/51 (25.5)	1/49 (2.0)	<b>12.49 (1.70, 91.90)</b>	SEC 300 mg	0.53 (0.17, 1.66)
	Meta-analysis (adalimumab vs placebo); I <sup>2</sup> = 0%			<b>8.85 (4.37, 17.94)</b>	'lumped'	0.50 (0.16, 1.55)
ETC	Mease 2000 (12 wk)	15/30 (50)	1/30 (3.3)	<b>15.00 (2.11, 106.49)</b>	SEC 150 mg	0.39 (0.11, 1.40)
	Mease 2004 (12 wk)	38/101 (37.6)	4/104 (3.8)	<b>9.78 (3.62, 26.41)</b>	SEC 300 mg	0.44 (0.13, 1.55)
	Meta-analysis (etanercept vs placebo); I <sup>2</sup> = 0%			<b>10.68 (4.40, 25.89)</b>	'lumped'	0.42 (0.12, 1.45)
INF	IMPACT (16 wk)	24/52 (46.2)	0/52 (0)	<b>49.0 (3.06, 785.06)</b>	SEC 150 mg	0.29 (0.07, 1.15)
	IMPACT2 (14 wk)	36/100 (36.0)	3/100 (3.0)	<b>12.00 (3.82, 37.70)</b>	SEC 300 mg	0.32 (0.08, 1.28)
	Meta-analysis (infliximab vs placebo); I <sup>2</sup> = 9%			<b>14.73 (5.11, 42.43)</b>	'lumped'	0.30 (0.08, 1.19)
GOL 50 mg	GO-REVEAL (14 wk)	44/146 (30.1)	2/113 (1.8)	<b>17.03 (4.22, 68.75)</b>	SEC 150 mg	0.25 (0.05, 1.31)
					SEC 300 mg	0.28 (0.05, 1.45)
					'lumped'	0.26 (0.05, 1.36)
Anti- TNF $\alpha$	Meta-analysis of all comparator bDMARDs (anti-TNF $\alpha$ agents excluding CZP) as per the submission; I <sup>2</sup> = 0%			<b>11.03 (6.95, 17.50)</b>	SEC 150 mg	0.38 (0.14, 1.06)
					SEC 300 mg	0.43 (0.16, 1.17)
					'lumped'	0.40 (0.15, 1.09)
CZP	RAPID-PsA (12 wk, subgp)					
	CZP 200 mg	NR	14/110 (12.7)	-	SEC 150 mg	1.59 (0.55, 4.53)
	CZP 400 mg	NR		-	SEC 300 mg	1.77 (0.63, 5.01)
	CZP ('lumped')	74/219 (33.8)		<b>2.65 (1.57, 4.48)</b>	'lumped'	1.68 (0.61, 4.66)
UST 45 mg	PSUMMIT-1 (24 wk)	51/205 (24.9)	18/206 (8.7)	<b>2.85 (1.72, 4.70)</b>	SEC 150 mg	1.47 (0.53, 4.08)
	PSUMMIT-2 (24 wk, subgp)	9/43 (20.9)	3/42 (7.1)	<b>2.93 (0.85, 10.08)</b>	SEC 300 mg	1.64 (0.60, 4.51)
	Meta-analysis (ustekinumab vs placebo); I <sup>2</sup> =0%			<b>2.86 (1.80, 4.55)</b>	'lumped'	1.56 (0.58, 4.19)

Abbreviations: ACR50 = at least 50% improvement in the American College of Rheumatology response criteria; ADA = adalimumab; CZP = certolizumab pegol; ETC = etanercept; GOL = golimumab; INF = infliximab; NR = not reported; OR = odds ratio; SEC = secukinumab; TNF $\alpha$  = tumour necrosis factor alpha; UST = ustekinumab

<sup>a</sup> secukinumab versus the meta-analysis (where relevant) for the comparators. RR >1 favours secukinumab.

Note: Bolding indicates that the 95% CI does not include the null value

Source: Adapted from Table 45, p136, Figure 8, p137, Table 50, p151, and Figure 12, p154 of the submission, CSR 24wk Table 14.2-1.4, pp409-414; CSR 24wk Table 14.2-7.4, pp710-715. . Additional data for CZP extracted from Table 3 of Mease et al (2015) and estimated from Figure 3 of Mease et al (2014), consistent with the data extracted from the Table 3, PSD of ustekinumab July 2015. Data for UST also extracted from an abstract by Ritchlin et al (2012) <http://acrabstracts.org/abstract/ustekinumab-in-active-psoriatic-arthritis-including-patients-previously-treated-with-anti-tnf-agents-results-of-a-phase-3-multicenter-double-blind-placebo-controlled-study/>

**Table 4: Indirect comparison of ACR20 (secukinumab vs comparators) via placebo as the common reference at the primary time point (Week 12 results for secukinumab) – anti-TNF $\alpha$  naïve patients only**

Tx	Trial	bDMARD n/N (%)	Placebo n/N (%)	RR (95% CI)	Indirect comparison RR (95% CI) <sup>a</sup>	
SEC	FUTURE2 (12 wk, subgp)					
	SEC 150 mg				-	-
	SEC 300 mg		19/63 (30.2)		-	-
	SEC ('lumped')				-	-
ADA	ADEPT (12 wk)	88/151 (58.3)	23/162 (14.2)	<b>4.10 (2.75, 6.14)</b>	SEC 150 mg	0.62 (0.32, 1.18)
	Genovese 2007 (12 wk)	20/51 (39.2)	8/49 (16.3)	<b>2.40 (1.17, 4.94)</b>	SEC 300 mg	0.65 (0.34, 1.24)
	Meta-analysis (adalimumab vs placebo); I <sup>2</sup> = 38%				<b>3.42 (2.08, 5.63)</b>	'lumped'
ETC	Mease 2000 (12 wk)	22/30 (73.3)	4/30 (13.3)	<b>5.50 (2.15, 14.04)</b>	SEC 150 mg	<b>0.49 (0.27, 0.89)</b>
	Mease 2004 (12 wk)	59/101 (58.4)	15/104 (14.4)	<b>4.05 (2.47, 6.65)</b>	SEC 300 mg	<b>0.52 (0.28, 0.94)</b>
	Meta-analysis (etanercept vs placebo); I <sup>2</sup> = 0%				<b>4.33 (2.79, 6.71)</b>	'lumped'
INF	IMPACT (16 wk)	34/52 (65.4)	5/52 (9.6)	<b>6.80 (2.89, 16.01)</b>	SEC 150 mg	<b>0.37 (0.19, 0.70)</b>
	IMPACT2 (14 wk)	58/100 (58.0)	11/100 (11.0)	<b>5.27 (2.95, 9.44)</b>	SEC 300 mg	<b>0.39 (0.21, 0.74)</b>
	Meta-analysis (infliximab vs placebo); I <sup>2</sup> = 0%				<b>5.71 (3.53, 9.25)</b>	'lumped'
GOL 50 mg	GO-REVEAL (14 wk)	74/146 (50.7)	10/113 (8.8)	<b>5.73 (3.10, 10.57)</b>	SEC 150 mg	<b>0.37 (0.18, 0.77)</b>
					SEC 300 mg	<b>0.39 (0.19, 0.81)</b>
					'lumped'	<b>0.38 (0.18, 0.79)</b>
Anti-TNF $\alpha$	Meta-analysis of all comparator bDMARDs (anti-TNF $\alpha$ agents excluding CZP) as per the submission; I <sup>2</sup> = 0%			<b>4.43 (3.55, 5.53)</b>	SEC 150 mg	<b>0.48 (0.30, 0.77)</b>
	SEC 300 mg	<b>0.50 (0.32, 0.80)</b>				
	'lumped'	<b>0.49 (0.31, 0.77)</b>				
CZP	RAPID-PsA (12 wk, subgp)					
	CZP 200 mg	66/107 (61.7)	29/110 (26.4)	<b>2.34 (1.66, 3.31)</b>	150 mg vs 'lumped'	1.00 (0.59, 1.72)
	CZP 400 mg	55/112 (49.1)			300 mg vs 'lumped'	1.06 (0.63, 1.80)
	CZP ('lumped')	121/219 (55.3)			'lumped' vs 'lumped'	1.03 (0.62, 1.73)
UST 45 mg	PSUMMIT-1 (24 wk)	87/205 (42.4)	47/206 (22.8)	<b>1.86 (1.38, 2.50)</b>	SEC 150 mg	1.13 (0.69, 1.86)
	PSUMMIT-2 (24 wk, subgp)	23/43 (53.5)	12/42 (28.6)	<b>1.87 (1.08, 3.26)</b>	SEC 300 mg	1.20 (0.74, 1.95)
	Meta-analysis (ustekinumab vs placebo); I <sup>2</sup> = 0%				<b>1.86 (1.43, 2.42)</b>	'lumped'

Abbreviations: ACR20 = at least 20% improvement in the American College of Rheumatology response criteria; ACR50 = at least 50% improvement in the American College of Rheumatology response criteria; ADA = adalimumab; bDMARDs = biological disease modifying antirheumatic drugs; RR = relative risk; SEC = secukinumab; TNF $\alpha$  = tumour necrosis factor alpha  
<sup>a</sup> secukinumab versus the meta-analysis (where relevant) for the comparators. RR >1 favours secukinumab.

Note: Bolding indicates that the 95% CI does not include the null value.

Source: Adapted from Table 45, p136, Figure 8, p137, Table 50, p151, and Figure 12, p154 of the submission, CSR 24wk Table 14.2-1.4, pp409-414; CSR 24wk Table 14.2-7.4, pp710-715. Additional data for CZP extracted from Table 10 of the EMA document 'Cimzia Assessment report EMA/CHMP/601513/2013' (available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Assessment\\_Report\\_-\\_Variation/human/001037/WC500159001.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001037/WC500159001.pdf))

- 6.14 All trials demonstrated that the active treatments resulted in a statistically significantly greater proportion of patients achieving a 50% or 20% improvement in the ACR response compared with placebo. The indirect comparisons indicated there was no statistically significant difference between secukinumab and any of the bDMARDs for the ACR50 outcome. However, secukinumab was demonstrated to be statistically significantly less effective than etanercept, infliximab, golimumab and the combined bDMARDs results for the ACR20 outcome using RRs.
- 6.15 It was unclear whether the PBAC had accepted a minimally clinically important difference (MCID) for the ACR50. However, a non-inferiority margin of 0.29 for the RR had been previously proposed by the July 2015 ustekinumab re-submission. If this non-stringent non-inferiority margin was applied, non-inferiority of secukinumab to adalimumab, etanercept, infliximab and golimumab (individually or combined) cannot be concluded for the ACR50 (lower limits of the 95% CIs ranged between 0.05 and 0.17). However, non-inferiority of secukinumab versus certolizumab pegol and ustekinumab was demonstrated, as the lower bounds of the 95% CI for the RR were all greater than 0.29 (between 0.53 and 0.63).
- 6.16 If the non-stringent non-inferiority margin on 0.46 for the ACR20 outcome (golimumab PSD March 2010) was applied to the indirect comparisons that were not statistically significantly in favour of the comparator, non-inferiority of secukinumab versus adalimumab could not be concluded (lower bounds of the 95% CI were 0.32 or 0.34). However, non-inferiority versus certolizumab pegol and ustekinumab was demonstrated (lower limits of the 95% CI were between 0.59 and 0.74).
- 6.17 The submission claimed that the placebo response rate was higher in the secukinumab trial versus all the comparator trials for both the ACR50 and ACR20 at Week 12-16, and argued that the higher placebo rate in the secukinumab trial would bias the indirect comparison against secukinumab. The ACR50 and ACR20 placebo response rate at Week 12-16 were numerically higher for the secukinumab trial versus the adalimumab, etanercept, infliximab, and golimumab trials. The ESC noted that no formal adjustment for these differences in placebo response rate appeared to have been made in the indirect comparison.
- 6.18 The submission also claimed that indirect comparisons of secukinumab versus certolizumab pegol were not conducted due to the high heterogeneity across the trials, presumably for the primary time point. The basis of this claim appeared to be the differing proportions of patient with prior anti-TNF $\alpha$  exposure (35% for the secukinumab trial versus 22.5% in the certolizumab pegol trial). The certolizumab pegol trial generally reported higher ACR50 placebo response rates at Week 12-16 compared to the secukinumab trial in both the anti-TNF $\alpha$  naïve and overall populations; therefore it could be argued that indirect comparisons using ACR50 would be biased in favour of secukinumab. The ACR20 placebo response rates at Week 12 appear broadly comparable between both trials for both the anti-TNF $\alpha$  naïve and overall populations. Overall, there appeared to be more heterogeneity between the secukinumab trial and the adalimumab, etanercept, infliximab, and golimumab trials; but the submission presented these unadjusted indirect comparisons.

- 6.19 The ESC advised that the results of the indirect comparisons should be interpreted with caution as:
- There were concerns that the included trials were not sufficiently exchangeable given the identified differences between the included trials across multiple exchangeability domains, therefore the validity of the indirect comparisons was uncertain.
  - There were variations in the placebo response rates across the included trials that may not have been adjusted for in the indirect comparison, also suggesting that the trials may not be exchangeable.
  - There were several important differences in trial methods and setting confounders including differences in eligibility criteria, a broad range of sample sizes, trial dates and trial durations and differences in rescue/escape provisions.
  - The small number of patients in each arm, as well as relatively low event rates for the ACR50, contributed to wide CIs around the indirect treatment estimates. The confidence intervals for indirect comparisons using ORs were generally wider than comparisons using RRs.
  - The results of the FUTURE2 (secukinumab), RAPID-PsA (certolizumab pegol) and PSUMMIT-2 (ustekinumab) trials represented a subgroup of enrolled patients (anti-TNF $\alpha$  naïve). The ESC noted that no sensitivity analyses were presented to test for influence of potential effect under-powering and/or point-estimate imprecision.
  - The 300 mg dose of secukinumab may not be the TGA-recommended dose for the majority of the patients included in the indirect comparisons, as these patients were not anti-TNF $\alpha$  inadequate responders. The proportion of patients with moderate to severe plaque psoriasis was unclear.
  - The ESC noted that the PSCR presented a sub-group analysis for secukinumab responders disaggregated by prior anti-TNF $\alpha$  exposure and SEC dose (Figure 1, PSCR): TNF $\alpha$ -naïve 150mg > 300mg for ACR20/50/70; TNF $\alpha$ -experienced 300mg > 150mg for ACR20/50/70. Both doses are expected to be used in clinical practice if listed.

### **Comparative harms**

- 6.20 The submission presented naïve informal comparisons of safety data of secukinumab versus its comparators in the overall trial population. The submission stated that secukinumab was associated with a similar percentage of adverse events versus the comparators. This claim was difficult to verify given the limited comparative safety data presented, and the limitations of the presented data (e.g. timing of assessment and method in adjusting for crossover during early escape). There were differences in the placebo events rates (e.g. between 42% and 79.6% for any adverse events), thus the exchangeability of the trials was uncertain. However, the PBAC has previously accepted a claim equivalent safety of secukinumab versus adalimumab and ustekinumab for the treatment of plaque psoriasis, and did not accept a claim of superior safety versus infliximab during its March 2015 meeting. There was no new safety signal from the FUTURE2 (secukinumab) trial.
- 6.21 The ESC noted that no formal adjustment for differences in placebo adverse event rates appears to have been undertaken. Furthermore no direct adjustment for imbalance of observed effect modifiers between trials was undertaken.

- 6.22 The Periodic Safety Update Report stated that the identified risks for secukinumab were infections and infestations, neutropenia and hypersensitivity. Potential risks were malignant or unspecified tumours, major adverse cardiovascular events, immunogenicity, Crohn disease, hepatitis B reactivation and interactions with live vaccines.

**Clinical claim**

- 6.23 The submission described secukinumab (150 mg and 300 mg) as non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety versus adalimumab, etanercept, infliximab, golimumab, and certolizumab pegol, alone or in combination.
- 6.24 The PBAC considered that the claim of non-inferior comparative effectiveness to adalimumab, etanercept, infliximab and golimumab was not adequately supported.
- 6.25 The PBAC considered that secukinumab was non-inferior in terms of comparative effectiveness and comparative safety to certolizumab pegol and ustekinumab, based on the data presented.

**Economic analysis**

- 6.26 A cost minimisation against adalimumab was presented.
- 6.27 The equi-effective doses were estimated as secukinumab 150 mg or 300 mg at weeks 0, 1, 2, 3, 4 then 150 mg or 300 mg every month and adalimumab 40 mg every 2 weeks. The equi-effective dose was based on an insufficiently adjusted indirect comparison of one secukinumab trial with two adalimumab trials with placebo as the common comparator. The equi-effective dose may not be appropriate as the claim of non-inferiority of secukinumab to adalimumab is not adequately supported by the clinical evidence.
- 6.28 The submission considered a two year treatment horizon in the cost minimisation, with 28 packs of secukinumab (7 initiating, 21 continuation) required for a two year treatment period at \$ [REDACTED] per pack (ex-manufacturer price), resulting in the same cost as 26.5 packs of adalimumab (4 initiating, 22.5 continuing) required for the same two year treatment period at \$ [REDACTED] per pack (ex-manufacturer price). There are several issues with the cost minimisation:
- There is no discounting in the second year of treatment;
  - The number of packs adalimumab is overestimated. For the 36-week continuing period in Year 1 (after the initial dosing period of 16 weeks) the number of packs of adalimumab should be 9, instead of 9.5. The dose at the beginning of this period (at the Week 16 time point) is included in the costings for both secukinumab and adalimumab, but the dose at the end of this period (at the Week 52 time point) is counted as part of Year 2 costs. The ESC noted the PSCR stated that in this case the number of packs in year 2 would be 13.5, instead of 13. The ESC considered that the PSCR sufficiently addressed this issue; and

- In the FUTURE2 trial, the frequency of secukinumab administration in continuation phase is 4 weekly (13 packs per year) and not monthly (12 packs per year).

Assuming 9 continuing scripts of adalimumab in Year 1 and 13 scripts of secukinumab in Year 2 (second year discounted at 5%), the ex-manufacturer price per pack of secukinumab required to achieve cost neutrality compared to adalimumab decreases to \$ [REDACTED].

**Drug cost/patient/year:**

- 6.29 \$ [REDACTED] for first year (\$ [REDACTED] for initiation and \$ [REDACTED] for continuation) and \$ [REDACTED] for the second year and beyond.
- 6.30 The cost for secukinumab is greater in the first year of treatment as the dose frequency during the initiation phase is greater than during the continuation phase. Comparatively, the cost per patient/year for adalimumab is \$ [REDACTED] irrespective of year of treatment.

**Estimated PBS usage & financial implications**

- 6.31 This submission was not being considered by DUSC. The submission used a market share approach to estimate the uptake of secukinumab. The uptake of secukinumab was assumed to be 70% of the uptake of golimumab from the first 5 years of PBS listing. Uptake rate and growth assumptions were based on historical PBS usage data.

**Table 5: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
bDMARD scripts for PsA	61,568	70,474	80,942	90,518	100,588	110,397
Secukinumab scripts	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Estimated net cost to PBS/RPBS/MBS</b>						
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]
Net cost to MBS <sup>a</sup>	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
<b>Estimated total net cost</b>						
<b>Net cost to PBS/RPBS/MBS</b>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]

<sup>a</sup> From reduced use of infliximab  
Source: Table 77, p187, table 80, p188, table 81, p190, Table 83, 84 and 85, p195 and Table 91, p 200 of the submission

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.

- 6.32 The submission’s estimate of the number of prescriptions/year of secukinumab for psoriatic arthritis (and change in adalimumab, etanercept, golimumab, infliximab and certolizumab pegol) is based on:
- A declining market growth from 17% annually to 10% annually at year 6 of listing, which may not be reasonable based on the PBAC’s consideration of the DUSC report in November 2015, in which it has stated that “the use of biological disease-modifying anti-rheumatic drugs (bDMARDs) to treat psoriatic arthritis was increasing with no indication of a slowing in the growth of this market.”; The ESC noted that the PSCR highlighted Medicare data provided with submission,

indicating a 28% to 17% decline from 2011/12 through 2014/15. The PCSR stated that these data supported the submission's original assumptions. The ESC considered this to be reasonable.

- PBS listing for secukinumab occurring in the financial year 2015/2016. This is not reasonable as PBS listing will only occur in the financial year 2016/2017;
- Secukinumab market share of 5% ,9%, 11%, 13%, 14%, and 15% in the first 6 years respectively, with a plateau in the number of patients initiating therapy at Year 5 which is not justified given the continued market growth and in light of secukinumab's alternate mechanism of action and different safety profile to other bDMARDs;
- Assumptions that secukinumab replaces 50% of newer agents (golimumab 40%; certolizumab 10%) and 50% established agents (adalimumab 25%; etanercept 23%; infliximab 2%). This is not entirely reasonable because the market share rates have not been adequately justified given the financial implications are sensitive to this assumption; and
- In the maintenance phase, 12 packs of secukinumab replaces 13 packs of adalimumab, etanercept and certolizumab. One pack of secukinumab replaces one pack of golimumab. This may not be reasonable as the pivotal FUTURE 2 trial has maintenance dosing of once every 4 weeks, equivalent to 13 packs per patient per year. The financial implications are also very sensitive to this variable. The PCSR claimed that prescribers would be likely guided by the monthly dosing, rather than four-weekly, as specified in the approved Product Information (PI).

All these issues are likely to lead to an underestimate of the overall number of scripts of secukinumab dispensed and therefore underestimate the financial impact of listing secukinumab for psoriatic arthritis. Further, it is unclear what the impact of the positive recommendation for listing of ustekinumab for psoriatic arthritis on the PBS would be on the uptake and usage rate of secukinumab.

- 6.33 Sensitivity analyses around the financial estimates showed that the estimates are most sensitive to assumptions around the secukinumab maintenance dosing regimen and relative market share from amongst the bDMARDs. The assumption of 12 script per year (as per PI and in the base case) compared to 13 scripts per year (as per FUTURE2 dosing) led to a lower overall cost of secukinumab to the budget. Assuming 13 scripts per year of secukinumab used for continuation therapy changes the estimates from a net saving in the base case to a net cost of less than \$10 million at year 6 of listing.

### ***Financial Management – Risk Sharing Arrangements***

- 6.34 The sponsor proposed a risk-share arrangement, where a rebate was proposed for patients treated with the 300 mg dose such that the price paid for the 300 mg dose by the Commonwealth would be the same as the 150 mg dose. However, the sponsor stated that it cannot propose a pricing arrangement until the details of the PBAC recommendations for the psoriatic arthritis and ankylosing spondylitis indications are known.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended General Schedule Authority Required listing of secukinumab for the treatment of severe active psoriatic arthritis on a cost-minimisation basis with certolizumab pegol and ustekinumab. The PBAC considered that any biological disease modifying antirheumatic drug (bDMARD) listed on the PBS for psoriatic arthritis could be an appropriate comparator and noted that certolizumab pegol or ustekinumab had the lowest cost of these comparators. Based on the available evidence, the PBAC was not satisfied that secukinumab provides a significant improvement in efficacy or reduction of toxicity over certolizumab pegol or ustekinumab for some patients. Therefore, there was no basis for secukinumab to have a price advantage over certolizumab pegol or ustekinumab for an equivalent treatment period.
- 7.2 The PBAC noted the submission's claims that there is no dose response relationship between secukinumab 150 mg and 300 mg and as such there would be no difference in price between the two strengths.
- 7.3 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.
- 7.4 The equi-effective doses are secukinumab 150 mg or 300 mg administered at weeks 0,1,2,3 and 4 then 150 mg or 300 mg every month, ustekinumab 45 mg administered at weeks 0, 4 and then every 12 weeks thereafter and certolizumab 400 mg at weeks 0, 2 and 4 followed by 200 mg every 2 weeks or 400 mg every 4 weeks.
- 7.5 The PBAC noted the clinical claim of non-inferior comparative effectiveness and safety compared with adalimumab, etanercept, infliximab, golimumab, and certolizumab pegol. 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 against certolizumab pegol and ustekinumab, but not against adalimumab, etanercept, infliximab or golimumab.
- 7.6 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.
- 7.7 The PBAC noted the ESC's advice regarding market growth for bDMARDs for PsA. The PBAC considered that the submission's estimates of market growth were reasonable.

- 7.8 The PBAC recommended the same restriction for secukinumab as for the other bDMARDs for PsA, noting that the availability of this will allow clinicians to choose from a range of bDMARDs depending on the circumstances of individual patients.
- 7.9 The PBAC advised, under Section 101(3BA) of the *National Health Act 1953*, that secukinumab and ustekinumab and certolizumab pegol for the treatment of PsA should be treated as interchangeable on an individual patient basis.
- 7.10 The PBAC advised that secukinumab is not suitable for prescribing by nurse practitioners.
- 7.11 The PBAC advised that there was no reason to exempt secukinumab for PsA from the Early Supply Rule.
- 7.12 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.