

6.13 USTEKINUMAB, Injection 45 mg in 0.5 mL, Stelara[®], Janssen-Cilag Pty Ltd

1 Purpose of Application

1.1 The submission requested an Authority Required General Schedule listing for ustekinumab for the treatment of paediatric patients with severe chronic plaque psoriasis (CPP). This was the first consideration of ustekinumab by the PBAC for this indication. Ustekinumab is currently listed on the PBS for the treatment of severe CPP, severe Crohn disease, and severe psoriatic arthritis in patients 18 years of age and over.

1.2 The requested basis for listing was a cost per responder analysis versus etanercept.

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 (CPP) defined as a PASI score of greater than 15. Patients must have failed treatment with two of three systemic treatments including methotrexate and/or acitretin and/or phototherapy (UVB or PUVA).
Intervention	Ustekinumab is administered subcutaneously at a dose of 0.75 mg/kg (for patients <60 kg), 45 mg (for patients ≥60 kg to ≤100 kg), or 90 mg (for patients >100 kg) at Wk 0, 4 and every 12 wks thereafter (q12w).
Comparator	Etanercept
Outcomes	PASI response rates (PASI 75 and PASI 90), quality of life, and adverse events.
Clinical claim	In paediatric patients with severe CPP, ustekinumab demonstrates superior effectiveness compared with etanercept as assessed by statistically and clinically significant improvements in PASI 75 and PASI 90 response rates. Ustekinumab is associated with a non-inferior safety profile compared with etanercept and demonstrates a safety profile consistent with its well established and accepted long-term safety profile in adults.

Source: Table 1-1, p14 of the submission.

PASI = Psoriasis Area and Severity Index; PUVA = psoralen and ultraviolet A; UVB = ultraviolet B; wk = week

2 Background

Registration status

2.1 Ustekinumab was registered by the TGA for moderate to severe plaque psoriasis in children and adolescent patients from 6 years of age on 16 November 2020.

3 Requested listing

3.1 The requested abridged listing for ustekinumab 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, a balance of supply restriction for both initial treatment and continuing treatment, and a grandfathering provision for an estimated < 500 patients treated as part of the

Public Summary Document – March 2021 PBAC Meeting

sponsor's compassionate access program. The submission requested a Special Pricing Arrangement.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty ^a	Proprietary Name and Manufacturer		
USTEKINUMAB Subcutaneous injection, 45 mg	1	2 (initial) 1 (continuing)	\$3,951.07 (published) \$ [REDACTED] (effective)	Stelara® Janssen-Cilag Pty Ltd		
Category/Program:	General Schedule					
PBS indication:	Paediatric severe chronic plaque psoriasis					
Restriction:	Authority required - written					
Treatment criteria:	Must be treated by a dermatologist					
Population criteria:	Patient must be under 18 years of age and a parent or authorised guardian must have signed a patient acknowledgement					
Treatment phase	Initial treatment [Initial 1, Face, hand, foot (New patients – No prior biological agent)]		Initial treatment [Initial 1, Whole body (New patients – No prior biological agent)]			
Clinical criteria	<p>The treatment must be as systemic monotherapy; OR The treatment must be in combination with methotrexate, AND</p> <table border="1"> <tr> <td>Patient must have severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot where the plaque or plaques have been present for at least 6 months from the time of initial diagnosis, AND</td> <td>Patient must have lesions present for at least 6 months from the time of initial diagnosis, AND</td> </tr> </table> <p>Patient must not have received any prior PBS-subsidised treatment with ustekinumab for this condition, AND</p> <p>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: (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 0.4 mg per kg per day for at least 6 weeks, AND</p> <p>Patient must not receive more than 28 weeks of treatment under this restriction</p>				Patient must have severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot where the plaque or plaques have been present for at least 6 months from the time of initial diagnosis, AND	Patient must have lesions present for at least 6 months from the time of initial diagnosis, AND
Patient must have severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot where the plaque or plaques have been present for at least 6 months from the time of initial diagnosis, AND	Patient must have lesions present for at least 6 months from the time of initial diagnosis, AND					
Treatment phase	Continuing treatment [Face, hand, foot]		Continuing treatment [Whole body]			
	<p>Patient must have received this drug as their most recent course of PBS-subsidised treatment with a biological agent for this condition, AND</p> <p>Patient must have demonstrated an adequate response to their most recent course of treatment with this drug, AND</p> <p>The treatment must be as systemic monotherapy (other than methotrexate), AND</p> <p>Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction</p>					

Source: adapted from Appendix 1 to the submission.

^a The submission requested the same current effective price as the ustekinumab 45 mg vial price in adults with severe CPP. This price was updated on 1 January 2021 (to an effective DPMQ of \$ [REDACTED]), and the evaluation updated financial implications for the PBS/RPBS and the Government health budget accordingly.

- 3.2 The proposed duration of initial therapy supply for ustekinumab patients is 28 weeks, with assessment of response for continuing treatment no later than 24 weeks (as per the restriction for ustekinumab in adult severe CPP).
- 3.3 The maximum requested quantity was not sufficient to allow for the recommended 90 mg dose in paediatric patients who weigh more than 100 kg. It was noted that

3/110 (2.7%) of patients enrolled in CADMUS, the pivotal trial which enrolled patients aged ≥ 12 years and < 18 years, weighed over 100 kg, but it was unclear if this was representative of the proposed PBS population. Based on ABS data, in 2014-2015 7.4% of children or adolescents aged 5-17 were obese (BMI > 35 kg/m²).

- 3.4 The proposed PBS population was wider than the approved TGA population with respect to patient age, as the requested PBS population is < 18 years, while the TGA indication limits treatment to patients aged ≥ 6 years. The age of the PBS population for the comparator, etanercept, is also < 18 years, while the TGA indication for etanercept limits treatment to patients aged ≥ 4 years.
- 3.5 The proposed PBS population for ustekinumab is limited to severe disease, compared to the wider moderate to severe disease approved by the TGA.

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

4 Population and disease

- 4.1 Psoriasis is a chronic disease with predominantly skin and joint manifestations affecting approximately 2% of the population. Overall, almost one third of psoriasis cases in the population begin in the patient's paediatric years (i.e. < 18 years old) and incidence rates of psoriasis in children have more than doubled since 1970. As a result, it is now estimated that psoriasis affects approximately 1% of children globally, with a median age of onset between 7 and 10 years. Plaque psoriasis is the most common form affecting approximately 80 to 90% of patients. The major manifestation is chronic inflammation of the skin characterised by disfiguring, scaling and erythematous plaques that may be painful or pruritic.
- 4.2 Patients diagnosed with mild disease are treated with topical treatments. Patients with moderate to severe disease are treated with non-biologic systemic therapies including methotrexate, ciclosporin and acitretin and/or phototherapy. After failing two of methotrexate, acitretin and phototherapy, patients may become eligible for PBS-subsidised etanercept. Etanercept is administered either as monotherapy or in combination with methotrexate.
- 4.3 The submission positioned ustekinumab (a monoclonal antibody that binds to human IL-12 and IL-23) as an alternative to etanercept. The restrictions proposed would allow that ustekinumab may be used before or after etanercept and patients may switch between the two biologics. The choice and/or order of biologic use will likely depend on clinician discretion and patient preference.
- 4.4 The proposed population for treatment with ustekinumab was broadly consistent with the PBS population eligible for treatment with etanercept except for:
 - Time of Psoriasis Area and Severity Index (PASI) response assessment. PASI response assessment with etanercept was expected to be conducted between 12

and 16 weeks after treatment initiation. With ustekinumab, PASI response assessment is conducted no later than 24 weeks after treatment initiation; and

- The maximum allowed duration of therapy. Patients may only receive a maximum of 24-weeks of treatment per course of etanercept based on the current restriction. They cannot be retreated with etanercept unless symptoms worsen, and any patient who failed to respond to treatment two times must have a break of at least 12 months before retreatment. With ustekinumab, a responding patient may receive continuous therapy.

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

5 Comparator

- 5.1 The submission nominated etanercept as the main comparator. The main arguments provided in support of this nomination were that in paediatric patients with severe CPP, etanercept is the only biologic currently PBS listed for this indication, and that etanercept is the only active treatment option for the paediatric severe CPP population after inadequate response to conventional therapies such as methotrexate, acitretin and/or phototherapy. As such, etanercept will be replaced by ustekinumab if listed on the PBS.
- 5.2 Best supportive care (BSC) would be an appropriate comparator for patients who had failed to respond to all other treatment options, including etanercept, or were unable or unwilling to be treated with etanercept due to safety concerns or treatment duration restrictions. However, the Economics Sub-Committee (ESC) considered this additional comparison would be complicated and clinical evidence would be limited.

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 an individual (1), health care professionals (23) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ustekinumab including fewer injections (3-monthly) compared to etanercept (weekly) and uninterrupted treatment. The health care professionals (HCPs) particularly emphasised the considerable psychosocial implications of severe CPP in the paediatric age group due to disfigurement in sensitive areas, such as the face and limbs/genital area. The HCPs commented on the significant improvement in patients' quality of life with ustekinumab, and several clinicians described patients' treatment as life-changing. The HCPs considered there is an unmet clinical need in childhood psoriasis treatment and strongly supported the PBS listing of ustekinumab.

6.3 The PBAC noted the advice received from the Australasian College of Dermatologists, specifically that there is a substantial unmet need for an alternative class of medication for the paediatric CPP population. The College noted that etanercept is the only biological agent available on the PBS, and there are limitations to its use. It further noted the well-established safety profile of ustekinumab. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.4 The submission was based on an indirect treatment comparison (ITC) of ustekinumab to etanercept via the common reference of placebo. For ustekinumab, the submission identified one trial of ustekinumab versus placebo in patients aged ≥ 12 and < 18 years (CADMUS) and one non-comparative trial of ustekinumab in patients aged ≥ 6 to < 12 years (CADMUS JR). For etanercept, the submission identified one randomised trial of etanercept versus placebo in patients aged ≥ 4 and < 18 years (Paller 2008). The Paller 2008 trial had previously been considered by the PBAC (etanercept for paediatric CPP, March 2012).

6.5 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Ustekinumab vs. placebo		
CADMUS	<p>A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Ustekinumab in the Treatment of Adolescent Subjects With Moderate to Severe Plaque-type Psoriasis.</p> <p>Landells I, Marano C, Hsu M 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.</p> <p>Landells I, Marano C, Hsu M 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.</p>	<p>2014</p> <p><i>J Am Acad Dermatol</i> 2015; Oct; 73(4): 594-603.</p> <p>73rd Annual Meeting of the American Academy of Dermatology. <i>J Am Acad Dermatol</i> 2015; 72(5 SUPPL.1), AB202.</p>
CADMUS Junior (JR)	<p>A Phase 3 Open-label Study to Assess the Efficacy, Safety, and Pharmacokinetics of Subcutaneously Administered Ustekinumab in the Treatment of Moderate to Severe Chronic Plaque Psoriasis in Pediatric Subjects ≥6 to <12 Years of Age.</p> <p>Philipp S, Menter A, Nikkels A et al. Ustekinumab for the treatment of moderate-to-severe plaque psoriasis in pediatric patients (≥ 6 to < 12 years of age): efficacy, safety, pharmacokinetic, and biomarker results from the open-label CADMUS Jr study.</p> <p>Philipp S, Menter A, Nikkels A et al. Ustekinumab for the treatment of moderate-to-severe plaque psoriasis in pediatric patients (>6 to <12 year of age): Results from CADMUS Jr.</p>	<p>2018</p> <p><i>Br J Dermatol</i> 2020; 183: 664-672.</p> <p>6th Congress of the Skin Inflammation and Psoriasis International Network. <i>J Eur Acad Dermatol Venereol</i> 2019; 33 (S3): 18.</p>
Etanercept vs. placebo		
Paller 2008	<p>Paller A et al. Etanercept treatment for children and adolescents with plaque psoriasis.</p> <p>Siegfried E et al. Intermittent etanercept therapy in pediatric patients with psoriasis.</p> <p>Langley R et al. Patient-reported outcomes in pediatric patients with psoriasis undergoing etanercept treatment: 12-week results from a phase III randomized controlled trial/</p> <p>Landells I et al. Efficacy and safety of etanercept in children and adolescents aged ≥ 8 years with severe plaque psoriasis</p> <p>Paller A et al. Subgroup analyses of etanercept in pediatric patients with psoriasis.</p> <p>Paller A et al. Long-term etanercept in pediatric patients with plaque psoriasis.</p> <p>Paller A et al. Long-term safety and efficacy of etanercept in children and adolescents with plaque psoriasis.</p> <p>Langley R et al. Pharmacokinetics, immunogenicity, and efficacy of etanercept in pediatric patients with moderate to severe plaque psoriasis.</p>	<p><i>NEJM</i> 2008; 358(3): 241-21.</p> <p><i>J Am Acad Dermatol</i> 2010; 63(5): 769-774.</p> <p><i>J Am Acad Dermatol</i> 2011; 64(1): 64-70.</p> <p><i>Eur J Dermatol</i> 2010; 20(3): 323-328.</p> <p><i>J Am Acad Dermatol</i> 2010; 63(2): e38-e41.</p> <p><i>J Am Acad Dermatol</i> 2010; 63(5): 762-768.</p> <p><i>J Am Acad Dermatol</i> 2016; 74(2): 280-287. e283.</p> <p><i>J Clin Pharmacol</i> 2018; 58(3): 340-346.</p>

Source: Table 2.5, pp43-44 of the submission.

6.6 The key features of the trials and studies are summarised in the table below.

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in cost per responder analysis
Ustekinumab vs. placebo						
CADMUS ^a	110	R, DB, MC up to 12 weeks, then crossover to OL ustekinumab with duration up to 60 weeks total	Low	Moderate to severe CPP ^b , poorly controlled on topical therapy. Age 12 to 17 years	PASI 75, PASI 90, PGA, CDLQI	Pooled PASI 75 responders at Week 24 with CADMUS JR Week 28
CADMUS Junior (JR)	44	Single-arm, up to 56 months	High	Moderate to severe CPP ^b , poorly controlled on topical therapy. Age 6 to 11 years	PASI 75, PASI 90, PGA, CDLQI	Pooled PASI 75 responders at Week 28 with CADMUS Week 24
Etanercept vs. placebo						
Paller 2008	211	R, DB up to 12 weeks, then crossover to OL etanercept for a total of 36 weeks and then 12 weeks of withdrawal	Low	Moderate to severe CPP ^b , poorly controlled on topical therapy. Age 4 to 17 years	PASI 75, PASI 90, PGA, CDLQI	PASI 75 response rate at Week 12 applied to Week 16 time point

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

DB=double blind; CDLQI=Children's Dermatology Life Quality Index; CPP=chronic plaque psoriasis; MC=multi-centre; OL=open label; PASI=Psoriasis Area and Severity Index; PGA= Physician's Global Assessment; R=randomised.

^a Including the 37 patients who received the ustekinumab half standard dose

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

6.7 In CADMUS, 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 sought listing only for the ustekinumab standard dose (at Week 0, 4, and every 12 weeks thereafter), which was consistent with the TGA approved dosage. CADMUS was considered to have a low risk of bias, but was restricted by small sample size with only 73 patients (36 at standard dose and 37 in placebo arm) analysed in the current submission.

6.8 In CADMUS, patients were treated with their randomised therapy at Week 0 and 4, and at Week 12, with clinical assessments occurring at Weeks 12, 28 and 52. Patients who experienced a worsening of symptoms as measured by PASI \geq 50% increase from baseline were allowed to enter 'early escape' and be treated with moderate to high potency topical steroid through Week 12, which was supposed to be discontinued by Week 16. At Week 12, patients randomised to placebo were re-randomised to either ustekinumab standard dose (n=18) or ustekinumab half-standard dose (n=19), with follow-up for up to Week 52. Patients randomised to ustekinumab received a placebo injection at Week 12 to maintain blinding.

6.9 In CADMUS JR, patients were treated with ustekinumab with a dosage identical to the ustekinumab standard dosage in CADMUS. Being a single arm non-randomised and non-comparative study, it was considered to have a high risk of bias.

- 6.10 In Paller 2008, patients were randomised to be treated with etanercept (n=106) or placebo (n=105) at baseline until Week 12. Patients who experienced a worsening of symptoms ($\geq 50\%$ increase from baseline PASI and ≥ 4 point increase at any visit or $\geq 25\%$ increase from baseline PASI and ≥ 4 point increase at two consecutive visits) could enter an early escape group in which all patients received etanercept. After Week 12, patients initially randomised to placebo crossed over and all patients received etanercept treatment. Clinical assessments were made at Weeks 12, 24, 36 and 48. Patients who did not achieve PASI 50 response at Week 24 and PASI 75 response at Week 36 were eligible for additional topical therapy. At Week 36, patients who achieved PASI 75 were re-randomised to etanercept (n=69) or placebo (n=69) and followed up until Week 48.
- 6.11 CADMUS and CADMUS JR did not allow concomitant use of methotrexate, although the proposed restriction allows use in combination with methotrexate. In general, PBS listings for biologics leave the choice of using concomitant methotrexate to clinician discretion.
- 6.12 Generally, baseline characteristics across CADMUS, CADMUS JR and Paller 2008 were relatively similar with the exception of the age of patients which varied according to the enrolment criteria. There was a potential difference in prior use of biologics, as a small proportion of patients enrolled in CADMUS and CADMUS JR were treated with biologics, but Paller 2008 excluded patients who had previously received anti-TNF α inhibitors. Patients in the CADMUS trial were also older than patients in Paller 2008. There was a large discrepancy in the proportion of patients randomised to placebo who entered the early escape group in CADMUS (0/37, 0%) and Paller 2008 (27/105, 25.7%). This may indicate that there were other unobserved differences between patients enrolled in CADMUS and Paller 2008 and that the transitivity assumption between CADMUS and Paller 2008 may not hold (see paragraph 6.27).
- 6.13 CADMUS, CADMUS JR and Paller 2008 all enrolled patients with less severe CPP (baseline PASI ≥ 12) compared to the proposed PBS population (baseline ≥ 15), and who were more treatment naïve (the trials and study did not require patients to have failed to achieve an adequate response to two of phototherapy, methotrexate or acitretin, as proposed in the requested listings).
- 6.14 The submission did not provide a specific subgroup analysis reflective of the proposed PBS population. While baseline PASI did not appear to be a treatment effect modifier for CADMUS (baseline PASI < 20 vs ≥ 20), given the small sample size of CADMUS, the subgroup analyses that were presented were likely biased towards showing no treatment effect modification.
- 6.15 The PBAC had previously considered results from a post-hoc subgroup analysis of patients in Paller 2008 with a PASI score > 15 and prior therapy as per the PBS restriction. The PBAC noted that this subgroup demonstrated a similar response rate to the ITT population (para 8.3 and 12.3, etanercept Public Summary Document,

March 2012). For this submission, the Pre-Sub-Committee Response (PSCR) analysed a subgroup of patients from the CADMUS and CADMUS JR trials with a baseline PASI score >15 or who received at least 2 of the 3 prior therapies of methotrexate, phototherapy or acitretin. The sponsor argued that the results of the subgroup analysis were consistent with the ITT population. The ESC noted that the subgroups comprised small patient numbers and did not specify patients who failed to respond to (not just received) at least 2 of the 3 specified prior therapies. Notwithstanding, the ESC considered the results supported that the findings in the trials were likely applicable to the requested PBS population.

Comparative effectiveness

6.16 The submission proposed that a 75% improvement (PASI 75) or 90% improvement (PASI 90) in the PASI score from baseline were relevant outcomes, with this being well established in clinical practice and measured using the same scoring system across trials, and having been the basis for the PBAC’s assessment of the effectiveness of etanercept in paediatric patients with CPP [which was acceptable in the context of high clinical need] (etanercept Public Summary Document (PSD), March 2012).

6.17 Results from the whole trial populations from CADMUS (Table 4), CADMUS JR (Table 5) and Paller 2008 (Table 6) are summarised below.

Table 4: Results of primary and secondary endpoints at Week 12 and 52 in CADMUS

	Week 12			Week 52
	Placebo	Ustekinumab	Difference RD (95%CI)	Ustekinumab
Patients randomised, N	37	36	-	35
Patients who achieved a PGA score of cleared (0) or minimal (1) ^a , n(%)	2 (5.4)	25 (69.4)	0.64 (0.45, 0.78)^b	20 (57.1%)
PASI 75 responders, n(%)	4 (10.8%)	29 (80.6%)	0.70 (0.53, 0.86)	28 (80.0%)
PASI 90 responders, n(%)	2 (5.4%)	22 (61.1%)	0.56 (0.38, 0.73)	23 (65.7%)
PedsQL Mean change from baseline, mean (SD)	3.35 (10.04)	8.03 (10.44)	4.68 (NR)^c	7.26 (10.92)
Change from baseline CDLQI, mean (SD)	-1.5 (3.18)	-6.7 (5.63)	-5.2 (-7.44,-2.96)	-7.6 (6.96)

Source: Table 11, p79 CADMUS CSR, Table 2-59, p129 and Table 2-75, p144 of the submission, Table 10, p78 and TEFASI07A, p192-193, CADMUS CSR

Bold indicates a statistically significant difference

PGA = physician’s global assessment; CDLQI = children’s dermatology life quality index; PASI = Psoriasis Area and Severity Index, PedsQL = Pediatric Quality of Life Inventory; NR = not reported, RD = risk difference

^a Primary outcomes

^b Reported as 0.64 (0.81, 18.25) in Table 2-40 in submission, which appeared to be incorrect and could not be reproduced. Value calculated using StatsDirect during evaluation reported here.

^c p=0.028

6.18 In CADMUS, a statistically significantly higher proportion of patients randomised to ustekinumab reported a PGA of 0 or 1, PASI 75 and PASI 90 response, and also reported higher quality of life, compared to patients randomised to placebo after 12 weeks of treatment. PASI 75 and PASI 90 also appeared to be maintained through to Week 52.

Table 5: Results of primary and secondary endpoints at Week 12 and 52 in CADMUS JR

	Week 12	Week 52
Patients enrolled at Week 0, N	44	41
Patients who achieved a PGA score of cleared (0) or minimal (1) ^a , n(%)	34 (77.3%)	31 (75.6%)
PASI 75 responders, n(%)	37 (84.1%)	36 (87.8%)
PASI 90 responders, n(%)	28 (63.6%)	29 (70.7%)
Change from baseline CLDQI, mean (SD)	-6.3 (6.43)	-6.4 (6.10)

Source: Table 2-59, p129 and Table 2-75, p144 of the submission, Table 7, p56 CADMUS JR CSR

PGA = physician's global assessment; CDLQI = children's dermatology life quality index; PASI = Psoriasis Area and Severity Index.

^a Primary outcomes

6.19 Due to the lack of a comparator, interpretation of CADMUS JR was limited. Ustekinumab appeared to be effective and the proportion of PGA, PASI 75 and PASI 90 responders as well as CDLQI improvement appeared similar to CADMUS.

Table 6: Results of primary and secondary endpoints at Week 12 and Weeks 24 in Paller 2008

	Week 12			Week 24
	Placebo	Etanercept	Difference RD (95%CI)	Etanercept
Patients randomised	105	106	-	106
Patients who achieved a PGA score of cleared (0) or minimal (1), n(%)	14 (13.3%)	56 (52.8%)	0.40 (0.20, 0.51)^b	60 (55.0%)
PASI 75 responders ^a , n(%)	12 (11.4%)	60 (56.6%)	0.45 (0.34, 0.56)	72 (67.9%)
PASI 90 responders ^a , n(%)	7 (6.7%)	29 (27.4%)	0.21 (0.11, 0.3)	39 (36.8%)
PedsQL Mean change from baseline, mean (SD)	3.8 (10.1)	6.8 (17.6)	3.0 (NR)	NR
Change from baseline CLDQI, mean (SD)	-3.1 (5.1)	-5.4 (5.6)	-2 (-3.48, 0.52)	NR

Source: Langley 2011. Table 2-30, p98, Table 2-32, p101, Table 2-34, p102, Table 2-41, p113 and Table 2-75, p144 of the submission.

Bold indicates a statistically significant difference, values in italics indicate estimated during evaluation

PGA = physician's global assessment; CDLQI = children's dermatology life quality index; SD = standard deviation; PASI = Psoriasis Area and Severity Index, PedsQL = Pediatric Quality of Life Inventory; NR = not reported, RD = risk difference

^a Primary outcomes

^b Reported as 0.39 (0.51, 52.75) in Table 2-41 in submission, which appeared to be incorrect and could not be reproduced. Value calculated using StatsDirect during evaluation reported here.

6.20 In Paller 2008, a statistically significantly higher proportion of patients randomised to etanercept reported a PGA of 0 or 1, PASI 75 and PASI 90 response, and also reported higher quality of life, compared to patients randomised to placebo after 12 weeks of treatment. However, the incremental benefit of etanercept over placebo was numerically lower than reported for ustekinumab in CADMUS.

6.21 In the absence of direct head-to-head trials, ITCs were conducted using the Bucher method (Mantel-Haenszel, fixed effect model) to compare ustekinumab and etanercept in the ITT populations at the end of induction time points (i.e., Week 24/28 for ustekinumab and Week 12 for etanercept, the timepoints at which PASI assessment following initial treatment should be conducted based on the proposed and current PBS restrictions, respectively) via a common placebo reference arm. (ITCs based on outcomes at the end of Week 12 for both etanercept and ustekinumab were presented as supporting analyses).

6.22 A summary of the submission’s ITC results, and the evaluation’s recalculated results after excluding the single-arm CADMUS JR, are presented below for the key outcomes of PASI 75 (Table 7) and PASI 90 (Table 8) responders and non-responders.

Table 7: Results of PASI 75 response and non-response rates for ustekinumab at Week 12 and Week 24/28 compared to etanercept at Week 12*

Trial	Biologic		PBO	Results		
	Wk	n/N (%)	n/N (%)	RD (95% CI)	RR (95% CI)	OR (95% CI)
Week 12						
Ustekinumab ^a versus placebo						
CADMUS	12	29/36 (80.6)	4/37 (10.8)	0.7 (0.53,0.86)	7.45 (2.91, 19.06)	34.18 (9.08, 128.7)
CADMUS JR	12	37/44 (84.1)	N/A	N/A	N/A	N/A
Pooled		66/80 (82.5)	4/37 (10.8)	0.72 (0.59, 0.85)	7.63 (3.01, 19.36)	38.89 (11.87, 127.48)
Etanercept versus placebo						
Paller 2008	12	60/106 (56.6)	12/105 (11.4)	0.45 (0.34, 0.56)	4.95 (2.83, 8.65)	10.11 (4.95, 20.63)
Indirect analysis UST vs ETN (response rate)				0.27 (0.09, 0.44)	1.54 (0.52, 4.56)	3.85 (0.96, 15.37)
Indirect analysis CADMUS vs Paller 2008 (response rate; excludes CADMUS JR)				0.25 (0.05, 0.45)	1.51 (0.50, 4.49)	3.38 (0.75, 15.23)
Indirect analysis UST vs ETN (non-response rate)^c				-0.27 (-0.44, -0.10)	0.41 (0.24, 0.70)	0.3 (0.10, 0.93)
Indirect analysis CADMUS vs Paller 2008 (non-response rate; excludes CADMUS JR)				-0.25 (-0.45, -0.05)	0.45 (0.22, 0.92)	0.3 (0.08, 1.10)
Week 24 or 28						
Ustekinumab ^a versus placebo						
CADMUS	24	29/36 (80.6)	4/37 (10.8) ^b	0.7 (0.53,0.86)	7.45 (2.91, 19.06)	34.18 (9.08, 128.7)
CADMUS JR	28	39/44 (88.6)	N/A	N/A	N/A	N/A
Pooled		68/80 (85.0)	4/37 (10.8) ^b	0.74 (0.61, 0.87)	7.86 (3.1, 19.93)	46.75 (14, 156.08)
Etanercept versus placebo						
Paller 2008	12	60/106 (56.6)	12/105 (11.4)	0.45 (0.34, 0.56)	4.95 (2.83, 8.65)	10.11 (4.95, 20.63)
Indirect analysis UST vs ETN (response rate)				0.29 (0.12, 0.46)	1.59 (0.54, 4.7)	4.62 (1.14, 18.77)
Indirect analysis CADMUS vs Paller 2008 (response rate; excludes CADMUS JR)				0.25 (0.05, 0.45)	1.51 (0.50, 4.49)	3.38 (0.75, 15.23)
Indirect analysis UST vs ETN (non-response rate)				-0.29 (-0.46, -0.12)	0.34 (0.19, 0.61)	0.22 (0.05, 0.88)
Indirect analysis CADMUS vs Paller 2008 (non-response rate; excludes CADMUS JR)				-0.25 (-0.45, -0.05)	0.45 (0.22, 0.92)	0.3 (0.08, 1.10)

Source: Table 2-69, p138 and Table 2-71, p140 of the submission.

Bold indicates a statistically significant difference

ETN= etanercept; ITT= intent to apply population; N/A= not applicable; PBO=placebo OR= odds ratio; RD= risk difference; RR= relative risk; UST= ustekinumab; PASI = Psoriasis Area and Severity Index; Wk = week

^a UST standard dosage is 0.75 mg/kg for ≤60 kg, 45 mg for >60 kg to ≤100 kg, and 90 mg for >100 kg

^b 12 week placebo results used

^c Submission erroneously used PASI 90 non-responder results for Paller 2008 in its calculation instead of PASI 75 non-responder. Corrected during evaluation.

*Note that the results presented in Table 7 are derived from 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 any of the included biologic trials. 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

6.23 Based on results of the ITCs, the submission concluded that there were statistically significantly fewer patients receiving the ustekinumab standard dosage who did not achieve a PASI 75 response compared with etanercept at both Week 12 (RR=0.41,

95% CI 0.24, 0.70) and Week 24/28 (RR=0.34, 95% CI 0.19, 0.61). However, no statistically significant difference was observed in the proportion of PASI 75 response at either Week 12 or Week 24/28, though the point estimate favoured treatment with ustekinumab.

Table 8: Results of PASI 90 response and non-response rates for ustekinumab at Week 12 and Week 24/28 compared to etanercept at Week 12*

Trial	Biologic		PBO	Results		
	Wk	n/N (%)	n/N (%)	RD (95% CI)	RR (95% CI)	OR (95% CI)
Week 12						
Ustekinumab ^a versus placebo						
CADMUS	12	22/36 (61.1)	2/37 (5.4)	0.56 (0.38, 0.73)	11.31 (2.86, 44.62)	27.5 (5.69, 132.8)
CADMUS JR	12	28/44 (63.6)	N/A	N/A	N/A	N/A
Pooled		50/80 (62.5)	2/37 (5.4)	0.57 (0.44, 0.7)	11.56 (2.97, 44.99)	29.17 (6.54, 130.08)
Etanercept versus placebo						
Paller 2008	12	29/106 (27.4)	7/105(6.7)	0.21 (0.11, 0.3)	4.1 (1.88, 8.95)	5.27 (2.19, 12.68)
Indirect analysis UST vs ETN (response rate)				0.36 (0.2, 0.53)	2.82 (0.59, 13.5)	5.53 (0.98, 31.32)
Indirect analysis CADMUS vs Paller 2008 (response rate; excludes CADMUS JR)				0.35 (0.15, 0.55)	2.76 (0.57, 13.4)	5.22 (0.86, 31.77)
Indirect analysis UST vs ETN (non-response rate) ^c				-0.36 (-0.52, -0.20)	0.51 (0.38, 0.70)	0.16 (0.03, 0.83)
Indirect analysis CADMUS vs Paller 2008 (non-response rate; excludes CADMUS JR)				-0.35 (-0.55, -0.15)	0.53 (0.34, 0.81)	0.21 (0.04, 1.20)
Week 24 or 28						
Ustekinumab ^a versus placebo						
CADMUS	24	24/36 (66.7)	2/37 (5.4) ^b	0.61 (0.44, 0.78)	12.33 (3.14, 48.42)	35 (7.18, 170.69)
CADMUS JR	28	34/44 (77.3)	N/A	N/A	N/A	N/A
Pooled		58/80 (72.5)	2/37 (5.4) ^b	0.67 (0.55, 0.79)	13.41 (3.46, 51.98)	46.14 (10.22, 208.24)
Etanercept versus placebo						
Paller 2008	12	29/106 (27.4)	7/105(6.7)	0.21 (0.11, 0.3)	4.1 (1.88, 8.95)	5.27 (2.19, 12.68)
Indirect analysis UST vs ETN (response rate)				0.46 (0.31, 0.62)	3.27 (0.68, 15.6)	8.75 (1.53, 50.05)
Indirect analysis CADMUS vs Paller 2008 (response rate; excludes CADMUS JR)				0.40 (0.21, 0.59)	3.01 (0.62, 14.5)	6.64 (1.09, 40.64)
Indirect analysis UST vs ETN (non-response rate) ^c				-0.46 (-0.62, -0.30)	0.37 (0.25, 0.55)	0.11 (0.02, 0.47)
Indirect analysis CADMUS vs Paller 2008 (non-response rate; excludes CADMUS JR) ^c				-0.40 (-0.60, -0.20)	0.45 (0.28, 0.73)	0.16 (0.03, 0.81)

Source: Table 2-70, p139 and table 2-72, p141 of the submission.

Bold indicates a statistically significant difference

ETN= etanercept; ITT= intent to apply population; N/A= not applicable; PBO= placebo OR= odds ratio; RD= risk difference; RR= relative risk; UST= ustekinumab; PASI= Psoriasis Area and Severity Index; Wk = week

^a UST standard dosage is 0.75 mg/kg for ≤60 kg, 45 mg for >60 kg to ≤100 kg, and 90 mg for >100 kg

^b 12 week placebo results used

^c Submission erroneously estimated 79/106 non-responders from 29/106 responders reported. Corrected to 77/106 non-responders during evaluation.

*Note that the results presented in Table 8 are derived from 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 any of the included biologic trials. 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 Based on results of the ITCs, the submission concluded that there were statistically significantly fewer patients receiving the ustekinumab standard dosage who did not achieve a PASI 90 response compared with etanercept at both Week 12 (RR=0.51, 95% CI 0.38, 0.70) and Week 24/28 (RR=0.37, 95% CI 0.25, 0.55). However, no statistically significant difference was observed in the proportion of PASI 90 response at either Week 12 or Week 24/28, though the point estimate favoured treatment with ustekinumab.
- 6.25 Overall, the submission concluded that ustekinumab demonstrated superior effectiveness compared with etanercept on the basis of PASI 75 and PASI 90 non-response rates (for RR measure) at Week 24/28 and Week 12.
- 6.26 The submission did not propose what lower bound of the 95% confidence interval for risk difference (RD), relative risk (RR), or odds ratio (OR) for ustekinumab versus etanercept would represent a minimally clinically important difference (MCID) required to establish superior efficacy. During evaluation, a systematic review of head-to-head trials of active comparators in psoriasis by Wan et al¹ 2019 was identified which noted that margins between 14% to 20% were used in superiority trials for the PASI 75 response outcome (and in non-inferiority trials, margins of -10% to -20% for PASI 75 have been used in the literature). However, it was unclear if these values were applicable to the current submission as all the trials identified by Wan et al were head-to-head active comparator trials (as opposed to ITC with placebo as common comparator) and were conducted in adults.
- 6.27 Issues with the submission's approach to the ITCs included:
- Combining the CADMUS RCT results with those from the single-arm CADMUS JR study, which confounded the consideration of comparative efficacy. Excluding CADMUS JR from the ITC resulted in numerically smaller incremental benefits in PASI response for ustekinumab, as well as loss of statistically significant differences in some measures (PASI 75 non-response OR at Week 12 and 24/28 and PASI 90 non-response OR at Week 12). While the sponsor maintained in the PSCR that it was appropriate and statistically valid to pool the active arms of the studies, based on consistent trial populations (with the exception of age) and absence of treatment effect modifiers, the ESC agreed with the evaluation that it was not appropriate to pool results from a single arm with a RCT. The ESC commented that while the pooling favoured ustekinumab in all the PASI response/non-response analyses, the ITC conclusions remain largely unchanged when the CADMUS JR study was not included.
 - Week 12 results for all treatments (ustekinumab, etanercept and placebo) should have been used in the primary analysis as this was reflective of the double blind

¹ Wan MT, Alvarez J, Shin DB, Dommasch ED, Wu JJ, Gelfand JM. Head-to-head trials of systemic psoriasis therapies: a systematic review of study design and maximum acceptable treatment differences. *J Eur Acad Dermatol Venereol*. 2019;33(1):42-55. doi:10.1111/jdv.15174

phase of the respective trials. This would also be consistent with the ustekinumab 2009 submission for treatment of severe CPP in adults, in which results at 12 weeks for ustekinumab were used in the indirect comparison with etanercept (and infliximab). The sponsor stated in the PSCR that results at Week 24/28 were applicable, as it is the time point consistent with (or as close to) the proposed timing of assessment for continuation of therapy on the PBS. The ESC noted that irrespective of whether Week 12 or Week 24/28 results for ustekinumab were used, the results from 12 and 24 weeks in CADMUS were numerically the same, and that the difference in timing of response may not be an issue given that response rate was stable over that time period.

- The submission did not consider transitivity issues between CADMUS, CADMUS JR and Paller 2008. There was a large difference in the proportion of patients randomised to placebo who entered early escape in CADMUS and Paller 2008 (0% and 25.7% respectively), which may have indicated that there were unobserved differences between the patient populations. The ESC considered that although the early escape rates in the placebo arms were different, the response rates in the placebo arms were similar, as was the early escape rate in the treatment arms, and overall, this was unlikely to be an issue.

- 6.28 Despite not being specifically measured in CADMUS, CADMUS JR or Paller 2008, the submission presented results for PASI 75 and PASI 90 non-responders (the complement to PASI 75 and PASI 90 responders) to support the clinical claim, particularly with respect to drawing inferences from the RR results. The main argument for using PASI 75 and PASI 90 non-responder RRs, instead of the responder RRs, was that statistical efficiency of the estimation (as measured by a lower variance/standard error) might be increased by using a non-response RR. However, the submission's approach was poorly justified.
- 6.29 The results of the response and non-response analyses were discordant. For example, at Week 12, PASI 75 and PASI 90 response for ustekinumab was not statistically different to etanercept when considering CADMUS pooled with CADMUS JR for either OR or RR. However, the PASI 75 and PASI 90 non-response OR and RR was statistically significantly lower for those treated with ustekinumab compared to etanercept. This was likely driven by the small sample size of CADMUS and CADMUS JR. The ESC commented that the conclusion should be consistent regardless of whether responders or non-responders are analysed. The pre-PBAC response argued that if relying on OR or RD measures, the RD is more appropriate than OR as it has the smaller variance and a lower risk of type II error, and is therefore the more statistically efficient measure.
- 6.30 Results of the submission's ITCs for the secondary endpoint of PGA score, and re-analysed results calculated during the evaluation after excluding the CADMUS JR study are presented in Table 9.

Table 9: Results of PGA response and non-response rates for ustekinumab at Week 12 and Week 24/28 compared to etanercept at Week 12

Trial	W k	PGA (0 or 1) response rate			Difference vs PBO		
		UST ^a	PBO	ETN	RD (95% CI)	RR (95% CI)	OR (95% CI)
		n/N (%)	n/N (%)	n/N (%)			
CADMUS	12	25/36 (69.4)	2/37 (5.4)	N/A	0.64 (0.45, 0.78) ^c	12.85 (3.28, 50.3)	39.77 (8.10, 195)
	24	26/36 (72.2)	2/37 (5.4) ^b	N/A	0.67 (0.50, 0.83)	13.36 (3.42, 52.2)	45.5 (9.18, 226)
CADMUS JR	12	34/44 (77.4)	N/A	N/A	N/A	N/A	N/A
	28	35/44 (79.5)	N/A	N/A	N/A	N/A	N/A
Paller 2008	12	N/A	14/105 (13.4)	56/106 (52.8)	0.40 (0.28, 0.51) ^d	3.96 (2.36, 6.66)	7.2 (3.69, 14.37)
PGA response rates							
Week 12 pooled ustekinumab versus etanercept					0.29 (0.12, 0.46)	3.44 (0.81, 14.69)	6.75 (1.29, 35.36)
Week 12 CADMUS vs Paller 2008 (excludes CADMUS JR)					0.24 (0.04, 0.44)	3.25 (0.75, 13.98)	5.45 (0.97, 30.8)
Week 24/28 pooled ustekinumab versus etanercept					0.31 (0.15, 0.48)	3.56 (0.84, 15.17)	7.72 (1.47, 40.61)
PGA non-response rates							
Week 12 pooled ustekinumab versus etanercept					-0.3 (-0.46, -0.13)	0.5 (0.32, 0.77)	0.14 (0.03, 0.75)
Week 12 CADMUS vs Paller 2008 (excludes CADMUS JR)					-0.24 (-0.44, -0.04)	0.59 (0.35, 1.01)	0.19 (0.02, 1.42)
Week 24/28 pooled ustekinumab versus etanercept					-0.32 (-0.49, -0.16)	0.45 (0.29, 0.71)	0.12 (0.02, 0.66)

Source: Tables 2-40 and 2-41, p113, 2-73, p142 and 2-74, p143 of the submission.

N/A= not applicable; PBO= placebo; PGA= Physician's Global Assessment; OR= odds ratio; placebo; RD= risk difference; RR= relative risk; UST= ustekinumab, WK = week

Bold indicates a statistically significant difference

Text in italics indicate values calculated during evaluation

^a UST standard dosage is 0.75 mg/kg for ≤60 kg, 45 mg for >60 kg to ≤100 kg, and 90 mg for >100 kg

^b 12 week results used

^c Reported as 0.64 (0.81, 18.25) in Table 2-40 in submission, which appeared to be incorrect and could not be reproduced. Value calculated using StatsDirect during evaluation reported here

^d Reported as 0.39 (0.51, 52.75) in Table 2-41 in submission, which appeared to be incorrect and could not be reproduced. Value calculated using StatsDirect during evaluation reported here

6.31 Based on results of the ITCs, the submission concluded that compared to etanercept at Week 12, statistically significantly fewer patients receiving the ustekinumab standard dosage failed to achieve a PGA score of cleared (0) or minimal (1) at Week 12 (48.1% vs 26.3%, respectively; RR: 0.50 [95% CI: 0.32, 0.77]) and at Week 24/28 (48.1% vs 23.8%, respectively; RR: 0.45 [95% CI: 0.29, 0.71]) and when using pooled data from CADMUS and CADMUS JR. Therefore, the submission concluded that ustekinumab demonstrated superior effectiveness compared with etanercept on the basis of PGA score 0 or 1 non-response rates at Week 24/28 and Week 12 using the RR measure. However, indirect comparison excluding CADMUS JR conducted during evaluation found no statistically significant differences in RR or OR for PGA responder or non-responder rates between ustekinumab and etanercept at Week 12.

6.32 Based on an ITC of the mean change from baseline in CDLQI scores, the submission claimed that patients treated with ustekinumab experienced statistically significantly higher reductions in the mean CDLQI score from baseline at Week 12 (RD = -3.0, 95% CI: -5.3, -0.7) and Week 24/28 (RD = -3.4, 95% CI: -5.7, -1.1) compared to patients treated with etanercept. Thus, the submission concluded that patients treated with ustekinumab experienced a significantly greater improvement in quality of life based on CDLQI scores compared to etanercept at Week 28 and Week 12. This may not be a reasonable conclusion, as:

- Langley 2011, using data from Paller 2008, proposed that the MCID for CLDQI should be 2.5, which was greater than the upper 95% confidence intervals reported. Therefore it could not be concluded with certainty that the numerical benefit from the ITC for CLDQI was clinically meaningful; and
- The change from baseline CLDQI in patients randomised to placebo was much larger in Paller 2008 (mean change [SD] =-3.4 [5.4]) than in CADMUS (mean change [SD] =-1.5 [3.18]), which may indicate a transitivity issue in the ITC and favoured treatment with ustekinumab.

Comparative harms

6.33 A naïve comparison of the adverse events reported at Week 12 in CADMUS, CADMUS JR and Paller 2008 is presented in Table 10.

Table 10: Summary of key adverse events in the CADMUS, CADMUS JR and Paller 2008 at Week 12

Trial	CADMUS		CADMUS JR	Paller 2008	
	PBO	UST standard dosage ^a	UST standard dosage ^a	PBO	ETN ^b
Patients treated, n	37	36	44	105	106
Patients with ≥ 1 AE	21 (56.8)	16 (44.4)	24 (54.5)	62 (59.0)	68 (64.2)
Patients who discontinued due to AE	0	0	0	0	1 (0.9)
Infections	14 (37.8)	8 (22.2)	17 (38.6)	33 (31.4)	50 (47.2)
Patients with ≥ 1 SAE	0	0	1 (2.3)	0	0
Serious infections	0	0	0	0	0
Death	0	0	0	0	0
Specific adverse events					
Upper respiratory tract infection	2 (5.4)	3 (8.3)	5 (11.4)	12 (11.4)	18 (17.0)
Gastroenteritis	1 (2.7)	0	0	0	6 (5.7)
Influenza	0	1 (2.8)	0	2 (1.9)	8 (7.6)
Nasopharyngitis	10 (27.0)	1 (2.8)	4 (9.1)	9 (8.6)	8 (7.6)
Injection site reaction	0	1 (2.8)	5 (11.4)	5 (4.8)	7 (6.6)

Source: Table 2-50, p120 and Table 2-56, p125 of the submission.

UST=ustekinumab; ETN=etanercept; AE=adverse events; SAE=serious adverse events; PBO=placebo

^a UST standard dosage is 0.75 mg/kg for subjects ≤60 kg, 45 mg for subjects >60 kg but ≤100 kg, and 90 mg for subjects >100 kg at Week 0 and 4 followed by q12w

^b 0.8 mg/kg ETN up to max. dose of 50 mg once weekly

6.34 The submission also provided Bucher ITCs for safety outcomes for ustekinumab (using pooled CADMUS and CADMUS JR safety outcomes) at Week 24/28 versus etanercept at Week 12. The comparative safety of ustekinumab versus etanercept was assessed for the induction phase only (Weeks 12 and 24/28), since the submission stated that maintenance data for etanercept was not available in the published documents. The adverse events reported for CADMUS Week 24 and CADMUS JR at Week 12 and 28 could not be independently verified.

6.35 The submission claimed that ustekinumab had non-inferior safety compared to etanercept with an overall similar proportion of patients experiencing AEs. There was a trend towards a lower incidence of specific AEs with ustekinumab such as upper

respiratory tract infections, influenza, gastroenteritis, and nasopharyngitis during the induction phase; however, the differences generally did not meet statistical significance during the induction period.

6.36 Overall, there was no evidence of any difference in adverse events between patients treated with ustekinumab standard dose in CADMUS and CADMUS JR and patients treated with etanercept in Paller 2008 except for:

- In the indirect comparison of CADMUS with Paller 2008, the proportion of patients who reported one or more infections at 12 weeks was statistically significantly lower (RD = -0.32, 95% CI = -0.56, -0.08) in patients treated with ustekinumab in CADMUS than in patients treated with etanercept in Paller 2008. No statistically significant differences were observed when using pooled ustekinumab data or at the end of ustekinumab induction (24 weeks) in CADMUS; and
- The proportion of patients who reported any nasopharyngitis at 12 weeks was statistically significantly lower (RD = -0.23, 95% CI = -0.30, -0.16) in patients treated with ustekinumab in CADMUS and when pooled with CADMUS JR (RD = -0.2, 95% CI = -0.37, -0.03) than in patients treated with etanercept in Paller 2008. However this was driven by an unusually high nasopharyngitis rate in patients randomised to placebo in CADMUS (10/37, 27%) compared to those randomised to placebo in Paller 2008 (9/105, 8.6%).

Benefits/harms

6.37 On the basis of the indirect comparison presented by the submission, for every 100 patients treated with ustekinumab in comparison with etanercept:

- Approximately 25 more patients would have a Psoriasis Area and Severity Index (PASI) 75 response after 12 weeks treatment.
- Approximately 35 more patients would have a PASI 90 response after 12 weeks treatment.

6.38 Comparative harms are not presented as the submission claimed non-inferior safety between ustekinumab and etanercept.

Clinical claim

6.39 The submission described ustekinumab as superior in terms of effectiveness and non-inferior in terms of safety compared to etanercept. The claims were based on a pooled analysis of PASI 75 and PASI 90 (non-)response rates and quality of life as measured by the CDLQI from CADMUS and CADMUS JR, and these results were compared in an ITC to results for etanercept from Paller 2008.

- 6.40 The PBAC considered that the claim of superior comparative effectiveness was reasonable, despite a number of limitations with the trials and the indirect comparison including: small trial sizes; applicability issues to the PBS population; potential transitivity issues; discordant results between responders/non-responders for some measures; a reliance on Week 24/28 CADMUS results for the primary analysis (not Week 12 in the supporting analysis); poorly defined MCIDs; and inappropriate pooling of the single-arm CADMUS JR with CADMUS results.
- 6.41 The PBAC noted that ustekinumab showed a statistically significant benefit compared with etanercept, measured by RD, at both Weeks 12 and 24, for both PASI 75 and PASI 90 responses. The PBAC also noted that ustekinumab showed a statistically significant benefit compared with etanercept, measured by OR, at Week 24 for PASI 90 response (after CADMUS JR was excluded). Non-response analyses consistently showed a statistical benefit at Weeks 12/24 for PASI 75/90 using both RD and RR. Whilst none of these measures definitively overcame potential transitivity issues or issues related to the small trial sizes, the PBAC considered the totality of the evidence presented supported a claim of superior effectiveness compared with etanercept. In particular, a claim of clinically meaningful superiority was reasonable in the context of an unmet need for an alternative to etanercept, which has a TGA indication limited to 24 weeks' treatment in the paediatric population, as its safety profile depicts only short term use². The claim was further supported by the subgroup analysis provided with the PSCR to demonstrate applicability of the trials to the PBS population; the general stability of responses between Weeks 12 and 24/28; and the broadly consistent results after CADMUS JR results were removed during evaluation. However, the magnitude of the benefit remained uncertain.
- 6.42 The PBAC considered that the claim of non-inferior comparative safety was reasonable, given the lack of evidence of an overall difference in adverse events between patients treated with ustekinumab and patients treated with etanercept.
- 6.43 BSC would be an appropriate comparator in some patients (see *Comparator* section). Although placebo in CADMUS may not be entirely representative of BSC, the PBAC considered that a claim of superiority over BSC was reasonable based on CADMUS results for induction of PASI 75 and PASI 90 response at Week 24/28 and Week 12. Whilst the magnitude was uncertain, the claim was reasonable in the context of the available clinical evidence. Comparative safety with respect to BSC was not assessed, although the PBAC considered it would not be worse than the safety of etanercept over placebo.

² See the TGA *Australian Public Assessment Report*, etanercept March 2012, p28: <https://www.tga.gov.au/auspar/auspar-etanercept>

Economic analysis

- 6.44 The submission presented a simple incremental cost per responder analysis (Table 11). The etanercept submission in March 2012 presented a trial-based cost per responder analysis, as determined by PASI 75 response to etanercept compared to best supportive care over a 12 week period, as the basis for the economic evaluation. While etanercept was recommended for paediatric patients with severe CPP on the basis of a cost per responder analysis, the PBAC considered that this approach was not ideal and a cost utility analysis was preferred (paragraph 12.5, etanercept PSD March 2012).
- 6.45 To show cost-effectiveness of ustekinumab compared with BSC (an appropriate comparison for some patients), the PSCR presented a trial-based cost per responder analysis of ustekinumab and placebo over 28 weeks of treatment, which resulted in an incremental cost of \$ [REDACTED] per PASI 75 responder. Placebo in the CADMUS trial may not be entirely representative of BSC. As this analysis was presented in the PSCR, it was not evaluated.

Table 11: Key components and assumptions of the cost per responder analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented, the submission stated that effectiveness was assumed to be superior to etanercept
Therapeutic claim: safety	Based on evidence presented, the submission stated that safety was assumed to be non-inferior to etanercept
Evidence base	Indirect comparison of three trials/studies; two with ustekinumab (CADMUS and CADMUS JR) and one with etanercept (Paller 2008) via a common placebo arm
Equi-effective doses ^b	For induction, ustekinumab 0.75 mg/kg (<60 kg), 45 mg (≥60 kg to <100 kg), or 90 mg (≥100 kg) at Weeks 0, 4 and 16 is equi-effective to etanercept 0.8 mg/kg ^a (up to maximum 50 mg etanercept) every week for a maximum 24-week treatment course. Note that ustekinumab is permitted for continuous use until inadequate response or treatment limiting intolerance develops.
Direct medicine costs	The treatment acquisition costs of ustekinumab (at Week 0, 4 and 16) and etanercept (weekly for a maximum 16-week treatment course) were included in the economic evaluation. A supplementary analysis of the treatment acquisition costs of ustekinumab (at Week 0, 4 and 16) and etanercept (weekly for a maximum 24-week treatment course) were also included in the economic evaluation.
Other costs or cost offsets	No, since the submission stated that both ustekinumab and etanercept are administered by subcutaneous injection, and most patients or carers are able to administer the injection after appropriate training. No costs were assumed for BSC for patients who fail to respond to treatment, or for hospitalisations due to severe disease.

Source: Table 3-1, p182 of the submission.

^a Table 3-1 in the submission stated 50 mg/kg, however this was considered to be an error as the Approved PI for etanercept states 0.8 mg/kg up to a maximum of 50 mg.

^b Inconsistent terminology with the clinical claim, as the submission claimed that ustekinumab was superior to etanercept.

- 6.46 The doses used in the cost component of the submission's cost per responder analysis were:
- 45 mg of ustekinumab at Weeks 0, 4 and 16, based on the approved dose of ustekinumab. The PBAC noted that analysis did not account for the 90 mg dose for

patients weighing >100 kg, or for the vial wastage associated with use in patients <60 kg.

- 47.32 mg etanercept weekly, assuming 10.7% use 25 mg and 89.3% use 50 mg for 24 weeks. The proportion of 25 mg and 50 mg dosing was based on PBS data from July 2018 to June 2020.

6.47 In the base case, the submission compared treatment with 28 weeks of ustekinumab (informed by the pooled CADMUS and CADMUS JR response rate for ustekinumab at Week 24/28) to 16 weeks of treatment with etanercept (informed by the response rate for etanercept at Week 12 from Paller 2008). A supplementary comparison was also provided comparing 28 weeks of treatment with ustekinumab to 24 weeks of etanercept.

6.48 The regimens in the cost per responder analysis may not capture the real-world use of either etanercept or ustekinumab:

- The current listing for etanercept allows for a patient to be treated with up to 16 weeks of treatment, and only patients who achieve a PASI 75 response (assessed at Week 12) may continue for another 8 weeks for a maximum of 24 weeks of treatment. This may be followed by another 24 weeks of treatment (with another PASI assessment at 12 weeks) after a disease flare, with a mandated 12-month break in PBS-subsidised therapy after a loss of response to two courses of treatment. The cost per responder analysis considered only 16 or 24 weeks of treatment with no consideration for continuation rules; and
- The proposed restriction for ustekinumab allowed for ongoing therapy until patients either lose response or develop treatment-limiting intolerance, whereas the cost per responder analysis was restricted to just 28 weeks. The cost effectiveness of ustekinumab beyond 28 weeks was unknown. The PSCR argued that the cost effectiveness of ustekinumab was appropriately presented based on a similar timepoint to etanercept's maximum duration of therapy (24 weeks). The ESC commented that 28 weeks is a short time horizon for an ongoing treatment, and ongoing ustekinumab treatment should have been compared with intermittent etanercept treatment. The pre-PBAC response argued that it was reasonable to assume that maintaining a response on continuous ustekinumab therapy is more effective than gaining (and losing) response on intermittent etanercept therapy. It noted the requested price of ustekinumab in paediatric severe CPP results in a total cost over 28 weeks that is \$ [REDACTED] ([REDACTED]%) higher than the cost of etanercept over 24 weeks (that is, \$ [REDACTED] and \$ [REDACTED], respectively). Thus, it argued that given the large additional benefit of ustekinumab continuous therapy versus etanercept's 24-week maximum treatment duration, and the small incremental cost of 28 weeks of ustekinumab versus 24 weeks of etanercept, which is based on the price currently paid for ustekinumab in adult CPP, ustekinumab should be

considered cost effective versus etanercept beyond the initial treatment period in paediatric severe CPP.

- 6.49 The results of the submission’s cost per responder analyses are presented in Table 12 and Table 13. The submission requested a price for ustekinumab 45 mg consistent with the current ustekinumab 45 mg vial price in adult severe CPP.

Table 12: Results of the base case cost per responder analysis (16 weeks of etanercept)

	Ustekinumab	Etanercept	Difference
Length of treatment period, weeks	28	16	12
Dose frequency	Week 0, 4, then q12w	Weekly	
Cost per script	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Scripts in the initial treatment period	3	4	
Cost of initial treatment period	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Incremental PASI 75 response rate over placebo (based on PBS initial treatment period of biologic)	74.2% ^a (Week 24/28)	45.2% (Week 12)	29.0%
Incremental cost per PASI 75 responder	\$ [REDACTED]		
Incremental PASI 90 response rate over placebo (based on PBS initial treatment period of biologic)	67.1% ^a (Week 24/28)	20.7% (Week 12)	46.4%
Incremental cost per PASI 90 responder	\$ [REDACTED]		

Source: Table 3-2 and 3-3, pp185-186 of the submission.

^a Estimated by submission by subtracting placebo response rate at 12 weeks from ustekinumab 24 week response rate in CADMUS pooled with ustekinumab 28 week response rate in CADMUS JR

Table 13: Results of the supplementary cost per responder analysis (24 weeks of etanercept)

	Ustekinumab	Etanercept ^a	Difference
Length of treatment period, weeks	28	24	4
Dose frequency	Week 0, 4, then q12w	Weekly	
Cost per script	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Scripts per 24-week treatment period	3	6	
Cost of initial treatment period	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Incremental PASI 75 response rate vs placebo	74.2% ^b (Week 24/28)	56.5% ^c (Week 24)	17.7%
Incremental cost per PASI 75 responder	\$ [REDACTED]		
Incremental PASI 90 response rate over placebo	67.1% ^b (Week 24/28)	30.1% ^c (Week 24)	37.0%
Incremental cost per PASI 90 responder	\$ [REDACTED]		

Source: Table 3-4 and 3-5, p187 of the submission.

^a Included all patients who received etanercept through the initial 12-week double-blind treatment period and the first 12 weeks of the 24-week open-label period that followed.

^b Estimated by submission by subtracting placebo response rate at 12 weeks from ustekinumab 24 week response rate in CADMUS pooled with ustekinumab 28 week response rate in CADMUS JR

^c Estimated by submission by subtracting placebo response rate at 12 weeks from etanercept 24 week response rate in Paller 2008.

- 6.50 Using the response rate from the CADMUS trial only, the cost per additional PASI 75 responder compared to etanercept increased to \$ [REDACTED] and \$ [REDACTED] for the base case and supplementary analyses respectively, and the cost per additional PASI 90 responder increased to \$ [REDACTED] and \$ [REDACTED] for the base case and supplementary analyses respectively.

- 6.51 An alternative scenario that compared 28 weeks of treatment with ustekinumab with up to 24 weeks of etanercept along with the following assumptions (to more

reasonably align with the most reliable clinical data and PBS listing), was considered during the evaluation:

- Using observed response rates from CADMUS and Paller 2008 only as these provided the least biased efficacy results, and removing any numerical differences in placebo response rate between trials; and
- Only patients treated with etanercept who achieve PASI 75 at Week 12 receive a further 8 weeks treatment.

The resultant cost per additional PASI 75 and PASI 90 responder was \$ [REDACTED] and \$ [REDACTED] respectively.

- 6.52 The ESC's preferred approach for a claim of superior efficacy would have been a cost-utility analysis that modelled the costs and quality adjusted life years over a number of years. In contrast, the analysis provided by the submission did not consider duration of effect or ongoing costs to the PBS for ustekinumab. The submission did not establish the health gain associated with the additional cost per responder for ustekinumab.
- 6.53 The PSCR stated that it strongly considered a trial-based cost per responder analysis remained an appropriate economic evaluation as it is consistent with the PBAC's acceptance and recommendation of etanercept for paediatric severe CPP where a trial-based cost per responder analysis versus BSC was presented and the PBAC noted that "there w[as] precedents in previous paediatric submissions" (etanercept PSD, March 2012). The pre-PBAC response reiterated that a trial-based cost per responder analysis is reasonable for a small group of patients with a high clinical need.

Drug cost/patient/28-week induction phase for assessment for continuation of treatment: \$ [REDACTED]

- 6.54 Based on the proposed restriction, patients would be assessed for PASI 75 response with ustekinumab after 24 weeks of initial treatment, with responders being eligible for another 24 weeks of treatment. The dosing schedule of ustekinumab is such that patients would not require another script for ustekinumab until 28 weeks after initiation of treatment. Accordingly, the cost of ustekinumab in the cost per responder analysis covers the period up to 28 weeks after initiation. For this induction phase for assessment of response prior to assessment for continuation of treatment, the cost of ustekinumab would be equal to \$ [REDACTED], assuming all patients remain on treatment and based on ex-manufacturer prices.
- 6.55 Comparatively, the cost of 16 weeks of treatment with etanercept (induction period) was \$ [REDACTED] (Table 12) and the cost of 24 weeks of treatment with etanercept (maximum treatment duration) was \$ [REDACTED] (Table 13).
- 6.56 As calculated during the evaluation, based on the PASI 75 response rates for ustekinumab in CADMUS after 24 weeks of treatment (80.6%, not considering placebo

response), and after a further 24 weeks of treatment, the cost for the first year of ustekinumab treatment would equal \$ [redacted] per responder (5 administrations at weeks 0, 4, 12, 28 and 40) and \$ [redacted] per non-responder (3 administrations at weeks 0, 4, and 12), equating to a weighted cost of \$ [redacted] per initiating patient. The ongoing treatment cost per year for responders would equal \$ [redacted], with administration of ustekinumab required every 12 weeks. Response beyond 52 weeks was not assessed in the trial or study for ustekinumab presented in the submission.

Table 14: Drug cost per patient for ustekinumab and etanercept

	Ustekinumab ^a Trial dose and duration	Ustekinumab Cost per responder analysis ^c	Ustekinumab Financial estimates ^m	Etanercept Trial dose and duration ^d	Etanercept Cost per responder analysis ^d	Etanercept Financial estimates ^m
Mean dose	42.32 mg in CADMUS and 29.73 mg in CADMUS JR ^b	45 mg at Week 0, 4 and 16	45 mg at Week 0, 4 and 16, then every 12 weeks	Based on median weight of 59.6 kg = 47.68 mg weekly ^g	42.37 mg weekly ^h	50 mg weekly
Mean duration	37.76 weeks CADMUS 37.28 weeks CADMUS JR ^f	24/28 weeks	[redacted] % x 28 weeks and [redacted] % x 24 weeks ongoing ⁿ	Not reported but up to 36 weeks	16 weeks	24 weeks
Cost/patient/4 weeks	\$ [redacted] averaged over first 24 weeks then \$ [redacted] ongoing ^j	\$ [redacted] averaged over first 24 weeks then \$ [redacted] ongoing	\$ [redacted] averaged over first 28 weeks then \$ [redacted] ongoing	\$ [redacted] ^k	\$ [redacted] ^h	\$ [redacted] ex-man price and \$ [redacted] corrected dispensed price
Cost/patient/course	\$ [redacted] for up to 40 weeks (\$ [redacted] for first 24/28 weeks) ^l	\$ [redacted] for the 24/28 weeks	\$ [redacted] for 28 weeks	\$ [redacted] for 16 weeks ^k	\$ [redacted] for 16 weeks ^h	\$ [redacted] for 24 weeks

Source: compiled during the evaluation from Sections 2, 3 and 4 of the submission and the CADMUS and CADMUS JR CSRs. Does not incorporate amendments to financials made in the PSCR (see *Estimated PBS usage & financial estimates*).

^a Standard dose group in CADMUS

^b Actual dose intensity in the trials: 207.38 mg over 4.9 administrations (Page 132 of the CADMUS CSR) and 142.7 mg in over 4.8 administrations (Page 213 of the CADMUS JR CSR)

^c Base case cost per responder analysis, and based on ex-manufacturer prices

^d Ex-manufacturer prices

^e Based on dose of 0.75 mg/kg for patients ≤60 kg, 45 mg for patients >60 kg to ≤100 kg, and 90 mg for patients >100 kg; at Week 0, 4, and every 12 weeks thereafter through Week 40

^f Page 214 of the CADMUS JR CSR and page 145 of the CADMUS CSR

^g 0.8 mg/kg up to 50 mg weekly.

^h Presumably based on split of 25 mg and 50 mg etanercept prescriptions for the paediatric patient population on the PBS

ⁱ Averaged over 24 weeks

^j With 1/36 in CADMUS and 1/44 in CADMUS JR receiving a 90 mg dose in CADMUS and 1/44 in CADMUS JR

^k Based on all patients receiving 50 mg weekly

^l Based on administration at Week 0, 4, 16, 28 and 40 and 2/80 patients receiving 90 mg dose and with 1/36 in CADMUS and 1/44 in CADMUS JR receiving a 90 mg dose in CADMUS and 1/44 in CADMUS JR,

^m Dispensed price for maximum quantity used in financial estimates, based on approved ex-manufacturer price.

ⁿ Persistence to therapy was assumed to be [redacted] % for initial treatment, and [redacted] % for continuing treatment.

Estimated PBS usage & financial implications

- 6.57 This submission was not considered by DUSC. The submission expected that once PBS-listed, ustekinumab will substitute for etanercept, which is the only biological agent listed on the PBS for paediatric severe CPP, and will also lead to an increase in the number of paediatric severe CPP patients receiving biological treatment who are not currently treated with etanercept.
- 6.58 Key assumptions and inputs for estimation of the financial estimates are presented in the table below.

Table 15: Key data sources and parameter values applied in the utilisation and financial estimates

Data	Value and Source	Comment
Eligible population		
Estimated etanercept-treated patients	Yr1: 36, Yr2: 36, Yr3: 37, Yr4: 37, Yr5: 38, Yr6: 38 Source: PBS/RPBS dispensed etanercept scripts (208) in 2019, divided by 6 scripts, assuming, on average, a patient received a full 24 wk course of treatment in the year. Extrapolated using ABS-projected population growth for the 4-17 age segment.	Assuming all etanercept patients completed the 24-wk treatment (6 scripts) resulted in the lowest possible number of current biologic-treated patients. Given that only 56.6% of patients achieved efficacy (PASI 75) at wk 12 with etanercept (required for continuation), the number of patients treated with etanercept was likely underestimated. Updated to 5 scripts the PSCR.
Estimated additional patients initiating ustekinumab (beyond those replacing etanercept)	Yr1: Double the number of patients that use ustekinumab in the replacement of etanercept Yr2-6: 7.6% per annum growth Source: Yr1: unclear/not reported. Yr2-6: Growth trend of ustekinumab in adult severe CPP following its PBS listing (PBS 10% sample data from January 2005-June 2020). Submission noted there is currently no published epidemiological data on paediatric severe CPP or the proportion of the patient population who would be eligible for treatment in Australia.	Yr1: There is likely to be a pool of paediatric patients eligible and ready to use PBS-subsidised ustekinumab once listed, but no details on how the magnitude of increase was determined. Yr2-6: 2010-2014 (first 5 years of listing) data was used to estimate annual growth. Yr6 was excluded because new biologics listed impacted the growth of ustekinumab initiations. If Yr6 was included, the growth rate would be higher (9.5%). 40 patients were proposed to be grandfathered to PBS supply upon listing, but they were not included in the submission's financial estimates. This was addressed in the PSCR.
Total prevalent population	Calculated via the sum of the estimated biologic-treated patients and the estimated additional patients initiating ustekinumab (beyond those replacing etanercept).	May be overestimated as the submission did not allow for the removal patients over the age of 18 in the forecast.
Treatment utilisation		
Uptake rate	Yr1-6: ■■■% Source: Expert advice from Australian dermatologists who treat paediatric severe CPP.	The sample of dermatologists involved, demographics/characteristics of the sample and what questions were asked were not provided.
Persistence to therapy	Initial treatment: ■■■%; calculated using patients who achieved PASI 75 and remained on treatment up until wk 28 from the CADMUS (30/36) and CADMUS JR (39/44) trials. Weighted based on the Australian distribution of ages. Continuing treatment: ■■■%; calculated using proportion who had PASI 75 at wk 28 and	The proportion of patients who continue treatment in the first year of initiation was underestimated. Given the initial treatment rate was a 28-wk rate, and the first continuing treatment is 24-wks, the continuing treatment rate for the first continuing treatment should be the 24-wk rate (92.7%), instead of the annual 52 wk rate (84.9%) used in the submission. This was addressed in the PSCR.

Public Summary Document – March 2021 PBAC Meeting

Data	Value and Source	Comment																
	continued treatment till wk 52 in CADMUS (28/30) and CADMUS JR trials (36/39). Averaged and weighted based on the based on the Australian distribution of ages, and then converted from a 24-wk rate to 52-wk rate.	Trial conditions in CADMUS may be different to real-world setting and the persistence to therapy may be uncertain.																
Scripts dispensed	<p>Number of scripts for ustekinumab</p> <table border="1"> <thead> <tr> <th>Ustekinumab</th> <th>Duration*</th> <th>Scripts</th> </tr> </thead> <tbody> <tr> <td>Initial treatment</td> <td>28</td> <td>3</td> </tr> <tr> <td>First continuing treatment</td> <td>24</td> <td>2</td> </tr> <tr> <td>Subsequent continuing treatments</td> <td>52</td> <td>4.33^</td> </tr> </tbody> </table> <p>*in wks ^based on 52wks/24wks*2 treatments</p>	Ustekinumab	Duration*	Scripts	Initial treatment	28	3	First continuing treatment	24	2	Subsequent continuing treatments	52	4.33^	Reasonable.				
Ustekinumab	Duration*	Scripts																
Initial treatment	28	3																
First continuing treatment	24	2																
Subsequent continuing treatments	52	4.33^																
Etanercept scripts replaced	<p>Calculated by assuming each etanercept patient received a full 24-wk treatment (6 scripts).</p> <p>Source: Sheet 4a of the submission's financial model.</p>	The submission was inconsistent applying continuation rates. While it was assumed that █% of patients would not achieve PASI 75 after initiation of ustekinumab and would discontinue treatment, it was assumed that 100% of patients who initiated etanercept would achieve PASI 75 (significantly higher than the 56.6% at wk 12 reported in Paller 2008). This would lead to an overestimate in the cost offset. The PSCR estimates assumed that etanercept patients received 5 scripts (on average).																
Costs																		
Proposed medicine	<p>Requested price for ustekinumab 45mg, initiating and continuing</p> <table border="1"> <thead> <tr> <th></th> <th>Max qty</th> <th>AEMP</th> <th>DPMQ</th> </tr> </thead> <tbody> <tr> <td>Published</td> <td>1</td> <td>\$3,809.08</td> <td>\$3,951.07</td> </tr> <tr> <td>Effective</td> <td>1</td> <td>\$█</td> <td>\$█</td> </tr> </tbody> </table>		Max qty	AEMP	DPMQ	Published	1	\$3,809.08	\$3,951.07	Effective	1	\$█	\$█	Requested same price as ustekinumab for adult CPP. Updated during evaluation to account for new PBS fees from 1 January 2021.				
	Max qty	AEMP	DPMQ															
Published	1	\$3,809.08	\$3,951.07															
Effective	1	\$█	\$█															
Comparator	<p>Current DPMQ for etanercept</p> <table border="1"> <thead> <tr> <th></th> <th>Max qty</th> <th>AEMP</th> <th>DPMQ</th> </tr> </thead> <tbody> <tr> <td>1954W 25mg vials</td> <td>2</td> <td>\$469.93</td> <td>\$1,066.68</td> </tr> <tr> <td>1963H 50mg syringes</td> <td>1</td> <td>\$939.25</td> <td>\$1,066.67</td> </tr> <tr> <td>1964J 50mg pens</td> <td>1</td> <td>\$939.25</td> <td>\$1,066.67</td> </tr> </tbody> </table>		Max qty	AEMP	DPMQ	1954W 25mg vials	2	\$469.93	\$1,066.68	1963H 50mg syringes	1	\$939.25	\$1,066.67	1964J 50mg pens	1	\$939.25	\$1,066.67	<p>The submission assumed all etanercept patients received 50 mg per dose. This was inconsistent with the approach taken in the economic evaluation, which assumed 10.7% of etanercept patients were dosed at 25 mg. AEMP for each dose of etanercept was estimated to be \$█ in the economic evaluation. This resulted in an overestimate in the cost offsets in the financial estimates. This was addressed in the PSCR.</p> <p>Updated during evaluation to account for new PBS fees from 1 January 2021.</p>
	Max qty	AEMP	DPMQ															
1954W 25mg vials	2	\$469.93	\$1,066.68															
1963H 50mg syringes	1	\$939.25	\$1,066.67															
1964J 50mg pens	1	\$939.25	\$1,066.67															

Source: Table 4-1, p193 of the submission, and compiled during evaluation.

ABS = Australia Bureau of Statistics; PASI = psoriasis area and severity index; CPP = chronic plaque psoriasis; PBS = pharmaceutical benefits scheme; RPBS = repatriation pharmaceutical benefits scheme; MBS = Medicare benefits schedule; AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity; qty = quantity; wk = week.

6.59 The submission used a mixed market share and epidemiological approach to estimate the utilisation and financial impact of listing ustekinumab on the PBS for paediatric severe CPP.

6.60 The estimated financial implications of listing ustekinumab for paediatric severe CPP are presented in the table below.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated use and financial implications of ustekinumab (PBS/RPBS)						
Initiating patients	1	1	1	1	1	1
Cont. patients (first cont. treatment)	1	1	1	1	1	1
Cont. patients (subsequent treatments)	1	1	1	1	1	1
Script numbers^a						
Initial treatment	1	1	1	1	1	1
First cont. treatment	1	1	1	1	1	1
Subsequent cont. treatments	1	1	1	2	2	2
Total ustekinumab scripts	1	2	2	2	2	2
Estimated financial implications of ustekinumab (PBS/RPBS cost less co-pay, effective prices)^b						
Initial treatment	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3
First cont. treatment	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3
Subsequent cont. treatments	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3
Total	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3
Estimated changes in use and financial implications of etanercept (PBS/RPBS)						
Changes in script numbers ^c	1	1	1	1	1	1
PBS/RPBS cost less co-pay (DPMQ) ^d	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3	-\$ 3
Estimated net implications for the PBS/RPBS						
Net change in PBS/RPBS scripts	1	1	2	2	2	2
Net cost to PBS/RPBS (effective)	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3

Source: Table 4-1 to 4-3, 4-5 to 4-10, p193-199 of the submission.

^a Assuming 3 scripts for initial treatment (28 weeks), 2 scripts for first continuing treatment (24 weeks), and 4.33 scripts per year for subsequent continuing treatment, as estimated by the submission.

^b The DPMQ of ustekinumab based on the proposed effective price was updated using pricing formula from 1 January 2021.

^c Assuming 6 scripts per patient (each patient completed the 24-week treatment), as estimated by the submission.

^d Updated during evaluation to account for changes to PBS fees from 1 January 2021.

Cont. = continuing; DPMQ = dispensed price for maximum quantity; PBS = pharmaceutical benefits scheme; RPBS = repatriation pharmaceutical benefits scheme.

The redacted values correspond to the following ranges:

¹<500

²500 to <5,000

³\$0 to <\$10 million

6.61 The estimated total cost to the PBS/RPBS of listing ustekinumab at the proposed effective price was \$0 to <\$10 million in Year 1, increasing to \$0 to <\$10 million in Year 6. The total cost over the first 6 years of listing was \$0 to <\$10 million. There were no estimated incremental costs for the MBS.

6.62 Overall, the submission's financial estimates were likely underestimated as the submission:

- May have underestimated the number of patients treated with ustekinumab, which was based on the estimated number of patients who would otherwise be treated with etanercept. The submission acknowledged that the number of patients initiating etanercept in a year may be underestimated if there were patients who did not receive the full course of treatment (i.e. scripts per patient is less than six). It also argued that there were also patients experiencing a disease flare and receiving a retreatment in the same year (i.e. scripts per patient is greater than six) who were not considered, and would offset each other. However, there was no

consideration of patients who discontinued from ustekinumab going back onto treatment when their disease worsens (similar to patients with disease flares being retreated with etanercept), and it was unlikely that the proportion of patients who experience a disease flare would be greater than the proportion who failed to respond to etanercept as only 56.6% of patients achieved PASI 75 at Week 12 in Paller 2008;

- May have overestimated the dosage of etanercept. The assumption that all patients would be treated with 50 mg etanercept dosing was inconsistent with the economic evaluation, which assumed that 10.7% of all patients would be treated with 25 mg of etanercept. This led to an overestimated cost offset for etanercept;
- Did not consider grandfathered patients (estimated to be 40 patients) in its estimates, underestimating the number of patients who may be treated with ustekinumab; and
- Erroneously applied a continuation rate for 52 weeks of treatment for the patients continuing treatment of ustekinumab after initiation. Given the initial treatment is 28-weeks and a 28-week continuation rate was used, and the first continuing treatment is 24-weeks, then the continuing treatment rate for the first continuing treatment should be the 24-week rate. Using the 52-week continuation rate as performed in the submission would result in an underestimation in the number of initiation patients who would continue treatment.

6.63 Additionally, there were other areas of uncertainty, including:

- Uncertainty regarding the uptake rate. The submission did not provide sufficient detail on how this rate was elicited; and
- Uncertainty around the paediatric severe CPP prevalent population. The submission likely underestimated the number of patients currently treated with etanercept but overestimated the eligible population by not accounting for the removal of eligible patients once they become over 18 years of age over the forecasted years.
- Wastage associated with use in patients <60 kg, and additional scripts associated with a 90 mg dose for patients weighing >100 kg.

6.64 The PSCR presented a revised financial analysis to address the concerns raised by the evaluation, specifically: (i) applying an average of 5 scripts to the current etanercept patients, derived based on ~■% of etanercept patients achieving PASI 75 response at Week 12 and receiving 6 scripts, and the other ■% receiving 4 scripts; (ii) applying a ■% increase in the number of ustekinumab initiations in Year 1 to include grandfathered patients, resulting in an increment of < 500 patients receiving ustekinumab; and (iii) applying the 24-week continuation rate to patients receiving the first continuing treatment. The DPMQ of the drugs and the patient co-payment were updated to those effective from January 2021, and the cost offset from etanercept was revised down to account for 10.7% of patients receiving the 25 mg

etanercept dose. The revised analysis is shown in the table below. These changes resulted in an estimated \$10 million to <\$20 million net cost for the health budget over the first six years of PBS listing, representing a \$0 to <\$10 million increase from the base case in the submission. As these calculations were provided with the PSCR, they have not been evaluated.

Table 17: Updated estimated use and financial implications (effective prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Initial submission						
Number of ustekinumab initiations	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Number of ustekinumab scripts	■ ¹	■ ²	■ ²	■ ²	■ ²	■ ²
Net cost to the PBS/RPBS (uncorrected)	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³
Revised for the PSCR						
Number of ustekinumab initiations	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Number of ustekinumab scripts	■ ¹	■ ²	■ ²	■ ²	■ ²	■ ²
Net cost to PBS/RPBS (ustekinumab)	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³
Net cost to PBS/PRBS (etanercept)	-\$■ ³	-\$■ ³	-\$■ ³	-\$■ ³	-\$■ ³	-\$■ ³
Net cost to the PBS/RPBS	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³
Variance vs. submission base case	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³

Source: Table 5, PSCR, p6, and sheets 3c and 4c of financial estimates spreadsheet provided with PSCR.

The redacted values correspond to the following ranges:

¹<500

²500 to <5,000

³\$0 to <\$10 million

6.65 The PSCR stated that since the financial estimates model continues to capture the utilisation of ustekinumab in patients after they turn 18 years of age, and also assumes grandfathered patients have the same utilisation as those initiated on the PBS, the true net cost of ustekinumab for the health budget will likely fall within the range of \$0 to <\$10 million (submission base case) and \$10 million to <\$20 million (revised for the PSCR) over the six-year listing period.

6.66 However, the PBAC considered that there remained a risk of leakage to less severe patients, given that ustekinumab has superior effectiveness and a lower frequency of injections compared to etanercept.

Financial Management – Risk Sharing Arrangements

6.67 The PBAC considered that a Risk Sharing Arrangement, based on the PSCR estimates with a rebate of ■% above the subsidy caps, would be needed to manage the risk that the market may grow beyond the estimates presented.

Quality Use of Medicines

- 6.68 The sponsor has a patient support program (PSP) for adults with severe CPP and intends for this PSP to also be available for paediatric severe CPP patients and carers. This will likely include multiple initiatives and information such as: a patient and carer starter pack; patient and carer injection/administration training and education to ensure the appropriate required dose is received; a reminder service for upcoming doses; free replacement services for sharps/swabs and syringes; and support material and resources.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of ustekinumab on the General Schedule for the treatment of paediatric patients with severe chronic plaque psoriasis (CPP), and is satisfied that ustekinumab provides, for some patients, a significant improvement in efficacy over etanercept. The PBAC's recommendation for listing was based on, among other matters, its assessment that ustekinumab would be cost-effective at a price no greater than the price for adults in the same indication.
- 7.2 The PBAC considered that the strong consumer support for ustekinumab reflected an unmet clinical need for a drug with an alternative mechanism of action to etanercept. It noted that although etanercept is currently available for the paediatric CPP population on the PBS, it has a TGA indication limited to 24 weeks' treatment, as its safety profile depicts only short term use.
- 7.3 In terms of the clinical place for ustekinumab, the PBAC agreed with the submission that ustekinumab will be used as an alternative to etanercept, and that choice and order of these therapies will likely depend on clinician discretion and patient preference.
- 7.4 The PBAC considered that the nominated main comparator of etanercept was appropriate, as it is the only biologic currently PBS listed for severe CPP in paediatric patients after inadequate response to conventional therapies. The PBAC also considered that best supportive care (BSC) would be an appropriate comparator for patients who had failed to respond to all other treatment options, including etanercept, or were unable or unwilling to be treated with etanercept due to safety concerns or treatment duration restrictions. However, it agreed with the ESC that this additional comparison would be complicated and clinical evidence would be limited.
- 7.5 The PBAC noted several issues with the reliability of the trial evidence presented in the submission; including the small sample size of the CADMUS trials; the non-randomised non-comparative nature of CADMUS JR; the difference in early escape rate in the placebo arm of CADMUS compared to Paller 2008 (signalling potential transitivity issues); and applicability to the PBS population both in terms of disease severity and prior and concomitant treatments. However, the PBAC considered that:

- the exclusion of CADMUS JR from the comparisons produced broadly consistent results.
 - the difference in early escape rates in the placebo arms were unlikely to be an issue given that the benefit of ustekinumab over placebo was greater than that achieved by etanercept, and the placebo arms response rates and the early escape rates in the treatment arms were similar.
 - in the context of the available evidence, and noting the limitations identified by ESC, the Pre-Sub-Committee Response (PSCR) subgroup analysis supported that the overall findings in the trials were likely applicable to the proposed PBS population (baseline PASI score >15 and patients who received 2 of prior methotrexate, acitretin or phototherapy).
- 7.6 In terms of comparative benefits, the submission presented indirect treatment comparisons (ITCs) of ustekinumab and etanercept. Along with the limitations in the studies (identified above), the PBAC noted: some statistical inconsistencies with the response and non-response analyses; poorly defined MCIDs; and a reliance on week 24/28 CADMUS results compared with week 12 Paller 2008 results in the primary analysis. The submission based its claim of superiority on PASI 75, PASI 90 and CLDQI results. Whilst none of these measures definitively overcame potential transitivity issues or the small trial sizes, the PBAC considered the totality of the evidence presented supported a claim of superior effectiveness compared with etanercept. The PBAC considered there was clinically meaningful superiority in the context of an unmet need for an alternative to etanercept, which is limited to 24 weeks' treatment due to its safety profile. The claim was further supported by: the general stability of responses between Weeks 12 and 24/28; and (as noted above) the PSCR subgroup analysis showing applicability of the trials to the PBS population; and the broadly consistent results after CADMUS JR results were removed during evaluation. However, the magnitude of the benefit remained uncertain.
- 7.7 The PBAC considered that a claim of superiority over BSC was reasonable based on CADMUS results for induction of PASI 75 and PASI 90 response at Week 24/28 and Week 12. Whilst the magnitude was uncertain, and the CADMUS placebo arm may not be entirely representative of BSC, the claim was reasonable in the context of the available clinical evidence.
- 7.8 The PBAC considered that the claim of non-inferior comparative safety was reasonable, given the lack of evidence of an overall difference in adverse events between patients treated with ustekinumab and patients treated with etanercept. Comparative safety with respect to BSC was not assessed, although the PBAC considered it would not be worse than the safety of etanercept over placebo.
- 7.9 The submission presented a simple incremental cost per responder analysis, consistent with the etanercept submission for the same population in March 2012. (A supplementary cost per responder analysis comparing ustekinumab with BSC was

presented in the PSCR). The PBAC did not see these analyses as ideal, and preferred a cost utility analysis, in view of the issues identified by the evaluation and ESC (see paragraphs 6.47–6.49), particularly the unknown cost-effectiveness beyond 28 weeks. However, it considered that it was not unreasonable to provide access to ustekinumab at the same price as the adult population.

- 7.10 The PBAC considered that the submission’s financial estimates likely underestimated the impact of listing ustekinumab for the paediatric population, as it overestimated the dosage and usage of etanercept. It also did not include ustekinumab patients to be grandfathered and underestimated patients continuing treatment with ustekinumab. The PBAC considered that the updated financial estimates in the PSCR addressed these concerns. However, the PBAC considered that there remained a risk of leakage to less severe patients, given that ustekinumab has superior effectiveness and a lower frequency of injections compared to etanercept. The PBAC considered that a Risk Sharing Arrangement, based on the PSCR estimates with a rebate of ■■■% above the subsidy caps would be needed to manage the risk that the market may grow beyond the estimates presented.
- 7.11 The PBAC noted that the restrictions (and those for etanercept) were complex, and as written Authority Required listings, will need to be finalised in consultation with Services Australia and the sponsor. Noting that the restrictions would require substantial revision, with flow-on changes to the etanercept listings where appropriate, the PBAC considered that:
- The restriction for ustekinumab should align to the general concepts of initiation, continuation, and balance of supply. A grandfathering restriction should be included.
 - Patients can swap between etanercept and ustekinumab 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, before taking a treatment break of at least 5 years (e.g. up to twice with one drug, and once with the other).
 - Patients who re-commence after a 5-year treatment break should not have to re-trial conventional therapies.
 - The restrictions should accommodate the treatment of patients greater than 100 kg (that is, requiring a 90 mg dose).
 - Definitions and instructions for determining response (and inadequate response to prior therapies) should align with the existing paediatric listings for etanercept for CPP, although assessment of response to access continuing therapy should take place no later than 24 weeks from initiation.
- 7.12 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for

ustekinumab:

- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies;
- b) The treatment is not expected to address a high and urgent unmet clinical need because an existing therapy is available;
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.13 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.