7.05 DUPILUMAB, 300 mg in 2 mL single use pre-filled syringe, Dupixent®, Sanofi-Aventis Australia Pty Ltd

1 Purpose of Application

1.1 The resubmission requested a Section 85 Authority Required listing for dupilumab for the treatment of atopic dermatitis (AD) in adult patients with moderate-to-severe disease who are inadequately controlled on topical therapies. The PBAC previously considered dupilumab at its July 2018 meeting.

1.2 The requested listing was based on a cost-utility analysis of dupilumab compared to 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

Component	Description
Population	Adults with moderate to severe AD who have had an inadequate response to topical therapies
Intervention	Dupilumab 600 mg subcutaneous (SC) initial dose, followed by 300 mg SC every other week (Q2W)
Comparator	Placebo (representing standard of care); and Ciclosporin A (representing immunosuppressants)
Outcomes in the trials	Primary: Proportion of patients with a 75% improvement in Eczema Area and Severity Index (EASI) score at week 16 (EASI-75); proportion of patients with an Investigator's Global Assessment (IGA) score of 0 or 1 and a change of ≥2 points from baseline at week 16 Secondary: Changes in physician and patient reported atopic dermatitis (AD) severity scores including EASI, SCORAD, DLQI, POEM, HADS, GISS, IGA, peak daily pruritus NRS and percent BSA involvement
Clinical claim	In the treatment of adults with moderate to severe atopic dermatitis, dupilumab has: • Superior efficacy and similar safety compared with standard of care. The claim of a similar safety profile may not be supported. • Similar efficacy and superior safety to ciclosporin A. The efficacy and safety claims for this comparison may not be supported due to uncertain evidence.

Source: Table 1.1 (pg.1 of the resubmission)
Abbreviations: AD: atopic dermatitis; SC: subcutaneous; Q2W: every two weeks; EASI: Eczema Area and Severity Index; SCORAD: Scoring atopic dermatitis; DLQI: Dermatology life quality index; POEM: Patient oriented eczema measure; HADS: Hospital anxiety and depression scale; GISS: Global individual signs score; IGA: Investigator's global assessment; NRS: Numerical rating scale; BSA: Body surface area

2 Requested listing

2.1 The resubmission proposed that a special pricing arrangement (SPA) apply. The proposed effective DPMQ for dupilumab was [redacted] with a published DPMQ of $1,743.62 per 2 pre-filled syringes.

2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
DUPILUMAB Dupilumab 300mg/2mL 2 x 2mL pre-filled syringe	1	2	4	[redacted] (effective) [redacted] (published)	Dupixent® Sanofi-aventis

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Severity:	Moderate to severe
Condition:	Atopic dermatitis
PBS Indication:	Chronic moderate to severe atopic dermatitis
Treatment phase:	*Initial* ~~1 (new patient or patient recommencing treatment after a break of five years or more)~~
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by a dermatologist OR Must be treated by a clinical immunologist
Clinical criteria:	*Patient must have moderate to severe atopic dermatitis with a PGA score of ≥3* AND ~~Patient must have moderate to severe atopic dermatitis where~~ *L*esions *must* have been present for at least 6 months from the time of initial diagnosis; AND Patient must not have received any prior PBS-subsidised treatment with ~~dupilumab~~ *this drug* for this condition; OR Patient must not have received PBS-subsidised treatment with ~~dupilumab~~ *this drug for this condition* for at least 5 years ~~for this condition~~ and wish to commence a new treatment cycle; AND Patient must have failed to achieve an adequate response to topical therapies (topical corticosteroids and/or topical calcineurin inhibitors); ~~AND~~ ~~Patient must have signed a patient and prescriber acknowledgement that PBS-subsidised treatment will cease if they do not meet the predetermined response criteria for ongoing PBS-subsidised treatment, as outlined for continuing treatment;~~ AND The treatment must be as systemic monotherapy (other than oral corticosteroids); AND Patient must not receive more than ~~16~~*18* weeks of treatment under this restriction.
Population criteria:	Patient must be 18 years of age or older
Prescriber Instructions	The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Atopic Dermatitis Authority Application – Supporting Information form which

	includes the following: (i) the completed current Physician's Global Assessment (PGA) calculation sheets including the date of assessment of the patient's condition; and (ii) the completed current Dermatology Life Quality Index (DLQI) calculation sheets including the date of assessment of the patient's condition; ~~and~~ ~~(iii) the signed patient and prescriber's acknowledgments.~~
Administrative Advice	Moderate to severe atopic dermatitis is defined as a Physician's Global Assessment (PGA) score of 3 or 4 on a five point PGA scale where scores range from 0 to 4. *Failure to achieve adequate response to topical therapies is defined as failure to achieve PGA 0-2 despite daily TCS of medium to higher potency for at least 28 days.* A Dermatology Life Quality Index (DLQI) assessment and a Physician's Global Assessment (PGA) assessment using a five point scale must be made at the time of this application, and after at least 12 weeks of treatment, so there is adequate time for a response to be demonstrated to this initial course of treatment. These assessments, which will be used to determine eligibility for continuing treatment, must be submitted to the Department of Human Services no later than 1 month from the completion of this initial course of treatment. Where a response assessment is not undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug. In circumstances where it is not possible to submit a response assessment within these timeframes, please call the Department of Human Services on 1800 700 270 to discuss. It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criteria for PBS-subsidised treatment with this drug. Any queries concerning arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday) Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov,au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001 Special Pricing Arrangements apply. N*o increase in the maximum quantity or number of units may be authorised.* *No increase in the maximum number of repeats may be authorised.*

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DUPILUMAB Dupilumab 300mg/2mL 2 x 2mL pre-filled syringe	1	2	2	[redacted] (effective) [redacted] (published)	Dupixent® Sanofi-aventis

Category/Program	GENERAL – General Schedule
Prescriber type	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners

	☐ Optometrists ☐ Midwives
Episodicity	Chronic
Condition	Atopic dermatitis
Severity	Moderate to severe
PBS Indication	Chronic moderate to severe atopic dermatitis
Treatment phase	*Initial treatment - Balance of supply* ~~Initial treatment (new patient or patient recommencing treatment after a break of five years or more)~~
Restriction Level/Method	☐ Restricted benefit ☒ Authority Required – In Writing ☐ Authority Required – Telephone ☐ Authority Required – Emergency ☐ Authority Required – Electronic ☐ Streamlined
Treatment criteria	Must be treated by a dermatologist OR Must be treated by a clinical immunologist.
Clinical criteria	Patient must have received insufficient therapy with this drug under the Initial restriction to complete ~~16~~ *18* weeks of treatment; AND The treatment must be as systemic monotherapy (other than oral corticosteroids); AND The treatment must provide no more than the balance of up to ~~16~~ *18* weeks of therapy
Population criteria	Patient must be 18 years of age or older
Administrative advice	Authority approval for sufficient therapy to complete a maximum of ~~16~~ *18* weeks of treatment must be requested by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Any queries concerning arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday) ~~Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov,au~~ ~~Applications for authority to prescribe should be forwarded to:~~ ~~Department of Human Services~~ ~~Complex Drugs~~ ~~Reply Paid 9826~~ ~~HOBART TAS 7001~~ Special Pricing Arrangements apply. *No increase in the maximum quantity or number of units may be authorised.* *No increase in the maximum number of repeats may be authorised.*

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2 x 2mL pre-filled syringe [redacted] (published)

Category/Program	GENERAL – General Schedule
Prescriber type	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity	Chronic
Condition	Atopic dermatitis
Severity	Moderate to severe
PBS Indication	Chronic moderate to severe atopic dermatitis
Treatment phase	~~Initial 2 –~~ *Grandfather* ~~patients~~
Restriction Level/Method	☐ Restricted benefit ☒ Authority Required – In Writing ☐ Authority Required – Telephone ☐ Authority Required – Emergency ☐ Authority Required – Electronic ☐ Streamlined
Treatment criteria	Must be treated by a dermatologist OR Must be treated by a clinical immunologist.
Clinical criteria	~~Patient must have a documented history of moderate-severe atopic dermatitis~~ *Patient must have a documented history of moderate to severe atopic dermatitis with a PGA score of ≥3* AND ~~Patient must have moderate to severe atopic dermatitis where~~ Lesions *must* have been present for at least 6 months from the time of initial diagnosis *prior to commencing non-PBS subsidised therapy with this drug for this condition;* AND Patient must have failed to achieve an adequate response to topical therapies (topical corticosteroids and/or topical calcineurin inhibitors); *prior to commencing non-PBS subsidised therapy with this drug for this condition* AND Patient must have received treatment with this drug for this condition prior to <PBS LISTING DATE>; AND ~~Patient must have demonstrated an adequate response to their most recent course of treatment with this drug;~~ ~~AND~~ ~~Patient must have signed a patient and prescriber acknowledgement that PBS-subsidised treatment will cease if they do not meet the predetermined response criteria for ongoing PBS-subsidised treatment, as outlined for continuing treatment;~~ ~~AND~~ The treatment must be as systemic monotherapy (other than oral corticosteroids); AND Patient must not receive more than ~~24~~*18* weeks of treatment under this restriction.
Population criteria	Patient must be 18 years of age or older
Prescriber instructions	The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Atopic Dermatitis Authority Application – Supporting Information form which includes the following:

	~~(i) the signed patient and prescriber's acknowledgments.~~ *(i) the completed current Physician's Global Assessment (PGA) calculation sheets including the date of assessment of the patient's condition; and* *(ii) the completed current Dermatology Life Quality Index (DLQI) calculation sheets including the date of assessment of the patient's condition;* ~~*and*~~ A patient may qualify for PBS-subsidised treatment under this restriction once only.
Administrative advice	Moderate to severe atopic dermatitis is defined as a Physician's Global Assessment (PGA) score of 3 or 4 on a five point PGA scale where scores range from 0 to 4. A Dermatology Life Quality Index (DLQI) assessment and a Physician's Global Assessment (PGA) assessment using a five point scale must be made at the time of this application, and after at least 12 weeks of treatment, so there is adequate time for a response to be demonstrated to this initial course of treatment. These assessments, which will be used to determine eligibility for continuing treatment, must be submitted to the Department of Human Services no later than 1 month from the completion of this initial course of treatment. Where a response assessment is not undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug. In circumstances where it is not possible to submit a response assessment within these timeframes, please call the Department of Human Services on 1800 700 270 to discuss. It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criteria for PBS-subsidised treatment with this drug. Any queries concerning arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday) Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov,au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001 Special Pricing Arrangements apply. *No increase in the maximum quantity or number of units may be authorised.* *No increase in the maximum number of repeats may be authorised.*

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Episodicity	Chronic
Condition	Atopic dermatitis
Severity	Moderate to severe
PBS Indication	Chronic moderate to severe atopic dermatitis
Treatment phase	Continuing treatment
Restriction Level/Method	☐ Restricted benefit ☒ Authority Required – In Writing ☐ Authority Required – Telephone ☐ Authority Required – Emergency ☐ Authority Required – Electronic ☐ Streamlined
Treatment criteria	Must be treated by a dermatologist, OR Must be treated by a clinical immunologist.
Clinical criteria	~~Patient must have a documented history of moderate-severe atopic dermatitis;~~ ~~AND~~ Patient must have received this drug as their most recent course of PBS-subsidised treatment for this condition ~~in the current treatment cycle~~; AND Patient must have demonstrated an adequate response to their most recent course of *PBS-subsidised* treatment with this drug; AND The treatment must be as systemic monotherapy (other than oral corticosteroids); AND Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction.
Population criteria	Patient must be 18 years of age or older
Prescriber instructions	The authority application must be made in writing and must include: (a) a completed authority prescription form; AND (b) a completed Atopic Dermatitis Authority Application – Supporting Information form which includes the following: (i) the completed current Physician's Global Assessment (PGA) calculation sheets including the date of assessment of the patient's condition; AND (ii) the completed current Dermatology Life Quality Index (DLQI) calculation sheets including the date of assessment of the patient's condition. The most recent PGA and DLQI assessments must be no more than 1 month old at the time of application. Approval will be based on the PGA/DLQI assessments of response to the most recent course of treatment with this drug. An adequate response to treatment is defined as either: • An improvement in Dermatology Life Quality Index (DLQI) score of at least 4 points, or sustained at that level, when compared to the prebiological treatment baseline value for this treatment cycle; OR

	• An improvement in Physician's Global Assessment (PGA) score of at least 2 points, or sustained at that level, when compared to the prebiological treatment baseline value for this treatment cycle. PGA and DLQI assessments of the patient's response must be conducted within 4 weeks prior to completion of this course of treatment. These assessments, which will be used to determine eligibility for further continuing treatment, must be submitted to the Department of Human Services no later than 1 week from the date of completion of this course of treatment. Where a response assessment is not undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug. In circumstances where it is not possible to submit a response assessment within these timeframes, please call the Department of Human Services on 1800 700 270 to discuss.
Administrative advice	~~Moderate to severe atopic dermatitis is defined as a Physician's Global Assessment (PGA) score of 3 or 4 on a five point PGA scale where scores range from 0 to 4.~~ It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criteria for PBS-subsidised treatment with this drug. Patients who fail to demonstrate a response to treatment with a biological treatment are deemed to have completed this treatment cycle and must cease PBS-subsidised therapy. These patients may recommence a new biological treatment cycle after a minimum of 5 years have elapsed between the date of the last prescription for a PBS-subsidised biological agent was approved and this cycle and the date of the first application under a new cycle. Any queries concerning arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday) Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov,au ~~Applications for authority to prescribe should be forwarded to:~~ ~~Department of Human Services~~ ~~Complex Drugs~~ ~~Reply Paid 9826~~ ~~HOBART TAS 7001~~ Special Pricing Arrangements apply. *No increase in the maximum quantity or number of units may be authorised.* *No increase in the maximum number of repeats may be authorised.*

2.3 Compared to the previous submission, the effective dispensed price per maximum quantity (DPMQ) decreased by approximately 3.7% from [redacted] to [redacted] and the published DPMQ increased by approximately 7.9% from [redacted] to [redacted] for 2 x 300mg/2ml dupilumab pre-filled syringes.

2.4 The number of packs and repeats for initial treatment has appropriately changed from 2 packs and 0 repeats (for dosing at Weeks 0, 2 and 4), relying on a balance of supply for the remainder of initial therapy, in the previous submission; to 1 pack and 4 repeats

(10 doses in total, allowing for dosing at Weeks 0 [2 doses], 2, 4, 6, 8, 10, 12, 14, 16) in the resubmission. This is consistent with the clinical trials measuring response at 16 weeks and the manner in which initial therapy for other bDMARDs are listed on the PBS for various indications. The PBAC considered that 16 weeks of initial treatment was appropriate and was consistent with listings for other bDMARDs.

2.5 The clinical criteria for disease severity changed from severe AD (Investigator's Global Assessment (IGA)=4) in the previous submission to moderate-to-severe AD (Physician's Global Assessment (PGA) ≥3) in the resubmission. The resubmission specified that the 5 point PGA scale should be used in the requested restriction. The PSCR noted that the term "investigator" is specific to the trial setting and the term "physician" in PGA is a more appropriate term for clinical practice. The PSCR clarified that In the dupilumab trials, a five point IGA scale ranging from 0 [clear] to 4 [severe] was used, and proposed that a five point PGA scale (0 [clear] to 4 [severe]), with the same definitions for scores as used in the clinical trials, be used to identify patients eligible for treatment for PBS-subsidised dupilumab.

2.6 The clinical criteria for prior treatment experience changed in the resubmission. Patients are no longer required to have a contra-indication, intolerance or unresponsiveness to ciclosporin A (CsA), but are now required to have failed to achieve an adequate response to topical therapies. The proposed restriction did not include a definition for 'failed to achieve an adequate response to topical therapies'. During the evaluation it was considered that a definition may be appropriate to align the patient population with the trial population, and to ensure that patients have adequately attempted other treatment options. The ESC considered that it would be appropriate to base these criteria on the trial definition of failure, but without the reference to PGA (i.e. failure to achieve adequate response despite daily topical corticosteroids (TCS) of medium to higher potency for at least 28 days).

2.7 The clinical criteria for eligibility for continuing treatment changed from a 75% improvement in the Eczema Area and Severity Index (EASI-75) in the previous submission to either a PGA score improvement of ≥2 from pre-treatment OR a Dermatology Life Quality Index (DLQI, 30 point scale) score improvement of ≥4 from pre-treatment. The submission stated this was based on an Australian Management Consensus for AD in adults (Foley et al, expected to be published in the in the first half of 2019), which indicated that 'treatment success can be defined as a DLQI score of ≤5 and/or an IGA improvement of ≥2 from a baseline of ≥3'. The PBAC previously "considered that "EASI-75 appears to be a valid clinical marker correlating with outcomes such as QoL" (Dupilumab PSD, July 2018, paragraph 7.5). During the evaluation it was considered that the revised response criteria may not be appropriate as:

- the composite outcome was not a primary outcome of the trials informing the resubmission and was not the basis of the clinical claim made by the resubmission

(both of which used the outcomes EASI-75 and an improvement in IGA score from pre-treatment values of ≥2).

- baseline DLQI scores were not specified as part of the initial treatment eligibility criteria. The PSCR and the pre-PBAC response maintained that the DLQI should not be used for diagnostic purposes but rather for assessing treatment response. The ESC noted that Foley et al suggest that baseline DLQI is suitable for use in quantifying AD severity. The pre-PBAC response stated the bands of DLQI scores relate to the impact of AD on the patient's quality of life and do not categorise the patient's disease as mild, moderate or severe. The ESC noted that if baseline DLQI values are not used for determining eligibility they would still be required to determine treatment response at 16 weeks (≥4 point change). The pre-PBAC response noted that the requirement for a baseline DLQI score for the purposes of monitoring response to therapy is included as part of the initiation restriction administrative advice;
- the change in DLQI (≥4 point change from pre-treatment) specified as a criteria for continuing treatment is not consistent with the recommendation in Foley et al that treatment success can be defined as a DLQI score of ≤5. The ESC considered that a change in DLQI score from 30 to 26 may not equate to an adequate response to treatment. The pre-PBAC response stated the proposed response criteria, PGA (≥2 point change) and DLQI (≥4 point change), can be used both to assess response to treatment, and to identify the overall treatment goal (a PGA score of at 0 or 1 or a DLQI score ≤5); and
- it is not clear that patients who respond by either a 2 point improvement in PGA or a 4 point improvement in DLQI scores achieve the same relative benefit. In the Pre-PBAC response the sponsor provided disaggregated outcome data by response definition (PGA alone, DLQI alone, composite outcome) as shown in Tables 9 and 10.

2.8 Table 2 compares the quantification criteria from the proposed listing, trial evidence and as recommended in Foley et al. The ESC noted that in the dupilumab trials IGA response required patients to have both IGA score 0 or 1 AND IGA improvement $\underline{>}$2.

Table 2: Comparison of quantification of severity and treatment success/failure

Parameter	Proposed listing	Trial evidence	Foley et al
Quantification of Moderate-severe	PGA ≥ 3 (using the same scale as the IGA)	IGA ≥3	Patient or Physician GS ≥3
		BSA≥10%	BSA≥10%
		EASI ≥16 (≥20 in CAFE trial)	DLQI≥10
		Pruritis (NRS) ≥3 (in CHRONOS and SOLO I/II trials)	Pruritis ≥4
Quantification of failure of TCS/TCI/treatment	None proposed	IGA>2 despite daily TCS of medium to higher potency for at least 28 days or the maximum duration recommended by the PI, in previous 6 months	DLQI≥6 and PGA not improved or improved by <2points (general treatment failure definition)
Quantification of Treatment success*	DLQI improvement ≥4 or PGA improvement ≥2	% EASI-75 responders (co-primary endpoint with IGA); IGA score 0 or 1 AND IGA improvement ≥2	If DLQI≤5 and/or PGA improved ≥2 from a baseline of ≥3

Source: Compiled for ESC, from the submission and Foley et al

BSA = body surface area; DLQI = dermatology life quality index; EASI = Eczema Area and Severity Index; GS = global score; IGA = investigators global assessment; NRS = numerical rating scale; PGA = physicians global assessment; PI = product information;TCS = topical corticosteroids; TCI = topical calcineurin inhibitors.

* Foley et al state that this is not a definitive measure of clinically meaningful improvement, rather a gauge as to whether the optimal goal for a patient's condition has been reached.

2.9 The PBAC considered a key issue in the resubmission was that the definitions for assessment of severity and response for continuation did not match trial criteria. The PBAC considered that initial assessment of moderate-to-severe AD should include both PGA and EASI scores, which is consistent with the clinical trial evidence. The PBAC considered that an assessment of response based on PGA score change of 2 or more and either DLQI <5 or EASI-75 response, would be more consistent with the clinical trial evidence and the criteria proposed by Foley et al. The PBAC considered that the EASI was an important measure to include in assessing severity and response because it includes consideration of the body surface area affected. The PBAC considered that dermatologists are familiar with PASI scoring in psoriasis, and will become familiar with EASI as it was developed by modifying the PASI.

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

3 Background

Registration status

3.1 Dupilumab was approved for registration by the TGA on 24 January 2018 for 'the treatment moderate to severe atopic dermatitis in adult patients who are candidates for chronic systemic therapy'. The TGA-recommended dose is two consecutive initial 300 mg doses followed by 300 mg given every other week (Q2W).

Previous PBAC consideration

3.2 This was the second submission to the PBAC for dupilumab for the treatment of adults with atopic dermatitis. The first submission was considered by the PBAC at its July 2018 meeting. Outstanding matters of concern from the July 2018 meeting are

summarised in Table 3.

Table 3: Summary of outstanding matters of concern

Component	Matter of concern (Paragraph references are to the Dupilumab July 2018 PSD)	How the resubmission addresses it
Proposed place of therapy	"The PBAC agreed with the ESC 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" (paragraph 7.4)	The proposed population in the resubmission is broader, and includes patients with moderate-to-severe AD who are inadequately controlled on topical therapies.
Economic model time horizon	"The PBAC noted several issues with the structure of the economic model which increased the uncertainty in the estimated ICER. The PBAC considered that the 5 year time horizon in the model, extrapolated from 16 weeks of trial data, increased uncertainty and was a key driver of the model" (paragraph 7.9)	The resubmission presented a new economic model which used a 10 year time horizon based on clinical data up to 44 weeks. As such, this outstanding matter of concern was not adequately addressed.
Utility values applied in the economic model.	"The PBAC noted that the utility values used for the responder health states in the model were highly uncertain due to small sample sizes (n=9 for placebo; n=28 for dupilumab), and because different utility values were assigned to each treatment arm despite no statistically significant differences in utility gain" (paragraph 7.9).	The resubmission used pooled utility values from four trials at Week 16, and from the CHRONOS trial for Weeks 16-42. The same utility values were reasonably applied for responders regardless of treatment arm.
Health state resource-utilisation estimates applied in the economic model.	"The PBAC noted that there were problems with the applicability of several other sources of data in the model, including health service use costs, which further increased the uncertainty of the estimate of cost-effectiveness" (paragraph 7.9).	The resubmission used resource-use estimates from a survey of Australian clinicians. There were issues associated with the estimates from this survey.
Base-case ICER in the economic model	"The PBAC noted that the base case ICER of $45,000/QALY - $75,000/QALY was relatively high" (paragraph 7.10).	The base-case ICER in the resubmission was $15,000/QALY - $45,000/QALY-gained. However, there were issues with the methodology and inputs used in the model that impacted the reliability of this result.

Source: Table 1.4 (p.10) of the resubmission

4 Population and disease

4.1 The resubmission changed the clinical place of dupilumab from adult patients with severe AD who are contra-indicated, intolerant or unresponsive to CsA (whereby CsA is indicated for patients inadequately controlled on topical therapies), to adult patients with moderate-to-severe AD who have failed to achieve an adequate response to topical therapies. This change was based on advice from the PBAC July 2018 meeting where the PBAC considered that "there was limited evidence that supported the contention that either severity of AD [moderate versus severe] or experience with CsA [yes versus no] are treatment effect modifiers" (Dupilumab PSD, July 2018, paragraph 6.21). The PBAC acknowledged there is significant disease burden from AD and a high clinical need for effective treatments for moderate to severe AD.

5 Comparator

5.1 The resubmission nominated placebo, representing standard of care (SoC), as the main comparator, whereby SoC involves topical therapy providing an inadequate response. The PBAC previously accepted placebo (representing SoC) as the comparator "on the justification that there are currently no safe and effective long-term treatment options available to patients. SoC would also include concomitant TCS ± TCI [topical calcineurin inhibitor] therapy for flaring" (Dupilumab PSD, July 2018, paragraph 5.1).

5.2 The resubmission also nominated cyclosporin A (CsA) as an additional relevant comparator. This additional comparator was not presented in the previous submission due to the narrower proposed population. The ESC considered nomination of CsA as an additional comparator was appropriate, however the clinical and economic evidence informing this comparison was poor, thus making the comparison uninformative.

5.3 The ESC considered that phototherapy could also be considered an additional comparator and noted that cost offsets for phototherapy were included in the financial estimates and sensitivity analyses in the economic model. The ESC acknowledged that uptake of phototherapy is limited by patient access to this service and the considerable out of pocket expenses associated with it. The ESC considered that there is unlikely to be suitable evidence for phototherapy to enable a comparison with dupilumab, however use of phototherapy in some patients may mean that the efficacy shown in the dupilumab trials is not realised in practice.

5.4 The PBAC considered that the resubmission appropriately nominated SoC as the main comparator. The PBAC considered CsA to be an additional relevant comparator given the broader proposed patient population, but acknowledged the likely limited use of CsA in clinical practice, and the limited clinical evidence available for CsA. Further, the PBAC noted the economic model presented in the resubmission comparing dupilumab and CsA was not informed by clinical evidence and thus was uninformative, and replacement of CsA was not considered in the financial estimates. The PBAC noted that there may be some use of phototherapy in the proposed population however there is likely to be limited clinical evidence to inform a comparison with dupilumab.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history of the disease, how the drug would be used in practice, and addressed other matters in response to the Committee's questions. The clinician stated that the vast majority of AD patients can be treated with topical

therapy; however, those patients who do not respond are treated with phototherapy or CsA, and off label therapy. The clinician indicated that patients treated with dupilumab describe treatment success as life changing as they have been able to return to normal life.

6.2 The clinician discussed the PGA, DLQI and EASI scales used in the assessment of AD and noted the EASI system is not well known or commonly used among clinicians, and although could be learnt, would be an involved process. The clinician emphasised that treatment targets (eg DLQI <5) are generally achieved over a 16-24 week period, and that if patients with moderate-to-severe AD stop therapy, the disease will gradually reappear and return to its previous level over 2-6 months.

6.3 The clinician stated that most children with AD improve in their teenage years; however, if the disease continues into their late teens and 20s, then they are likely to have AD for life. The clinician confirmed the estimate of approximately 500 new moderate-to-severe AD patients per year appears reasonable, although noted epidemiology data are scarce. The clinician stated that dermatologists (90%) would perform the majority of prescribing, with immunologists covering the remainder, although there is variation between the states.

6.4 The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease.

Consumer comments

6.5 The PBAC noted and welcomed the input from individuals (159), health care professionals (47) and organisations (3) via the Consumer Comments facility on the PBS website.

6.6 The comments from healthcare professionals described the high disease burden for patients with AD and the lack of safe and effective treatments currently available, in particular noted renal failure associated with CsA and serious infection associated with immunosuppressants in general. Healthcare providers also commented on the high success rate for patients currently accessing dupilumab on compassionate supply programs. The comments from individuals currently accessing dupilumab described a range of benefits of treatment including dramatic improvements in quality of life in terms of work, sleep, relationships, psychological well-being and relief from incessant itch, bleeding and tenderness of the skin for patients with severe AD. These individuals noted that side effects from treatment were well tolerated and easily resolved. Comments from patients not currently accessing dupilumab described the very high impact AD has on their quality of life and some patients reported being hospitalised due to infection.

6.7 The PBAC noted the support for PBS listing of dupilumab received from Allergy & Anaphylaxis Australia, Eczema Association of Australasia Inc, and Eczema Support Australia.

6.8 The PBAC noted the advice from Allergy & Anaphylaxis Australia regarding the

extremely negative impact of AD on physical and mental health, and that the use of dupilumab may improve the quality of life and be a lifeline for patients were it to become affordable for them. The PBAC noted the advice from 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 term periods because of side effects that require close monitoring. The PBAC noted the advice from Eczema Support Australia that the use of dupilumab may reduce the extremely negative impact of AD on patients' careers and relationships and noted the expense incurred by the individual, both on expensive creams/dressings/prescriptions, as well as lost productivity in the workplace.

6.9 The PBAC also noted the advice provided by the Australasian College of Dermatologists (ACD) and Australasian Society of Clinical Immunology and Allergy (ASCIA) in response to the PBAC request for advice regarding the appropriate patient population and assessment measures. The PBAC noted that both organisations supported PBS listing of dupilumab in patients with moderate to severe AD and considered the proposed population appropriate, including that patients should not be required to have failed CsA. The ACD and ASCIA provided information on the PGA, DLQI and EASI and their current use by dermatologists and clinical immunologists. The ACD advised a 2 point improvement in PGA and DLQI of less than or equal to 5 would be appropriate to assess patient response, or alternatively an improvement in DLQI of 4 or more could be used. The PBAC noted that the ASCIA favoured the combined use of PGA and DLQI for both assessment of severity and response to treatment.

Clinical trials

6.10 Unchanged from the previous submission, 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 previous submission) (n=380)] comparing dupilumab 300 mg fortnightly (Q2W) to placebo in patients with moderate-to-severe AD (IGA ≥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.

6.11 CAFÉ was considered the pivotal trial in the previous submission due to the inclusion criteria of requiring prior CsA treatment experience, with the remaining trials considered supplementary. The resubmission appropriately considered all five trials as relevant clinical evidence. Additionally, the previous submission relied on sub-group analyses of patients with severe AD (IGA = 4) from the CAFÉ trial, whereas the resubmission appropriately relied on whole trial data from all five trials.

6.12 The resubmission conducted a literature search for clinical evidence to inform the comparison with CsA. No head-to-head trial evidence was identified, nor any RCTs that could be used to inform a traditional pairwise indirect comparison. To inform the

comparison of dupilumab to CsA, the resubmission conducted two separate indirect comparisons:

- a matching-adjusted indirect comparison (MAIC) using patient-level CHRONOS trial data for dupilumab and aggregate-level data from two randomised studies of CsA; and
- a logistic regression analysis using patient-level CHRONOS trial data for dupilumab and patient-level data from a CsA registry in the Netherlands for CsA.

6.13 Details of the trials presented in the resubmission are provided 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, Gadkari A, Simpson E et al.Dupilumab improves patient-reported outcomes in atopic dermatitis inadequately controlled, intolerant, or inadvisable for cyclosporine-A. Annals of Allergy, Asthma and Immunology.	Annals of Allergy, Asthma and Immunology. 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).	British Journal of Dermatology. 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
	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).	Australasian Journal of Dermatology. 2017; 58:55.
	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.	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.

Trial ID	Protocol title/ Publication title	Publication citation
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 (p48-49 of the resubmission)

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

Table 5: Key features of the included evidence

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Primary outcome(s) in the trials	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]	Not used
CHRONOS	740	DB, R, MC; 64 weeks	Low	Moderate to severe AD		Post-hoc analysis of Week 16 and week 44 IGA/DLQI[c] response; Baseline, Week 16 and Week 44 EQ-5D utility data
SOLO 2	671	DB, R, MC; 28 weeks	Low	Moderate to severe AD		Post-hoc analysis of Week 16 IGA/DLQI[c] response; Baseline and Week 16 EQ-5D utility data
SOLO 2	708	DB, R, MC; 28 weeks	Low	Moderate to severe AD		
Phase IIb	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; DLQI = dermatology life quality index; EQ-5D = Euro Qol 5 dimensions; IGA = investigator's global assessment

Source: Table 3 (5.04.COM.8) in the previous submission commentary & Sections 2 and 3 of the resubmission

[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] defined using a post-hoc outcome of ≥2 score reduction from baseline in IGA score OR ≥4 score reduction from baseline in DLQI score

Comparative effectiveness

6.15 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 submission; all trials show a statistically significantly higher response in favour of dupilumab (for both weekly (QW) and fortnightly (Q2W) administration, noting the latter is TGA-approved). The PBAC previously considered that "EASI-75 appears to be a valid clinical marker correlating with outcomes such as QoL" (Dupilumab PSD, July 2018, paragraph 7.5).

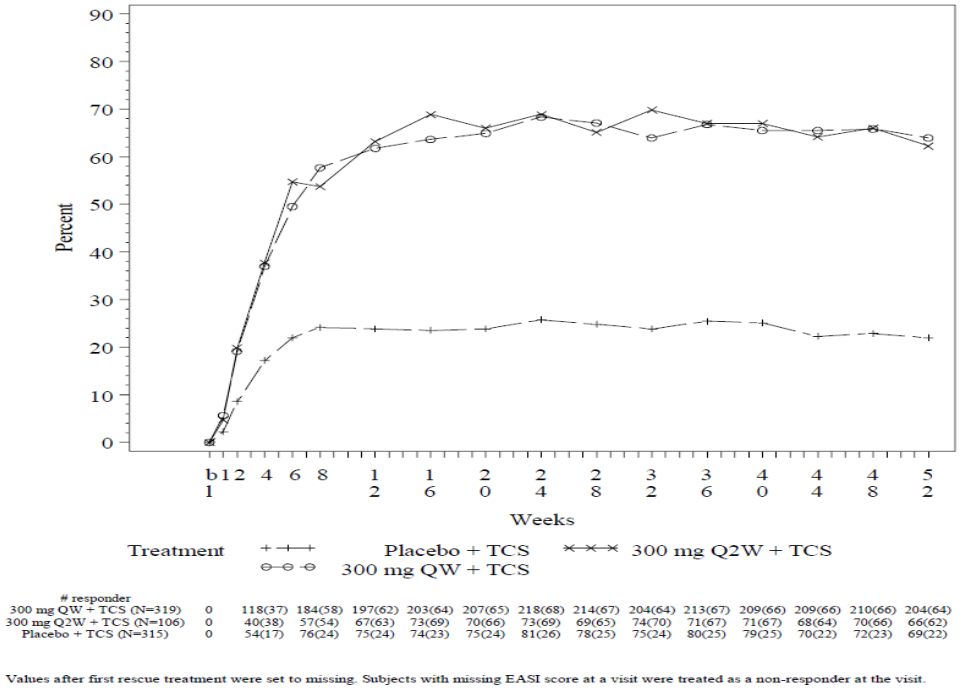
Table 6: The proportion of patients achieving the EASI-75 at week 16 (and week 52 in CHRONOS) across trials

	N	Patients achieving EASI-75 n (%)	Difference vs placebo % (95% CI)	P-value vs placebo
CAFÉ				
Dupilumab 300 mg QW	110	65 (59.1)	29.5 (16.87, 42.05)	<0.0001
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 QW	319	204 (63.9)	40.8 (33.74, 47.81)	<0.0001
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 QW	223	117 (52.5)	37.7 (29.70, 45.77)	<0.0001
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 QW	239	138 (57.7)	42.1 (34.27, 49.86)	<0.0001
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 QW	63	38 (60.3)	48.8 (34.35, 63.33)	<0.0001
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 QW	319	204 (63.9)	42.0 (35.07, 49.02)	<0.0001
Dupilumab 300 mg Q2W	106	66 (62.3)	40.4 (30.06, 50.66)	<0.0001
Placebo	315	69 (21.9)	-	-

Source: Table 2.5.1 (p 86 of the resubmission) & Table 2.5.7 (p.94) 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.
Note: The dupilumab 300mg QW arm results are not relevant to the resubmission, and are provided here for additional context
[a] Secondary endpoint. Results for dupilumab 300 mg Q4W, 200 mg Q2W and 100 mg Q4W treatment arms not presented;

6.16 The EASI-75 response over 52 weeks in CHRONOS is shown in Figure 1. As stated in the commentary for the previous submission, it is unclear whether the plateaued dupilumab treatment effect from 16 weeks is due to Week 16 responders who maintain their response, or different patients moving in and out of response.

Figure 1: Proportion of patients achieving EASI 75 over time in CHRONOS



Source: Figure 2.5.4, p94 of the resubmission

6.17 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 all dupilumab arms across all trials (for both QW and Q2W administration (the latter is TGA-approved)).

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
CAFE[a]				
Dupilumab 300 mg QW	110	43 (39.1)	25.2 (13.99, 36.41)	<0.0001
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 QW	319	125 (39.2)	26.8 (20.33, 33.28)	<0.0001
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 QW	223	83 (37.2)	27.0 (19.47, 34.44)	<0.0001
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 QW	239	87 (36.4)	27.9 (20.87, 34.99)	<0.0001
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 QW	64	19 (29.7)	28.0 (16.41, 39.69)	<0.0001
Dupilumab 300mg Q2W	63	21 (33.3)	31.7 (19.63, 43.76)	<0.0001
Placebo	61	1 (1.6)	-	

Source: Table 2.5.2, 2.5.4 & 2.5.5 (pg88-92) 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.

6.18 Meta-analysis data for CAFÉ, CHRONOS, SOLO1/2 and Study 1021 presented in the resubmission remained unchanged from the previous submission 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).

6.19 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 (for both QW and Q2W administration (latter is TGA-approved) (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 QW	110	13.8 (8.03)	-8.7 (6.94)	-8.8 (0.45)	-4.3 (-5.60, -3.04)	<0.0001
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 QW	319	14.4 (7.17)	-10.8 (6.71)	-10.7 (0.31)	-4.9 (-5.82, -4.08)	<0.0001
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 QW	223	14.1 (7.51)	-8.8 (6.79)	-9.0 (0.40)	-3.7 (-4.87, -2.49)	<0.0001
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 QW	239	16.0 (7.33)	-10.3 (6.75)	-9.5 (0.39)	-5.9 (-7.10, -4.72)	<0.0001
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 QW	63	15.0 (7.07)	-10.7 (7.29)	-9.7 (0.80)	-7.0 (-9.1, -4.8)	<0.0001
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 QW	270	14.9 (7.19)	-11.1 (7.00)	-11.1 (0.36)	-3.9 (-4.89, -2.99)	<0.0001
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 2.5.15 (p101) of the resubmission
Abbreviations: CI = confidence interval; DLQI = dermatology life quality index; FAS = full analysis set; QW = weekly; Q2W = fortnightly
Note: The dupilumab 300mg QW arm results are not relevant to the resubmission, and are provided here for additional context

6.20 The EQ-5D utility results remain unchanged from the previous submission. As stated in the previous commentary, there were differences in mean baseline utility both within trials (between treatment arms) and between trials making it difficult to interpret the comparative effect of dupilumab to placebo on health related quality of life. The magnitude and direction of quality of life change from baseline to Week 16 for both patients treated with dupilumab and patients treated with placebo reported across the trials were inconsistent.

6.21 The resubmission proposed that the criteria for continuation of dupilumab use on the PBS be based on response defined as a 2 point improvement in PGA and/or a 4 point improvement DLQI, although this composite outcome did not form the basis of the clinical claim. The results are presented in Table 9. These results are based on *post hoc* analyses and patient numbers could not be verified in the clinical study reports (CSRs).

Table 9: Proportion of patients achieving a 2 point improvement in IGA and/or a 4 point improvement DLQI

	N	Patients achieving IGA or DLQI endpoint; n (%)	Difference vs placebo % (95% CI)	P-value vs placebo
[redacted] **(Pooled analysis of CsA-naïve sub-group responders from Study 1021, SOLO1, SOLO2, CHRONOS)**				
Dupilumab 300 mg [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	-	-
[redacted], **conditional on response at** [redacted] **(CHRONOS)**				
Dupilumab 300 mg [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	-	-

Source: Table 3.6 (p.178) of the resubmission

6.22 No data for the proportion of patients achieving an improvement in DLQI of ≥4 points were provided in the resubmission, and nor was it available in any CSRs. These data were provided in the pre-PBAC response (Table 10 below). For each of the three definitions of response (PGA alone, DLQI alone, composite outcome), the proportion of dupilumab-treated patients was statistically significantly greater than placebo ($p<0.0001$ for all definitions), with similar risk differences, for achieving a response compared to placebo. This applied to both CsA-naïve and CsA-experienced patients at baseline. The PBAC agreed with the ESC that these data inform interpretation of the composite outcome used as the basis of response in the resubmission.

Table 10: Proportion of responders at Week 16 by response definition

	CsA-naive			CsA-experienced		
	% responders	RD (95% CI)	p-value vs placebo	% responders	RD (95% CI)	p-value vs placebo
Improvement in DLQI ≥4 OR improvement in PGA ≥2						
Placebo ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab 300mg Q2W ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Improvement in DLQI ≥4						
Placebo (N[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab 300mg Q2W ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Improvement in PGA ≥2						
Placebo ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab 300mg Q2W ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Improvement in DLQI ≥4 AND improvement in PGA ≥2						
Placebo ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab 300mg Q2W ([redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 1 (p4) of the pre-PBAC response

Abbreviations: CI = confidence interval; DLQI = dermatology life quality index; PGA = Physician's Global Assessment; Q2W = fortnightly; RD = risk difference

6.23 Data included by the sponsor in the pre-PBAC response showed the change in utility from baseline to week 16 for responders by response definition (PGA alone, DLQI alone, composite outcome) (Table 11 below). The sponsor stated that amongst CsA-naïve patients, the change in utility from baseline to week 16 in dupilumab arms was [redacted] for all three definitions of response, whilst for CsA-experienced patients it was [redacted] (DLQI alone), [redacted] (PGA alone), and [redacted] (DLQI PGA composite). The sponsor stated that the clinical benefit achieved by patients defined as responders by either

the PGA or the DLQI criteria in terms of improvement in QoL are comparable, and similar to that for patients achieving response according to the proposed composite response criteria.

Table 11: Change in utility from baseline to week 16 for responders by response definition

	CsA-naive		CsA-experienced	
	Placebo	Dupilumab	Placebo	Dupilumab
Improvement in DLQI ≥4 OR improvement in PGA ≥2				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]
Improvement in DLQI ≥4				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]
Improvement in PGA ≥2				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]
Improvement in DLQI ≥4 AND improvement in PGA ≥2				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (Min, Max)	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 2 (p4) of the pre-PBAC response

Abbreviations: DLQI = dermatology life quality index; PGA = Physician's Global Assessment; Q2W = fortnightly; RD = risk difference; SD = standard deviation

6.24 The ESC considered that the comparison with CsA was not informative because:

- The use of 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. 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" (Dupilumab PSD, July 2018, paragraph 6.35).

Benefits/harms

6.26 A summary of the comparative benefits and harms for dupilumab versus placebo are presented in Table 12. This is based on the same trial data as the previous submission, however EASI-75 response at Week 52, an IGA improvement ≥2 at Week 16 and an IGA improvement ≥2 or DLQI improvement ≥4 at Week 16 (and Week 44) are additional relevant outcomes.

Table 12: 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)**
IGA improvement ≥2 or DLQI improvement ≥4 at Week 16						
Pooled CsA-naïve sub-group (Study 1021, SOLO1, SOLO2, CHRONOS)	323/436	227/590	**1.93 (1.72, 2.17)**	74.1	38.5	**36 (30, 41)**
IGA improvement ≥2 or DLQI improvement ≥4 at Week 44, contingent on response at Week 16						
CHRONOS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[b]	104/1089	24/645	**2.67 (1.73, 4.11)**	9.6	3.7	**5.9 (1.1, 10.6)**
Blepharitis[c]	17/425	3/315	**5.73 (1.59, 20.6)**	5.0	1.0	**4.5 (1.2, 10.5)**
Allergic rhinitis[d]	11/217	1/108	**7.07 (1.16, 43.7)**	5.1	0.9	**5.6 (0.7, 12.1)**

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

- Approximately 38 additional patients 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 would have at least a 2 point improvement in IGA score from baseline;
- Approximately [redacted] patients would have at least a [redacted] point improvement in IGA and/or a [redacted] point improvement in DLQI score, ;
- Approximately 3 additional patients will have conjunctivitis;
- Approximately 2 additional patients will have oral herpes;

- Approximately 7 additional patients will have an injection site reaction;
- Approximately 6 additional patients will have allergic conjunctivitis;
- Approximately 5 additional patients will have blepharitis; and
- Approximately 6 additional patients will have allergic rhinitis.

6.28 The ESC 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.

Clinical claim

Dupilumab vs. SoC

6.29 The resubmission claimed superior clinical efficacy and a similar safety profile of dupilumab compared with placebo (SoC). The claim of superior clinical efficacy was supported by the clinical evidence with respect to the co-primary outcomes of most trials (EASI-75 response and IGA score of 0-1 and a reduction of ≥2 points from baseline at Week 16 (and week 52 for CHRONOS)). The claim of a similar safety profile was not supported by the clinical evidence due to a higher incidence of conjunctivitis and injection-site reaction events in dupilumab patients. The efficacy and safety claims may only be reasonable up to 52 weeks as none of the trial provided data beyond 52 weeks of treatment.

6.30 In its consideration of the previous submission, the PBAC considered the claim of superior efficacy to placebo to be reasonably supported by the clinical evidence for the treatment of adults with severe AD (IGA = 4) who have had an inadequate response or intolerance to CsA of a severity to necessitate permanent treatment withdrawal, or for whom CsA is contraindicated; but considered a claim of a comparable safety profile to placebo not to be supported due to a higher incidence of conjunctivitis and injection site reactions in dupilumab patients (Dupilumab PSD, July 2018, paragraphs 6.33 and 6.35).

6.31 For the resubmission, the PBAC considered that the claim of superior comparative effectiveness of dupilumab compared with SoC for patients with moderate to severe AD was reasonable based on EASI-75 response and IGA score. The PBAC noted that this claim may only be reasonable up to 52 weeks as data are not available to support efficacy beyond this time.

6.32 For the resubmission, the PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data due to a higher incidence of conjunctivitis and injection-site reaction events in dupilumab patients. The PBAC noted that the long-term safety for dupilumab is unknown.

Dupilumab vs. CsA: ITC

6.33 For the comparison of dupilumab to CsA, the resubmission acknowledged the high degree of uncertainty with the clinical evidence. As such, the resubmission claimed that, despite the indirect comparisons indicating that dupilumab had superior clinical efficacy to CsA, dupilumab is at least non-inferior to CsA in terms of efficacy. The evaluation considered this claim was not supported due to the uncertainty associated with the clinical evidence. The resubmission also stated that the long-term safety profile of CsA is known, and it is recommended that the duration of CsA therapy be as short as possible and generally not longer than 12 months of continuous therapy. As such, the resubmission claimed dupilumab has a superior safety profile to CsA. During the evaluation this claim was not considered supported due to a lack of comparative safety data provided for dupilumab versus CsA. The ESC noted that the long-term safety of dupilumab is unknown.

6.34 The PBAC acknowledged the submission's attempt to undertake an indirect comparison of dupilumab and CsA, however the limited evidence for CsA and differences across the trials resulted in the comparison being uninformative.

6.35 The PBAC acknowledged CsA is associated with considerable toxicity, of note renal toxicity, and the need to limit the duration of exposure. However, the limited safety data presented for CsA, and the unknown long-term safety of dupilumab, prevent an overall conclusion regarding the relative safety of the two agents.

Economic analysis

6.36 The resubmission presented a stepped modelled cost-utility analysis. The summary of the model is provided in Table 13.

Table 13: Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case versus 44 weeks in trial data
Outcomes	% of patients with an improvement of IGA of at least 2 points or DLQI of at least 4 points, life years, quality adjusted life years, resource utilisation
Methods 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: • Induction treatment (16 weeks) • Responder (DLQI Δ ≥4 or IGA Δ ≥2) • Non-Responder (DLQI Δ <4 and IGA Δ <2) • All-cause death
Cycle length	6 months (but 16 weeks for the initial treatment component of the decision tree)
Transition probabilities	Week 16 response: pooled CHRONOS, SOLO 1, SOLO 2 and Study 1021 response (DLQI Δ ≥4 or IGA Δ ≥2) data Week 42 maintenance of response: CHRONOS response data Maintenance of response past 42 weeks: time-to-event analysis using CHRONOS time to rescue treatment or withdrawal data All-cause death: Age and sex specific Australian mortality rates (Australian lifetables)

Source: Section 3 of the resubmission
Abbreviations: DLQI = dermatology life quality index; IGA = Investigator's Global Assessment

6.37 The main differences in the model presented in the resubmission are summarised in Table 14. Given the numerous differences between the models in both structure and inputs, they are not directly comparable. The ESC noted that the changes to the model inputs have the most impact on the results, rather than changes in the model structure.

Table 14: Main differences to Section 3 between the submission considered at the July 2018 PBAC meeting and this resubmission

	July 2018 Submission	Current resubmission	Comment
Population	Adults with severe AD (defined as an IGA score of 4) who have had an inadequate response or intolerance to CsA, or for whom CsA is contra-indicated.	Moderate-to-severe AD (defined as PGA or 3 or 4) 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".
Comparator	Placebo for standard of care	Placebo for standard of care; CsA, representing immunosuppressants	Reasonable given the broader proposed population in the resubmission.
Evidence	The IGA=4 sub-group of the CAFÉ trial for week 16 response rates. CHRONOS (week 52 data) for response rates between weeks 16-52.	CHRONOS, SOLO 1, SOLO 2 & Study 1021 for week 16 response rates. CHRONOS (week 44 data) for week 42 response rates.	Appropriate given the broader proposed population in the resubmission.
Outcome for response	EASI-75 Dupilumab=[redacted]% at [redacted] weeks; Placebo=[redacted]% at [redacted] weeks	Improvement in IGA or DLQI of 2 and 4 points, respectively Dupilumab=[redacted]% at [redacted] weeks; Placebo=[redacted]% at [redacted] weeks	Issues with the resubmission's definition of response are discussed above. The ESC noted that there was a higher proportion of responders using the composite outcome as per the resubmission for both dupilumab and placebo.
Model structure	Markov model	Decision tree for initiation (Cycle 1) and first maintenance cycle (Cycle 2; to Week 44) followed by a Markov model	Reasonable. Change to model structure allows for accumulation of dupilumab costs as would be expected on the PBS. The ESC considered the changes to model structure were appropriate.
Time horizon	Five years	Ten years	Not supported, given the PBAC questioned the appropriateness of a 5 year time horizon. The ESC considered that the 5 year time horizon should be used in the base case.
Health states	Induction, responder (where responder was based on EASI-75 response), non-responder, death	Induction, responder (where responder was based on IGA improvement of 2 points or DLQI improvement of 4 points), non-responder, death	Reasonable, if definition of 'response' accepted.
Cycle length	Three months	First cycle 16 weeks, followed by 6-monthly (26 week) cycles	Reasonable. Change to model structure allows for accumulation of dupilumab costs as would be

	July 2018 Submission	Current resubmission	Comment
			expected on the PBS for initial therapy. Slight disparity in terms of maintenance doses (26 weeks in the model versus 24 weeks on the PBS).
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.	Unreasonable. The change in maintenance of response rates used in the model substantially favours dupilumab as compared to the rates used in the previous submission model.
Utility	Source: IGA=4 CAFÉ sub-group EQ-5D data. Baseline & non-responder: [redacted] Dupilumab responder: [redacted] Placebo responder: [redacted]	Source: Pooled analysis of EQ-5D data from CHRONOS, SOLO 1, SOLO 2 & Study 1021 at week 16, and from CHRONOS at week 44. It was unclear whether the utility data was from CsA-naïve sub-groups or total trial populations. Baseline to week [redacted] & non-responders: [redacted] Week [redacted] dupilumab arm patients utility: [redacted] Week [redacted] placebo-arm patients utility: [redacted] Week [redacted] responders onwards (regardless of treatment arm) utility: [redacted]	An increase in the baseline utility in the model presented in the resubmission is consistent with an overall less severe group. In the resubmission, while response is measured at 16 weeks, the model applies the mean change in utility observed in the trials (0.1741 and 0.0800 in dupilumab and placebo arms, respectively) to the baseline utility resulting in differing utilities in the dupilumab and placebo arms for this period. These values could not be verified. Responder utilities applied between the models are comparable. Utilities applied in the resubmission could not be verified. The ESC considered the high utility values for responders lack face validity.
Cost of dupilumab	$[redacted] (requested effective price)	$[redacted] (requested effective price)	As requested
Other health care costs	Derived from a 2005 economic evaluation and a 1997 Australian outpatient survey (n=48). These sources of data were deemed highly uncertain, and inapplicable for the most-part. Annual responder health-state cost: $1,509.50 Annual non-responder health-state cost: $3,292.61	Derived from a survey of Australian dermatologists and immunologists. This source of data is more applicable than the source used in the previous submission, however some of the results lack face validity. Annual responder health-state cost: $1,168.16 Annual non-responder health state cost:$11,067.72	Although issues with the derivation of health state costs were identified in the previous submission, the estimates in the resubmission are also uncertain. In particular, it appears counter-intuitive that the non-responder health state costs have increased 3-fold, in the resubmission, when the population is overall less severe. The majority of these costs come from additional hospitalisations for non-responders.

[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

6.38 The submission 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 A summary of the key model drivers is presented in Table 15. The extrapolation of loss of response and the time horizon were also key model drivers in the previous submission. Non-responder health state costs were not considered a key model driver in the previous submission; however, the resubmission model was sensitive to health state costs.

Table 15: Key drivers of the model

Description	Method/Value	Impact
Time horizon	Base-case of 10 years. This was increased from 5 years in the original submission with inadequate justification given the 5 year time horizon was considered optimistic in the previous commentary based on the length of comparative clinical data.	High, favours dupilumab. A one-year time horizon results in an 825% increase in base-case ICER.
Extrapolation of loss of response	Derived from time-to-event regression analyses from CHRONOS time-to-rescue treatment or treatment withdrawal data.	High, favours dupilumab.
Non-responder annual health state costs	Derived from a survey of Australian clinicians.	High, favours dupilumab. Using the non-responder health state costs from the previous model approximately doubled the ICER.

Source: Evaluation of Section 3 of the resubmission

6.40 The model presented in the resubmission was particularly sensitive to:

- health state costs (particularly those for non-responders). The incremental treatment costs per patient ($42,088) were substantially offset (-$23,170) by the incremental health state costs which are driven by the substantial difference in annual health state costs between responders and non-responders. The costs were derived from a clinician survey (n=13) with limited information provided regarding how descriptions of the health states were phrased or quantification of uncertainty around the estimates. The non-responder health state cost was 3-fold higher than that applied in the previous submission, despite the population in the resubmission being less severe overall. Annual costs for hospitalisations (average annual frequency of 2.5 hospitalisations, annual cost $8,010) and emergency room visits (annual frequency of 3, annual cost $2,034) contributed the largest costs to the non-responder health state cost ($11,068 total annual cost). The PBAC agreed with the ESC that the frequency and resulting annual costs for

hospitalisations and emergency room visits for non-responders did not appear plausible, particularly given the less severe population proposed.

- estimation of maintenance of response, particularly the assumption of differential maintenance of response for dupilumab and placebo. The PSCR clarified how the maintenance of response rates, derived from time-to-event regression analyses from CHRONOS time-to-rescue treatment or treatment withdrawal data, were applied for the dupilumab arm in the model. The ESC noted that it was assumed that the treatment effect observed at the end of CHRONOS would persist but only for the dupilumab arm. The ESC noted that modelled response rates resulted in no responders in the SoC arm beyond 3 years and considered that this did not appear plausible. The PBAC agreed with the ESC that the differential maintenance of response rates applied to the treatment arms in the model were not reasonable and considered that extrapolation of these rates over the 10-year time horizon further increased uncertainty in the modelled outcomes. The ESC also noted that the 3.7% annual dupilumab discontinuation rate could not be verified, nor is it clear at what time point this discontinuation rate was measured and whether it was therefore appropriate for the resubmission to have assumed that this discontinuation rate did not increase through the ten year model time-horizon, though the model was less sensitive to this value.

6.41 The trial EQ-5D scores were converted to Australian utility values for use in the economic model. The ESC noted that the model assumed that a proportion of dupilumab non-responders respond to SoC and accrue a utility of 0.9. The ESC considered that the utility values in the resubmission lacked face validity as the value for responders was higher than the population norm (0.89 for males and females aged 35-44, from Clemens et al, 2014) and the difference in utility between responders and non-responders was large. The sponsor stated in the pre-PBAC response it did not agree that a difference of 0.01 represents a real difference in health-related QoL. This assumes that responders' QoL would be equal to that of the general population, ie they do not experience any impact on QoL from the underlying condition. The pre-PBAC response also argued that it is widely acknowledged that patients with moderate to severe AD have very poor QoL, as reflected in the utility value of 0.7 used at baseline and for patients not responding to treatment and the large difference in utility values applied to responders and non-responders reflects this significant improvement in QoL experienced by patients successfully treated with dupilumab. The results of the stepped modelled economic evaluation are presented in Table 16.

Table 16: Results of the stepped economic evaluation

		Step 1[a]	Step 2[b]	Step 3[c] (base case)
Dupilumab	Active treatment costs	[redacted]	[redacted]	[redacted]
	Other medical costs	$2269	$4135	$68,029
	Administration costs	$59	$59	$59
	% of cohort with response	74.1%	56.1%	15.5%
	QALYs			6.60
SoC	Active treatment costs	$0	$0	$0

	Other medical costs	$2810	$6437	$91,199
	Administration costs	$0	$0	$0
	% of cohort with response	38.5%	11.4%	0.4%
	QALYs			6.16
Incremental	Total cost	[redacted]	[redacted]	[redacted]
	% of cohort with response	35.6%	44.7%	15.0%
	QALYs			**0.45**
ICER	Incremental cost per responder	[redacted]	[redacted]	[redacted]
	Incremental cost per QALY gained			[redacted]

Source: Table 3.14 (p188) of the resubmission

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care

a: Step 1 = incremental cost per DLQI Δ ≥4 or IGA Δ ≥2 responder at 16 weeks, including estimation of non-drug resource use

b: Step 2 = As for Step 1 + extrapolated to include the first six months of maintenance treatment associated following the application of the requested continuation rule, taking the total period of this step to approximately 42 weeks.

c: Step 3 = As for Step 2, extrapolated to 10 years using the economic model that allows for all-cause mortality, loss of response, and discounting. Utility values are also applied in this step allowing the calculation of cost per QALY gained.

6.42 The base-case ICER estimated by the resubmission is $15,000/QALY to $45.000/QALY gained. This has been reduced from $45,000/QALY - $75,000/QALY gained in the previous submission, however, as noted above, the models are not directly comparable given numerous changes to the approach and inputs.

6.43 The PBAC considered that the ICER of $15,000/QALY to $45.000/QALY gained was highly uncertain and likely to be underestimated based on the some of the key drivers which favoured dupilumab (time horizon, extrapolation of loss of response and costs in the non-responder health states). The PBAC considered that the true ICER is likely to be unacceptably high at the proposed price.

6.44 Sensitivity analyses provided in the resubmission and conducted during the evaluation are shown in Table 17. Sensitivity analyses provided in the submission were mostly univariate sensitivity analyses, with three additional scenario analyses. Sensitivity analyses conducted during the evaluation, using the non-responder health state costs from the previous model approximately doubled the ICER.

Table 17: Sensitivity analyses of resubmission model

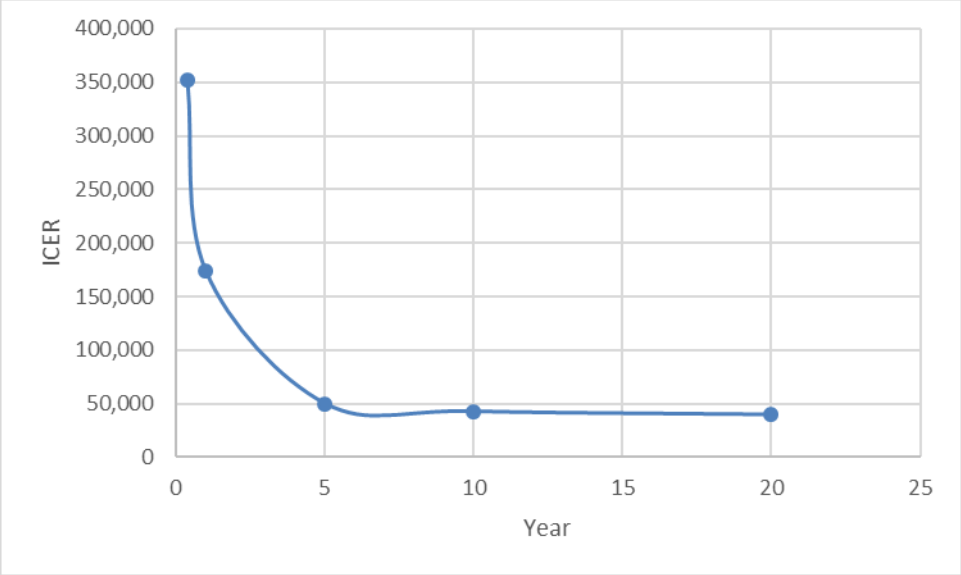
Analysis	Values and source	Incremental Costs	Incremental QALYs	ICER
Base-case	10-year time horizon (assumption); Annual non-responder ($11,067.72) and responder ($1,168.16) health state costs from survey of Australian clinicians presented in resubmission	[redacted]	[redacted]	[redacted]
Time horizon	Time horizon changed to 5 years only, no change to any other parameters	[redacted]	[redacted]	[redacted]
Annual non-responder health state costs	Non-responder annual health state cost changed from $11,067.72 to $3,292.61 (assumed non-responder health state cost in July 2018 submission)	[redacted]	[redacted]	[redacted]
Annual non-responder and responder health state costs	Non-responder annual health state cost changed from $11,067.72 to $3,292.61 and responder annual health state cost changed from $1,168.16 to $1,509.50 (assumed health state costs in July 2018 submission)	[redacted]	[redacted]	[redacted]
Time horizon and annual non-responder health state costs	Time horizon changed to 5 years Non-responder annual health state cost changed from $11,067.72 to $3,292.61	[redacted]	[redacted]	[redacted]
Time horizon and annual non-responder and responder health state costs	Time horizon changed to 5 years Non-responder annual health state cost changed from $11,067.72 to $3,292.61 and responder annual health state cost changed from $1,168.16 to $1,509.50	[redacted]	[redacted]	[redacted]

Source: constructed during the evaluation

The redacted table shows ICERs in the range of $15,000/QALY -$105,000/QALY.

6.45 Varying the time horizon had a substantial impact on the ICER (see Figure 2). Given the uncertainty with the maintenance of response rates and the 10-year time horizon of the model, there was inadequate testing of loss of response rates in univariate analyses and inadequate testing of loss of response rates and model time horizon in multi-variate analyses.

Figure 2: A graph of changes in ICER as model time horizon changes



Source: Evaluator-conducted sensitivity analysis using the resubmission Excel economic model

Drug cost/patient/year

6.46 A cost of [redacted] per year for dupilumab patients on maintenance treatment, based on an effective DPMQ of [redacted] and [redacted] scripts per year. This is decreased from the [redacted] annual cost in the previous submission due to the reduced proposed effective DPMQ.

Estimated PBS usage & financial implications

6.47 This submission was considered by DUSC. The DUSC considered the financial cost presented in the resubmission to be underestimated.

6.48 Compared to the previous submission, the resubmission made the following changes to the financial estimates:

- Financial estimates for a broader population (moderate-to-severe AD inadequately controlled on topical therapies) were presented. As such, the financial estimations increased substantially from the previous submission.
- An epidemiological approach was taken whereby data on the size of the eligible population was derived largely from commissioned local market research data, and uptake and treatment discontinuation rates were derived from international market data. The previous submission utilised the psoriasis PBS bDMARD market as a proxy to calculate the size of the eligible population and uptake rates. The PBAC considered that the reliance on the psoriasis market as a proxy for dupilumab uptake was not well supported and was likely to have underestimated the patient numbers (Dupilumab PSD, July 2018, paragraph 6.52).
- Health budget cost-savings were incorporated into the financial estimates through annual health state costs applied in the economic model. The same method was used in the previous submission, however, because the annual non-responder health state costs increased substantially in the resubmission compared to the previous submission, the impacts on the estimated cost-savings to the health budget substantially increased.

6.49 Table 18 presents the estimated use and financial implications as provided in the resubmission. The resubmission estimated that at year 6, the estimated number of continuing patients was less than 10,000 and the net cost to the PBS would be more than $100 million based on the effective price and more than $100 million based on the published price.

Table 18: Summary of the utilisation and financial impact estimates of listing dupilumab

Parameter	2020	2021	2022	2023	2024	2025
Estimated extent of use						
Patient initiators						
Initiators discontinuing at week 16						
Initiators discontinuing at 10 months						
Initiating patients transition to continuing treatment						
Continuing patients from the previous the year						
Total continuing patients [b]						
Total scripts						
Estimated financial implications of dupilumab						
Net effective cost - PBS/RPBS						
Net published cost - PBS/RPBS						
Net financial implications						
Effective health budget cost						
Published health budget cost						

Source: Sections 4.1-4.6 of the resubmission

Abbreviations: ABS = Australian Bureau of Statistics; AD = atopic dermatitis; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; MBS = Medicare Benefits Schedule; TCS = topical corticosteroids

[a] This number was derived by applying the treatment persistence rate (88%) to the number of requested grandfathered patients.

[b] These values represent the number of patients in the year who receive a full year of treatment (i.e. continuers from the previous year + initiators who respond at week 16 and at month 10)

The redacted table shows that over 6 years, the estimated number of patients was less than 10,000 and the net cost to the PBS would be more than $100 million.

6.50 The estimates are likely to be under-estimated due to low estimated market uptake rates (% in Year 1 to % in Year 6, informed from dupilumab uptake in Germany). The DUSC stated that the uptake rate is likely to be higher due to the high unmet need of moderate-to-severe AD patients in Australia and the relative familiarity of biologics by clinicians. However, workforce constraints of dermatologists and/or immunologists may limit access to specialists. The sponsor stated in the pre-PBAC response that the specific factors raised by DUSC would apply to all countries where dupilumab is currently marketed, and would therefore be expected to have the same impact on uptake in Australia as in those countries.

6.51 The DUSC stated that based on global estimates, the prevalence of AD and moderate-to-severe AD is likely underestimated. The DUSC noted that a prevalence estimate of 6.9% has been used for AD, and suggested that this is as underestimate as the prevalence of AD is increasing and the DUSC considered an AD prevalence of 8% would be consistent with global trends (7.05.DUSC ADV.3). The sponsor stated in the pre-PBAC response that evidence for this assumption has not been provided, however the sponsor noted that a sensitivity analysis was provided in Section 4.7 of the submission which assessed the impact of a prevalence rate for AD of 8% on the financial estimates. Results of this analysis increased the estimated net financial impact of the listing of

dupilumab to the PBS from approximately $20-$30 million to approximately $30 - $60 million in year 1, and from approximately more than $100 million in year 6.

6.52 The estimates were most sensitive to the proportion of patients who have moderate-to-severe disease, and the proportion of patients who are considered uncontrolled on topical therapies, with the assumptions used for both considered to be uncertain. The DUSC considered that the patient pool may potentially be larger than proposed moderate-to-severe AD population, as patients who failed optimised topical therapy, and/or those with reduced quality of life due to overly complex topical regimens may qualify for treatment with dupilumab. The sponsor stated in the pre-PBAC response that, of those patients with moderate-to-severe AD who are currently treated by a specialist, 89% reported having been treated with topical therapies and, of these, 48% report that their disease is still uncontrolled. The sponsor stated that since the requested PBS population is moderate-to-severe patients who have failed to achieve an adequate response to topical therapy, it is appropriate that the financial estimates exclude patients with moderate disease who are treated by a specialist but whose disease can be controlled with more complex and/or high potency topical regimens.

6.53 The DUSC noted that it may have been more appropriate to assume 100% of moderate-to-severe AD patients are likely to see a specialist. The sponsor stated in the pre-PBAC response that their market research showed that 22% of moderate to severe AD patients reported they no longer engaged with a specialist due to the lack of long-term effective treatments available.

6.54 The DUSC stated that the number of continuing patients was uncertain. Use of the composite DLQI/PGA outcome to assess for responders might not be appropriate, as it has not been correlated with a 75% improvement in the EASI-75, a primary outcome of the trials that was previously accepted by the PBAC as a valid clinical marker for AD in the July 2018 submission. The sponsor stated in the pre-PBAC response that response rates (and therefore continuing patients) from the model, used in financial impact estimates, are in CsA naïve patients and would be expected to slightly overestimate the population considered responders. Response rates are [redacted]% for CsA-naïve patients vs. [redacted]% for CsA-experienced patients at week 16.

6.55 The DUSC stated that MBS cost-savings were overestimated due to the high non-responder health state costs applied and the assumption that all SOC patients do not respond.

6.56 The PBAC considered that there is substantial risk for use beyond the proposed restriction, which may apply to several groups of patients: those with less severe AD, those with co-morbid conditions such as asthma, those with reduced QoL due to overly complex topical regimens, and also paediatric patients with a high unmet need. The PBAC also considered that usage may occur beyond expectations within the requested restriction because there is no stopping rule for indefinite dupilumab therapy.

6.57 The PBAC considered that the financial cost was very high and uncertain, noting the total cost over the first 6 years of listing increased from more than $100 million in the July 2018 submission to more than $100 million in the resubmission. The PBAC agreed with DUSC that the financial cost presented in the resubmission was underestimated. The PBAC considered that patient numbers were uncertain with respect to the patient population for initiation, uptake and continuation.

Quality Use of Medicines

6.58 No additional information was provided in the resubmission on quality of use of medicines compared to the previous submission. The resubmission identified the (i) accurate use of the PGA and DLQI by clinicians, (ii) correct administration of dupilumab, (iii) appropriate storage and handling of dupilumab, and (iv) comprehensive pharmacovigilance plan for dupilumab as QUM issues. No consideration of potential use beyond the restriction was discussed.

6.59 The DUSC considered that a potential Quality use of Medicines (QUM) issue is there could be barriers with the accurate use of the composite DLQI/PGA outcome in practice, as both DQLI and PGA are new tests which require additional training of their respective instruments. The sponsor noted in the pre-PBAC response that currently no clinical measurement scales are routinely used in Australian practice for the management of AD; therefore, regardless of the scale(s) used to monitor response to treatment with dupilumab, additional training will be required. The sponsor also noted that both the PGA and DLQI are simpler, easier to complete, and less time consuming that the previously proposed EASI score. It is the sponsor's intention to undertake face-to-face and online training of dermatologists and clinical immunologists in the use of the PGA and DLQI as part of the QUM Program for dupilumab.

Financial Management – Risk Sharing Arrangements

6.60 The resubmission stated the sponsor is willing to work with the Department of Health to develop a suitable risk share arrangement.

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

7 PBAC Outcome

7.1 The PBAC did not recommend dupilumab for the treatment of adult patients with moderate-to-severe AD who are inadequately controlled on topical therapies. The PBAC acknowledged the effectiveness of dupilumab in a therapeutic area of high clinical need, however considered that dupilumab was not cost-effective at the price proposed in the resubmission. The PBAC also considered that the criteria for defining the patient population for initial and continuing treatment did not appropriately consider the extent of disease in terms of the body surface area affected. The PBAC considered that the estimated financial implications were very high and uncertain, and

that a risk sharing arrangement would be necessary to manage the uncertainty in patient estimates, likely treatment duration and the potential for use outside the proposed restriction.

7.2 The PBAC acknowledged there is significant disease burden from AD and a high clinical need for effective treatments for moderate to severe AD. The PBAC noted the consumer comments from professionals and individuals which reflected the substantial impact AD has on patients' QoL, the high clinical need in this patient population and the treatment success reported for many patients currently accessing dupilumab. The PBAC also noted the support for the PBS listing of dupilumab from several professional organisations and patient representative organisations.

7.3 The PBAC noted, consistent with its advice from the July 2018 meeting that restricting eligibility to patients with severe AD unable to be effectively treated with CsA may be inappropriately narrower than the TGA indication and the trial data, that the proposed patient population in the resubmission was expanded to moderate-to-severe AD inadequately treated with topical therapies.

7.4 The PBAC noted that the listing criteria proposed in the resubmission for the assessment of disease severity were based on the PGA (score of ≥3), and for treatment response (and hence continuing treatment) were based on the PGA (≥2 point improvement) and/or DLQI (≥4 point improvement). The PBAC considered that, although these measures would be easier to implement in clinical practice, criteria based on the EASI were important to include in the initial listing to ensure appropriate consideration of the body surface area affected. The PBAC considered that initial assessment of moderate-to-severe AD should be based on both PGA and EASI scores, consistent with the clinical trial inclusion criteria. The PBAC noted that EASI-75 response was the co-primary trial outcome and captures the extent of affected body surface area. The PBAC also noted that DPMQ <5 was considered a measure of treatment success in the Australian Management Consensus for AD and a change in DPMQ of ≥4 was considered to be the minimal clinically important difference for the DPMQ scale. The PBAC considered that both DLQI and EASI-75 were therefore important measures of response and should be included as response criteria. The PBAC considered the requirement for the EASI measure to be used in clinical practice was reasonable as dermatologists are familiar with using the analogous PASI measure to assess disease severity and treatment response for accessing bDMARDs through the PBS for psoriasis.

7.5 The PBAC considered that the resubmission appropriately nominated SoC as the main comparator. The PBAC considered CsA to be an additional relevant comparator given the broader proposed patient population, but acknowledged the toxicity of CsA limited its use in clinical practice, and the paucity of clinical evidence prevented a reliable indirect comparison of the efficacy of dupilumab versus CsA. The PBAC noted the economic model comparing dupilumab and CsA was based on assumptions regarding efficacy and duration of treatment rather than clinical data, and hence was not considered informative. The PBAC further noted the replacement of CsA was not

considered in the financial estimates. Overall, the PBAC considered that the information presented in the resubmission did not enable a meaningful comparison of dupilumab and CsA. The PBAC considered that presentation of data from the dupilumab trials, for patients who have failed systemic therapy, would be informative. The PBAC noted there may be some use of phototherapy in the proposed population however, did not consider it a main comparator noting that access to this treatment is limited.

7.6 The PBAC noted that the evidence for dupimumab compared with SoC consisted of five double-blind, phase 3, randomised controlled trials [CAFÉ (n=325); CHRONOS (n=740); SOLO 1 (n=671); SOLO 2 (n=318) and Study 1021 (n=380) comparing dupilumab 300 mg Q2W to placebo in patients with moderate-to-severe AD (IGA ≥3). The PBAC noted that in the resubmission the clinical claim was appropriately informed by the data from all five trials using the intention-to treat populations.

7.7 The PBAC noted that all trials showed:

- a statistically significantly higher proportion of patients treated with dupilumab achieved an EASI-75 response;
- a statistically significantly higher proportion of patients treated with dupilumab achieved an IGA score reduction (improvement) of ≥2 from baseline; and
- a statistically significant larger reduction (improvement) in DLQI scores from baseline in patients treated with dupilumab.

7.8 The PBAC noted that based on the pooled data for patients naïve to CsA, 74.1% of dupilumab treated patients at week 16 met the response criteria proposed for the listing (change of DLQI ≥4 and/or PGA ≥2) compared with 38.5% of placebo patients. The PBAC noted the additional data provided in the pre-PBAC response which showed that a higher proportion of patients met the DLQI criteria of at least a 4 point change (dupilumab 72.3%, placebo 37.8%) compared with the PGA criteria of at least a 2 point change (dupilumab 50.5%, placebo 16.3%), with only 46.8% of dupilumab treated patients and 14.1% of placebo patients meeting both criteria. Thus, the DLQI criteria is a less stringent assessment of response compared with the PGA criteria. As noted above, the PBAC considered response should include EASI-75, and the PBAC noted that approximately 55% of dupilumab patients met this criteria at week 16 (see paragraph 6.18). The PBAC noted that the pre-PBAC response provided pooled data by response definition for change in utility from baseline to week 16, which indicated that the improvement in QoL was dependent on the definition of response.

7.9 The PBAC considered 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. The PBAC noted that this claim may only be reasonable up to 52 weeks as data are not available to support efficacy beyond this time.

7.10 The PBAC reaffirmed its conclusion from the July 2018 meeting that the claim of a non-inferior safety profile versus SoC was not considered to be supported by the evidence

due to a higher incidence of conjunctivitis events and injection-site reactions in dupilumab treated patients. The PBAC noted that the long-term safety of dupilumab is unknown.

7.11 The PBAC acknowledged the submission's attempt to undertake an indirect comparison of dupilumab and CsA, however the limited evidence for CsA and differences across the trials resulted in the comparison being uninformative. The PBAC acknowledged CsA is associated with considerable toxicity, of note renal toxicity, and the need to limit the duration of exposure. However, the limited safety data presented for CsA, and the unknown long-term safety of dupilumab, prevented an overall conclusion regarding the relative safety of the two agents.

7.12 The PBAC noted that the resubmission presented a cost-utility evaluation based on patients who achieved response defined as meeting either improvement in PGA ≥2 points or improvement in DLQI≥4 points after 16 weeks of treatment. The PBAC noted the structure of the economic model was revised substantially from that presented in the July 2018 submission, and although the ESC considered some revisions to the model structure were reasonable, a number of the model inputs were not considered appropriate. Given the substantial revisions, it was not possible to directly compare the results of the previous and current models. The PBAC noted that compared with the July 2018 submission, a higher ICER would have been expected in the resubmission because the population was expanded to include patients with moderate disease and the criteria for response were less stringent. The impact of these changes on the ICER would not be offset by the small (3.7%) reduction in the proposed price for dupilumab. However, the base case ICER in the resubmission was actually substantially lower ($15,000/QALY - $45,000/QALY) than that in the July 2018 submission ($45,000/QALY - $75,000/QALY) which suggested that overall the model presented in the resubmission included less conservative assumptions regarding the benefits and/or the cost-offsets associated with dupilumab treatment.

7.13 The PBAC noted that the key drivers for the model included in the resubmission were non-responder annual health state costs, estimation of maintenance of response, and the time horizon.

7.14 Regarding the non-responder health state costs, the PBAC noted that the annual cost in the resubmission was three fold higher than in the previous submission, despite the less severe patient population. The annual cost ($11,068) included an average of 2.5 hospitalisations (cost of $8,010) and 3 emergency room visits (cost of $2,034). The PBAC agreed with the ESC, that the frequency of hospitalisations and emergency visits did not appear plausible for patients with moderate to severe AD. The PBAC noted the ICER approximately doubled when the non-responder health state cost from the July 2018 submission was applied in the resubmission's model.

7.15 Regarding the maintenance of response, the PBAC agreed with the ESC, that differential rates applied to the treatment arms in the model was not reasonable, and that extrapolation of these rates over the 10-year time horizon further increased

uncertainty in the modelled outcomes.

7.16 The PBAC noted its concern from the July 2018 meeting that a 5-year model time horizon, extrapolated from 16 weeks of trial data, increased uncertainty in the results and was a key driver of the model. The PBAC noted that the model time horizon in the resubmission was increased 10 years, extrapolated from 44 weeks of trial data. Acknowledging that the ICER was reasonably stable with time horizons of 5 years or longer (see Figure 2), the PBAC considered the 10-year time horizon used in the resubmission was not adequately justified and that the model time horizon should be no more than 5 years given the available clinical evidence.

7.17 Overall, the PBAC considered that the resubmission base-case ICER of $15,000/QALY - $45,000/QALY gained was uncertain and appeared to be significantly underestimated due to assumptions in the model described above. The PBAC considered that the true ICER was likely to be unacceptably high at the proposed price. The PBAC noted that a lower ICER, providing greater certainty in the cost-effectiveness of dupilumab, would be required as the proposed indication was broader, encompassing moderate-to-severe AD patients and therefore with a much higher potential budget impact.

7.18 The PBAC considered that the financial cost was very high at the proposed price and remained uncertain. The PBAC noted the estimated total cost over the first 6 years of listing increased from more than $100 million in the July 2018 submission to more than $100 million in the resubmission. The PBAC agreed with the DUSC that the financial cost presented in the resubmission was likely to be underestimated. The PBAC considered that patient numbers were uncertain with respect to patient population for initiation, uptake and continuation. The PBAC noted that the financial estimates would need to be revised to reflect the criteria considered appropriate for assessment of severity and response.

7.19 The PBAC considered that there is substantial risk for use beyond the proposed restriction, which may apply to several groups of patients: those with less severe AD, those with co-morbid conditions such as asthma, those with reduced QoL due to overly complex topical regimens, and also paediatric patients with a high unmet need. The PBAC considered an RSA would be necessary to manage the uncertainty in patient estimates, likely treatment duration and the potential for use outside the proposed restriction.

7.20 The PBAC considered that any future submission would need to be a major submission and should consider the following:

- The inclusion of the EASI scale in the restriction to assess initial disease severity.
- The sponsor should propose revised response criteria that include EASI-75 and either DLQI <5, or DLQI improvement of ≥4 points, and may also include PGA, given its use in the trials and as suggested in the AD management consensus

statement.

- An economic model that incorporates the revised patient population, and addresses the issues noted in paragraphs 7.14 to 7.16.
- Revised financial forecasts that incorporate the revised patient population and address the uncertainties outlined in paragraph 7.18.

7.21 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Sanofi is disappointed with the PBAC's decision not to recommend dupilumab but welcomes the Committee's recognition of the need for a safe and effective treatment for patients with moderate-to-severe atopic dermatitis unresponsive to current therapies, and its acknowledgement of dupilumab's effectiveness. Sanofi remains committed to working with the PBAC to enable access for Australian patients to this effective and innovative therapy.