

**5.13 SECUKINUMAB,
Injection 75 mg in 0.5 mL pre-filled syringe,
Injection 150 mg in 1 mL pre-filled pen,
Injection 300 mg in 2 mL pre-filled pen,
Injection 300 mg in 2 mL pre-filled syringe,
Cosentyx[®],
Novartis Pharmaceuticals Australia Pty Limited**

1 Purpose of submission

- 1.1 The Category 2 submission requested Authority Required listing for secukinumab for the treatment of paediatric patients with severe chronic plaque psoriasis (CPP).
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) comparing secukinumab and ustekinumab as the near-market secondary comparator (Table 1).

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

Component	Description
Population	Paediatric patients with severe chronic plaque psoriasis
Intervention	Secukinumab (based on body weight, at Week 0,1,2,3 and 4 followed by same dose every month).
Comparator	Etanercept (0.8 mg/kg, up to max. of 50 mg every week) as the main comparator and ustekinumab (weight-based dosing at Week 0,4 then every 12 weeks) ^a as the near market secondary comparator.
Outcomes	Clinical response: proportion of patients meeting PASI response criteria (PASI 75 and 90) and IGA 0/1 response; change in safety and tolerability.
Clinical claim	In paediatric patients with severe psoriasis, secukinumab demonstrates superior effectiveness compared with etanercept as assessed by statistically significant improvements in PASI 75, PASI 90 and IGA 0/1.

Source: Table 1.1, p.26 of the submission.

IGA = Investigator's Global Assessment; PASI = Psoriasis Area and Severity Index.

^a There was an error in the submission which stated ustekinumab had dosing at week 0,2 then every 12 weeks.

2 Background

Registration status

- 2.1 **TGA status at time of PBAC consideration:** The submission was made under the TGA/PBAC Parallel Process. The TGA application requested an extension of the indication to moderate to severe paediatric plaque psoriasis, and also to register a new strength (75 mg/0.5 mL syringe). A concurrent separate TGA application was made for an additional strength (300 mg/2 mL) in 2 dosage forms (syringe and pen device). At the time of PBAC consideration, the Clinical Evaluation Report (Second Round for the paediatric psoriasis application, First Round for the additional strength application) was available for both applications.

- 2.2 The TGA Delegate provided a file note prior to PBAC consideration confirming the applications would not be considered by the Advisory Committee on Medicines and stated “no major issues or concerns are noted with the efficacy and safety data that the Sponsor has provided to support the extension of indication.” The Delegate stated:
- “The [TGA] evaluator has recommended the indication as *COSENTYX is indicated for the treatment of moderate to severe plaque psoriasis in patients 6 years and older who are candidates for systemic therapy or phototherapy. At this stage, as the delegate for this submission, I agree with the evaluator’s recommendation.*”
- 2.3 The PBAC noted that paediatric patients over 50 kg may require a 300 mg dose. The PBAC supported the PBS listing of the 300 mg strength for paediatric patients if the following wording is included in the paediatric psoriasis dose section in the final Product Information: "Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg."
- 2.4 Secukinumab was TGA registered on 8 January 2015 for moderate to severe plaque psoriasis in adult patients.

Previous PBAC consideration

- 2.5 This is the first consideration of secukinumab by the PBAC for this indication. Secukinumab is currently listed on the PBS for the treatment of severe CPP, ankylosing spondylitis, severe psoriatic arthritis and non-radiographic axial spondyloarthritis in patients 18 years of age and over.

3 Requested listing

- 3.1 The requested abridged listing for secukinumab is provided below (for initial phase patients with no prior biologic treatment, and for continuing phase treatment). The submission also requested a restriction for change or recommencement of treatment of <5 years and >5 years, a balance of supply restriction for both initial treatment and continuing treatment, and a grandfathering provision for patients treated as part of the Sponsor’s patient familiarisation and compassionate access programs. While the submission did not request a Special Pricing Arrangement (SPA), it is noted that a SPA applies to the secukinumab listing for adults in severe CPP.

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Name, Restriction, Manner of administration and form	Max. Qty (units)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
Secukinumab Injection, 75mg/0.5mL, 150mg/1mL, 300mg/2mL	1	0 (initial) 3 (initial) 5 (continuing)	\$██████ per pack ^a	Cosentyx [®]	Novartis Pharmaceuticals
Category/Program:	GENERAL – General Schedule (Code GE)				
PBS indication	Severe chronic plaque psoriasis				
Restriction:	Authority Required - In Writing/HPOS				
Treatment criteria:	Must be treated by a dermatologist				
Treatment phase:	Initial treatment 1, Face, hand, foot (new patient)		Initial treatment 1, Whole body (new patient)		
Clinical criteria:	<ul style="list-style-type: none"> • The treatment must be as systemic monotherapy; OR • The treatment must be in combination with methotrexate, AND • Patient must have lesions present for at least 6 months from the time of initial diagnosis, AND • Patient must not have received any prior PBS-subsidised treatment with a biological medicine for this condition; OR • Patient must not have received any PBS-subsidised treatment with a biological medicine for this condition for at least 5 years, AND • Patient must have failed to achieve an adequate response, as demonstrated by a Psoriasis Area and Severity Index (PASI) assessment, to at least 2 of the following 3 treatments: <ul style="list-style-type: none"> (i) phototherapy (UVB or PUVA) for 3 treatments per week for at least 6 weeks; and/or (ii) methotrexate at a dose of at least 10 mg or 10 mg per square metre weekly (whichever is lowest) for at least 6 weeks; and/or (iii) acitretin at a dose of at least 0.4mg per kg per day for at least 6 weeks, AND • Patient must not receive more than 16 weeks of treatment with secukinumab under this restriction 				
Population criteria:	Patient must be under 18 years of age and a parent or authorised guardian must have signed a patient acknowledgement.				
Prescriber criteria:	<p>The following criterion indicates failure to achieve an adequate response to prior treatment and must be demonstrated in the patient at the time of the application:</p> <p>(a) Chronic plaque psoriasis classified as severe due to a plaque or plaques on the face, palm of a hand or sole of a foot where:</p> <p>(i) at least 2 of the 3 Psoriasis Area and Severity Index (PASI) symptom subscores for erythema, thickness and scaling are rated as severe or very severe, as assessed, preferably whilst still on treatment, but no longer than 1 month following cessation of the most recent prior treatment; or</p> <p>(ii) the skin area affected is 30% or more of the face, palm of a hand or sole of a foot, as assessed, preferably whilst still on treatment, but no longer than 1 month following cessation of the most recent prior treatment;</p>		<p>The following criterion indicates failure to achieve an adequate response to prior treatment and must be demonstrated in the patient at the time of the application:</p> <p>(a) A current Psoriasis Area and Severity Index (PASI) score of greater than 15, as assessed, preferably whilst still on treatment, but no longer than 1 month following cessation of the most recent prior treatment.</p> <p>(b) A PASI assessment must be completed for each prior treatment course, preferably whilst still on treatment, but no longer than 1 month following cessation of each course of treatment.</p> <p>(c) The most recent PASI assessment must be no more than 1 month old at the time of application.</p>		

	(b) A PASI assessment must be completed for each prior treatment course, preferably whilst still on treatment, but no longer than 1 month following cessation of each course of treatment. (c) The most recent PASI assessment must be no more than 1 month old at the time of application.	
Treatment phase	Continuing treatment [Whole body or Face, hand, foot]	
Restriction:	Authority Required - In Writing/HPOS	
Clinical Criteria	<ul style="list-style-type: none"> • Patient must have previously received this drug as their most recent course of PBS-subsidised biologic medicine treatment with for this condition, AND • Patient must have demonstrated an adequate response to treatment with this drug for this condition, AND <p>The treatment must not exceed a maximum of 24 weeks with this drug per authorised course under this restriction.</p>	
Prescriber Instructions	<p>An adequate response to treatment is defined as:</p> <p>For Whole body A Psoriasis Area and Severity Index (PASI) score which is reduced by 75% or more, or is sustained at this level, when compared with the baseline value for this treatment cycle.</p> <p>For Face, hand, foot (i) a reduction in the Psoriasis Area and Severity Index (PASI) symptom subscores for all 3 of erythema, thickness and scaling, to slight or better, or sustained at this level, as compared to the baseline values; or (ii) a reduction by 75% or more in the skin area affected, or sustained at this level, as compared to the baseline value for this treatment cycle.</p>	

Source: adapted from Table 1.8, p40-45.

^aThe submission used the pre 1 July dispensing fee (\$7.74) instead of \$7.78; the effective DPMQ should be \$█ for an ex-manufacturer price of \$█.

- 3.2 The submission proposed an effective dispensed price for maximum quantity (DPMQ) of \$█ for three strengths (75 mg/0.5 mL, 150 mg/1 mL and 300 mg/2 mL).
- 3.3 The proposed restriction is narrower than the proposed TGA indication with respect to psoriasis severity. The restriction is for 'severe chronic plaque psoriasis' while the TGA indication is 'moderate to severe plaque psoriasis'. This restriction is consistent with the etanercept and ustekinumab listing.
- 3.4 The proposed PBS population was wider than the proposed TGA population with respect to patient age, as the PBS population is <18 years, while the TGA indication limits treatment to patients aged ≥6 years. The same respective PBS and TGA age limits also apply to ustekinumab. The age of the PBS population for etanercept is also <18 years, while the TGA indication for etanercept limits treatment to patients aged ≥4 years.
- 3.5 The proposed PBS population and circumstances of use for treatment with secukinumab is broadly consistent with those for ustekinumab and etanercept, except for:

- Maximum duration of initial therapy, which is 16 weeks for secukinumab and etanercept, and 28 weeks for ustekinumab.
 - Total maximum duration of therapy for etanercept, which is limited to 24 weeks' treatment due to its safety profile (see paragraph 6.33); this limit does not apply to ustekinumab or secukinumab.
 - Time of Psoriasis Area and Severity Index (PASI) response assessment for continuing treatment. PASI response assessment with etanercept and secukinumab is conducted at least 12 weeks after treatment initiation. PASI response assessment with ustekinumab is conducted 24 weeks after treatment initiation.
 - The maintenance dosing schedule. Patients receive etanercept weekly, ustekinumab every 12 weeks, and secukinumab monthly.
- 3.6 Currently, ustekinumab may be used before or after etanercept and patients may switch between the biologics. Neither the current restrictions for etanercept and ustekinumab, or the proposed restriction for secukinumab, prevent sequential use of one biologic before (or after) the other. The choice and/or order of biologic use will likely depend on the clinician discretion and patient preference (paragraph 4.3, ustekinumab Public Summary Document (PSD), March 2021).
- 3.7 The submission requested a 5-year break after 3 failures of biologics. This is consistent with both the etanercept and ustekinumab PBS listings for paediatric severe CPP.

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

4 Population and disease

- 4.1 Psoriasis is a chronic relapsing disease of the skin characterised by variable clinical features. Skin lesions are characterised by prominent erythema, induration, and scaling. Plaque-type psoriasis is the most frequent clinical presentation. Psoriasis tends to be underdiagnosed, especially in children, as their symptoms are often atypical and overlap with those of other skin conditions such as dermatitis.
- 4.2 The submission estimated that the incidence of severe paediatric psoriasis in Australia was 30–40 patients per year, based on the PBS 10% sample of Medicare data analysing etanercept's listing from 1 August 2012. The submission assumed that the prevalence of severe paediatric psoriasis was 0.25%.
- 4.3 Secukinumab is a high-affinity, recombinant, fully human monoclonal antibody that binds to and neutralises the activity of the proinflammatory cytokine IL-17A. By inhibiting the interaction of IL-17A with its receptor, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage, and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases, including psoriasis.

5 Comparator

- 5.1 The submission proposed the following two comparators:
- Etanercept as the main comparator; and
 - Ustekinumab as a near-market secondary comparator.
- 5.2 The submission nominated etanercept as the main comparator. The main argument provided in support of this nomination was that it is the only biologic agent currently PBS listed at the time of submission for treatment of severe paediatric psoriasis. The submission nominated ustekinumab as a near-market secondary comparator as it had received a positive recommendation at the PBAC March 2021 meeting. The comparator used for the economic evaluation was ustekinumab.
- 5.3 After the application was submitted, ustekinumab was listed on the PBS on 1 October 2021 for severe CPP in patients under 18 years of age.
- 5.4 Under Section 101(3B) of the National Health Act (1953), the PBAC cannot recommend listing a therapy that is substantially more costly than an alternative therapy unless it is satisfied that the therapy provides, for some patients, a significant improvement in efficacy and/or reduction in toxicity. The submission claimed that secukinumab provides a significant improvement in efficacy compared to etanercept, and has non-inferior efficacy and safety to ustekinumab.

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 and welcomed the input from 3 health care professionals (HCPs) via the Consumer Comments facility on the PBS website. The comments from the HCPs emphasised the benefits of secukinumab in severe CPP for paediatric patients in terms of effectiveness, safety, quality of life, and access/equity. One HCP stated that secukinumab is efficacious and safer than other therapeutic options currently available. Another HCP noted that current medication options require blood test monitoring in children to check liver and kidney function, which would not be required for most children using secukinumab. A third HCP commented on the issue of access and equity; i.e. that biological medicines have been life changing for adults with psoriasis but PBS funding for those aged under 18 is extremely limited. The HCPs also commented on the significant improvement in quality of life for children who have severe CPP, as their symptoms of bright red itchy skin and disfigurement improve, leading to normal progress in terms of socialising, education and emotional development.

Clinical studies

6.3 The submission was based on a direct comparison between secukinumab and etanercept:

- Study 2310 (N=162): a phase III, double-blind, randomised trial in severe plaque psoriasis patients ≥ 6 years comparing secukinumab high dose (HD) and low dose (LD), to etanercept [and placebo].

6.4 The submission was also based on an indirect comparison, using placebo as the common reference, in order to compare secukinumab to ustekinumab:

- Study 2310 (N=162), comparing secukinumab HD and LD, to placebo.
- CADMUS (N=110), a phase III, double-blind, randomised trial in patients aged 12 to 17 years who had moderate-to-severe plaque psoriasis, comparing ustekinumab to placebo.

6.5 Details of the studies included for analysis are provided in Table 2.

Table 2: Trials/studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Study 2310 (NCT02471144)	A Randomized, Double-blind, Placebo- and Active Controlled Multicenter Trial to Demonstrate Efficacy of Subcutaneous Secukinumab Compared to Placebo and Etanercept (in a Single-blinded Arm) After Twelve Weeks of Treatment, and to Assess the Safety, Tolerability, and Long-term Efficacy in Subjects From 6 to Less Than 18 Years of Age With Severe Chronic Plaque Psoriasis	Clinical Study Report Ongoing study Estimated completion date July 19, 2023
	Bodemer et al. Secukinumab demonstrates high efficacy and a favourable safety profile in paediatric patients with severe chronic plaque psoriasis: Week 52 results from a Phase 3 double-blind randomized, controlled trial.	Journal of the European Academy of Dermatology and Venereology 2021, 35 (4): 938-947.
Indirect randomised trials		
CADMUS ^a (NCT01090427)	A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the of Efficacy and Safety of Ustekinumab in the Treatment of Adolescent Subjects With Moderate to Severe Plaque-type Psoriasis (CADMUS)	Clinical Study Report 2014
	Landells et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: Results of the randomized phase 3 CADMUS study.	Journal of the American Academy of Dermatology 2015 73 (4): 594-603.
	Landells et al. Safety and efficacy of ustekinumab in adolescent patients with moderate to severe plaque psoriasis: Results through 1 year of the phase 3 CADMUS trial.	73rd Annual Meeting of the American Academy of Dermatology. J Journal of the American Academy of Dermatology (2015) 72:5 SUPPL. 1 (AB202).

Source: Table 2.10, p53-55 of the submission.

^a The PBAC has previously considered the CADMUS trial for ustekinumab in paediatric severe CPP in March 2021.

6.6 The key features of the studies are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Primary outcomes
Direct comparison					
Secukinumab vs etanercept					
Study 2310	162	R, DB 52 weeks	Moderate	Severe paediatric CPP	PASI 75 response and IGA mod 2011 0 or 1 response at Week 12
Indirect comparison					
Secukinumab vs ustekinumab (with placebo as common reference)					
Secukinumab vs placebo Study 2310	162	R, DB 52 weeks	Moderate	Severe paediatric CPP	PASI 75 response and IGA mod 2011 0 or 1 response at Week 12
Ustekinumab vs placebo CADMUS	110 ^b	R, DB	Low	Moderate to severe CPP ^a poorly controlled on topical therapy. Age 12 to 17 years	PGA 0/1 response at Week 12

Source: Compiled during the evaluation from Section 2 of the submission.

BSA = body surface area; CPP = chronic plaque psoriasis; DB = double blind; IGA = Investigator's Global Assessment; MC = multi-centre; OL = open label; OS = overall survival; PASI = Psoriasis Area and Severity Index; PFS = progression-free survival; PGA = Physician Global Assessment; R = randomised.

^a Defined by a PASI ≥ 12 , PGA ≥ 3 , and BSA involvement $\geq 10\%$.

^b Only 73 patients were analysed in the submission, reflecting patients receiving the ustekinumab standard dose (0.75 mg/kg for patients ≤ 60 kg, at Week 0, 4, and every 12 weeks thereafter), which was consistent with the TGA approved dosage for ustekinumab for the paediatric population.

6.7 Study 2310 is a phase 3, randomised, double blind trial that enrolled 162 children and adolescents aged 6 to 18 years with severe CPP. This was defined as a PASI >20 , an Investigator's Global Assessment 2011 modified version (IGA mod 2011) score of ≥ 4 , and body surface area (BSA) involvement $\geq 10\%$. Patients were stratified by weight (<25 kg, 25 to <50 kg, ≥ 50 kg) and age (6 to <12 years, ≥ 12 to <18 years). Patients were randomised 1:1:1:1 to receive LD (75 mg/75 mg/150 mg) or HD (150 mg/300 mg)^a subcutaneous secukinumab or placebo or etanercept (0.8 mg/kg up to a maximum of 50 mg). Patients who were on placebo during induction and who at Week 12 were PASI 75 non-responders could be switched to either secukinumab LD or secukinumab HD treatment group in the maintenance phase according to their baseline randomisation. The dosing frequency was secukinumab injections at weeks 0, 1, 2, 3, 4, and followed by every 4 weeks.

6.8 Study 2310 had an overdosing error in a high proportion of patients in the secukinumab arm (total 36/80 secukinumab patients: 45%). Thirty-six patients who were assigned to the secukinumab groups (LD: 16 patients and HD: 20 patients) were

^a Patients weighing ≥ 50 kg received 150 mg (low dose group) and 300 mg (high dose group); patients weighing 25 to <50 kg received 75 mg (low dose group) and 150 mg (high dose group); and patients weighing <25 kg received 75 mg for both dose groups.

dispensed active secukinumab medication at Week 13, 14, 15 visits instead of placebo medication (p49 of PM-2020-06312 Clinical Evaluation Report for Cosentyx), and thus received 3 additional doses of active treatment. This increases the uncertainty of the Week 52 analysis of Study 2310, but not the Week 12 analysis. The Pre-Sub-Committee Response (PSCR) provided an analysis of patients both affected and not affected by the dosing error. There was no statistical analysis provided, but the results suggest that patients who were not affected by the dosing error had lower response rates at Week 52 compared to those who were affected.

- 6.9 Study 2310 had a moderate risk of bias due to the unblinding of participants to etanercept treatment. Etanercept was single (efficacy assessor) blinded to prevent observer bias, and not patient-blinded. The rationale presented in the submission was that since the dosing regimens of the two products are different (weekly dosing in etanercept vs monthly in secukinumab), double blinding would be inappropriate in children due to the number of additional placebo injections needed in order to achieve a true double-blind administration. The unmasking of etanercept increased the risk of bias for secukinumab compared to etanercept.
- 6.10 CADMUS was a phase 3 randomised, double-blind, placebo-controlled, parallel-group, multi-centre three-arm study that enrolled 110 adolescent patients (≥ 12 to < 18 years) with moderate to severe CPP defined by PASI ≥ 12 , a Physician's Global Assessment (PGA) ≥ 3 , and BSA involvement $\geq 10\%$. Patients were randomised in a 1:1:1 ratio to ustekinumab standard dose ($n=36$), ustekinumab half-standard dose ($n=37$) and placebo ($n=37$). The submission only presented the ustekinumab standard dose (0.75 mg/kg for patients ≤ 60 kg, at Week 0, 4, and every 12 weeks thereafter), which was consistent with the TGA approved dosage for ustekinumab for the paediatric population. CADMUS was considered to have a low risk of bias. The PBAC has previously considered the CADMUS trial for ustekinumab in paediatric severe CPP in March 2021.
- 6.11 CADMUS and Study 2310 did not allow concomitant use of methotrexate, and as such, although the proposed restriction allows use in combination with methotrexate, the efficacy and safety of this combination was unknown. Study 2310 did not allow a topical corticosteroid treatment for the face, scalp, hands, feet and genitoanal area after the patient had been randomised. This differs to the CADMUS trial which allowed topical steroids.
- 6.12 Generally, baseline characteristics across CADMUS and Study 2310 were different with regards to the age of patients, prior biologics, and severity grade. There was a higher proportion of patients in the CADMUS study who had received biologic therapy prior to enrolment (10.9%), compared to only 2.5% of patients in Study 2310. In terms of patient age, the ustekinumab study (CADMUS) included children and adolescents aged 12 to 17 years, and the secukinumab study (2310) included children and adolescents aged 6 years to < 18 years. However, the mean age across the studies did not differ greatly. Compared with 53% in Study 2310, the number of patients who had received

prior systemic therapy was numerically lower in the ustekinumab CADMUS study (43%).

6.13 CADMUS and Study 2310 enrolled patients with different severity CPP compared to the proposed PBS population as:

- In CADMUS, the severity grade was PASI >12 (moderate-to-severe) while Study 2310 included only with PASI ≥20 (severe). This differs to the proposed PBS restriction of PASI >15 (severe).
- The trials did not require patients to have failed to achieve an adequate response to two of phototherapy, methotrexate or acitretin, as proposed in the requested listing.

Comparative effectiveness

Direct comparison between secukinumab and etanercept

6.14 Table 4 presents Study 2310 results of the co-primary clinical response outcomes (PASI 75 and IGA 0/1) at Week 12 and 52.

Table 4: Summary of clinical response at Week 12 and 52 in Study 2310

Outcome	Treatment comparison	Secukinumab n/N (%)	Control	OR	p-value
			n/N (%)	estimate (95% CI)	
At Week 12^a					
PASI 75	SKB LD vs. placebo	32/40 (80.0)	6/41 (14.6)	25.78 (7.08, 114.66)	<0.0001
	SKB HD vs. placebo	31/40 (77.5)	6/41 (14.6)	22.65 (6.31, 98.93)	<0.0001
PASI 75	SKB LD vs etanercept	32/40 (80.0)	26/41 (63.4)	2.25 (0.73, 7.38)	0.1819
	SKB HD vs etanercept	31/40 (77.5)	26/41 (63.4)	1.92 (0.64, 6.07)	0.2919
IGA 0/1	SKB LD vs. placebo	28/40 (70.0)	2/41 (4.9)	51.77 (10.02, 538.64)	<0.0001
	SKB HD vs. placebo	24/40 (60.0)	2/41 (4.9)	32.52 (6.48, 329.52)	<0.0001
IGA 0/1	SKB LD vs etanercept	28/40 (70.0)	14/41 (34.1)	4.49 (1.60, 13.42)	0.0027
	SKB HD vs etanercept	24/40 (60.0)	14/41 (34.1)	2.86 (1.05, 8.13)	0.0395
At Week 52^{a,b}					
PASI 75	SKB LD vs etanercept	35/40 (87.5)	28/41 (68.3)	3.25 (1.03, 10.21)	0.04
	SKB HD vs etanercept	35/40 (87.5)	28/41 (68.3)	3.25 (1.03, 10.21)	0.04
IGA 0/1	SKB LD vs etanercept	29/40 (72.5)	23/41 (56.1)	2.06 (0.82, 5.22)	0.08
	SKB HD vs etanercept	30/40 (75.0)	23/41 (56.1)	2.35 (0.91, 6.04)	0.13

Source: Table 2.30, p88-89 of the submission.

CI = confidence interval; HD = high dose; IGA = Investigator's Global Assessment; LD = low dose; N = number of patients evaluable; n = the number of responders; NRI = non-responder imputation; OR = odds ratio; PASI = Psoriasis Area and Severity Index; SKB = secukinumab.

Bold indicates statistical significance.

^a Non-responder imputation was used to handle missing values in full analysis set for outcomes at Week 12 and Week 52.

^b Week 52 analysis includes 36 patients out of 80 secukinumab patients (16 in low dose and 20 in high dose) who received an extra dose at Weeks 13, 14, 15.

- 6.15 Secukinumab demonstrated significantly higher response compared to etanercept for IGA 0/1 at Week 12 and for PASI 75 at Week 52. However, there was no significant difference for PASI 75 at Week 12 or IGA 0/1 at Week 52.

Indirect comparison between secukinumab and ustekinumab

- 6.16 In the absence of a direct head-to-head trial, an indirect comparison was conducted using the Bucher method (Mantel-Haenszel, fixed effect model) to compare secukinumab to ustekinumab at Week 12, using placebo as the common reference. The PBAC previously considered that Week 12 results for all treatments (ustekinumab, etanercept and placebo) should have been used in the indirect comparison in the ustekinumab submission as this was reflective of the double-blind phase of the respective trials (paragraph 6.27, ustekinumab PSD, March 2021).
- 6.17 Table 5 presents the results of the indirect comparison for the PASI 75 response at Week 12, on which the claim of non-inferiority effectiveness of secukinumab compared to ustekinumab is based.

Table 5: Summary of results of the indirect comparison for PASI 75 response

Trial type or estimate	Intervention	Placebo	OR	RD
	n/N (%)	n/N (%)	(95% CI)	(95% CI)
Secukinumab versus placebo (Week 12)				
Study 2310 (LD)	32/40 (80.0%)	6/41 (14.6%)	23.33 (7.30, 74.58)	0.65 (0.49, 0.82)
Study 2310 (HD)	31/40 (77.5%)	6/41 (14.6%)	20.09 (6.42, 62.86)	0.63 (0.46, 0.80)
Study 2310 (combined doses)	63/80 (78.8%)	6/41 (14.6%)	21.62 (7.81, 59.85)	0.64 (0.50, 0.78)
Ustekinumab versus placebo (Week 12)				
CADMUS	29/36 (80.6%)	4/37 (10.8%)	34.18 (9.08, 128.7)	0.70 (0.53, 0.86)
Indirect comparisons				
Secukinumab (LD) vs ustekinumab			0.68 (0.12, 3.98)	-0.05 (-0.28, 0.18)
Secukinumab (HD) vs ustekinumab			0.59 (0.10, 3.38)	-0.07 (-0.30, 0.16)
Secukinumab (combined doses) vs ustekinumab			0.63 (0.12, 3.37)	-0.06 (-0.27, 0.15)

Source: Table 2.5.1, p113 of the submission.

CI = confidence interval; ETN = etanercept; HD = high dose; LD = low dose; OR = odds ratio; PBO = placebo; RD = risk difference; SEC = secukinumab; UST = ustekinumab.

Bold indicates statistical significance.

- 6.18 For PASI 75 response, the indirect comparison of secukinumab (LD or HD) and ustekinumab showed no statistically significant difference for either odds ratio or risk difference. The indirect comparison had a small sample size (40:40:41 patients in each of the secukinumab HD, LD and placebo arms, respectively, for Study 2310 [total 121 patients]; and 36:37 patients in each of the ustekinumab and placebo arms, respectively, for CADMUS [total 73 patients]).
- 6.19 There were key differences between CADMUS and Study 2310 (paragraph 6.12). CADMUS and Study 2310 had differences in the trial population for severity grade of CPP and child age. Treatment differences included prior use of biologics and systemic therapy. The lack of applicability of the CADMUS population (moderate to severe) to

the proposed PBS population (severe), and its small sample size (n=76) creates uncertainty regarding the lack of difference in PASI 75 response between ustekinumab and secukinumab.

- 6.20 The submission nominated a non-inferiority margin of 10% for PASI 75 with respect to risk difference. While 10% is the same non-inferiority margin used for the PASI 75 and PASI 90 outcomes in guselkumab and risankizumab submissions for severe CPP in adults (guselkumab PSD March 2018; risankizumab PSD July 2019), it is unclear whether it is appropriate to apply to the paediatric population. Moreover, the submission did not apply the non-inferiority margin to the PASI 75 outcomes. The evaluation noted that the lower risk difference confidence intervals for the indirect comparison of secukinumab LD, HD and combined doses vs ustekinumab (Table 6) were outside the proposed 10% margin, and therefore the proposed non-inferiority margin was not met.
- 6.21 The submission claimed that no minimal clinically important difference (MCID) was specified in the trials and so proposed a 75% reduction from the baseline PASI score (i.e. PASI 75 response) as the MCID. However, this is not a MCID, rather a justification of the clinical relevance of the PASI 75 outcome. The MCID suggested for the secondary outcome of Children's Dermatology Life Quality Index (CDLQI) was from the Langley 2011^a publication on the Study 20030211^b (etanercept versus placebo; 2.5 mean change in score).
- 6.22 Table 6 presents the change in health-related quality of life (HRQoL) of CDLQI from baseline in Study 2310. Both secukinumab and etanercept show improved HRQoL from baseline via the CDLQI score. Study 2310 reports mean changes in HRQoL of 5.26 for secukinumab and 3.92 for etanercept above placebo, respectively. While these scores were above the MCID of 2.5 mean change in CDLQI proposed by Langley 2011, according to Waters et al. (2010)^c identified during the evaluation, these mean changes would be considered small.

^a Langley RG et al. Patient-reported outcomes in pediatric patients with psoriasis undergoing etanercept treatment: 12-week results from a phase III randomized controlled trial. *J Am Acad Dermatol* 2011;64:64-70.

^b Study 20030211 was a phase III, double-blind, randomised, placebo-controlled trial in moderate-to-severe plaque psoriasis, aged 4 to 17 years, comparing etanercept to placebo.

^c Waters A, Sandhu D, Beattie P, Ezughah F, Lewis-Jones S. Severity stratification of Children's Dermatology Life Quality Index (CDLQI) scores. *Br J Dermatol* 2010; 163 (Suppl 1): 121.

Table 6: Summary of CDLQI from Study 2310*

Treatment arm	N	Mean change from baseline	SD	% Mean change from baseline	SD	% Median change from baseline (range)
Secukinumab LD	38	-9.05	7.17	-67.43	41.6	-80 (-100, -54)
Secukinumab HD	38	-7.71	7.74	-62.5	50.08	-80 (-100, -50)
Etanercept	40	-6.49	7.31	-62.8	34.4	-66.6 (-91.6, -42.8)
Placebo	41	-3.79	6.2	-18.4	80.01	-37.5 (-61.9, 0)

Source: Table 2.34, p95 of the submission. *Modified during the evaluation to isolate the direct comparison.*

CDLQI = Children's Dermatology Life Quality Index; ETN = etanercept; HD = high dose; LD = low dose; NR = not reported; PASI = Psoriasis Area and Severity Index; PBO = placebo; SEC = secukinumab.

*Note that the results presented in Table 6 are derived from ad-hoc/ post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for study 2310. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Comparative harms

Direct comparison between secukinumab and etanercept

6.23 The summary of adverse events (AEs) in direct comparison in Study 2310 is presented in Table 7.

Table 7: Summary of key adverse events in Study 2310, up to Week 24*

Trial ID	Secukinumab n (%)	Etanercept n (%)	RR (95% CI) ^a	RD (95%CI) ^a
Secukinumab low dose				
Any AE (at least one)	23 (57.5)	25 (61.0)	0.94 (0.66, 1.35)	-0.03 (-0.25, 0.18)
Nasopharyngitis	7 (17.5)	4 (9.8)	1.79 (0.57, 5.66)	0.08 (-0.07, 0.23)
Headache	2 (5.0)	1 (2.4)	2.05 (0.19, 21.72)	0.03 (-0.06, 0.11)
Abdominal pain	2 (5.0)	3 (7.3)	0.68 (0.12, 3.88)	-0.02 (-0.13, 0.08)
Pharyngitis	2 (5.0)	0 (0.0)	NA	0.05 (-0.02, 0.12)
Any SAE (at least one)	1 (2.5%)	4 (9.8%)	0.26 (0.03, 2.19)	-0.07 (-0.18, 0.03)
AEs resulting in discontin.	0 (0%)	1 (2.4%)	NA	-0.02 (-0.07, 0.02)
Secukinumab high dose				
Any AE (at least one)	25 (62.5)	25 (61.0)	1.03 (0.73, 1.44)	0.02 (-0.20, 0.23)
Nasopharyngitis	6 (15.0)	4 (9.8)	1.54 (0.47, 5.04)	0.05 (-0.09, 0.20)
Headache	3 (7.5)	1 (2.4)	3.08 (0.33, 28.34)	0.05 (-0.04, 0.14)
Abdominal pain	2 (5.0)	3 (7.3)	0.68 (0.12, 3.88)	-0.02 (-0.13, 0.08)
Pharyngitis	2 (5.0)	0 (0.0)	NA	0.05 (-0.02, 0.12)
Any SAE (at least one)	1 (2.5%)	4 (9.8%)	0.26 (0.03, 2.19)	-0.07 (-0.18, 0.03)
AEs resulting in discontin.	1 (2.5%)	1 (2.4%)	1.03 (0.07, 15.83)	0.00 (-0.07, 0.07)

Source: Table 2.35, p102-103 and Table 2.36, p104 of the submission.

Abbreviations: AE = adverse event; CI = confidence interval; discontin. = discontinuation; NA = not applicable; RR = relative risk; RD = risk difference; SAE = serious adverse event; SD = standard dose.

^a Modified during the evaluation to focus on the direct comparison between secukinumab and etanercept, and to add RR (95% CI) and RD (95% CI).

*Note that the results presented in Table 7 are derived from ad-hoc/ post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for study 2310. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.24 There were no significant differences between secukinumab and etanercept for any AEs in Study 2310. Secukinumab LD and HD has fewer serious AEs, and fewer AEs

resulting in discontinuation at LD compared to etanercept. The majority of the AEs reported at Week 12 were of mild to moderate severity. The difference between the treatment groups were marginal. The small sample size limits the ability to observe serious AEs and to detect a difference between groups.

Indirect comparison between secukinumab and ustekinumab

6.25 The summary of AEs in the indirect comparison is presented in Table 8.

Table 8: Summary of results of the indirect comparison for adverse events*

	Secukinumab/ ustekinumab	Placebo	OR	p-value
	n/N (%)	n/N (%)	(95% CI)	
Any AE				
Secukinumab versus placebo (Week 12)				
Study 2310 (combined doses)	48/80 (60.0)	22 / 41 (53.7)	1.30 (0.61,2.77)	0.50
Ustekinumab versus placebo (Week 12)				
CADMUS	16/36 (44.4)	21 / 37 (56.8)	0.61 (0.24,1.54)	0.29
Any SAE				
Secukinumab versus placebo (Week 12)				
Study 2310 (combined doses)	2/80 (2.5)	0/40 (0)	NA	0.33
Ustekinumab versus placebo (Week 12)				
CADMUS	0/36 (0)	0/37 (0)	NA	1.00
Any AE resulting in discontinuation				
Secukinumab versus placebo (Week 12)				
Study 2310 (combined doses)	1/80 (1.25)	1/41 (2.44)	0.51 (0.03,8.31)	0.66
Ustekinumab versus placebo (Week 12)				
CADMUS	0/36 (0)	0/37 (0)	NA	1.00
INDIRECT COMPARISONS				
Any AE				
Secukinumab (combined doses) vs ustekinumab			2.13 (0.64, 7.06)	NR

Source: Table 2.5.1, p116 of the submission.

AE = adverse event; CI = confidence interval; ETN = etanercept; NA = not applicable due to zero value; NR = not reported; OR = odds ratio; PBO = placebo; SAE = serious adverse event; SEC = secukinumab; UST = ustekinumab.

*Note that the results presented in Table 8 are derived from ad-hoc/ post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for study 2310. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.26 Based on pooled dose of secukinumab there was no significant difference in any AE between secukinumab and ustekinumab. The submission did not present an indirect comparison using LD and HD separately.

6.27 Previously, the PBAC considered that secukinumab for adults with severe CPP is likely to be non-inferior to ustekinumab in terms of comparative efficacy and safety (paragraph 7.3, secukinumab PSD, March 2015).

6.28 Similar to comparative efficacy (paragraph 6.12), there are uncertainties with the indirect comparison safety data and this may limit the reliability of the indirect comparison for assessing AEs.

Benefits/harms

6.29 A summary of the comparative benefits for the direct comparison of secukinumab versus etanercept is presented in Table 9. A summary of comparative harms was not presented given there were no statistically significant differences between the arms and the results generally supported similar safety.

Table 9: Summary of comparative benefits for secukinumab versus etanercept in Study 2310

Trial	SKB LD n/N (%)	SKB HD n/N (%)	Etanercept n/N (%)	RD (95% CI) SKB LD vs etanercept ^a	RD (95% CI) SKB HD vs etanercept ^a
PASI 75 at Week 12	32/40 (80.0)	31/40 (77.5)	26/41 (63.4)	0.17 (-0.03, 0.36)	0.14 (-0.06, 0.34)
IGA 0/1 at Week 12	28/40 (70.0)	24/40 (60.0)	14/41 (34.1)	0.36 (0.16, 0.56)	0.26 (0.05, 0.47)
PASI 75 at Week 52	35/40 (87.5)	35/40 (87.5)	28/41 (68.29)	0.19 (0.02, 0.37)	0.19 (0.02, 0.37)
IGA 0/1 at Week 52	29/40 (72.5)	30/40 (75.0)	23/41 (56.1)	0.16 (-0.04, 0.37)	0.19 (-0.01, 0.39)

Source: Table 2.30, p91 of the submission.

CI = confidence interval; HD = high dose; IGA = Investigator's Global Assessment; LD = low dose; n = number of participants with event; N = total participants in group; PASI = Psoriasis Area and Severity Index; RD = risk difference; SKB = secukinumab.

Bold indicates statistical significance.

^a Calculated during the evaluation.

6.30 On the basis of the direct comparison presented by the submission, for every 100 patients treated with secukinumab in comparison with etanercept:

- Approximately 36 additional patients on LD secukinumab would have an IGA 0/1 response at Week 12.
- Approximately 26 additional patients on HD secukinumab would have an IGA 0/1 response at Week 12.
- Approximately 19 additional patients on LD and HD secukinumab would have a PASI 75 response at Week 52.

Clinical claim

Direct comparison between secukinumab and etanercept

6.31 The submission described secukinumab as having superior effectiveness over the main comparator (etanercept) based on a direct comparison. The claim was based on the main trial population of Study 2310 as measured by PASI 75 response and IGA 0/1.

6.32 The ESC agreed with the evaluation that clinical claim of superior effectiveness of secukinumab over etanercept is uncertain because:

- A statistically significant favourable result for secukinumab compared to etanercept was observed for IGA 0/1 but not PASI 75 at Week 12 in Study 2310. A statistically significant favourable result for secukinumab compared to etanercept

was observed for PASI 75 but not IGA 0/1 at Week 52 in Study 2310. The ESC noted the lack of superiority for secukinumab with respect to PASI 75 at Week 12, and that the result was only marginally significant at Week 52.

- There was an overdosing error in 45% of secukinumab patients (36/80 total, 20/40 in HD, 16/40 in LD) which increases the uncertainty in the Week 52 analysis of secukinumab. The analysis provided in the PSCR suggests that patients who were not affected by the dosing error had lower response rates at Week 52 compared to those who were affected (paragraph 6.8).
- Unmasking of the main comparator, etanercept, due to the dosing regimen of etanercept (weekly) vs secukinumab (monthly), may impact treatment effect.
- Inadequate source, specification and application of a MCID (paragraph 6.21).

6.33 The PBAC recalled it had previously considered a claim of superiority for ustekinumab over etanercept was reasonable in the context of an unmet need for an alternative to etanercept, which is limited to 24 weeks of treatment due to its safety profile (paragraph 6.41, ustekinumab PSD, March 2021).

6.34 The PBAC noted that while the PASI 75 outcome was not significantly different between secukinumab and etanercept at Week 12, the point estimate favoured secukinumab and the confidence intervals were wide due to small patient numbers. The PBAC considered that the claim of superior comparative effectiveness of secukinumab compared to etanercept was uncertain but reasonable.

6.35 The submission described secukinumab as equivalent in terms of safety compared to etanercept. The ESC agreed with the evaluation that this claim may be reasonable, however noted there were limited comparative safety data presented in the submission to support a claim of equivalent safety. The PBAC considered that the claim of equivalent comparative safety was reasonable.

Indirect comparison between secukinumab and ustekinumab

6.36 The submission described secukinumab as having non-inferior effectiveness over the secondary comparator (ustekinumab) based on an indirect comparison. The claim was based on CADMUS and Study 2310, as measured by PASI 75 response at Week 12.

6.37 The evaluation considered the claim may not be adequately supported for the following reasons:

- Inadequate source, specification and application of a non-inferiority margin (paragraph 6.20). The evaluation noted that the proposed 10% margin was not met. The PSCR noted that the 10% non-inferiority margin previously applied to the guselkumab and risankizumab submissions was for adults, there is no published non-inferiority margins in paediatric CPP identified during the evaluation, nor has the PBAC previously accepted any specific non-inferiority margin.
- Both Study 2310 and the CADMUS trial had small sample sizes.

- While not statistically significant, the point estimate for the primary outcome (PASI 75) favoured ustekinumab over secukinumab at Week 12 (secukinumab combined doses vs ustekinumab OR=0.63, 95% CI: 0.12, 3.27).
- 6.38 The trial populations are different to the proposed eligible PBS population, in terms of:
- The number of prior systemic treatments failed. The proposed PBS population must have failed to achieve an adequate response to at least 2 of 3 prior treatments (phototherapy, methotrexate or acitretin). The 2310 and CADMUS trials did not require patients to meet this criterion.
 - The presence of lesions prior to treatment. The proposed PBS population must have lesions present for at least 6 months from the time of initial diagnosis. The 2310 and CADMUS trials did not require patients to meet this criterion.
 - Child's age (12-17 years in CADMUS and 6-18 years old in Study 2310, compared to under 18 years in the proposed restriction).
- 6.39 The submission described secukinumab as equivalent in terms of safety compared to ustekinumab. The ESC agreed with the evaluation that this claim may be reasonable, however noted there were limited comparative safety data presented in the submission to support a claim of equivalent safety. Previously, the PBAC considered that secukinumab for adults with severe CPP is likely to be non-inferior to ustekinumab in terms of comparative efficacy and safety (paragraph 7.3, secukinumab PSD, March 2015). Ustekinumab is considered to have non-inferior safety compared to etanercept in the paediatric population (paragraph 6.43, ustekinumab PSD, March 2021).
- 6.40 The ESC considered the non-inferiority claim against ustekinumab with respect to efficacy to be uncertain. The ESC noted the significant transitivity issues and the wide confidence intervals that cross the nominated non-inferiority margin of 10%, indicating secukinumab could have inferior efficacy. The ESC acknowledged that the wide confidence intervals may be associated with the small sample sizes in the studies.
- 6.41 The pre-PBAC response stated that there are no published non-inferiority margins in paediatric CPP identified during the evaluation, nor has the PBAC previously accepted any specific non-inferiority margin. The Sponsor noted that for ustekinumab in paediatric CPP, a claim of superiority was accepted by the PBAC based on the indirect comparison in PASI 75 response compared with etanercept at Week 12 (RD = 0.27, 95% CI 0.09, 0.44). The lower risk difference confidence interval was outside the proposed 10% margin (ustekinumab PSD, March 2021, Table 7).
- 6.42 The PBAC considered that the claim of non-inferior comparative effectiveness of secukinumab compared to ustekinumab was uncertain but reasonable, noting that the PASI 75 response rate was similar across treatments (approximately 80%, Table 5). It also noted that some transitivity issues between the trials may have favoured ustekinumab, such as:

- Study 2310 did not allow a topical corticosteroid treatment for the face, scalp, hands, feet and genitoanal area after the patient had been randomised, and ustekinumab would be expected to perform better in the CADMUS trial because of allowed topical corticosteroid use (paragraph 6.11).
- In CADMUS, the severity grade was PASI >12 (moderate-to-severe) while Study 2310 included only with PASI ≥20 (severe) (paragraph 6.13).

6.43 While the PBAC acknowledged the uncertainties with the indirect safety comparison between secukinumab and ustekinumab (paragraph 6.28), it considered that the claim of non-inferior comparative safety was reasonable, noting that it previously accepted non-inferior safety for secukinumab compared to ustekinumab in adults with severe CPP (March 2015).

Economic analysis

Indirect comparison between secukinumab and ustekinumab

6.44 The submission presented a CMA comparing secukinumab and ustekinumab, based on the clinical evidence that secukinumab is demonstrated to have non-inferior effectiveness to ustekinumab. Given the clinical claim of non-inferior effectiveness and safety over ustekinumab, the choice of a cost-minimisation economic evaluation method is reasonable.

6.45 The submission stated equi-effective doses were secukinumab weight-based dosing for Week 0, 1, 2, 3 and 4 followed by the same dose once a month over 2 years, and ustekinumab weight-based dosing for Week 0, 4 and followed by the same dose every 12 weeks over 2 years. The recommended doses are presented in Table 10.

Table 10: Recommended dose of secukinumab and ustekinumab for paediatric psoriasis

	Body weight at the time of dosing	Recommended Dose
Secukinumab	<25 kg	75 mg
	25 to <50 kg	75 mg (may be increased to 150 mg)
	≥50 kg	150 mg (may be increased to 300 mg)
Ustekinumab	<60 kg	0.75 mg/kg
	60-100 kg	45 mg
	>100 kg	90 mg

Source: Table 1.5, p40 of the submission, Table 1a, p2 of ustekinumab PI

6.46 The Sponsor proposed the same price for secukinumab across the three strengths (75 mg/0.5 mL, 150 mg/1 mL and 300 mg/2 mL). The cost minimisation calculation presented in the submission was conducted based on 150 mg secukinumab and 45 mg of ustekinumab.

6.47 The frequency of use is consistent with the approved PI for ustekinumab and the approved PI for secukinumab, but there is inconsistency in the exact dosing frequency of secukinumab across the clinical trial (four-weekly) and the PI (monthly). The PBAC previously considered patients would likely find four-weekly dosing with secukinumab less confusing than monthly dosing, and “therefore considered four-weekly dosing was the most appropriate frame of reference for considering equi-effective doses.”

(paragraph 7.2, secukinumab ankylosing spondylitis PSD, March 2016). As a result, a sensitivity analysis was conducted during evaluation using four-weekly as the dosing frequency for secukinumab.

6.48 The ESC estimated the equi-effective doses for secukinumab and ustekinumab to be:

- Secukinumab (75 mg, 150 mg, or 300 mg) weight-based dosing at Week 0, 1, 2, 3 and 4, and then every 4 weeks over 2 years, and
- Ustekinumab (45 mg) weight-based dosing at Week 0 and 4, and then every 12 weeks over 2 years.

6.49 The submission claimed no administration costs given the proposed medicine will be administered in the same form as the comparators (as subcutaneous injection via pre-filled syringe or pen). This is reasonable. The submission claimed no difference in the safety or toxicity profiles between secukinumab and ustekinumab and applied no additional costs on safety and toxicity management. This is reasonable based on the non-inferior safety claims over ustekinumab.

6.50 The results of the CMA are presented in Table 11.

Table 11: Results of the cost-minimisation approach using published prices

Component	Cost minimisation calculation		
	Secukinumab (monthly dose)	Secukinumab (four-weekly dose) ^a	Ustekinumab
Cost per dose (AEMP)	\$1307.38	\$1217.21	\$3782.07 ^b
Dose duration	two years	two years	two years
Doses over two years	27	29	9.3333
Total medicine cost over 2 yrs	\$35,299	\$35,299	\$35,299

Source: Table 3.3, p126 of the submission.

AEMP = approved ex-manufacturer price.

^a Modified during the evaluation.

^b The published AEMP for ustekinumab is \$3,809.08. Ustekinumab was listed on the PBS for paediatric severe CPP on 1 October 2021, with the same published AEMP.

6.51 There is a special pricing arrangement for ustekinumab, however the effective price was not available to the Sponsor. As a result, the Sponsor conducted the cost minimisation analysis using the published price only.

6.52 On the basis of equivalence to the ustekinumab cost over two years, the ex-manufacturer price (EMP) for secukinumab in paediatric psoriasis was calculated as \$1,307.38 in the submission using published prices of ustekinumab, adjusted during the evaluation to \$1,217.21 if using four-weekly as dosing frequency.

6.53 The submission stated the requested EMP for secukinumab in paediatric psoriasis is \$█ per dose, stating that “On the basis of equivalence to the secukinumab price for adults in the same indication, the requested AEMP for secukinumab in paediatric psoriasis is \$█ (instead of \$1,307.38).” This ambiguously compared the proposed effective price (\$█) to the published cost-minimised price (\$1,307.38) derived from the ustekinumab published price. The Sponsor clarified in the PSCR that the requested

effective EMP (\$████) was the price for secukinumab in adult severe CPP when first listed in this indication (March 2015, cost-minimised to adalimumab [AEMP \$████]).

- 6.54 The ESC considered that, if the PBAC accept the claim of non-inferiority, it would be appropriate to conduct a CMA against ustekinumab, using the effective price for paediatric CPP and the equi-effective doses in paragraph 6.48.

Drug cost/patient/year

- 6.55 In the submission, assuming a DPMQ of \$████ (MQ = 1) and \$████ (MQ = 4) and 12 scripts required for the first year of treatment inclusive of initial and continuing therapy with loading regimen, the cost per patient per year for secukinumab is \$████. Using the updated DPMQ of \$████ (MQ = 1) and \$████ (MQ = 4) based on the 1 July 2021 mark-ups, the cost per patient per year for secukinumab slightly increased to \$████. For ustekinumab using the published price for current indication DPMQ of \$3943.17 (MQ = 1) and 5 scripts required for the first year of treatment with loading regimen, the cost per patient per year is \$19,716.

Estimated PBS usage & financial implications

- 6.56 This submission was not considered by DUSC.
- 6.57 The submission used a market share approach by starting with etanercept scripts and applying market growth, with these scripts then split based on the estimated market share of ustekinumab and etanercept. Key inputs for the financial estimates are shown in Table 12. The uptake of secukinumab is then applied. This approach is reasonable given the proposed medicine is expected to represent a direct substitution of etanercept and ustekinumab. An alternative method would be a mixed market share and epidemiological approach which was used in the submission of ustekinumab for paediatric severe psoriasis (paragraph 6.59, ustekinumab PSD, March 2021).

Table 12: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Market size for etanercept (scripts) in 2021	250 Source: The Medicare Statistics database	This estimation is uncertain but reasonable.
Market growth	Yr 1-2: 10% Yr 2-6: 2 % Source: Assumption	This is uncertain and may underestimate the market growth. A higher estimated number of additional patients initiating ustekinumab beyond those replacing etanercept were applied in Y1 in the ustekinumab PSD.
Ustekinumab market share in absence of a PBS listing for secukinumab	Yr 1: 30% Yr 2: 40% Yr 3-6: 50% Source: The PBS 10% sample in the juvenile idiopathic arthritis (JIA) market	It is unclear if the juvenile idiopathic arthritis (JIA) market would be a good proxy since the comparative effectiveness is different between the two pairs of comparators: adalimumab was found to be non-inferior over etanercept for JIA (p6, adalimumab PSD, March 2010), while ustekinumab was found to be superior over etanercept for paediatric psoriasis.
Secukinumab market share	Yr 1: 10%; Yr 2: 15% Yr 3: 20%; Yr 4: 25% Yr 5: 30%; Yr 6: 33% Source: Assumption	This is uncertain. It is possible that secukinumab will share a bigger market with ustekinumab since both of these medicines are claimed to be superior to etanercept. It is also possible that secukinumab will have a smaller market share since a similar biologic treatment is near market (ustekinumab) with many patients expected to stay with first biologic due to prohibitive switching rules in the indication.
Annual script number for secukinumab and the comparators	Etanercept 13 Ustekinumab: 4.33 Secukinumab: 12 Source: PBS restrictions, PIs and clinicians' input.	The assumption on script number for etanercept is uncertain. The Sponsor tested the impact of 5 etanercept scripts per year in sensitivity analysis based on the ustekinumab PSD (paragraph 6.64, ustekinumab PSD, March 2021). Monthly scripts was used as the dosing frequency for secukinumab when calculating annual script numbers. This is consistent with the approved PI but inconsistent with the clinical trial where four-weekly dosing was used as the frequency.
Script breakdown for secukinumab (initial)	Yr 1: 10% Yr 2-6: 5% Source: Assumption	This is uncertain and may underestimate the financial impact of secukinumab. The proportion of patients initiating scripts for secukinumab was higher in the adult psoriasis market after listing.

Source: Table 4.4-12, p129-133 of the submission

6.58 The estimated financial implications of listing secukinumab for paediatric severe CPP are presented in Table 13. The PSCR clarified that the proposed prices (EMP \$ [REDACTED], DPMQ \$ [REDACTED]) are proposed effective prices for paediatric severe CPP, not published prices. However, this price was used together with the published prices of the comparators in the submission's estimation of the financial impact.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed ^a	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Estimated financial implications of secukinumab						
Cost to PBS/RPBS less copayments (corrected) ^b	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Estimated financial implications for etanercept and ustekinumab						
Cost to PBS/RPBS less copayments	-■ ²	-■ ²	-■ ²	-■ ²	-■ ²	-■ ²
Net financial implications						
Net cost to PBS/RPBS (corrected) ^b	■ ²	-■ ²	-■ ²	-■ ²	-■ ²	-■ ²

Source: Table 4.12, p133; Table 4.18, p135 of the submission.

^a Assuming 12 per year as estimated by the submission.

^b Corrected during the evaluation using the DPMQ generated using the 1 July 2021 mark-ups.

The redacted values correspond to the following ranges:

¹ < 500

² \$0 to < \$10 million

6.59 The net cost saving to the PBS/RPBS of listing secukinumab is estimated to be \$0 to < \$10 million in Year 6 based on the corrected price generated using the 1 July 2021 mark-ups (based on the published price of ustekinumab).

6.60 The estimated financial impact may be underestimated. There would be net financial costs to the PBS if different assumptions were used on the annual scripts for etanercept, and the split of initiating/continuing scripts for secukinumab: assuming 5 scripts of etanercept per year will cost the PBS \$0 to < \$10 million in Year 6; and assuming a higher proportion of initial scripts for secukinumab as in the adult psoriasis market will cost the PBS \$0 to < \$10 million in Year 1, \$0 to < \$10 million in Year 2, and minor costs from Year 3 to 6.

6.61 The submission requested a grandfathering clause for paediatric patients currently receiving secukinumab as trial patients or under the patient familiarisation and compassionate use programs. The submission did not state the proposed number of grandfathered patients, and they were not counted separately in the submission but may already be covered in the predicted market for etanercept in 2021, given a higher script number was used comparing to the observed script number for etanercept in 2020.

Financial Management – Risk Sharing Arrangements

6.62 The submission did not propose a risk-sharing arrangement. For ustekinumab, the PBAC considered that there was a risk of ustekinumab use outside the restriction to less severe patients, given that ustekinumab has superior effectiveness and a lower frequency of injections (3 monthly) compared to etanercept (weekly) (paragraph 6.66 ustekinumab PSD, March 2021). The Sponsor for secukinumab claimed that this was not expected to be applicable to secukinumab since the frequency of administration for secukinumab is more often (monthly) than ustekinumab (3 monthly). The risk of secukinumab use outside the proposed restriction remains, given the frequency of

injections for secukinumab (monthly) is still less often compared to etanercept (weekly).

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of secukinumab on the General Schedule for the treatment of paediatric patients with severe chronic plaque psoriasis (CPP). The PBAC's recommendation was based on, among other matters, its assessment that secukinumab would be cost-effective at a price no greater than the price for ustekinumab in the same indication for the paediatric population.
- 7.2 The PBAC considered that the equi-effective doses are secukinumab (75 mg, 150 mg, or 300 mg) weight-based dosing at Week 0, 1, 2, 3 and 4, and then every 4 weeks, and ustekinumab (45 mg or 90 mg) weight-based dosing at Week 0 and 4, and then every 12 weeks. The cost-minimisation calculation should be performed over two years.
- 7.3 The PBAC noted that ustekinumab was listed on the PBS for severe CPP in paediatric patients on 1 October 2021. The PBAC commented that when etanercept was the only medicine available on the PBS for this population, the Australasian College of Dermatologists indicated there was substantial unmet need for an alternative class of medication. The PBAC noted the positive consumer comments received from healthcare professionals that supported the use of secukinumab in paediatric patients.
- 7.4 The PBAC noted that the restrictions for secukinumab (and those for ustekinumab and etanercept) were complex, and as written Authority Required listings, will need to be finalised in consultation with Services Australia and the Sponsor. Noting that there may be revisions required to the proposed secukinumab restrictions, with flow on changes to the ustekinumab and etanercept listings where appropriate, the PBAC considered that:
 - The restriction for secukinumab should align to the general concepts of initiation, continuation, and balance of supply. A grandfathering restriction should be in operation for 12 months after listing.
 - Patients can swap between secukinumab, ustekinumab and etanercept without having to experience a disease flare within a treatment cycle. Patients should be allowed to trial and fail therapy no more than 3 times within a treatment cycle (once with each agent), before taking a treatment break of at least 5 years.
 - Definitions and instructions for determining response (and inadequate response to prior therapies) should align with the existing paediatric listings for etanercept and ustekinumab for CPP. Assessment of response to access continuing secukinumab therapy should take place after 12 weeks of therapy (assessment of response occurs after 24 weeks for ustekinumab and after 12 weeks for etanercept).

- 7.5 The PBAC agreed with the submission that the clinical place for secukinumab is as an alternative to etanercept (and ustekinumab), and that the choice and order of these therapies will likely depend on clinician discretion and patient preference.
- 7.6 The PBAC considered that the nominated main comparator of etanercept was appropriate, as it was the only biologic currently PBS listed for severe CPP in paediatric patients at the time the submission was lodged. On the 1 October 2021, the near-market comparator, ustekinumab, was PBS listed for the same indication and population, and the PBAC indicated that, as a biological agent most likely to be replaced by secukinumab, ustekinumab could be considered the main comparator at the time of its consideration.
- 7.7 The PBAC noted several issues with the reliability of the trial evidence presented in the submission. Study 2310 had an overdosing error in 45% of secukinumab patients, and a moderate risk of bias due to the unblinding of participants to etanercept treatment. Consistent with its consideration of ustekinumab for paediatric severe CPP in March 2021, the PBAC noted the small sample size of the CADMUS [and Study 2310] arms, and applicability to the PBS population in terms of disease severity and prior/concomitant treatments. However, the PBAC considered that in the context of the available evidence, the overall findings of both trials were likely applicable to the proposed PBS population (baseline PASI score >15 and patients who received 2 of prior methotrexate, acitretin or phototherapy).
- 7.8 In terms of comparative benefits, the submission presented a direct treatment comparison against etanercept. The PBAC noted the claim of superior comparative effectiveness of secukinumab compared to etanercept was uncertain (as discussed in paragraph 6.32) but considered that, overall, it was reasonable. The PBAC considered that, despite the availability of ustekinumab for this population, there remained a need for additional treatment options. The PBAC accepted the clinical claim that secukinumab is equivalent in terms of safety compared to etanercept.
- 7.9 The submission also presented an indirect comparison against ustekinumab using placebo as the common reference. While the PBAC acknowledged the uncertainties associated with the clinical claim of non-inferior effectiveness (inadequate source, specification and application of a non-inferiority margin, small sample sizes, point estimate favouring ustekinumab), it considered it was reasonable in the context of several factors that may have favoured ustekinumab (concomitant topical corticosteroid use allowed in CADMUS but not Study 2310, and moderate-to-severe patients in CADMUS compared to severe patients in Study 2310). The PBAC also acknowledged the uncertainties associated with the indirect safety claim of non-inferiority, but overall considered the claim was reasonable. The PBAC recalled that it considered that secukinumab for adults with severe CPP is likely to be non-inferior to ustekinumab in terms of comparative efficacy and safety (paragraph 7.3, secukinumab PSD, March 2015).
- 7.10 The PBAC considered there is a risk of secukinumab use outside the restriction to less

severe patients and noted that the frequency of injections for secukinumab (monthly) is less often compared to etanercept (weekly). The PBAC advised that secukinumab should be subject to the same Risk Sharing Arrangement in place for ustekinumab in this population.

- 7.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because secukinumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over ustekinumab, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

Restriction to be finalised.

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.