

7.03 DUPILUMAB, Injection 300 mg in 2 mL single use pre-filled syringe, Dupixent[®], Sanofi-Aventis Australia Pty Ltd.

1 Purpose of submission

- 1.1 The resubmission requested a Section 85 Authority Required listing for dupilumab for the treatment of atopic dermatitis (AD) in adult patients with severe disease who are inadequately controlled on topical therapies.
- 1.2 Listing was requested on the basis of a cost-utility analysis versus placebo representing standard of care (SoC). Table 1 presents the key components of the clinical issue addressed by the resubmission.

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

Component	Description
Population	Adults with severe atopic dermatitis who have had an inadequate response to topical therapies
Intervention	Dupilumab 600mg initial dose, followed by 300mg Q2W
Comparator	Main comparator: Placebo representing standard of care (SoC) Secondary comparator: Cyclosporin A (CsA)
Outcomes (trial)	Primary: Proportion of patients with a 75% improvement in EASI score at week 16 (EASI-75); proportion of patients with and IGA score of 0 or 1 and a change ≥ 2 points from baseline at week 16 Secondary: Changes in physician and patient reported severity scores including EASI, SCORAD, DLQI, POEM, HADS, GISS, IGA, peak daily pruritus NRS and percent BSA involvement
Clinical claim	In the treatment of adult with severe atopic dermatitis unresponsive to topical therapies, dupilumab has: <ul style="list-style-type: none"> • Superior efficacy to standard of care with an increased risk of injection site reactions and conjunctivitis. • Similar efficacy and superior safety to CsA.

Source: Table 1.1, p1 of the resubmission

Abbreviations: BSA: Body surface area; CsA: cyclosporin A; DLQI: Dermatology life quality index; EASI: Eczema area and severity index; GISS: Global individual signs score; HADS: Hospital anxiety and depression scale; IGA: Investigator's global assessment; NRS: Numerical rating scale; POEM: Patient oriented eczema measure; Q2W = fortnightly; SCORAD: Scoring atopic dermatitis

2 Background

Registration status

- 2.1 Dupilumab was TGA registered on 24 January 2018 for 'the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for chronic systemic therapy'. The dupilumab product information (PI; revised on 25 October 2019) states that dupilumab is TGA indicated:
- for the treatment of moderate to severe atopic dermatitis in patients aged 12 years and older who are candidates for chronic systemic therapy;

Public Summary Document – March 2020 PBAC Meeting

- as add on maintenance treatment in patients aged 12 years and older with moderate to severe asthma with type 2 inflammation (elevated eosinophils or elevated FeNO); and
- as maintenance therapy for oral corticosteroid dependent asthma.

2.2 Dosage in adult patients is two consecutive initial 300 mg doses followed by 300 mg given every other week (Q2W). The PBAC noted for patients 12 to 17 years of age with atopic dermatitis, the recommended every other week dose is 200 mg (<60 kg) or 300 mg (≥60 kg).

Previous PBAC consideration

2.3 Dupilumab has previously been considered by the PBAC in July 2018 and July 2019. A summary of the key matters for concern in the previous resubmission (July 2019) and how these have been addressed in the current resubmission is provided in Table 2.

Table 2: Summary of key matters of concern

Component	Matter of concern (July 2019 PSD)	How the resubmission addresses it
Initial eligibility criteria	Initial assessment of disease severity should be based on both the PGA and EASI scores, consistent with the clinical trial inclusion criteria (Para 7.4)	Addressed. Restriction amended to reflect PBAC comments.
Response criteria for eligibility for continuation	Both DLQI and EASI-75 were important measures of response and should be included in the response criteria (Para 7.4)	Partially addressed. Response criteria is defined as EASI-50 (not EASI-75) and 4 point improvement in DLQI
Economic model – key drivers	The frequency of hospitalisations (2.5/year) and emergency visits (3/year) did not appear plausible for patients with moderate to severe AD (Para 7.14)	Addressed. Resubmission provides evidence for resource use from new clinician survey (n=63)
	Differential rates of maintenance of response applied in the treatment arms of the model were not reasonable (Para 7.15)	Not addressed. The sponsor disagrees with the PBAC and maintains differential maintenance of response
	The 10 year time horizon was not adequately justified and that the model time horizon should be no more than 5 years given the available evidence (Para 7.15, 7.16)	Addressed. Model time horizon is 5 years.
Financial estimates	The financial cost was very high and remained uncertain; the estimated total cost over the first 6 years of listing increased.....to \$500 million to < \$600 million (Para 7.18)	Addressed. Updated financial estimates are provided for a narrower population (severe compared with moderate to severe AD)
	An RSA would be necessary to manage uncertainty in patient estimates, likely treatment duration and the potential for use outside the proposed restriction (Para 7.19)	The sponsor is willing to negotiate a RSA to address any residual uncertainty

Source: Table 1.4, pp12-13 of the resubmission

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

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
DUPILUMAB Dupilumab 300mg/2mL 2 x 2mL pre-filled syringe	1	4 ^a 2 ^b 5 ^c	\$1,743.77 (published) \$ [REDACTED] (effective)	Dupixent® Sanofi-Aventis
Category/Program:	General Schedule			
PBS indication:	Chronic severe atopic dermatitis			
Treatment phase:	Initial, Continuing and Grandfather			
Restriction:	Authority Required – In writing			
Treatment criteria:	Must be treated by a dermatologist or clinical immunologist			
Clinical criteria:	<p>Whole body Initial: Patient must have severe atopic dermatitis with a PGA score of 4 and an EASI score ≥ 20; and must have failed to achieve an adequate response to topical therapies (topical corticosteroids and/or topical calcineurin inhibitors) Continuing: An improvement in Dermatology Life Index (DLQI) score of at least 4 points, or sustained at that level, when compared to the prebiologic treatment baseline value for this treatment cycle; AND An improvement in the Eczema Area and Severity Index (EASI) score of at least 50%, or sustained at that level, when compared to the prebiologic treatment baseline value for this treatment cycle.</p> <p>Face, hand Initial: Patient must have severe atopic dermatitis of the face or palm of hand and the treatment must be as systemic monotherapy (other than oral corticosteroids) Continuing: A reduction in the Eczema Area and Severity Index (EASI) of at least 3 of the 4 subscores for erythema, oedema/papulation, excoriation and lichenification to mild or better, or sustained at this level, as compared to the prebiologic baseline values; OR A reduction by 75% or more of the skin area affected, or sustained at this level, as compared to the prebiologic baseline value.</p>			
Population criteria:	Patient must be 18 years of age or older			
Prescriber criteria:	Completed current Dermatology Life Quality Index (DLQI) calculation sheets including the date of assessment of the patient's condition. Completed Eczema Area and Severity Index (EASI) calculation sheets including the date of assessment of the patient's condition.			

^a Initial, whole body and face and hand

^b Initial (balance of supply)

^c Continuing: whole body; face and hand *and foot and genitals*; and grandfather

3.1 The key differences with the restrictions requested in the current resubmission, compared with the July 2018 and July 2019 (re)submissions are summarised in Table 3.

Public Summary Document – March 2020 PBAC Meeting

Table 3: Main differences to Section 1 between the three (re)submissions

	Original submission (July 2018)	First resubmission (July 2019)	Current resubmission (March 2020)
Population¹	Adults with severe AD (defined as an Investigator’s Global Assessment [IGA] score of 4) who have had an inadequate response or intolerance to cyclosporin A (CsA), or for whom CsA is contra-indicated.	Moderate to severe atopic dermatitis AD (defined as Physician’s Global Assessment [PGA] score of 3 or 4) who have had an inadequate response to topical therapy (topical corticosteroids [TCS]/topical calcineurin inhibitor [TCI])	Adults with severe AD (defined as a PGA of 4 AND an Eczema Area and Severity Index [EASI] of ≥ 20) who have had an inadequate response to topical therapies (TCS/TCI)
Price	Price: \$ [REDACTED] (effective); \$1,615.39 (published)	Price: \$ [REDACTED] (effective); \$1,743.62 (published)	Price: \$ [REDACTED] (effective); \$1,743.77 (published)
Listings	Initial and continuing restriction requested listings for all eligible patients		Initial and continuing restriction requested listings separate for whole body AD patients and for AD patients affected on the hands or face
	Requested restrictions for patients who are returning to therapy after a break in treatment of less than 5 years	No requested restrictions for patients who are returning to therapy after a break in treatment of less than 5 years	Requested restrictions for patients who are returning to therapy after a break in treatment of less than 5 years
Clinical criteria	Initial restriction criteria: IGA=4 ¹	Initial restriction criteria: PGA=3 or 4 ¹	Initial restriction criteria (whole body): PGA=4 ¹ and EASI ≥ 20
Eligibility for continuation	Continuing restriction criteria: EASI-75 response	Continuing restriction criteria: change in baseline in DLQI of ≥ 4 OR an improvement from baseline in PGA score of ≥ 2	Continuing restriction criteria: change in baseline in DLQI of ≥ 4 AND EASI-50

Abbreviations: AD = atopic dermatitis; CsA = cyclosporin A; DLQI = dermatology life quality index; EASI = Eczema Area and Severity Index; EASI-50 = reduction from baseline in EASI score of 50% or more; EASI-75 = reduction from baseline in EASI score of 75% or more; IGA = Investigator’s Global Assessment; PGA = Physician’s Global Assessment; SoC = standard of care; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid

¹The IGA and PGA are synonymous outcome measures, differing only by the name used based on the setting administered (discussed in Section 1.1).

3.2 In its consideration of the July 2019 resubmission, the PBAC stated the measurement of response should “include EASI-75 [a 75% improvement in Eczema Activity and Severity Index score] and either DLQI [Dermatology Life Quality Index] < 5 , or DLQI improvements of ≥ 4 points, and may also include the PGA [Physician’s Global Assessment]” (paragraph 7.20, dupilumab, PSD, July 2019). The resubmission defines response and eligibility criteria for continuing treatment as an EASI-50 (50% improvement in EASI) AND DLQI improvements of ≥ 4 points (DLQI 4) based on a series of post-hoc sub-group analyses and the impacts of changing the definition of response on the ICER. The commentary stated that choosing criteria based on the most cost-effective combination of response definition may not be appropriate as this decision should be made on what is most clinically meaningful and what most appropriately aligns with the clinical evidence; noting that EASI-75 was the primary or co-primary outcome of most trials. The Pre-Sub-Committee Response (PSCR) argued that “the choice of scales and definitions of response proposed appropriately target continued therapy to patients who are deriving and will continue to derive a clinically meaningful

benefit from treatment with dupilumab whilst avoiding inappropriately excluding patients who do not achieve maximal benefit for either scale by week 16”.

- 3.3 The ESC noted that using a marker of lesions and patient impact for continuing criteria is broadly consistent with Australian consensus guidelines¹. The ESC considered the proposed approach is likely to be clinically reasonable and able to capture patients with the best response to treatment. The ESC noted that the proportion of responders appeared to plateau at around week 16 in data from the CHRONOS trial and the number of additional patients who respond in terms of EASI-75 following this time point may be small.
- 3.4 This resubmission, unlike the previous re (submissions), requests a separate listing for patients with severe AD of the face or hands who have a baseline EASI of less than 20 but in whom their AD is considered severe due to the intensity and/or locations affected. The requested criteria for this listing also included the foot and genitals, however the PSCR clarified that the intention of this listing was to include patients with severe AD of face or hands only. The resubmission provided no data to inform the efficacy of dupilumab in patients who exclusively had face or hand AD. The PSCR referred to a recent publication (letter to the editor)² which reported the efficacy of dupilumab in different body regions (head and neck, upper extremities, trunk, lower extremities) in patients included in the dupilumab clinical trials. The PSCR claimed that results of this post hoc analysis indicated that similar and statistically significant improvements in EASI score were observed in all of the body areas assessed. The ESC agreed with the PSCR that this study supported the claim that dupilumab is equally effective in all anatomical regions and the ESC considered that the proposed listing was clinically appropriate.
- 3.5 The requested face and hand continuing treatment restriction included wording around the requirement to assess eligibility based on the DLQI, however change in DLQI is not included in the criteria for continuing treatment. The PSCR acknowledged that, as patients who achieve successful resolution of severe AD lesions on the face or hands are likely to experience a significant improvement in quality of life, a continuation criterion based on improvement in DLQI score would be appropriate for this restriction. The sponsor suggested that this be consistent with the continuing criteria for the proposed “whole body” listing (improvement in DLQI score of ≥ 4 points). The ESC considered that this addition to the criteria for continuing treatment was appropriate.

¹ Smith, Saxon, et al. "Atopic dermatitis in adults: An Australian management consensus." *Australasian Journal of Dermatology* (2019).

² Blauvelt, A., et al. "Improvement of atopic dermatitis with dupilumab occurs equally well across different anatomical regions: data from phase III clinical trials." *The British journal of dermatology* 181.1 (2019): 196

- 3.6 The PBAC noted the requested listing for adults was inconsistent with the TGA registered indication which is for patients aged 12 years and older.

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

4 Population and disease

- 4.1 AD is a chronic inflammatory disease characterised by dry skin, itching and extensive skin lesions. Symptoms may be continuous or of a relapsing-remitting nature. The clinical presentation of symptoms varies based on phase (chronic or acute) and severity of AD. Patients with severe AD have more frequent symptom flaring, and their disease is characterised by skin with pronounced dryness, red lesions, papulation, crusting and skin thickening. Patients can suffer from itchy painful skin, bleeding, sleep deprivation, an increased risk of skin infections, depression, anxiety and/or suicidal intentions.
- 4.2 Consistent with the previous resubmission (July 2019), the proposed clinical management algorithm indicates that patients can choose either dupilumab or cyclosporin A (CsA) as first-line systemic therapy following inadequate response to topical corticosteroids [TCS]/topical calcineurin inhibitor [TCI]), with the alternative treatment (CsA or dupilumab) as second-line.
- 4.3 Dupilumab (ATC D11AH05) is a recombinant human IgG4 monoclonal antibody which selectively binds to and inhibits signalling of IL-4 and IL-13, the key cytokines of atopic disease. The inhibition of IL-4 and IL-13 signalling reduces type 2 inflammatory response and is also believed to induce altered epidermal responses, inhibit terminal differentiation proteins, and produce and/or amplify the skin barrier defect in AD thereby restoring skin barrier function.
- 4.4 The ESC noted that the clinical algorithm presented was similar to that presented in the Australian AD consensus document. The consensus document included consideration of treatment with phototherapy in patients with moderate to severe disease or with reduced QoL, where there was requisite availability, suitability and patient compliance.

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

5 Comparator

- 5.1 Standard of care (represented by placebo) was nominated as the main comparator, and CsA as a relevant secondary comparator. SoC “would also include concomitant TCS ± TCI therapy for flaring” (paragraph 5.1, dupilumab, PSD, July 2018). The PBAC previously accepted placebo representing standard of care as the appropriate main comparator (paragraph 5.4, dupilumab, PSD, July 2019). The PBAC also “considered CsA to be an additional relevant comparator...but acknowledged the likely limited use of CsA in clinical practice, and the limited clinical evidence for CsA...did not enable a

meaningful comparison of dupilumab and CsA” (paragraph 5.4, dupilumab, PSD, July 2019). As in the July 2019 resubmission, whilst nominating CsA as an appropriate comparator, the current resubmission did not indicate the CsA dosage or treatment regimen that would be applicable.

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 individuals (323), health care professionals (61) and organisations (6) via the Consumer Comments facility on the PBS website.

6.3 The comments from healthcare professionals including dermatologists, immunologists, allergists, nurses, pharmacists and surgeons, described the very high disease burden for patients with severe AD. Healthcare professionals described the impact on patients’ lives of itch, sleep disruption, pain and infections and the resulting effects on their ability to work and maintain relationships. Healthcare professionals also noted the detrimental impact on mental health from uncontrolled severe AD. Healthcare professionals noted the lack of safe and effective treatments currently available, and that other systemic treatments have high AE burden including steroid-induced diabetes, osteoporosis and fractures, raised liver function tests, hypertension and nausea. Many healthcare professionals reported having patients with access to dupilumab through compassionate access programs who experienced substantial improvement in their AD, mental health and quality of life as a result of their treatment. Healthcare professionals reported the high cost of self-funding dupilumab which was described as inequitable and precludes many patients from accessing treatment. One healthcare professional noted intense lobbying by the sponsor for support of the proposed listing, and several also mentioned the high price requested by the sponsor for dupilumab and the need to weigh this high and ongoing cost against the benefits of treatment. Healthcare providers also compared dupilumab with biological treatments for psoriasis, many of which are available on the PBS.

6.4 Comments from patients not currently accessing dupilumab described the very high and ongoing impact AD has on all aspects of their daily functioning, relationships, financial security and their quality of life. Some patients reported being hospitalised due to infection and sepsis, some also reported the impact of their suffering on their mental health including clinical depression and suicide attempts or suicidal ideation. Many patients noted the high cost of dupilumab, which made it unsustainable or impossible for patients to access.

- 6.5 Comments from individuals currently accessing dupilumab described treatment as life-changing, with a range of benefits of treatment including dramatic improvements in terms of being able to care for themselves and family, to work, sleep improvements, relationships, psychological well-being and relief from incessant itch, bleeding and pain. These individuals noted that, where experienced, side effects from treatment were well-tolerated and easily resolved.
- 6.6 The PBAC noted the support for PBS listing of dupilumab received from Allergy & Anaphylaxis Australia, The Eczema Association of Australasia Inc, Eczema Support Australia, The Australasian College of Dermatologists, National Allergy Strategy and the Royal Melbourne Hospital Department of Dermatology.
- 6.7 The PBAC noted the advice from Allergy & Anaphylaxis Australia (A&AA) that their stance on the need for dupilumab remains unchanged from previous advice. A&AA noted that dupilumab “has given people with severe AD hope and for some, a will to go on”. A&AA considered that PBS listing of dupilumab will be life-changing for patients with severe AD and urged that listing of dupilumab be given urgent and serious consideration.
- 6.8 The PBAC noted the advice from The Eczema Association of Australasia Inc that the use of dupilumab may provide a much needed treatment option in a therapeutic area that has few treatments available and no new treatments approved for a long time. The Association stated that dupilumab can be used long-term, unlike other treatments which can only be used for short periods because of side effects that require close monitoring.
- 6.9 The PBAC noted the advice from Eczema Support Australia that patients with severe AD can experience “social isolation, sleep deprivation, co-morbidities, pain, infection and intense itch”, which “can result in depression, anxiety and suicidal thoughts in conjunction with the negative impact on schooling, loss of work or career choice and relationship breakdown”. The advice noted a recent systematic review and meta-analysis that found patients with AD are 44% more likely to exhibit suicidal ideation and 36% more likely to attempt suicide compared to patients without AD³. The advice also noted the financial burden associated with AD treatment and the hope that access to dupilumab offers to patients with debilitating AD.
- 6.10 The PBAC noted the advice provided by the Australasian College of Dermatologists (ACD) in support of the proposed listing. The ACD noted the currently available treatments options are limited and often costly or ineffective. The ACD noted that “while dupilumab will not address all needs it will offer a more effective treatment for a proportion of patients, for whom AD can be debilitating”.
- 6.11 The PBAC noted advice from the National Allergy Strategy in support of the proposed

³ Sandhu et al. Association between atopic dermatitis and suicidality. A systematic review and meta-analysis. JAMA Dermatol 2019; 155(2): 178-187

listing. The advice referred to submissions to the Parliamentary Inquiry for Allergies and Anaphylaxis which mentioned dupilumab and the need for patient access to this treatment for AD.

- 6.12 The PBAC noted advice from the Royal Melbourne Hospital Department of Dermatology in support of the proposed listing. The advice described the extensive impact on patients' lives and the frequent hospital admissions due to complications of the disease and current treatments.

Clinical trials

- 6.13 Unchanged from the previous (re)submissions, the resubmission was based on five double-blind, randomised controlled trials [CAFÉ (n=325); CHRONOS (n=740); SOLO 1 (n=671); SOLO 2 (n=318) and Study 1021 (referred to as 'Phase IIb' in the July 2018 submission) (n=380)] comparing dupilumab 300 mg fortnightly (Q2W) to placebo in patients with moderate to severe AD (IGA \geq 3). SOLO 1, SOLO 2 and Study 1021 did not allow concomitant TCS/TCI therapy during treatment, whereas CAFÉ and CHRONOS allowed low to medium potency TCS but not TCI. The resubmission appropriately considered all five trials as relevant clinical evidence. The ESC noted longer term (76 week) data was recently published for weekly dosing⁴.
- 6.14 The patient populations enrolled in the trials were broader than that for whom listing is sought, thus the resubmission relied on sub-group analyses of patients defined as having severe AD (defined as PGA=4 AND an EASI score \geq 20 at baseline), presenting results for those who were CsA-naive and CsA-experienced separately.
- 6.15 Details of the trials presented in the resubmission are provided in Table 4.

Table 4: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
CAFÉ R668-AD-1424 NCT02755649	A phase 3 study investigating the efficacy, safety, and tolerability of dupilumab administered to adult patients with severe atopic dermatitis who are not adequately controlled with or are intolerant to oral cyclosporine A, or when this treatment is not medically advisable.	08/07/2015
	de Bruin-Weller M, Gadhari A, Simpson E et al. Dupilumab improves patient-reported outcomes in atopic dermatitis inadequately controlled, intolerant, or inadvisable for cyclosporine-A. <i>Annals of Allergy, Asthma and Immunology</i> .	<i>Annals of Allergy, Asthma and Immunology</i> . 2017; 119(5S1):S94-S95.
	de Bruin-Weller M, Thaci D, Smith K et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ).	<i>British Journal of Dermatology</i> . 2018; 178:1083-1101.
CHRONOS R668-AD-1224 NCT02260986	A randomised, double-blind, placebo-controlled study to demonstrate the efficacy and long-term safety of dupilumab in adult patients with moderate to severe atopic dermatitis.	02/10/2015

⁴ Deleuran, Mette, et al. "Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study." *Journal of the American Academy of Dermatology* 82.2 (2020): 377-388

Public Summary Document – March 2020 PBAC Meeting

Trial ID	Protocol title/ Publication title	Publication citation
	Blauvelt A, Bruin-Weller M, Gooderham M et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial.	Lancet. 2017; 389:2287-303.
	Blauvelt A, Gooderham M, Foley P et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids for up to 1 year in moderate-to-severe atopic dermatitis: a randomized, placebo-controlled phase III trial (CHRONOS).	British Journal of Dermatology. 2017; 177(S1):10.
	Blauvelt A, Gooderham M, Foley P et al. Dupilumab with concomitant topical corticosteroids in moderate-to-severe atopic dermatitis: a randomised, placebo-controlled phase 3 clinical trial (CHRONOS). de Bruin-Weller M, Blauvelt A, Simpson E et al. Analysis of the long-term consistent of clinical response with dupilumab plus concomitant topical corticosteroids.	Australasian Journal of Dermatology. 2017; 58:55. British Journal of Dermatology. 2018; 179: e41-42
SOLO 1 R668-AD-1334 NCT02277743	A phase 3 confirmatory study investigating the efficacy and safety of dupilumab monotherapy administered to adult patients with moderate to severe atopic dermatitis.	05/02/2015
	Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.	N Engl J Med. 2016 Dec 15;375(24):2335-2348.
SOLO 2 R668-AD-1416 NCT02277769	A phase 3 confirmatory study investigating the efficacy and safety of dupilumab monotherapy administered to adult patients with moderate to severe atopic dermatitis.	05/02/2015
	Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.	N Engl J Med. 2016 Dec 15;375(24):2335-2348.
Phase IIb R668-AD-1021 NCT01859988	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study Investigating the Efficacy, Safety, Pharmacokinetic and Biomarker Profiles of Dupilumab (REGN668) Administered to Adult Patients with Moderate-to-Severe Atopic Dermatitis.	03/12/2013
	Thaci D, Simpson EL, Beck LA et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial.	Lancet. 2016; 387:40-52
	Simpson EL, Gadkari A, Worm M et al. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): A phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD).	J Am Acad Dermatol. 2016; 75(3): 506-15.
	Simpson EL, Bieber T, Eckert L et al. Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults.	J Am Acad Dermatol. 2016; 74(3): 491-98.

Source: Table 2.2.1 (pp54-55 of the resubmission)

6.16 The key features of the direct randomised trials are summarised in Table 5.

Table 5: Key features of the included evidence, dupilumab vs. placebo

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
CAFÉ	325	DB, R, MC; 28 weeks	Low	Moderate to severe AD; previous intolerance, lack of efficacy or contra-indication to CsA	EASI-75 ^a IGA 0 or 1 ^b	<i>Post-hoc</i> analysis of EASI-50 ^c AND DLQI 4 ^d at Week 16 (all trials) and Week 44 (CHRONOS) (PGA=4 AND EASI ≥20 subgroup)
CHRONOS	740	DB, R, MC; 64 weeks	Low	Moderate to severe AD		
SOLO 1	671	DB, R, MC; 28 weeks	Low	Moderate to severe AD		
SOLO 2	708	DB, R, MC; 28 weeks	Low	Moderate to severe AD		
Study 1021	318	DB, R, MC; 28 weeks	Low	Moderate to severe AD		

DB=double blind; MC=multi-centre; R=randomised; AD = atopic dermatitis; CsA = cyclosporin A

Source: compiled during the evaluation

^a 75% improvement/reduction in the EASI score from baseline

^b achievement of a score of 0 or 1 from a baseline of 3 or 4 on the 5 point IGA scale

^c 50% improvement/reduction in the EASI score from baseline

^d at least 4 point improvement in DLQI

Comparative effectiveness

6.17 Table 6 presents the results of EASI-75 response in the trials. The EASI was developed for use in AD by modifying the Psoriasis Area Severity Index (PASI), as such, the EASI and the PASI are similar in construct. The individual trial results remain unchanged from the previous (re)submissions; all trials show a statistically significantly higher response in favour of dupilumab (TGA-approved fortnightly (Q2W) administration). The PBAC previously considered that “EASI-75 appears to be a valid clinical marker correlating with outcomes such as QoL” (paragraph 7.5, dupilumab PSD, July 2018,).

Public Summary Document – March 2020 PBAC Meeting

Table 6: The proportion of patients achieving the EASI-75 at week 16 (and week 52 in CHRONOS) across trials

	N	Patients achieving EASI-75 n (%)	Difference vs placebo % (95% CI)	P-value vs placebo
CAFÉ				
Dupilumab 300 mg Q2W	107	67 (62.6)	33.0 (20.41, 45.47)	<0.001
Placebo	108	32 (29.6)	-	-
CHRONOS				
Dupilumab 300 mg Q2W	106	73 (68.9)	45.7 (35.72, 55.66)	<0.0001
Placebo	315	73 (23.2)	-	-
SOLO 1				
Dupilumab 300 mg Q2W	224	115 (51.3)	36.6 (28.58, 44.63)	<0.0001
Placebo	224	33 (14.7)	-	-
SOLO 2				
Dupilumab 300 mg Q2W	233	116 (49.8)	34.1 (26.19, 42.03)	<0.0001
Placebo	236	37 (15.7)	-	-
Study 1021^a				
Dupilumab 300 mg Q2W	64	34 (53.1)	41.6 (27.04, 56.26)	<0.0001
Placebo	61	7 (11.5)	-	-
CHRONOS (Week 52)				
Dupilumab 300 mg Q2W	106	66 (62.3)	40.4 (30.06, 50.66)	<0.0001
Placebo	315	69 (21.9)	-	-

Table 2.5.1 (p71 of the resubmission) & Table 2.5.5 (p75 of the resubmission)

Abbreviations: CI = confidence interval; EASI = eczema area and severity index; FAS = full analysis set; QW = weekly; Q2W = fortnightly

Note: Values after initiation of rescue treatment were set to missing (censored). Patients with missing EASI score at week 16 were considered non-responders.

^a Secondary endpoint.

6.18 Table 7 presents the results of the proportion of patients achieving an IGA score reduction (improvement) of ≥ 2 from baseline. The IGA used in the trials was a 5 point scale where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe. The proportion of patients achieving at least a 2 point improvement in IGA was statistically significantly higher in dupilumab (TGA-approved fortnightly (Q2W) administration) compared with placebo across all trials.

Table 7: The proportion of patients achieving an IGA score reduction of ≥ 2 at week 16 across trials

	N	Patients achieving IGA endpoint n (%)	Difference vs placebo % (95% CI)	P-value vs placebo
CAFÉ^a				
Dupilumab 300 mg Q2W	107	43 (40.2)	26.3 (14.95, 37.65)	<0.0001
Placebo	108	15 (13.9)	-	-
CHRONOS^b				
Dupilumab 300 mg Q2W	106	41 (38.7)	26.3 (16.34, 36.26)	<0.0001
Placebo	315	39 (12.4)	-	-
SOLO 1^b				
Dupilumab 300 mg Q2W	224	85 (37.9)	27.7 (20.18, 35.17)	<0.0001
Placebo	224	23 (10.3)	-	-
SOLO 2^b				
Dupilumab 300 mg Q2W	233	84 (36.1)	27.6 (20.46, 34.69)	<0.0001
Placebo	236	20 (8.5)	-	-
Study 1021^c				
Dupilumab 300mg Q2W	63	21 (33.3)	31.7 (19.63, 43.76)	<0.0001
Placebo	61	1 (1.6)	-	-

Source: Tables 2.5.2 & 2.5.5 (p72 & 75 of the resubmission)

Abbreviations: CI = confidence interval; FAS = full analysis set; IGA = investigator's global assessment; PBO = placebo; QW = weekly; Q2W = fortnightly

^a Values after first rescue treatment used were set to missing (censoring) and these patients were considered non-responders. Difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by Cochran-Mantel-Haenszel test stratified by disease severity [IGA 3 vs IGA 4] and prior CsA use [Yes, No].

^b Values after initiation of rescue treatment were set to missing (censored). Patients with missing IGA score at week 16 were considered non-responders.

6.19 Meta-analyses of CAFÉ, CHRONOS, SOLO1/2 and Study 1021 presented in the resubmission remained unchanged from the previous (re)submissions and showed a statistically significant difference in favour of dupilumab for the outcomes of EASI-75 at Week 16 (55% vs 19%, $p < 0.001$) and the proportion of patients achieving an IGA score reduction of ≥ 2 at Week 16 (37.3% vs 10.6%, $p < 0.001$).

6.20 The mean DLQI change from baseline to Week 16 or Week 52 are relevant to the resubmission because improvement in DLQI of ≥ 4 points was added as a continuation criterion in the proposed restriction. The DLQI is a series of 10 questions, nine of which are rated and scored as follows: 'not at all' or 'not relevant' = 0, 'a little' = 1, 'a lot' = 2 and 'very much' = 3; with the remaining question being 'yes' = 3 and 'no' = 0. The maximum possible score is 30 points, with higher scores indicating greater impact on a patient's life (0-1 = no effect at all; 2-5 small effect; 6-10 = moderate effect; 11-20 = very large effect; 21-30 = extremely large effect). The mean change in DLQI in each of the trials showed statistically significant differences in favour of dupilumab (Table 8).

Table 8: The mean change in DLQI score (reduction in score indicates improvement) - FAS

	N	Baseline mean (SD)	Mean change (SD)	LS mean change (SE)	LS mean difference vs PBO (95% CI)	P-value
Week 16						
CAFÉ						
Dupi 300 mg Q2W	107	14.5 (7.63)	-9.8 (6.52)	-9.5 (0.46)	-5.0 (-6.31, -3.74)	<0.0001
Placebo	108	13.2 (7.60)	-4.1 (5.60)	-4.5 (0.49)	-	-
CHRONOS						
Dupi 300 mg Q2W	106	14.5 (7.31)	-10.0 (7.33)	-10.0 (0.50)	-4.2 (-5.31, -3.02)	<0.0001
Placebo	315	14.7 (7.37)	-6.0 (6.33)	-5.8 (0.34)	-	-
SOLO 1						
Dupi 300 mg Q2W	224	13.9 (7.37)	-9.0 (6.61)	-9.3 (0.40)	-4.0 (-5.16, -2.80)	<0.0001
Placebo	224	14.8 (7.21)	-5.6 (5.86)	-5.3 (0.50)	-	-
SOLO 2						
Dupi 300 mg Q2W	233	15.4 (7.07)	-9.7 (6.20)	-9.3 (0.38)	-5.7 (-6.86, -4.47)	<0.0001
Placebo	236	15.4 (7.69)	-4.0 (5.75)	-3.6 (0.50)	-	-
1021						
Dupi 300 mg Q2W	64	14.5 (7.20)	-8.5 (6.90)	-7.7 (0.81)	-5.0 (-7.2, -2.8)	<0.0001
Placebo	61	12.8 (6.20)	-2.5 (6.10)	-2.7 (0.90)	-	-
Week 52						
CHRONOS						
Dupi 300 mg Q2W	89	15.0 (7.32)	-11.5 (7.07)	-11.4 (0.57)	-4.2 (-5.54, -2.94)	<0.0001
Placebo	264	15.2 (7.35)	-7.4 (6.23)	-7.2 (0.40)	-	-

Source: Table 2.5.3 (p73) of the resubmission & Table 2.5.15 (p.101) of the July 2019 resubmission

Abbreviations: CI = confidence interval; DLQI = dermatology life quality index; FAS = full analysis set; QW = weekly; Q2W = fortnightly

- 6.21 The resubmission requested listing for a severe AD population (defined as PGA=4 AND EASI ≥20) and proposed that the criteria for continuation of dupilumab use on the PBS be based on response defined as a 50% in EASI score (EASI-50) AND a 4 point improvement in DLQI (DLQI 4), although this composite outcome did not form the basis of the clinical claim. The results for this composite outcome in the sub-group of interest are presented in Table 9, along with results for the outcomes individually. These results are based on *post hoc* analyses and patient numbers could not be verified in the clinical study reports (CSRs).
- 6.22 The change in utility among patients with baseline PGA=4 AND EASI ≥20, according to EASI-50 and/or DLQ 4 response are presented in Table 10.
- 6.23 These results consistently show statistically significant differences in favour of dupilumab at both Week 16 and Week 44 for all definitions of response in both CsA-naïve and CsA-experienced sub-groups. The utility results at Week 16 consistently show higher utility improvements in dupilumab patients compared to placebo patients in responders and non-responders across all definitions of response. However, these utility results are not replicated at Week 44 (in CHRONOS), with placebo responders and non-responders showing higher utility improvements than dupilumab responders and non-responders (respectively) for many definitions of response.

Public Summary Document – March 2020 PBAC Meeting

Table 9: Response rates at Week 16 (pooled 1021, SOLO 1, SOLO 2, CHRONOS) and maintenance of response rates at Week 44 (CHRONOS) – Baseline IGA=4 AND EASI ≥20, CsA-naïve and CsA-experienced;

Analysis	Week 16			Week 44		
	n/N (%) responders		RD (95%CI) p-value	n/N (%) responders ^a		RD (95%CI) p-value
	Placebo	Dupilumab Q2W		Placebo	Dupilumab Q2W	
CsA-naïve						
EASI-50	59/246 (24.0)	111/166 (66.9)	42.9 (34.0, 51.8) p<0.0001	23/91 (25.3)	22/28 (78.6)	53.3 (35.7, 70.9) p<0.0001
DLQI 4	78/246 (31.7)	114/166 (68.7)	37.0 (27.8, 46.1) <0.0001	20/91 (22.0)	24/28 (85.7)	63.7 (48.2, 79.2) p<0.0001
DLQI 4 and EASI-50	49/246 (19.9)	99/166 (59.6)	39.7 (30.7, 48.7) p<0.0001	16/91 (17.6)	22/28 (78.6)	61.0 (43.9, 78.1) p<0.0001
CsA-experienced						
EASI-50	36/178 (20.2)	102/152 (67.1)	46.9 (37.4, 56.4) P<0.0001	9/53 (17.0)	18/23 (78.3)	61.3 (41.6, 80.9) P<0.0001
DLQI 4	49/178 (27.5)	105/152 (69.1)	41.6 (31.7, 51.4) P<0.0001	12/53 (22.6)	17/23 (73.9)	51.3 (30.1, 72.5) P<0.0001
DLQI 4 and EASI-50	25/178 (14.0)	91/152 (59.9)	45.8 (36.5, 55.1) P<0.0001	8/53 (15.1)	17/23 (73.9)	58.8 (38.4, 79.2) P<0.0001

Source: Table 2.6.3 (p81 of the resubmission) and Table 2.6.4 (p82 of the resubmission)

Bold typography indicates statistically significant differences

^a Responders at Week 16 AND Week 44

* Note that the results presented in Table 9 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 plans for Studies 1021, SOLO 1, SOLO 2 and CHRONOS. 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.

Table 10: Change in EQ-5D utility from baseline to Week 16 (pooled 1021, SOLO 1, SOLO 2, CHRONOS) and Week 44 (CHRONOS) – Baseline IGA=4 AND EASI ≥20, CsA-naïve and CsA-experienced

Analysis	Week 16				Week 44			
	Responders		Non-responders		Responders		Non-responders	
	Placebo	Dupilumab Q2W	Placebo	Dupilumab Q2W	Placebo	Dupilumab Q2W	Placebo	Dupilumab Q2W
CsA-naïve								
EASI-50	0.17 (0.246)	0.28 (0.262)	0.05 (0.272)	0.15 (0.287)	0.22 (0.230)	0.19 (0.128)	0.11 (0.261)	0.12 (0.336)
DLQI 4	0.21 (0.249)	0.28 (0.266)	0.02 (0.258)	0.13 (0.269)	0.26 (0.246)	0.16 (0.160)	0.11 (0.251)	0.31 (0.285)
DLQI 4 and EASI-50	0.20 (0.250)	0.31 (0.254)	0.05 (0.266)	0.12 (0.271)	0.27 (0.252)	0.19 (0.128)	0.12 (0.250)	0.12 (0.336)
CsA-experienced								
EASI-50	0.15 (0.274)	0.27 (0.274)	0.04 (0.266)	0.10 (0.228)	0.28 (0.212)	0.28 (0.265)	0.18 (0.266)	0.05 (0.101)
DLQI 4	0.19 (0.295)	0.28 (0.264)	0.01 (0.243)	0.07 (0.226)	0.41 (0.224)	0.26 (0.259)	0.13 (0.234)	0.14 (0.253)
DLQI 4 and EASI-50	0.23 (0.277)	0.30 (0.273)	0.03 (0.260)	0.09 (0.214)	0.31 (0.207)	0.26 (0.259)	0.17 (0.264)	0.14 (0.253)

Source: Table 2.6.5 (p83 of the resubmission) and Table 2.6.6 (p84 of the resubmission)

* Note that the results presented in Table 10 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 plans for Studies 1021, SOLO 1, SOLO 2 and CHRONOS. 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 The resubmission also re-presented an indirect comparison of dupilumab versus CsA that was presented in the July 2019 resubmission. At that time the ESC considered that the comparison with CsA was not informative because:

- The use of matched adjusted indirect comparison (MAIC) approach methods and logistic regression modelling methods based on registry data are not considered robust methods for comparing clinical data, and are inherently associated with uncertainty.
- A thorough presentation of trial/study design, execution and characteristics according to the PBAC guidelines was not provided in the resubmission.
- The resubmission did not provide explicit details on the most applicable CsA treatment regimen in the Australian target population, and the CsA dosing regimens across the two CsA trials and the CsA registry patients varied.
- The MAIC approach included no results for EASI or IGA outcomes, limiting the comparability of the efficacy evidence to that of the dupilumab to placebo (SoC) comparison. The sample sizes of the two CsA trials within the MAIC analysis were also small (n=26; n=17).
- Other than treatment discontinuation, no safety outcomes were provided.

Comparative harms

6.25 The resubmission did not present any new evidence relating to comparative safety compared with the previous (re)submissions. The PBAC previously considered that the safety evidence presented in the July 2018 submission showed dupilumab patients

“reported a higher incidence of conjunctivitis and injection site reactions compared to patients treated with placebo” (paragraph 6.35, dupilumab, PSD, July 2018,). The ESC considered that the recently published 76 week data provided some reassurance of long term safety beyond 52 weeks.

Benefits/harms

- 6.26 A summary of the comparative benefits and harms for dupilumab versus standard of care (placebo) is presented in the table below. This is based on the same trial data as the previous (re)submissions, however EASI-50 AND DLQI improvement ≥ 4 at Weeks 16 and 44 are additional relevant outcomes.

Public Summary Document – March 2020 PBAC Meeting

Table 11: Summary of comparative benefits and harms for dupilumab and placebo

Benefits						
Trial	Dupilumab	Placebo	RR (95% CI)	Events/100 patients		RD, % (95% CI)
				Dupilumab	Placebo	
EASI-75 response at Week 16						
Meta-analysis (whole trial populations)	405/734	182/944	2.98 (2.44, 3.64)	55.2	19.3	38 (33, 42)
EASI-75 response at Week 52						
CHRONOS	204/319	69/315	2.92 (2.34, 3.67)	63.9	21.9	40 (30, 51)
IGA improvement ≥2 at Week 16						
Meta-analysis (whole trial populations)	210/563	82/775	3.53 (2.80, 4.44)	37.3	10.6	27 (23, 32)
EASI-50 AND DLQI improvement ≥4 at Week 16*						
Pooled Baseline IGA=4, EASI ≥20 CsA-naïve sub-group (Study 1021, SOLO1, SOLO2, CHRONOS)	99/166	49/246	2.99 (2.27, 3.97)	59.6	19.9	40 (31, 49)
Pooled Baseline IGA=4, EASI ≥20 CsA-experienced sub-group (Study 1021, SOLO1, SOLO2, CHRONOS)	91/152	25/178	4.26 (2.93, 6.30)	59.9	14.0	46 (37, 55)
EASI-50 AND DLQI improvement ≥4 at Week 44 (Responders at Week 16 AND 44)*						
Baseline IGA=4, EASI ≥20 CsA-naïve sub-group (CHRONOS)	22/28	16/91	4.47 (2.76, 7.28)	78.6 ^a	17.6	61 (44, 78)
Baseline IGA=4, EASI ≥20 CsA-experienced sub-group (CHRONOS)	17/23	8/53	4.90 (2.54, 9.74)	73.9 ^a	15.1	59 (38, 79)
Harms (meta-analysis – combined population from all trials)						
	Dupilumab	Placebo	RR (95% CI)	Events/100 patients		RD (95% CI)
				Dupilumab	Placebo	
Conjunctivitis	65/1562	11/879	2.93 (1.37, 6.23)	4.2	1.3	2.8 (0.9, 4.7)
Oral herpes	57/1562	17/879	1.79 (1.04, 3.08)	3.6	1.9	2.0 (0.7, 3.2)
Injection site reaction	205/1562	53/879	2.24 (1.68, 3.00)	13.1	6.0	7.0 (2.0, 12.0)
Allergic conjunctivitis	104/1089	24/645	2.67 (1.73, 4.11)	9.6	3.7	5.9 (1.1, 10.6)
Blepharitis	17/425	3/315	5.73 (1.59, 20.6)	5.0	1.0	4.5 (1.2, 10.5)
Allergic rhinitis	11/217	1/108	7.07 (1.16, 43.7)	5.1	0.9	5.6 (0.7, 12.1)

Source: compiled during the evaluation

NC = not calculable as n/N not reported; NR = not reported; and RD = risk difference; RR = risk ratio

^a response rates at Week 16 include all trials (59.6% and 59.9% for CsA-naïve and experienced patients, respectively), whereas the response rates at Week 44 are those reported in CHRONOS for those who responded at Week 16 AND 44 (78.6% and 73.9% for CsA-naïve and experienced patients, respectively). For reference, response rates at Week 16 in CHRONOS were 23/28 (82.1%) and 18/23 (78.3%) for CsA-naïve and experienced patients, respectively

* Note that the results presented in these rows of Table 11 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 plans for Studies 1021, SOLO 1, SOLO 2 and CHRONOS. 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.

6.27 On the basis of direct evidence presented by the resubmission, for every 100 patients treated with dupilumab in comparison to placebo over 16 weeks of treatment:

- Approximately 38 additional patients with moderate to severe AD would have at least a 75% improvement in EASI score from baseline (for example, a patient with

a baseline EASI score of 20, would need to achieve an EASI score of 5 at 16 weeks to achieve a 75% improvement);

- Approximately 27 additional patients with moderate to severe AD would have at least a 2 point improvement in IGA score from baseline (for example, patients with AD classified as severe (4) would move to mild (2), almost clear (1) or clear (0));
- Approximately 40 additional patients with a baseline PGA score of 4 and EASI score of 20 or above who are CsA-naïve would have at least a 50% improvement in EASI AND a 4 point improvement in DLQI score from baseline (for example, a patient with a baseline EASI score of 20, would need to achieve an EASI score of 10 at 16 weeks to achieve a 50% improvement AND would need a 4 point improvement in DLQI score from baseline);
- Approximately 46 additional patients with a baseline PGA score of 4 and EASI score of 20 or above who are CsA-experienced would have at least a 50% improvement in EASI AND a 4 point improvement in DLQI score from baseline (for example, a patient with a baseline EASI score of 20, would need to achieve an EASI score of 10 at 16 weeks to achieve a 50% improvement AND would need a 4 point improvement in DLQI score from baseline);
- Approximately 3 additional patients with moderate to severe AD will have conjunctivitis;
- Approximately 2 additional patients with moderate to severe AD will have oral herpes;
- Approximately 7 additional patients with moderate to severe AD will have an injection site reaction;
- Approximately 6 additional patients with moderate to severe AD will have allergic conjunctivitis;
- Approximately 5 additional patients with moderate to severe AD will have blepharitis; and
- Approximately 6 additional patients with moderate to severe AD will have allergic rhinitis.

6.28 The ESC previously noted that the additional risk from injection site reactions may be underestimated compared with clinical practice due to the use of a sham injection in the trials (paragraph 6.28, dupilumab, July 2019 PSD).

Clinical claim

6.29 The resubmission presented a claim of clinical superiority of dupilumab versus placebo based on pooled trial results at Week 16 (and sustained results over time at Week 52 in CHRONOS) for EASI-75 response and for the IGA score of 0 or 1 and a ≥ 2 point reduction from baseline, and based on DLQI results across trials, all of which showed statistically significant results in favour of dupilumab. The ESC agreed with the commentary that this claim was supported by the evidence presented in the resubmission.

- 6.30 In support of this claim, the resubmission also noted that post-hoc sub-group data indicated statistically significant results in favour of dupilumab in the PGA=4 and EASI ≥ 20 sub-group of interest for a range of relevant DLQI, EASI and/or PGA outcomes.
- 6.31 In respect to a safety claim for dupilumab versus placebo, the resubmission stated ‘dupilumab is associated with an increased risk of injection site reactions and conjunctivitis’. As such, the safety claim made for dupilumab versus placebo in the current resubmission may be better described as ‘dupilumab has inferior safety compared with placebo’. The ESC agreed with the commentary that the claim of inferior safety was reasonable.
- 6.32 The resubmission also claimed that dupilumab had at least non-inferior efficacy, and a superior safety profile, compared to CsA. This remains unchanged from the claims made in the previous resubmission. The PBAC considered that “limited safety data...prevented an overall conclusion regarding the relative safety of these two agents” (Dupilumab July 2019 PSD, paragraph 7.11) and that “the paucity of clinical evidence prevented a reliable indirect comparison of the efficacy of dupilumab versus CsA” (Dupilumab July 2019 PSD, paragraph 7.5). The ESC noted that the evidence presented and the clinical claim for dupilumab compared with CsA was unchanged from the previous resubmission.
- 6.33 The PBAC maintained that the claim of superior comparative effectiveness of dupilumab compared with SoC was reasonable, and that an improvement in quality of life for patients treated with dupilumab was demonstrated.
- 6.34 The PBAC considered the claim of inferior comparative safety of dupilumab compared with SoC was reasonable due to increased incidence of conjunctivitis and injection site reactions.
- 6.35 The PBAC noted that the evidence presented and the clinical claims in terms of safety and efficacy for dupilumab compared with CsA were unchanged from the previous resubmission.

Economic analysis

- 6.36 The resubmission presented a stepped modelled cost-utility analysis. The structure of the model was largely unchanged from the economic evaluation presented in the July 2019 resubmission, however the population and some assumptions and inputs varied. The summary of the model is provided in Table 12.

Public Summary Document – March 2020 PBAC Meeting

Table 12: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	% of patients with DLQI 4 and EASI-50, life years, quality adjusted life years, resource utilisation
Time horizon	5 years
Method(s) used to generate results	Markov cohort model (with a prior decision tree for initial treatment and the first cycle of maintenance treatment)
Health states	Four possible health states: <ul style="list-style-type: none"> • Induction treatment (16 weeks)^b • Responder (DLQI Δ \geq4 and EASI-50) • Non-Responder (DLQI Δ <4 and/or EASI score <50% from baseline) • All-cause death
Cycle length ^a	6 months
Transition probabilities	% of patients with response (DLQI Δ \geq 4 and EASI-50), maintenance of response (DLQI Δ \geq 4 and EASI-50), All-cause death: Age and sex specific Australian mortality rates (Australian lifetables)
Software	Microsoft® Office® 365

Source: Table 3.2 (p106) of the resubmission

Abbreviations: DLQI: Dermatology Quality of Life Index; EASI = eczema area and severity index

^a For the Markov component of the model

^b Health state within the decision tree only

6.37 While the structure remained the same, the main changes were shortening the time horizon from 10 to 5 years; changes in the initial and continuing response rates (as a result of changing the definition of response) and other health state costs (informed by a new clinician survey), see Table 13. Given the numerous differences between the models in patient population and inputs, the results are not directly comparable.

Table 13: Main differences to Section 3 between the three dupilumab (re)submissions

	July 2018 Submission	July 2019 Resubmission	Current Resubmission	Comment
Population	Adults with severe atopic dermatitis (AD; defined as an Investigator's Global Assessment [IGA] score of 4) who have had an inadequate response or intolerance to cyclosporin A (CsA), or for whom CsA is contraindicated.	Moderate to severe atopic dermatitis AD (defined as Physician's Global Assessment [PGA] or 3 or 4) who have had an inadequate response to topical therapy (topical corticosteroids [TCS]/topical calcineurin inhibitors [TCI]).	Adults with severe AD (defined as patients with PGA=4 and EASI \geq 20) who have had an inadequate response to topical therapy (TCS/TCI)	Appropriate based on previous PBAC consideration that "restricting eligibility to patients with severe AD and prior CsA exposure or contraindication may be inappropriately narrower than the TGA indication and the trial data" (Dupilumab July 2019 PSD, para.6.22) and given the PBAC advice that "any future submission...should include the EASI scale in the restriction to assess initial disease" (Dupilumab July 2019 PSD, para.7.20)
Comparator	Placebo for standard of care (SoC)	Placebo for SoC CsA, representing immunosuppressant's	Same as July 2019	Reasonable
Evidence	The IGA=4 sub-group of the CAFÉ trial for Week 16 response rates.	CHRONOS, SOLO 1, SOLO 2 & Study 1021 for Week 16 response	PGA=4 and EASI \geq 20 sub-group of CHRONOS, SOLO 1,	Appropriate given the proposed population

Public Summary Document – March 2020 PBAC Meeting

	July 2018 Submission	July 2019 Resubmission	Current Resubmission	Comment
	CHRONOS (Week 52 data) for response rates between Weeks 16-52.	rates. CHRONOS (Week 44 data) for Week 42 response rates.	SOLO 2 & Study 1021 for Week 16 response rates and CHRONOS (Week 44 data) for Week 42 response rates.	
Outcome for response	EASI-75 Dupilumab=54% at 16 weeks; Placebo=11.5% at 16 weeks	Improvement in IGA or DLQI of 2 and 4 points, respectively Dupilumab=74.1% at 16 weeks; Placebo=38.5% at 16 weeks <i>See footnote b</i>	Improvement in DLQI of ≥ 4 points and EASI-50 Dupilumab=59.1% at 16 weeks; Placebo=19.4% at 16 weeks <i>See footnote b</i>	The resubmission's definition of response is discussed above (paragraph 3.2).
Model structure	Markov model from Cycle 1	Decision tree for initiation (Cycle 1) and first maintenance cycle (Cycle 2; to Week 44) followed by a Markov model	Same as July 2019	Reasonable
Time horizon	Five years	Ten years	Five years	Reasonable
Health states	Induction, responder, non-responder, death (where responder was based on EASI-75 response)	Induction, responder, non-responder, death (where responder was based on IGA or DLQI improvement of 2 or 4 points, respectively).	Same as July 2019, except with new definition of 'response' (see above)	Reasonable, if definition of 'response' accepted.
Cycle length	All 3 months	First cycle 16 weeks, followed by 6-monthly (26 week) cycles	Same as July 2019	Reasonable
Maintenance of response	CHRONOS Week 52 EASI-75 response data (for patients who were considered EASI-75 responders at Week 16) and kept constant (i.e. the same loss of response rate per cycle) through the remainder of the model Dupilumab = 93.1% and placebo = 88.2% per 3-month cycle	Extrapolation of time-to-event data of treatment withdrawal or use of rescue treatment, considered time to first rescue treatment or treatment discontinuation to be a proxy for loss of effect to estimate loss of response. Response rates applied as time-dependent estimates that change in Year 2, 3, 4 and 5+. Different values assumed for dupilumab and placebo.	Same as July 2019	Unreasonable. The change in maintenance of response rates used in the model substantially favours dupilumab as compared to the rates used in the July 2018 submission model. The PBAC, in consideration of the July 2019 resubmission, found "the differential maintenance of response rates...were not reasonable" (Dupilumab July 2019 PSD, para 6.40).
Utility	Source: IGA=4 CAFÉ sub-group EQ-5D data. Baseline & non-responder utility: 0.64 Dupilumab responder: 0.916	Source: Pooled analysis of EQ-5D data from CHRONOS, SOLO 1, SOLO 2 & Study 1021 at Week 16, and from CHRONOS at Week 44.	Source: Pooled analysis of EQ-5D data from CHRONOS, SOLO 1, SOLO 2 & Study 1021 at Week 16, and from CHRONOS at Week 44,	A decrease in baseline utility is consistent with a severe AD group. The current resubmission no longer applies Week 44 CHRONOS utility values at

Public Summary Document – March 2020 PBAC Meeting

	July 2018 Submission	July 2019 Resubmission	Current Resubmission	Comment
	Placebo responder: 0.866	Baseline to Week 8 & non-responders utility: 0.70 Week 8-16 dupilumab arm patients utility: 0.8741 ^a Week 8-16 placebo-arm patients utility: 0.7800 ^a Week 16 responders onwards (regardless of treatment arm) utility: 0.90 <i>See footnote b</i>	for PGA=4 and EASI ≥20 baseline sub-groups Baseline to Week 8 & non-responders utility: 0.60 Week 8-16 dupilumab arm patients utility: 0.847 ^a Week 8-16 placebo-arm patients utility: 0.686 ^a Week 16-42 responders (regardless of treatment arm) utility: 0.91 Post week 42 responders onwards (regardless of treatment arm): 0.79 <i>See footnote b</i>	Week 16 onwards in the model (unlike the previous resubmission). Instead, the Week 44 utilities are appropriately applied at Week 42 onwards in the model.
Cost of dupilumab	\$█ (requested effective price)	\$█ (requested effective price)	\$█ (requested effective price)	As requested by the sponsor
Other health care costs	Derived from a 2005 economic evaluation and a 1997 Australian outpatient survey (n=48). Annual responder health-state cost: \$1,509.50 Annual non-responder health-state cost: \$3,292.61 Conjunctivitis costs <u>not</u> included	Derived from a survey of Australian dermatologists and immunologists (n=13). Annual responder health-state cost: \$1,168.16 Annual non-responder health state cost: \$11,067.72 Conjunctivitis costs <u>not</u> included Phototherapy and TCS/TCI costs <u>not</u> included	Derived from an updated clinician survey to that used in the July 2019 resubmission, with a larger sample size (n=61). Annual responder health-state cost: \$3,975.90 Annual non-responder health state cost: \$13,439.15 Conjunctivitis costs included Phototherapy and TCS/TCI costs included	A clinician survey with a larger sample size was included to address issues with the low sample size of the clinician survey in the previous resubmission. Incremental changes to responder and non-responder annual health state costs (estimated from this survey) are of similar magnitude and direction compared to the previous resubmission. The inclusion of phototherapy costs is a significant driver of the model. The phototherapy cost values used in the resubmission may not be plausible or appropriate. The previous submissions did not include phototherapy costs in the base-case.

^a response measured at 16 weeks, utilities for 8-16 weeks in the model are “half-cycle corrected” between baseline non-response and proportion who become responders at Week 16

^b Note that the results presented in these cells 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 plans for Studies 1021, SOLO 1, SOLO 2 and CHRONOS. 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.

6.38 The resubmission presented a stepped cost-utility analysis based on direct randomised trial evidence. The Markov model included an initial decision tree for

induction treatment (16 weeks) and the first cycle (26 weeks) of maintenance treatment prior to the Markov component (all subsequent maintenance treatment cycles). Patients began the model in the induction health state (considered to be non-responders), and could not transition back to induction treatment at any point in the model. Patients could transition to be responders, non-responders or die (death was only relevant in the Markov component of the model), accumulating relevant costs and utilities for each health state. Patients in the responder health state could remain a responder or transition to non-responder or die. Patients in the non-responder health state could not transition to the responder health state at any point in the model, but could transition to death.

- 6.39 The ESC noted that baseline utilities were lower than those used in the previous submission and considered this is likely to be appropriate, given the more severe patient population. The ESC also noted that the responder utilities were higher than the values used in the previous resubmission and considered these utilities appeared implausibly high for a chronic disease. The ESC noted that the PSCR did not clarify what patient population was the basis of the utility values used in the resubmission. The ESC also noted that the commentary suggested that it may not be appropriate to attribute any utility from baseline to week 16, however the ESC considered that it may be appropriate to attribute half the utility benefit over this time.
- 6.40 A summary of the key model drivers is presented in Table 14. The extrapolation of loss of response and the time horizon were also key model drivers in the previous (re)submissions. Non-responder health state costs were not considered a key model driver in the July 2018 submission; however, the July 2019 resubmission and this resubmission’s models were sensitive to health state costs.

Table 14: Key drivers of the model

Description	Method/Value	Impact
Time horizon	Base-case of 5 years. This was decreased from 10 years in the previous resubmission.	High, favours dupilumab. A one-year time horizon results in an 83% increase in base-case ICER.
Maintenance of response (Year 2+)	Derived from time-to-event regression analyses from CHRONOS time-to-rescue treatment or treatment withdrawal data.	High, favours dupilumab.
Health state costs including phototherapy	Assumed three sessions of phototherapy per week on the basis of a study (Patrizi et al 2015)	High, favours dupilumab. Removing phototherapy costs increased the ICER by 47%.

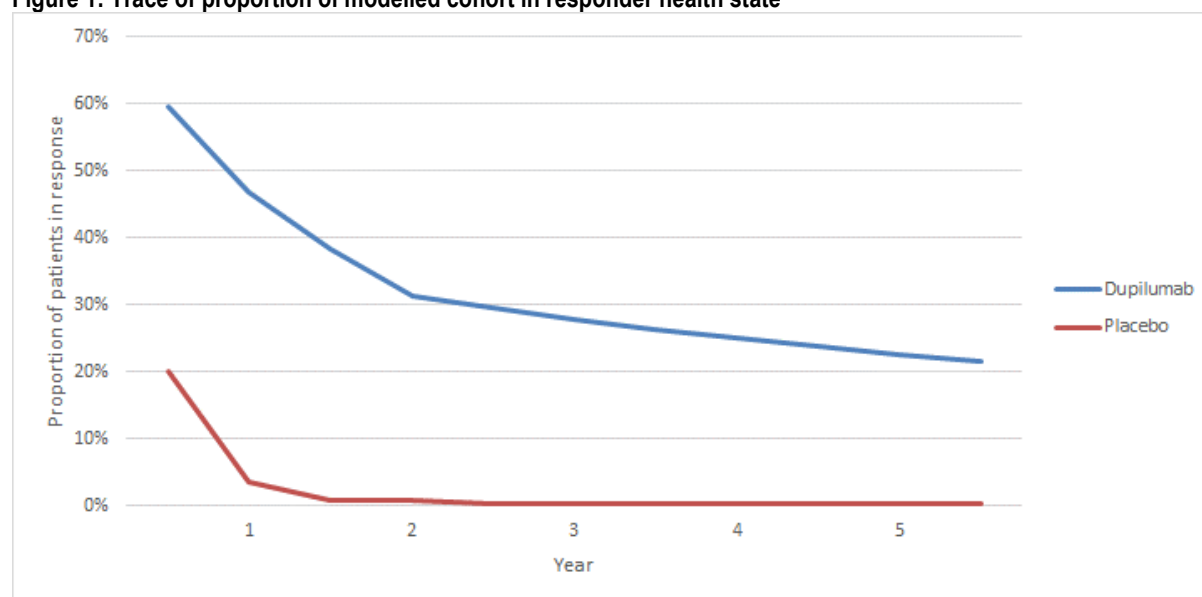
Source: Evaluation of Section 3 of the resubmission

- 6.41 As for the model presented in the July 2019 resubmission, this resubmission assumed a differential maintenance of response for dupilumab and placebo, see Figure 1. The PBAC previously stated that “the differential maintenance of response rates applied to treatment arms in the model were not reasonable” (Dupilumab July 2019 PSD, paragraph 6.40). However, the current resubmission (p123) ‘maintains that it is appropriate that differential rates of maintenance of response beyond Week 42 should be applied to the dupilumab and SoC arms’ based on the same justifications provided in the July 2019 resubmission: namely, (i) a panel of dermatologists and

interviews with eight AD patients lead to a list of behavioural and clinical factors that justified the need for clinical and utility benefit used in the model to be considered separately for dupilumab and SoC arms; and (ii) UK HTA appraisals (by NICE and the SMC) accepted that SoC patients would revert to pre-trial health within less than one year. The PBAC considered that the same issues and uncertainty associated with these values as applied in the previous resubmission remain.

- 6.42 The ESC maintained that the approach to modelling of maintenance of response rates was not appropriate. The ESC considered that the application of differential maintenance of response highly favoured dupilumab and was not justified for the following reasons:
- The financial estimates assumed that there was a proportion of patients with severe AD who were adequately controlled without systemic treatment (32%) and this was inconsistent with assuming that all placebo-treated patients would revert to pre-trial health within less than one year.
 - The ESC noted that the PSCR argued that differences between the trial setting and the real-world clinical setting would result in patients in the SoC arm rapidly reverting to pre-trial health, however the ESC considered that there would also be differences between the trial setting and the real-world setting for patients treated with dupilumab and this was not accounted for in the submission's approach to maintenance of response.
 - The ESC noted that, in the regression analysis used to estimate continued response from time to first rescue treatment or discontinuation, the full data set from CHRONOS from baseline was applied for the SOC arm, whereas only the data for patients who met the efficacy endpoint at 16 weeks was used for the dupilumab arm. The ESC considered the maintenance of response rates from these different approaches was not comparable and this approach favoured dupilumab.
- 6.43 The pre-PBAC response argued that patients with severe AD accounted for in the financial estimates were not relevant to consideration of duration of response as all patients in the clinical trials demonstrated inadequate response to topical medications or CsA. The pre-PBAC response also acknowledged that the efficacy of dupilumab outside the clinical trial setting may also differ from that seen within the trial but argued that it is "it is implausible that the response rate for dupilumab-treated patients would decline to the same extent over the same time period as placebo-treated patients".
- 6.44 The ESC noted that the discontinuation due to "other" reasons for dupilumab (3.7%) was applied from year 2 onwards. The ESC noted that the source for this rate could not be verified and it was unclear whether application of this rate was appropriate.

Figure 1: Trace of proportion of modelled cohort in responder health state



Source: Figure 3.7.1 (p130) of the re-submission

- 6.45 The resubmission presented and applied annual healthcare resource-use estimates for responders and non-responders from a revised clinician survey from September 2019 with a larger sample size (n=61) compared to the previous resubmission (n=13). The annual responder and non-responder health state costs applied in the model have increased by \$2,711.86 and \$1,788.23 respectively as compared to the July 2019 resubmission. Increases to both estimates are to be expected given the targeting of severe AD patients in the current resubmission (versus moderate to severe in the previous resubmission). These increases benefit the SoC arm (compared to the previous resubmission) given a larger cost increase for responders as compared to non-responders. Importantly, as compared to the previous resubmission, the mean annual frequency estimates for hospitalisations and ED visits have remained approximately the same for responders in the current resubmission, whilst noticeably decreasing (from 2.49 to 1.0 for hospitalisations and from 3.12 to 1.5 for ED visits) for non-responders. This addresses the PBAC’s concerns about the implausibility of hospitalisation and ED visit frequencies (see Table 2).
- 6.46 The revised clinician survey benefits from an increased sample size, thereby reducing uncertainty in the estimates. However, there are a number of issues that exist with the use of these estimates in the resubmission model:
- The survey provided clinicians with definitions of ‘controlled’ and ‘uncontrolled’ disease, which were used in the resubmission model to be applicable to responder and non-responder, respectively. It is unclear whether the definitions provided for ‘controlled’ and ‘uncontrolled’ in this survey adequately align with a DLQI ≥ 4 and EASI-50 responder versus a DLQI ≥ 4 and EASI-50 non-responder for patients with baseline severe AD (PGA=4 and EASI ≥ 20).

- Whilst the incremental difference between responders and non-responders for hospitalisations and ED visits are now decreased from the previous resubmission (with this variable representing a key model driver and source of uncertainty in the previous resubmission model – see above), the current resubmission included phototherapy and TCS/TCI-usage costs in the base-case analysis. The previous resubmission did not apply either of these resource-uses in the base-case.
 - The inclusion of TCS/TCI costs may be reasonable, and these costs do not constitute a significant component of the annual health state costs.
 - The annual cost of phototherapy applied comprises the majority of both annual responder and non-responder health state costs in the model, and non-responders have an incrementally higher annual cost by approximately \$4,467. The resubmission assumed three sessions of phototherapy per week on the basis of a review (Patrizi et al 2015). The resubmission stated (p22) “advice from Australian clinicians experienced in the treatment of AD is that, due to its poor availability and significant burden on patients (frequency and length of treatment and cost), its use in the treatment of AD in Australia is limited”. The incremental difference in annual phototherapy costs between responders and non-responders of \$4,467 may not be a plausible estimation given the unit cost of \$52.75 for a phototherapy session (MBS Item no. 14050). The PSCR argued that the patient population with severe disease is at high risk of disease flare and phototherapy is likely to be a viable option where patients have access. The ESC considered that though it was clinically reasonable to assume that some patients would access phototherapy, the extent of phototherapy costs included for non-responders was not consistent with the availability of phototherapy in Australia, nor with the total number of MBS claims for phototherapy (around 700,000 services for financial year 2018/19, the majority of which would be in patients with psoriasis). The pre-PBAC response maintained that these costs were reasonable to include in the economic model as they were based on a physician feedback in a high quality survey.
 - Additionally, the model presented in the resubmission did not incorporate the effectiveness of phototherapy, and only fractionally incorporated the effectiveness of TCS use (as SOLO 1, SOLO 2 and Study 1021 did not allow TCS use during the trials), the exclusion of which favours dupilumab. The PSCR noted that patients in the CHRONOS trial were able to use phototherapy as rescue medication in the case of a flare from week 3 of treatment onwards. The ESC noted that 2.8% of patients in CHRONOS used phototherapy (2.2% in the placebo arm, 5.5% in the dupilumab arm, Table 4.4.2/11a of the CSR). The ESC also noted that no benefit from phototherapy treatment was incorporated for non-responders in the SoC arm as after year 2 there are no responders in this arm despite the ongoing costs for phototherapy. The Pre-PBAC response noted benefit was not truncated at 2 years, however the PBAC noted that only 1% of patients in the SoC are remain responders after year 2. The PBAC agreed

with the ESC that the effectiveness of phototherapy was effectively not incorporated in the model and therefore the inclusion of substantial incremental costs from phototherapy favoured dupilumab.

6.47 Table 15 presents the results of the stepped economic evaluation.

Table 15: Results of the stepped economic evaluation

		Step 1 16 weeks	Step 2 42 weeks	Step 3 (base case) 5 years
Dupilumab	Active treatment costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	Other medical costs	\$3,125	\$6,887	\$48,881
	Administration costs	\$59	\$59	\$59
	% of cohort with response	59.64%	57.1%	26.09%
	QALYs	n/a	n/a	3.57
SoC	Active treatment costs	\$0	\$0	\$0
	Other medical costs	\$3,668	\$9,199	\$64,258
	Administration costs	\$0	\$0	\$0
	% of cohort with response	19.92%	13.3%	0.51%
	QALYs	n/a	n/a	3.22
Incremental	Total cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	% of cohort with response	39.72%	43.8%	25.57%
	QALYs	n/a	n/a	0.34
ICER	Incremental cost per responder	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	Incremental cost per QALY gained	n/a	n/a	\$ [REDACTED]

Source: Table 3.15 (p131) of the resubmission

Abbreviations: ICER: incremental cost-effectiveness ratio; n/a: not applicable; SoC: standard of care; QALY: quality-adjusted life year

6.48 The base-case ICER estimated by the resubmission was \$45,000 to < \$55,000/QALY for the CsA-naïve population. Applying the correct conditional probabilities resulted in an ICER of \$45,000 to < \$55,000/QALY (a 2.5% decrease from the ICER presented in the resubmission). This has increased from \$35,000 to < \$45,000/QALY in the July 2019 resubmission, and decreased from \$55,000 to < \$75,000/QALY in the July 2018 submission. However, these three models are not directly comparable due to:

- Different populations (severe AD inadequately controlled on topical therapies in the current resubmission, versus severe AD CsA-contraindicated, inadequately controlled or intolerant in the July 2018 submission or versus moderate to severe AD inadequately controlled on topical therapies in the July 2019 resubmission).
- Differences in the definition of ‘responder’.
- The inclusion of phototherapy resource-usage in the current resubmission.

6.49 As was done in the July 2019 resubmission, the current resubmission provided a scenario analysis whereby Week 16 and Week 42 response and utility inputs for a CsA-experienced were used instead of for a CsA-naïve population as was done in the base-case. This scenario analysis decreased the ICER from \$45,000 to < \$55,000/QALY to \$25,000 to < \$35,000/QALY, driven mostly by changes in incremental QALYs. The PBAC noted that the CsA-experienced and CsA naïve populations could have been combined but considered that the lower ICER for the CsA-experienced population provided

confidence that the use of the CsA-naïve population in the base-case was a conservative approach.

- 6.50 The results of key univariate / multivariate sensitivity analyses (conducted on the corrected ICER) are summarised below. The ESC noted that the model was not particularly sensitive to the definition of response used (EASI-50 or EASI-75). The PBAC noted that the ICER was impacted by the measures chosen for response criteria, and considered it was not clear whether this reflects a true difference in cost-effectiveness.
- 6.51 The pre-PBAC response argued that the assumption adopted in the sensitivity analysis, whereby SoC patients receive the same maintenance of response as the dupilumab patients, was clinically implausible and unfairly biases against dupilumab. The pre-PBAC response noted that this approach assumed the same proportional (relative) reductions in response. Whereas in the base case of the model, over five years, dupilumab response falls 31% in absolute terms (from approximately 60% to 29%) versus a drop in SoC response of 19% in absolute terms (from approximately 20% to 1%). The pre-PBAC response also provided a respecified base case applying the same absolute reduction in response to both arms at year 2, which resulted in a small increase in the ICER from \$45,000 to < \$55,000/QALY to \$45,000 to < \$55,000/QALY.

Public Summary Document – March 2020 PBAC Meeting

Table 16: Results of key univariate and multivariate sensitivity analyses presented by the resubmission and conducted during the evaluation

	Variable (base case)	Sensitivity analysis	Dupilumab		SoC		Incremental		ICER
			Costs	QALYs	Costs	QALYs	Costs	QALYs	
Base case			\$ [redacted]	3.57	\$ [redacted]	3.22	\$ [redacted]	0.34	\$ [redacted]
1	Time horizon: 5 years	1 year	\$ [redacted]	0.61	\$ [redacted]	0.53	\$ [redacted]	0.09	\$ [redacted]
		10 years	\$ [redacted]	5.76	\$ [redacted]	5.29	\$ [redacted]	0.47	\$ [redacted]
2	DLQI4 and EASI-50 as definition of response (Week 16 dup=59.6%; SoC=19.9%) (Week 42 dup=95.7%; SoC=66.7%)	DLQI4 and EASI 75 as definition of response (Week 16 dup=41.0%; SoC=12.6%) (Week 42 dup=89.5%; SoC=61.1%) ^a	\$ [redacted]	3.45	\$ [redacted]	3.21	\$ [redacted]	0.23	\$ [redacted]
3	DLQI4 and EASI-50 as definition of response (Week 16 dup=59.6%; SoC=19.9%) (Week 42 dup=95.7%; SoC=66.7%)	DLQI4 and EASI 50 and PGA2 as definition of response (Week 16 dup=45.8%; SoC=13.4%) (Week 42 dup=80.0%; SoC=56.3%) ^b	\$ [redacted]	3.45	\$ [redacted]	3.21	\$ [redacted]	0.24	\$ [redacted]
4	Differential (years 2 to 5) maintenance of response rates in dupilumab and SoC patients	Dupilumab maintenance of response rates also applied to SoC patients	\$ [redacted]	3.95	\$ [redacted]	3.80	\$ [redacted]	0.15	\$ [redacted]
5	Health state costs including phototherapy (responder = \$3,880 per year; non-responder = \$12,856 per year) Difference = \$8,976)	Exclude phototherapy costs. Responder= \$984; non-responder = \$5,493 per year) Difference = \$4,509	\$ [redacted]	3.57	\$ [redacted]	3.22	\$ [redacted]	0.34	\$ [redacted]
2+4			\$ [redacted]	3.90	\$ [redacted]	3.79	\$ [redacted]	0.11	\$ [redacted]
2+4+5			\$ [redacted]	3.90	\$ [redacted]	3.79	\$ [redacted]	0.11	\$ [redacted]

Source: Table 3.21 (p136-7) of the resubmission

Abbreviations: CI = confidence interval; DLQI = dermatology life quality index; IGA = investigator's global assessment; QALY = quality-adjusted life year; SoC = standard of care

^a dupilumab 17/19 (89.5%) and SoC 11/18 (61.1%) Week 16 responders maintained response at Week 44 from Attachment t5.2b.1, Attachment 13

^b dupilumab 16/20 (80%) and SoC 9/16 (56.3%) Week 16 responders maintained response at Week 44 from Attachment t5.2b.1, Attachment 13

The redacted table shows ICERs in the range of \$35,000 to < \$165,000/QALY.

Drug cost/patient/year

Table 17: Drug cost per patient for dupilumab and standard of care

	Dupilumab Trial dose and duration	Dupilumab Model	Dupilumab Financial estimates	Comparator Trial dose and duration	Comparator Model	Comparator Financial estimates
Mean dose	600mg loading 300mg Q2W	600mg loading 300mg Q2W	600mg loading 300mg Q2W	-	-	-
Cost/patient/month ^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$0	\$0	\$0
Cost/patient/year	\$ [REDACTED] ^b	\$ [REDACTED] ^c	\$ [REDACTED] ^d	\$0	\$0	\$0

Source: compiled during the evaluation

^a effective price

^b for a maintenance patient, assuming 13.05 scripts

^c over first 44 weeks, incorporates discontinuers (non-responders at Week 16)

^d incorporates discontinuation (non-responders at Week 16) and grandfathered patients

Estimated PBS usage & financial implications

- 6.52 This resubmission was not considered by DUSC. The previous submissions were considered by DUSC in July 2018 and July 2019.
- 6.53 The financial estimates presented in the resubmission have substantially decreased compared to those presented in the July 2019 resubmission. This is primarily due to the narrower (severe AD) population proposed in the current resubmission. Compared to the July 2018 submission (also requesting use in a severe AD group, but defined differently), the financial estimates in the current resubmission are substantially higher. This is primarily due to increases in input values such as prevalence of AD, proportion with severe disease and uptake rates. The uptake of dupilumab in the July 2018 submission was based on the observed uptake of bDMARDs when first listed on the PBS for psoriasis. DUSC considered that uptake of dupilumab was likely to be higher as: the biologics market had evolved compared to the uptake rates based on earlier listings; and the submission’s estimate based on market research of the percentage of patients that would fulfil the restriction criteria was higher than the projected uptake of dupilumab. Compared to the July 2018 submission, the PBAC noted that the July 2019 and March 2020 submissions used a different, epidemiological approach to estimate the proportion of AD patients accessing dupilumab. The higher projections of severe AD patients accessing dupilumab in the March 2020 vs. July 2018 submission is mainly from substantially higher treatment uptake assumptions (Table 18).
- 6.54 The key differences between the approaches taken in the three (re)submissions are provided in Table 18.

Public Summary Document – March 2020 PBAC Meeting

Table 18: Main relevant differences to Section 4 between the three submissions

	July 2018 original submission	July 2019 resubmission	Current resubmission
Approach	The number of adult Australians with a diagnosis of AD were estimated for 2019-2024. From these patients, the total number of patients on dupilumab treatment for 2019-2024 (i.e. the number of eligible patients and the expected uptake rate in these patients) as well as treatment persistence rates, using the PBS 2006-2011 bDMARD market for chronic plaque psoriasis as a proxy were estimated. In this way, a mixed epidemiological and market share approach was used. <i>Ultimately, the PBAC considered that the reliance on the psoriasis market as a proxy for dupilumab uptake was not well supported and was likely underestimated (Dupilumab PSD, July 2018, paragraph 6.52).</i>	An epidemiological approach was taken to estimate the financial impacts of dupilumab from 2020-2025. The main change in the approach used in the re-submission was no longer using the chronic plaque psoriasis bDMARD market as a proxy to inform expected dupilumab usage in AD patients, but rather relying on local and international market data to inform the estimated number of eligible patients, the expected uptake rates and the anticipated treatment persistence rates.	The same approach from the July 2019 resubmission was used, estimating costs for Years 1-6 rather than explicitly for years 2020-2025.
Population	Financial estimates were produced for the Australian adult population with severe AD who were contra-indicated or previously intolerant or unresponsive to CsA.	Financial estimates were produced for a population of the Australian adult population with moderate to severe AD who were inadequately controlled on topical therapies.	Financial estimates were produced for a population of the Australian adult population with severe (PGA=4 and EASI ≥20) who were inadequately controlled on topical therapies.
Annual uptake rate	0.05% in Year 1 to 0.21% in Year 6 informed by the psoriasis bDMARD market. The previous commentary considered these rates implausibly low.	1.7% (Year 1) to 4.2% (Year 6), informed from dupilumab uptake in Germany.	5% (Year 1) to 7.5% (Year 6) based on an assumption.

Abbreviations: AD = atopic dermatitis; bDMARD = biologic disease-modifying anti-rheumatic agent; CsA = cyclosporin; PBS = Pharmaceutical Benefits Scheme

Public Summary Document – March 2020 PBAC Meeting

Table 19: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Proportion of adult Australians who have severe AD	0.45%: 9% of Australian adults assumed to have AD * 5% assumed to be severe (METIS 2019a)	Definition of severe disease may not align with PGA=4. Resubmission does not account for those with severe face or hand AD
Proportion severe AD patients with EASI ≥20	95% (EAP patient data)	Reasonable
Proportion of TCS therapy patients who have uncontrolled AD	68% (METIS 2019b)	Inappropriate to have assumed some severe AD patients would be 'adequately controlled' on treatment. This is a major source of uncertainty in the financial estimates and may underestimate the eligible patients.
Uptake rate	5.0% in Year 1 (in addition to continuing grandfathered patients) increasing to 7.5% in Year 6. Increased uptake assumption based on PBAC feedback and severe disease only.	Uncertain
Grandfathered patients	n=500 to < 5,000 (these 500 to < 5,000 patients are subtracted from the prevalent pool)	Reduced from n=850 in the July 2019 submission, which included patients with moderate AD, based on sponsor estimates
Initial response	59.6% (Pooled results from trials for those meeting EASI-50/DLQI 4 response criteria)	Consistent with the economic evaluation
Responders at Week 42	46.85% (Apply the proportion who respond at Week 16 AND 44 to Week 16 response rate). Amended to 95.7% (as per economic evaluation)	Underestimate as the proportion who respond at Week 16 AND 44 is not the probability of response at Week 44 based on response at Week 16. Changed during the evaluation to be consistent with the economic evaluation.
Continuing patients treatment persistence	Year 2 = 83.2% Year 3 = 79.87% Year 4 = 77.16% Year 5+ = 74.76% from time to first rescue treatment or treatment discontinuation analysis	Reasonable
MBS phototherapy cost offsets	Assumed three sessions of phototherapy per week on the basis of a study (Patrizi et al 2015)	Consistent with the economic evaluation. Phototherapy cost offsets may be overestimated.

Source: compiled during the evaluation

6.55 Table 20 summarises the estimated use and financial implications of dupilumab on the PBS/RPBS and associated MBS cost-offsets. The PBAC noted that the starting point for estimating the patient numbers was the Australian population aged 18 years and older.

Table 20: Estimated use and financial implications (effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Patients (initiation)	█	█	█	█	█	█
Patients (continuing)	█	█	█	█	█	█
Number of scripts dispensed ^a	█	█	█	█	█	█
Estimated financial implications of dupilumab at the effective price						
Cost to PBS/RPBS less copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net financial implications						
Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net saving to MBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to PBS/RPBS/MBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

Source: compiled during the evaluation

^a Assuming 13.05 per year for continuing patients as estimated by the resubmission.

- 6.56 The PBAC noted that the uptake rates of 5% in year 1, increasing to 7.5% in year 6 were applied to the prevalent pool of eligible patients each year to calculate the number of patients initiating treatment. When continuing patients are taken into account the overall uptake is higher, and by year 6 continuing patients represent 14% of the eligible patients (5,000 to < 10,000 patients out of 40,000 to < 50,000 patients). The PBAC considered that it was reasonable that the overall uptake of dupilumab would increase in each year, accounting for both new and continuing patients. However, the PBAC considered it is not reasonable to assume the uptake rate of new patients from the prevalent pool would increase each year. The PBAC considered that the uptake rates of 5.5% in year 2, increasing to 7.5% in year 6 should be applied such that they reflect the proportion of continuing patients in each year (e.g. 500 to < 5,000 continuing patients in year 6 is 7.5% (500 to < 5,000 patients out of 40,000 to < 50,000 patients) of the eligible patients).
- 6.57 The total cost to the PBS/RPBS of listing dupilumab was estimated in the resubmission to be \$80 million to < \$90 million in Year 6, and a total of \$300 million to < \$400 million in the first 6 years of listing. This includes 500 to < 5,000 grandfathered patients who are assumed to continue treatment according to the proportions reported for “Continuing patients treatment persistence” in Table 19.
- 6.58 The evaluation noted that the estimates may be underestimated as the resubmission did not account for patients with severe face or hand AD and some of the inputs relating to patient eligibility may be underestimated.
- 6.59 The PSCR noted that patients with severe AD of the face and hands only were included in the survey on which estimates of prevalence were based. However, the financial estimates provide prevalence of AD of 9% and assume 5% are severe and 95% of severe meet the EASI ≥20 criteria. Patients with face and hands only affected may not have an EASI score ≥20, so may not be accounted for in the financial estimates.
- 6.60 The ESC noted that it was unclear how many patients would re-engage with specialist care if dupilumab is listed.

- 6.61 The ESC noted that net cost savings were driven by reduced phototherapy costs and considered that these cost savings were not consistent with current MBS costs for phototherapy items and were overestimated.
- 6.62 The PBAC considered there is potential for substantial use beyond the requested restriction to those with less severe AD, those with comorbid conditions such as asthma, those with reduced QoL due to overly complex topical regimens. Regarding this concern the PBAC noted recent changes to the dupilumab TGA-approved indications to include use in patients with asthma.

Financial Management – Risk Sharing Arrangements

- 6.63 The resubmission stated that the sponsor is willing to negotiate a RSA. No further details were provided.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of dupilumab for the treatment of patients aged 12 years and older with severe atopic dermatitis (AD) who are inadequately controlled on topical therapies. The PBAC has previously acknowledged the significant reduction in the extent of disease and improved patient quality of life with dupilumab over standard of care in a therapeutic area of high clinical need. The PBAC considered that the proposed measures of disease assessment were adequately addressed in the resubmission. The PBAC considered that the incremental cost effectiveness ratio (ICER) was likely underestimated in the resubmission and that this could be addressed with a reduced effective price. The PBAC considered the potential for use of dupilumab outside the proposed restriction could be managed through a risk sharing arrangement.
- 7.2 The PBAC acknowledged there is significant disease burden from AD and a high clinical need for effective treatments for severe AD. The PBAC noted the considerable number of consumer comments from professionals and individuals which reflected the substantial impact AD has on patients' physical and emotional wellbeing and the financial impact of AD and existing treatments for patients and their families. The PBAC also noted the support for the PBS listing of dupilumab from several professional organisations and patient representative organisations which reflected the same considerations as provided in the consumer comments.
- 7.3 The PBAC noted that the resubmission proposed revised measures of disease assessment for initiation and continuation of treatment compared with previous submissions. The resubmission proposed initial assessment of disease severity based on both the PGA and EASI scores, consistent with the clinical trial inclusion criteria. The PBAC noted that this was consistent with its previous advice (paragraph 7.4 dupilumab, PSD, July 2019 PBAC meeting) and considered this was appropriate.

- 7.4 The resubmission defined response and eligibility criteria for continuing treatment as an EASI-50 (50% improvement in EASI) AND DLQI improvement of ≥ 4 points (DLQI 4) based on a series of post-hoc sub-group analyses and the impact of changing the definition of response on the ICER. The PBAC noted that EASI-75 was the primary or co-primary outcome of most trials and was the basis of the clinical claim, however also noted that dupilumab demonstrated statistically significant improvements over SoC across both measures. The ESC noted that using a marker of lesions and patient impact for continuing criteria is broadly consistent with Australian consensus guidelines. The PBAC agreed with the ESC that the proposed approach is likely to be clinically reasonable and able to capture patients with a meaningful response to treatment.
- 7.5 The PBAC noted the resubmission proposed an additional initial and continuing restriction for patients with chronic severe AD on the face and hands, which was not considered in the previous submissions. The sponsor argued that these patients would not be eligible for treatment under the original restriction due to the relatively small body surface involved but that severe lesions in these specific areas have a significant impact on patients' quality of life. The PBAC agreed with the ESC that this additional listing may be clinically appropriate and that the listing should include improvement in DLQI as a criterion for continuing treatment.
- 7.6 The PBAC noted that the TGA registered indication has been expanded to include patients aged 12 years and older, and considered the proposed listing should be consistent with the TGA registered indication. The PBAC noted that for patients 12 to 17 years of age, the recommended every other week dose is 200 mg (<60 kg) or 300 mg (≥ 60 kg). The PBAC recommended that the 200 mg strength should also be listed, noting only the 300 mg strength was requested for listing.
- 7.7 The PBAC considered that the main comparator, SoC, remained appropriate and noted that no additional data were available to further inform the comparison with CsA.
- 7.8 The PBAC noted that no additional trial data were available, however post-hoc analyses of responders according to the proposed criteria for continuing treatment were provided in the resubmission. The PBAC noted that post-hoc sub-group data indicated statistically significant results in favour of dupilumab in the PGA=4 and EASI ≥ 20 sub-group of interest for a range of relevant DLQI, EASI and/or PGA outcomes. The PBAC noted that estimates of the number of patients who were responders at both week 16 and week 44 were based on data from the CHRONOS trial only. In these analyses week 44 response was conditional on response at week 16 and as such these estimates were not based on a randomised comparison and the PBAC considered they were much less robust than the whole of trial response rates. The PBAC noted that for the conditional response rates, for dupilumab versus placebo the risk difference at week 44 was higher than the risk difference at week 16 (absolute difference of 21%), which was not consistent with the overall CHRONOS trial data for the full population.
- 7.9 The PBAC noted that no direct clinical evidence supporting the proposed listing for patients with severe AD exclusively of the hands and face, was presented. The PBAC

noted the post-hoc analysis of the clinical trials for dupilumab that indicated similar and statistically significant improvements in EASI score were observed in all of the body areas assessed, however the PBAC considered that this would not necessarily translate to the equivalent incremental effectiveness or quality of life improvements and therefore equivalent cost-effectiveness to the whole body listing is uncertain.

- 7.10 The PBAC maintained that the claim of superior comparative effectiveness of dupilumab compared with SoC was reasonable, and that an improvement in quality of life for patients treated with dupilumab was demonstrated.
- 7.11 The PBAC considered the claim of inferior comparative safety of dupilumab compared with SoC was reasonable due to increased incidence of conjunctivitis and injection site reactions.
- 7.12 The PBAC noted that the evidence presented and the clinical claims in terms of safety and efficacy for dupilumab compared with CsA were unchanged from the previous resubmission.
- 7.13 The PBAC noted that the resubmission proposed a continuation criteria based on less stringent measures than previously requested by the PBAC, by using EASI-50 and DLQI 4 rather than EASI-75 and DLQI 4. The PBAC noted that using the EASI-75 and DLQI 4 as criteria for response resulted in an increase in the ICER from \$45,000 to < \$55,000/QALY to \$45,000 to < \$55,000/QALY. The PBAC noted that the ICER was impacted by the measures chosen for response criteria, and considered it was not clear whether this reflects a true difference in cost-effectiveness.
- 7.14 The PBAC noted that response rates for the CsA-experienced and CsA-naïve populations could have been combined for use in the model but considered that the lower ICER for the CsA-experienced population (\$25,000 to < \$35,000/QALY), driven mostly by changes in incremental QALYs, provided confidence that the use of the CsA-naïve population in the base-case was a conservative approach.
- 7.15 The PBAC noted that a revised clinician survey with an increased sample size was used as the source of healthcare resource use. Despite reducing uncertainty in some resource use estimates (such as hospitalisations), the PBAC agreed with the ESC that the magnitude of cost offsets from phototherapy applied in the model was not reasonable, particularly as the model included no effectiveness from phototherapy utilisation. The PBAC noted that excluding the cost offsets from phototherapy increased the ICER to \$55,000 to < \$75,000/QALY.
- 7.16 The PBAC noted, as for the model presented in the July 2019 resubmission, this resubmission assumed a differential maintenance of response for dupilumab and SoC. The PBAC noted the pre-PBAC response argued that, in the absence of active treatment and outside of the highly controlled clinical trial environment which would encourage adherence, it is reasonable to assume that patients treated with SoC would revert back to their baseline level of disease activity but argued that it is implausible that the response rate for dupilumab-treated patients would decline to the same

extent over the same time period as placebo-treated patients. The pre-PBAC response argued that the assumption adopted in the sensitivity analysis conducted during the evaluation, whereby SoC patients receive the same maintenance of response as the dupilumab patients, was clinically implausible and unfairly biases against dupilumab. The pre-PBAC response noted that this approach resulted in the same relative reductions in response over time but a much larger absolute reduction for dupilumab given the higher number of responders initially. Specifically over five years, the dupilumab response was reduced by 31% in absolute terms (from approximately 60% to 29%) versus a reduction in SoC response of 19% in absolute terms (from approximately 20% to 1%). The pre-PBAC response proposed an alternative sensitivity analysis in which the absolute reduction in response from year 1 to year 2 was approximately the same for both the dupilumab and SoC arms (approximately 13%). The resulting ICER was \$45,000 to < \$55,000/QALY. The PBAC considered the base case ICER as presented in the resubmission was a likely underestimate due to the assumptions regarding maintenance of response.

- 7.17 Overall in relation to the cost-effectiveness of dupilumab, the PBAC noted the base case ICERs presented in the resubmission were \$45,000 to < \$55,000/QALY for the CsA-experienced population and \$25,000 to < \$35,000/QALY for the CsA-naïve population. The PBAC considered the ICERs to be underestimated due to overestimating the extent of phototherapy use, however noted in the extreme case of removing the phototherapy costs, the ICER for the CsA experienced population increased to \$55,000 to < \$75,000/QALY. The PBAC also considered the ICER to be underestimated due to the submission's assumptions regarding maintenance of response, and noted that there are limited data currently available to inform these assumptions. The PBAC considered that the effective price for dupilumab should be reduced to address the likely underestimation of the ICER.
- 7.18 The PBAC noted the financial estimates as presented in Table 20 would need to be revised to:
- Include patients aged 12-17 years. The PBAC considered it would be reasonable to expand the population on which the estimates are based to include the Australian population aged 12-17 years with the remaining assumptions regarding the proportion of patients treated unchanged. The PBAC noted, based on the population data included in the submission, that expanding the population increases the population size by approximately 9%. The PBAC noted that a reduced dose (200 mg every other week) is recommended in patients aged 12-17 years with a body weight of <60 kg and considered the reduced dose should be accounted for in the financial estimates.
 - Apply the uptake rates of 5% in year 1, increasing to 7.5% in year 6 such that they reflect the proportion of continuing patients in each year rather than only the initiating patients (paragraph 6.56).

- 7.19 The PBAC considered that the estimated MBS cost offsets from phototherapy were likely overestimated, as due to the limited availability and significant burden on patients (frequency and length of treatment and cost), its use in the treatment of AD in Australia is limited. The PBAC considered that overall phototherapy services are unlikely to be reduced as a result of listing dupilumab as they are largely at capacity and therefore should not be included as cost-offsets in the financial estimates.
- 7.20 The PBAC considered there is potential for substantial use beyond the requested restriction to those with less severe AD, those with comorbid conditions such as asthma, and those with reduced QoL due to overly complex topical regimens. Regarding this concern the PBAC noted recent changes to the dupilumab TGA-approved indications to include use in patients with asthma. The PBAC considered that there remains a high risk of leakage to patients who do not have sufficient response according to the continuing criteria.
- 7.21 The PBAC noted that the sponsor indicated a willingness to enter a risk sharing agreement. The PBAC considered that a [REDACTED] % rebate would be required for expenditure exceeding the estimated financial cost for dupilumab (as per Table 20 with revisions noted in paragraph 7.18) to address the potential for use outside the intended population, and to address the potential continuing use in patients who do not have adequate response, where use of dupilumab is likely to be less cost-effective. The PBAC considered that it would not be appropriate for the caps to be increased to account for patients with severe AD exclusively of the hands or face as the cost-effectiveness in these patients is unknown.
- 7.22 The PBAC recommended that the grandfather listing be in operation for 12 months to transition patients commenced on non-PBS subsidised treatment to PBS subsidised supply, where these patients would otherwise have met the initial treatment criteria. The PBAC noted the sponsor's request that the assessment of grandfather patient eligibility to continue treatment, following their transition to PBS-subsidised treatment with dupilumab, be based on EASI score alone, because the baseline DLQI score would not be recorded in these patients.
- 7.23 The PBAC advised that dupilumab is not suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements as the treatment criteria specify that the patient must be treated by a dermatologist or clinical immunologist.
- 7.24 The PBAC considered that dupilumab should be exempt from the Early Supply Rule for initial treatment as the first repeat would need to be dispensed within 20 days according to the dosing directions in the Product Information. However, for continuing supply, the PBAC considered that dupilumab should not be exempt from the Early Supply rule.
- 7.25 The PBAC noted that an Authority Required (Written only) restriction level was requested. The PBAC considered that the authority approval method may need further refinement between the Department and Services Australia. The expected

number of applications requiring processing, logistics and nature of any collected clinical evidence as stated in the restriction are to be considered in determining the authority approval method.

- 7.26 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.
- 7.27 The PBAC found that the criteria prescribed by the National Health (Pharmaceutical 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 dupilumab:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over SoC;
 - b) The treatment is expected to address a high and urgent unmet clinical need, however alternative treatments (including cyclosporin) are available and therefore this criterion is not met; and
 - 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.

Outcome:

Recommended

8 Recommended listing

- 8.1 Restrictions to be finalised.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

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.