

## 5.04 DUPILUMAB

### Injection 300 mg in 2 mL single dose pre-filled syringe,

### Dupixent<sup>®</sup>,

### Sanofi-Aventis Australia Pty Ltd

#### 1 Purpose of application

- 1.1 Authority Required listing for dupilumab for treatment of atopic dermatitis. The PBAC has not previously considered a submission for dupilumab.
- 1.2 The requested basis for the listing was a cost-utility analysis compared with placebo (for standard care). Table 1 summarises the key components of the clinical issue addressed by the submission.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Adults with severe AD who have had an inadequate response or intolerance to CsA, or for whom CsA is contra-indicated. Severe AD is defined as an IGA score of 4.
Intervention	Dupilumab 600mg at baseline followed by dupilumab 300mg every other week (Q2W). Dupilumab is used concomitantly with topical corticosteroid (TCS), topical calcineurin inhibitor (TCI) and emollient use.
Comparator	Placebo (representing standard of care). This is better described as concomitant TCS, TCI and emollient use alone (see 'Comparator' below).
Outcomes	<b>Primary:</b> proportion of patients with a 75% improvement in Eczema Area and Severity Index (EASI) score (EASI-75) at Week 16. This was the primary outcome of the pivotal clinical trial. <b>Secondary:</b> change in physician and patient reported AD severity scores, including EASI, SCORAD, DLQI, POEM, HADS, GISS, IGA, peak daily pruritus NRS, and percent BSA involvement.
Clinical claim	Superior efficacy, demonstrated by an EASI-75 response and improvement in other AD severity measures, and non-inferior safety, compared to placebo.

Source: Table 1.1.1 (pg. 2) of the main submission

Abbreviations: CsA = Cyclosporin A; AD = atopic dermatitis; IGA = Investigator's Global Assessment; Q2W = fortnightly; EASI = Eczema Area and Severity Index; BSA = body surface area; DLQI = dermatology life quality index; GISS = global individual signs score; HADS = hospital anxiety and depression scale; NRS = numerical rating scale; POEM = patient oriented eczema measure; SCORAD = scoring atopic dermatitis; TCS = topical corticosteroid; TCI = topical calcineurin inhibitor

#### 2 Requested listing

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

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DUPILUMAB 300 mg in 2 mL pre-filled syringe	4	0	\$ [REDACTED]	Dupixent <sup>®</sup> Sanofi-Aventis

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<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Chronic
<b>Severity:</b>	Severe
<b>Condition:</b>	<del>Severe</del> atopic dermatitis
<b>PBS Indication:</b>	<i>Chronic severe atopic dermatitis</i>
<b>Treatment phase:</b>	<del>Initial 1<sup>a</sup></del> -Initial treatment – Initial 1 ( <i>new patient or patient recommencing treatment after a break of 5 years or more</i> )
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by a dermatologist, OR Must be treated by a clinical immunologist.
<b>Clinical criteria:</b>	<p>Patient must have severe<sup>b</sup> chronic atopic dermatitis where lesions have been present for at least 6 months from the time of initial diagnosis; AND</p> <p>Patient must not have received any prior PBS-subsidised treatment with a <del>biological agent</del> <i>dupilumab</i> for this condition; OR</p> <p>Patient must not have received PBS-subsidised treatment with a <del>biological agent</del> <i>dupilumab</i> for at least 5 years, if they have previously received PBS-subsidised treatment with a <del>biological agent</del> <i>dupilumab</i> for this condition and wish to commence a new Treatment Cycle; AND</p> <p>Patient must have failed to achieve an adequate response to oral cyclosporin at a dose of at least 2 mg per kg per day for at least 6 weeks; OR</p> <p>Patient must have had prior intolerance to cyclosporin of a severity to necessitate permanent treatment withdrawal; OR</p> <p>Patient <del>was</del> <i>must not be</i> a candidate for cyclosporin due to: -Medical contraindication, or -Hypersensitivity to cyclosporin active substance or excipients, or -Use of concomitant medications which prohibited cyclosporine; AND</p> <p>Patient must have signed a patient and prescriber acknowledgment <i>indicating they understand and acknowledge</i> that PBS-subsidised treatment will cease if they do not meet the predetermined response <del>criteria</del> <i>criteria</i> for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment (<i>whole body</i>); AND</p> <p>The treatment must be as systemic monotherapy (other than oral corticosteroids); AND</p> <p>Patient must not receive more than 16 weeks of treatment under this restriction.</p>
<b>Population criteria:</b>	<del>Adults aged ≥ 18 years with severe atopic dermatitis</del> <i>Patient must be aged</i>

	18 years or older
<b>Definitions</b>	<p><sup>a</sup> <del>New patient (no prior biological agent) or patient recommencing treatment after a break of 5 years or more</del></p> <p><sup>b</sup> <del>Severe atopic dermatitis is defined as an Investigator's Global Assessment (IGA) score of 4</del></p>
<b>Prescriber Instructions</b>	<p>Where treatment with cyclosporin is contraindicated according to the relevant TGA-approved Product Information, details must be provided at the time of application.</p> <p>Where a patient has a history of intolerance to treatment with cyclosporin, which was of a severity to necessitate permanent treatment withdrawal, details of the degree of this toxicity must be provided at the time of application.</p> <p>The following criterion indicates failure to achieve an adequate response to prior treatment and must be demonstrated in the patient at the time of the application: An inadequate response to cyclosporin is defined as a flare of atopic dermatitis after dosing of at least 2 mg/kg/day for at least 6 weeks. A flare is defined as an increase in signs and/or symptoms of atopic dermatitis.</p> <p>The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Severe Chronic Atopic Dermatitis PBS Authority Application - Supporting Information form which includes the following: (i) the completed current Investigator's Global Assessment (IGA) calculation sheets including the date of assessment of the patient's condition; and (ii) details of previous cyclosporin therapy, including dosage, date of commencement and duration of therapy; and (iii) the signed patient and prescriber acknowledgements.</p>
<b>Administrative Advice</b>	<p>Details of the toxicities, including severity, which will be accepted as a reason for exempting a patient from the requirement for 6 weeks treatment with cyclosporin can be found on the Department of Human Services website (<a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a>).</p> <p><i>Severe atopic dermatitis is defined as an Investigator's Global Assessment (IGA) score of 4 on a five point IGA scale where scores range from 0 to 4.</i></p> <p>An Eczema Area and Severity Index (EASI) assessment 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. This assessment, 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 date of 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.</p> <p>In circumstances where it is not possible to submit a response assessment within these timeframes, please call the Department of Human Services on</p>

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	<p>1800 700 270 to discuss.</p> <p><i>It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior to the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.</i></p> <p><i>Any queries concerning the 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).</i></p> <p><i>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></i></p> <p><i>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</i></p> <p><i>Special Pricing Arrangements apply.</i></p>
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<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Chronic
<b>Severity:</b>	Severe
<b>Condition:</b>	<del>Severe</del> atopic dermatitis
<b>PBS Indication:</b>	Chronic <del>Severe</del> atopic dermatitis
<b>Treatment phase:</b>	<del>Initial 2<sup>a</sup></del> -Initial 2 (change or recommencement of treatment after a break of less than 5 years)
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by a dermatologist, OR Must be treated by a clinical immunologist.
<b>Clinical criteria:</b>	Patient must have a documented history of severe <sup>b</sup> chronic atopic dermatitis;

	<p>AND                  Patient must have received prior PBS-subsidised treatment with a biological agent <i>dupilumab</i> for this condition in this Treatment Cycle;                  AND                  Patient must not have failed, or ceased to respond to, PBS-subsidised treatment with this drug during the current Treatment Cycle;                  AND                  The treatment must be as systemic monotherapy (other than oral corticosteroids);                  AND                  Patient must not receive more than 16 weeks of treatment under this restriction.</p>
<b>Population criteria:</b>	<p><del>Adults aged ≥ 18 years with severe atopic dermatitis</del> <i>Patient must be aged 18 years or older</i></p>
<b>Definitions</b>	<p><sup>a</sup> <del>Change or recommencement of treatment after a break of less than 5 years</del>  <sup>b</sup> <del>Severe atopic dermatitis is defined as an Investigator’s Global Assessment (IGA) score of 4</del></p>
<b>Prescriber Instructions</b>	<p>The authority application must be made in writing and must include:                  (a) a completed authority prescription form; and                  (b) a completed Severe Chronic Atopic Dermatitis PBS Authority Application - Supporting Information form which includes the following:                  (i) the completed current Investigator’s Global Assessment (IGA) calculation sheets including the date of assessment of the patient’s condition; and                  (ii) details of prior biological treatment, including dosage, date and duration of treatment.</p> <p>Applications for patients who have demonstrated a response to PBS-subsidised treatment with this drug within this Treatment Cycle and who wish to recommence treatment with this drug within the same Cycle following a break in therapy, will only be approved where evidence of the patient’s response to their most recent course of PBS-subsidised treatment with this drug has been submitted within 1 month of cessation of treatment.</p> <p>An adequate response to treatment is defined as an Eczema Area and Severity Index (EASI) score which is reduced by 75% or more, or is sustained at this level, when compared with the prebiological treatment baseline value for this Treatment Cycle.</p>
<b>Administrative Advice</b>	<p><i>Severe atopic dermatitis is defined as an Investigator’s Global Assessment (IGA) score of 4 on a five point IGA scale where scores range from 0 to 4.</i></p> <p>An Eczema Area and Severity Index (EASI) assessment 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. This assessment, 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 date of 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.</p>

	<p><i>It is recommended that an application is submitted to the Department of Human Services no later than 2 weeks prior to the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.</i></p> <p>Patients who fail to demonstrate a response to treatment with a biological agent are deemed to have completed this Treatment Cycle and must cease PBS-subsidised therapy. These patients may recommence a new <del>Biological</del> Treatment Cycle <i>with dupilumab</i> after a minimum of 5 years has elapsed between the date the last prescription for a PBS-subsidised <del>biological agent</del> <i>dupilumab</i> was approved in this Cycle and the date of the first application under the new Cycle.</p> <p>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.</p> <p><i>Any queries concerning the 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).</i></p> <p><i>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></i></p> <p><i>Applications for authority to prescribe should be forwarded to:</i>  Department of Human Services  Complex Drugs  Reply Paid 9826  HOBART TAS 7001</p> <p><i>Special Pricing Arrangements apply.</i></p>
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DUPILUMAB 300 mg in 2 mL pre-filled syringe	2	2	\$ [REDACTED]	Dupixent® Sanofi-Aventis

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Chronic
<b>Severity:</b>	Severe
<b>Condition:</b>	Severe atopic dermatitis
<b>PBS Indication:</b>	Chronic Severe atopic dermatitis
<b>Treatment phase:</b>	Initial 1 <sup>a</sup> or Initial 2 <sup>b</sup> -Initial 1 (new patient or patient recommencing)

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	<i>treatment after a break of 5 years or more) or Initial 2 (change or recommencement of treatment after a break of less than 5 years) – balance of supply</i>
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	<p>Must be treated by a dermatologist, OR          Must be treated by a clinical immunologist.</p>
<b>Clinical criteria:</b>	<p>Patient must have received insufficient therapy with this drug under the Initial 1 restriction to complete 16 weeks treatment, OR          Patient must have received insufficient therapy with this drug under the Initial 2 restriction to complete 16 weeks treatment;          AND          The treatment must be as systemic monotherapy (other than oral corticosteroids);          AND  <del>Patient must not receive more than 16 weeks of treatment under this restriction.</del>  <i>The treatment must provide no more than the balance of up to 16 weeks of therapy (new patients or change/re-commencement patients; Initial 1 or Initial 2).</i></p>
<b>Population criteria:</b>	<p><del>Adults aged ≥ 18 years with severe atopic dermatitis</del> <i>Patient must be aged 18 years or older</i></p>
<b>Definitions</b>	<p><del><sup>a</sup> New patient (no prior biological agent) or patient recommencing treatment after a break of 5 years or more</del>  <del><sup>b</sup> Change or recommencement of treatment after a break of less than 5 years</del></p>
<b>Administrative Advice</b>	<p>Authority approval for sufficient therapy to complete a maximum of 16 weeks of treatment may 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).</p> <p><i>Any queries concerning the 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).</i></p> <p><i>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></i></p> <p><i>Applications for authority to prescribe should be forwarded to:</i>  <i>Department of Human Services</i>  <i>Complex Drugs</i>  <i>Reply Paid 9826</i>  <i>HOBART TAS 7001</i></p> <p><i>Special Pricing Arrangements apply.</i></p>

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<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Chronic
<b>Severity:</b>	Severe
<b>Condition:</b>	Severe atopic dermatitis
<b>PBS Indication:</b>	Chronic Severe atopic dermatitis
<b>Treatment phase:</b>	Initial 3 – <i>grandfather patients</i>
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by a dermatologist, OR Must be treated by a clinical immunologist.
<b>Clinical criteria:</b>	Patient must have a documented history of severe <sup>a</sup> chronic atopic dermatitis; AND Patient must have failed to achieve an adequate response to oral cyclosporin at a dose of at least 2 mg per kg per day for at least 6 weeks, OR Patient must have had prior intolerance to cyclosporin of a severity to necessitate permanent treatment withdrawal, OR Patient <del>was</del> <i>must not be</i> a candidate for cyclosporin due to: -Medical contraindication, or -Hypersensitivity to cyclosporin active substance or excipients, or -Use of concomitant medications which prohibited cyclosporine; AND Patient must have been receiving treatment with this drug for this condition prior to <PBS listing date>; AND Patient must have demonstrated an adequate response <sup>b</sup> to their most recent course of treatment with this drug; AND Patient must have signed a patient and prescriber acknowledgment <i>indicating they understand and acknowledge</i> that PBS-subsidised treatment will cease if they do not meet the predetermined response criteria <sup>a</sup> for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment ( <i>whole body</i> ); AND The treatment must be as systemic monotherapy (other than oral

	<p>corticosteroids); AND Patient must not receive more than 24 weeks of treatment under this restriction.</p>
<b>Population criteria:</b>	<p><del>Adults aged ≥ 18 years with severe atopic dermatitis</del> <i>Patient must be aged 18 years or older</i></p>
<b>Definitions</b>	<p><del><sup>a</sup> Severe atopic dermatitis is defined as an Investigator’s Global Assessment (IGA) score of 4</del> <del><sup>b</sup> An adequate response to treatment is defined as an Eczema Area and Severity Index (EASI) score which is reduced by 75% or more, or is sustained at this level, when compared with the prebiological treatment baseline value for this Treatment Cycle.</del></p>
<b>Prescriber Instructions</b>	<p>Where treatment with cyclosporin is contraindicated according to the relevant TGA-approved Product Information, details must be provided at the time of application.</p> <p>Where a patient has a history of intolerance to treatment with cyclosporin, which was of a severity to necessitate permanent treatment withdrawal, details of the degree of this toxicity must be provided at the time of application.</p> <p>The following criterion indicates failure to achieve an adequate response to prior treatment and must be demonstrated in the patient at the time of the application: An inadequate response to cyclosporin is defined as a flare of atopic dermatitis after dosing of at least 2 mg/kg/day for at least 6 weeks. A flare is defined as an increase in signs and/or symptoms of atopic dermatitis.</p> <p><i>An adequate response to treatment is defined as an Eczema Area and Severity Index (EASI) score which is reduced by 75% or more, or is sustained at this level, when compared with the prebiological treatment baseline value for this Treatment Cycle.</i></p> <p>The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Severe Chronic Atopic Dermatitis PBS Authority Application - Supporting Information form which includes the following: (i) the Investigator’s Global Assessment (IGA) calculation sheets completed prior to commencing treatment with this drug; and (ii) details of previous cyclosporin therapy, including dosage, date of commencement and duration of therapy; and (iii) the signed patient and prescriber acknowledgements.</p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only.</p>
<b>Administrative Advice</b>	<p>Details of the toxicities, including severity, which will be accepted as a reason for exempting a patient from the requirement for 6 weeks treatment with cyclosporin can be found on the Department of Human Services website (<a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a>).</p> <p><i>Severe atopic dermatitis is defined as an Investigator’s Global Assessment (IGA) score of 4 on a five point IGA scale where scores range from 0 to 4.</i></p>

	<p>An Eczema Area and Severity Index (EASI) assessment of the patient’s response to this initial course of treatment must be made within 4 weeks prior to completion of this course of treatment. This assessment, 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 date of 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.</p> <p>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.</p> <p>It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior to the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.</p> <p><i>Any queries concerning the 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).</i></p> <p><i>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></i></p> <p><i>Applications for authority to prescribe should be forwarded to:</i>  <i>Department of Human Services</i>  <i>Complex Drugs</i>  <i>Reply Paid 9826</i>  <i>HOBART TAS 7001</i></p> <p><i>Special Pricing Arrangements apply.</i></p>
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<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Chronic
<b>Severity:</b>	Severe
<b>Condition:</b>	Severe atopic dermatitis

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<b>PBS Indication:</b>	<i>Chronic Severe atopic dermatitis</i>
<b>Treatment phase:</b>	Continuing <i>treatment</i>
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be treated by a dermatologist, OR Must be treated by a clinical immunologist.
<b>Clinical criteria:</b>	<p>Patient must have a documented history of severe<sup>a</sup> chronic atopic dermatitis;            AND            Patient must have received this drug as their most recent course of PBS-subsidised treatment <del>with a biological agent</del> for this condition in the current Treatment Cycle;            AND            Patient must have demonstrated an adequate response<sup>b</sup> to their most recent course of 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.</p>
<b>Population criteria:</b>	<del>Adults aged ≥ 18 years with severe atopic dermatitis</del> <i>Patient must be aged 18 years or older</i>
<b>Definitions</b>	<p><del><sup>a</sup> Severe atopic dermatitis is defined as an Investigator's Global Assessment (IGA) score of 4</del>  <del><sup>b</sup> An adequate response to treatment is defined as an Eczema Area and Severity Index (EASI) score which is reduced by 75% or more, or is sustained at this level, when compared with the prebiological treatment baseline value for this Treatment Cycle.</del></p>
<b>Prescriber Instructions</b>	<p>The authority application must be made in writing and must include:            (a) a completed authority prescription form; and            (b) a completed Severe Chronic Atopic Dermatitis PBS Authority Application - Supporting Information form which includes the following:            (i) the completed Eczema Area and Severity Index (EASI) calculation sheets including the date of assessment of the patient's condition.            The most recent EASI assessment must be no more than 1 month old at the time of application.            Approval will be based on the EASI assessment of response to the most recent course of treatment with this drug.</p> <p><i>An adequate response to treatment is defined as an Eczema Area and Severity Index (EASI) score which is reduced by 75% or more, or is sustained at this level, when compared with the prebiological treatment baseline value for this Treatment Cycle.</i></p> <p>An EASI assessment of the patient's response must be conducted within 4 weeks prior to completion of this course of treatment. This assessment,</p>

	<p>which will be used to determine eligibility for further continuing treatment, must be submitted to the Department of Human Services no later than 1 month 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.</p> <p>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.</p>
<p><b>Administrative Advice</b></p>	<p><i>Severe atopic dermatitis is defined as an Investigator's Global Assessment (IGA) score of 4 on a five point IGA scale where scores range from 0 to 4.</i></p> <p>It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior to the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.</p> <p>Patients who fail to demonstrate a response to treatment with a biological agent 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 has elapsed between the date the last prescription for a PBS-subsidised biological agent was approved in this Cycle and the date of the first application under the new Cycle.</p> <p><i>Any queries concerning the 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).</i></p> <p><i>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></i></p> <p><i>Applications for authority to prescribe should be forwarded to:</i>  <i>Department of Human Services</i>  <i>Complex Drugs</i>  <i>Reply Paid 9826</i>  <i>HOBART TAS 7001</i></p> <p><i>Special Pricing Arrangement apply.</i></p>

- 2.2 The submission proposed a special pricing arrangement (SPA), with a proposed published dispensed price per maximum quantity (DPMQ) of \$ [REDACTED] and an effective DPMQ of \$ [REDACTED].
- 2.3 The PBAC noted that the initial 2 restriction may not be necessary as there are currently no other biologicals listed on the PBS for this indication and the PBAC considered that multiple re-trials of dupilumab after inadequate response would not be appropriate.

- 2.4 The PBAC noted that there are several IGA scales, including a 4 point scale referenced in the sponsor's Pre-Sub-Committee Response (PSCR)<sup>1</sup>, however considered that the IGA scale should be specified in the restriction as a 5 point scale.
- 2.5 The PBAC questioned whether prescribing by clinical immunologists would be appropriate as dermatologists would be better placed to rate skin disease severity at initiation and assess EASI response.
- 2.6 The PBAC noted that a grandfather restriction was requested for 440 patients, including 101 in an early access program, 39 in the open label extension study (who do not all meet the requested restriction in terms of baseline IGA score and prior CsA use) and 300 patients expected to be enrolled in a patient familiarisation program. The PBAC considered that this was a large number of patients and may not be reasonable to include patients who had not yet commenced on the program.

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

### **3 Background**

#### ***Registration status***

- 3.1 Dupilumab was approved for registration by the TGA on the 24th 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 300mg doses followed by 300mg given every other week.
- 3.2 As dupilumab is a newly registered prescription medication, it is subject to additional monitoring by the TGA for the 5 years following registration.

### **4 Population and disease**

- 4.1 AD is a chronic inflammatory disease characterised by dry skin, itching and extensive skin lesions. Symptoms may be continuous or of a relapsing-remitting nature. The clinical presentation of symptoms varies based on phase (chronic or acute) and severity of AD. Patients with severe AD have more frequent symptom flaring, and their disease is characterised by skin with pronounced dryness, red lesions, papulation, crusting and skin thickening. Patients can suffer from itchy painful skin, bleeding, sleep deprivation, an increased risk of skin infections, depression, anxiety and/or suicidal intentions.
- 4.2 Dupilumab 300mg fortnightly (Q2W) is proposed as last-line therapy in patients who have not adequately responded to topical corticosteroids (TCS) ± topical calcineurin inhibitors (TCI), and who have not adequately responded to systemic therapy (cyclosporin A), or are intolerant or contra-indicated to systemic therapy. The ESC noted that the proposed place in therapy is use after CsA, which may not be clinically

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<sup>1</sup> Chopra et al 2017, British Journal of Dermatology 177, pp1316-1321.

necessary as it is narrower than the TGA indication and much of the trial data. Therefore it is unclear if dupilumab should be considered to be a last line therapy.

- 4.3 Dupilumab would be used concomitantly with TCS ± TCI therapy as TCS/TCI are used to help manage flaring.
- 4.4 The proposed patient population is narrower than the TGA-approved indication, the clinical guidelines, and the enrolment criteria for the trials supporting the submission. The main trials for dupilumab did not require prior CsA exposure and therefore the proposed place in therapy does not align with the available clinical trials. The PSCR and pre-PBAC response argued that these patients had the greatest unmet clinical need, and that the restriction was aligned with that of biologics for chronic plaque psoriasis.

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

## **5 Comparator**

- 5.1 The submission appropriately nominated placebo (representing standard of care (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 therapy for flaring. As noted above, the ESC considered it may not be appropriate to restrict use of dupilumab to after CsA use. The PBAC noted that positioning dupilumab earlier in the clinical algorithm would have implications for the comparator.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (54), health care professionals (28) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with dupilumab 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. The comments noted the safety profile of dupilumab appears better than other currently available AD treatments such as CsA. Several comments noted that there is a population of patients who are currently receiving chronic combination immunosuppressive therapy including drugs other than CsA, such as azathioprine, methotrexate and mycophenolate mofetil, and suggested that the indication for use should be broadened to include patients who

have had an inadequate response, intolerance, or contraindication to any systemic immunosuppression. The comments also suggested that treatment roll-out should consider the population of patients who are currently receiving chronic combination immunosuppressive therapy to control disease activity who should have the opportunity to access dupilumab without the requirement to first experience exacerbation of AD. Some of the consumer comments also referred to use of dupilumab in children.

- 6.3 The PBAC received comments received from Allergy & Anaphylaxis Australia and the Eczema Association of Australasia describing the burden of disease for severe AD on patients physically, emotionally and financially. Comments from these organisations outlined the need for safe and effective long term treatments for patients with severe AD and noted that the use of dupilumab may allow patients to move from a restricted lifestyle that limits many activities, including employment, sport, outdoor activities, and therefore improve patient quality of life.
- 6.4 The PBAC noted the advice received from the Australasian Society of Clinical Immunology and Allergy (ASCIA) of in-principle support for the proposed listing for dupilumab. The PBAC noted that the ASCIA supported the listing of dupilumab in patients with severe AD and stated its intention to write to the ASCIA to ask whether it would also be in support of a listing in moderate to severe AD. The ASCIA noted that clinical immunology/allergy specialists are suitably qualified and well-placed to prescribe this treatment in appropriate patients and monitor treatment outcomes.
- 6.5 The PBAC noted the comments received from the International Centre for Community-Driven Research describing a recent report on the experience and expectations of 100 patients with AD. In structured interviews the most common themes were impact in relation to self-esteem and confidence, leading to social isolation, relationships with family and friends, not being able to work, not being able to do everyday activities and the impact of itchiness on quality of sleep. Participants felt that they were not provided with adequate treatment options and noted the hope that access to safe, effective, affordable treatments would become available.

### **Clinical trials**

- 6.6 The submission was based on:
  - one head-to-head randomised trial (CAFÉ, n=325) comparing dupilumab 300mg once weekly (QW) (n=110) with dupilumab 300mg fortnightly (Q2W) (n=107) and placebo (n=108). All patients enrolled in CAFÉ had moderate to severe AD (defined as an Investigator's Global Assessment (IGA) of 3 or 4, respectively at baseline) and were intolerant/contraindicated/had an inadequate response to cyclosporin A (CsA). It should be noted that listing for dupilumab 300mg Q2W only was requested, which was appropriate given this was the only TGA-approved dose; and

- four supplementary randomised, placebo-controlled trials: CHRONOS (n=740), SOLO 1 (N=671), SOLO 2 (N=708) and a phase IIb trial (referred to as Phase IIb herein) (N=318). Patients enrolled in these trials had moderate to severe AD (IGA 3-4) and were not required to have prior exposure to CsA (thus were considered supplementary as the trial population were not entirely representative of the proposed PBS population). The ESC noted that the majority of the clinical evidence for dupilumab didn't require failure with or contraindication to CsA.
- 6.7 All trials compared dupilumab 300mg Q2W and dupilumab 300mg weekly (QW) treatment arms to placebo.
- 6.8 The submission made the claim of superior clinical effectiveness compared with SoC based on the outcome of a 75% improvement in Eczema Area Severity Index (EASI) score (EASI-75) from baseline.
- 6.9 The patients enrolled in the trials were broader than those for whom listing is sought, thus the submission relies on a sub-group analysis of patients defined as having severe AD (defined as IGA=4 at baseline) and prior intolerance/contraindication/inadequate response to CsA.
- 6.10 Details of the trials presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Pivotal direct randomised trial</b>		
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.  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. <i>Annals of Allergy, Asthma and Immunology</i> .	08/07/2015  <i>Annals of Allergy, Asthma and Immunology</i> . 2017; 119(5S1):S94-S95.
<b>Supplementary direct randomised trials</b>		
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.  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.	02/10/2015  <i>Lancet</i> . 2017; 389:2287-303.

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	<p>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).</p> <p>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).</p>	<p>British Journal of Dermatology. 2017; 177(S1):10.</p> <p>Australasian Journal of Dermatology. 2017; 58:55.</p>
<p>SOLO 1 R668-AD-1334 NCT02277743</p>	<p>A phase 3 confirmatory study investigating the efficacy and safety of dupilumab monotherapy administered to adult patients with moderate to severe atopic dermatitis.</p> <p>Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.</p>	<p>05/02/2015</p> <p>N Engl J Med. 2016 Dec 15;375(24):2335-2348.</p>
<p>SOLO 2 R668-AD-1416 NCT02277769</p>	<p>A phase 3 confirmatory study investigating the efficacy and safety of dupilumab monotherapy administered to adult patients with moderate to severe atopic dermatitis.</p> <p>Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.</p>	<p>05/02/2015</p> <p>N Engl J Med. 2016 Dec 15;375(24):2335-2348.</p>
<p>Phase IIb R668-AD-1021 NCT01859988</p>	<p>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.</p> <p>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.</p> <p>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).</p> <p>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.</p>	<p>03/12/2013</p> <p>Lancet. 2016; 387:40-52</p> <p>J Am Acad Dermatol. 2016; 75(3): 506-15.</p> <p>J Am Acad Dermatol. 2016; 74(3): 491-98.</p>

Source: Tables 2.2.1 (pp44-45) and 2.2.3 (p50) of the submission

6.11 The key features of the direct randomised trials are summarised in Table 3.

**Table 3: Key features of the included evidence, dupilumab vs. placebo**

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
CAFÉ	325	DB, R, MC; 28 weeks	Low	Moderate to severe AD; previous intolerance, lack of efficacy or contra-indication to CsA	EASI-75 <sup>a</sup> IGA 0 or 1 <sup>b</sup>	EASI-75 at Week 16 (IGA=4 subgroup)
CHRONOS	740	DB, R, MC; 64 weeks	Low	Moderate to severe AD		EASI-75 at Week 52 (for achievers of EASI-75 at Week 16)
SOLO 2	671	DB, R, MC; 28 weeks	Low	Moderate to severe AD		Not used
SOLO 2	708	DB, R, MC; 28 weeks	Low	Moderate to severe AD		Not used
Phase IIb	318	DB, R, MC; 28 weeks	Low	Moderate to severe AD		Not used

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

Source: compiled during the evaluation

<sup>a</sup> 75% improvement/reduction in the EASI score from baseline

<sup>b</sup> achievement of a score of 0 or 1 from a baseline of 3 or 4 on the 5 point IGA scale.<sup>6,7</sup> The submission (p73) stated that the EASI is a validated measure used to assess the severity and extent of AD which was developed based on the Psoriasis Area Severity Index (PASI). While the PBAC has previously accepted PASI-75 as a clinically meaningful outcome (e.g. secukinumab for chronic plaque psoriasis, March 2015 meeting), the EASI score has not previously been considered by the PBAC.

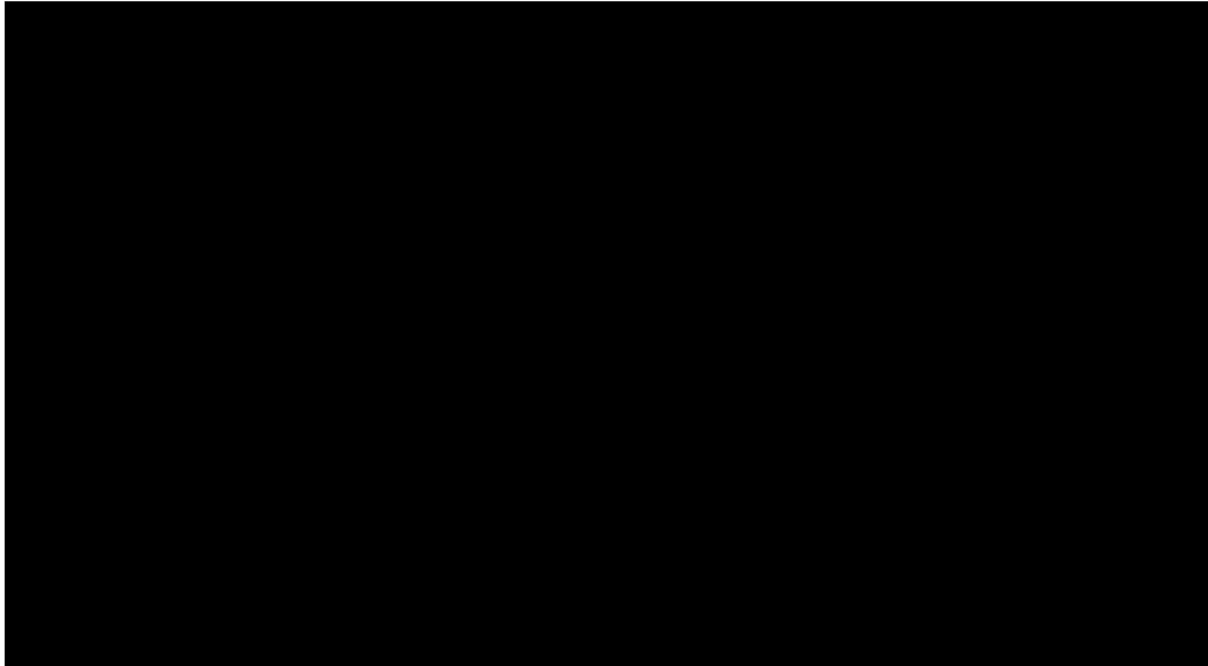
6.12 A 75% improvement in Eczema Area Severity Index (EASI) score (EASI-75) has not been previously considered by the PBAC. Data sourced during the evaluation from Kimball et al 2017<sup>2</sup> indicated that, overall, it appears that achieving EASI-75 is associated with significant improvement in patient quality of life and may be a clinically meaningful outcome in AD. The PBAC agreed with the evaluation that EASI-75 appears to be a valid clinical marker correlating with outcomes such as QoL. The PBAC also noted that SCORAD may be a relevant outcome.

### **Comparative effectiveness**

6.13 The proportion of patients achieving an EASI-75 response in the whole trial populations in the individual trials and meta-analysis is presented in Figure 1.

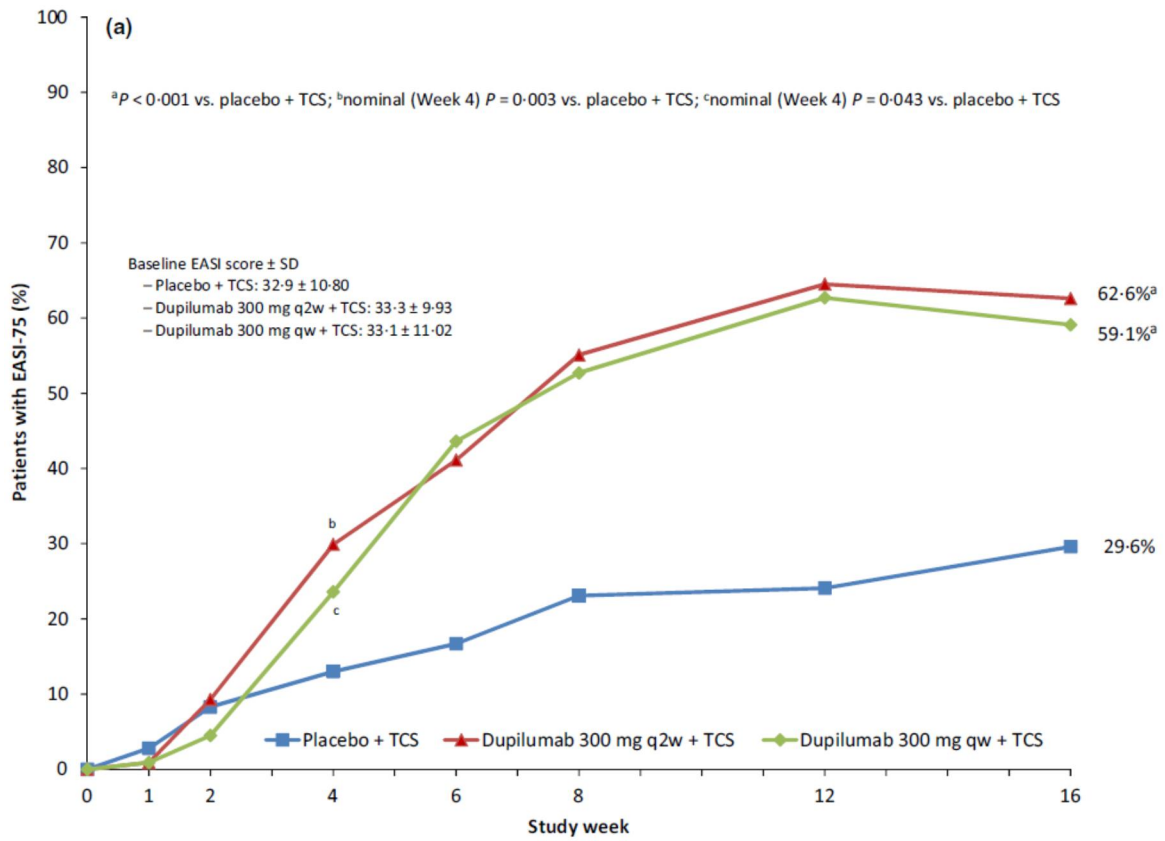
<sup>2</sup> Kimball et al. 2017. "Interpretation of EASI-75 from a patient perspective—A post hoc analysis from a phase 2b trial of dupilumab in adults with moderate-to-severe atopic dermatitis". Journal of the American Academy of Dermatology , Volume 76 , Issue 6 , AB416 Accessed 30/4/18

Figure 1: The proportion of patients achieving EASI-75 at Week 16 in the randomised trials



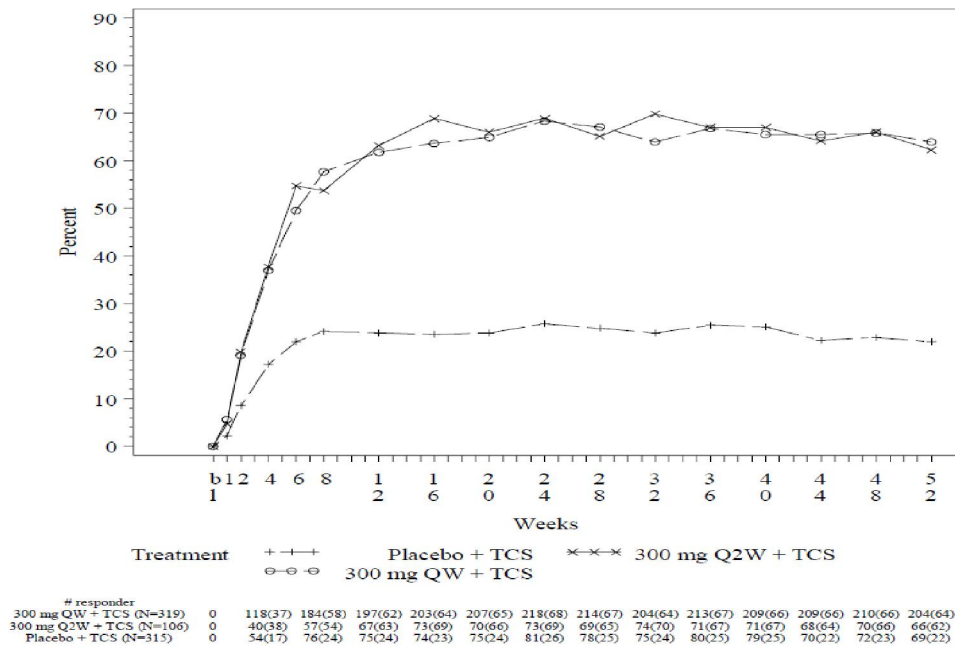
- 6.14 In all the trials and the meta-analysis, a statistically significantly higher proportion of patients treated with dupilumab 300mg Q2W achieved an EASI-75 response at Week 16 than patients treated with placebo. The ESC noted that the trials showed a large placebo response, which may have contributed to the relatively large proportion of patients achieving EASI-75 response.
- 6.15 Results of EASI-75 response over 16 weeks in the CAFÉ trial is shown in Figure 2, and over 52 weeks in the CHRONOS trial are presented in Figure 3. It appears that the dupilumab treatment effect plateaued at approximately 16 weeks of treatment, but it is unclear whether the plateauing of response rate indicates that patients are moving in and out of EASI-75 response or if patients who respond at Week 16 will continue to maintain the EASI-75 response. The ESC noted that both the short term and the long term studies showed that response to dupilumab was maintained over time.

Figure 2: Proportion of patients achieving EASI 75 over 16 weeks in CAFÉ



Source: Adapted from Figure 2 of *Dupilumab treatment in adults with atopic dermatitis (LIBERTY AD CAFÉ)* (p. 1091), by M. de Bruin-Weller et al, 2017: British Journal of Dermatology.

Figure 3: Proportion of patients achieving EASI 75 over time in CHRONOS

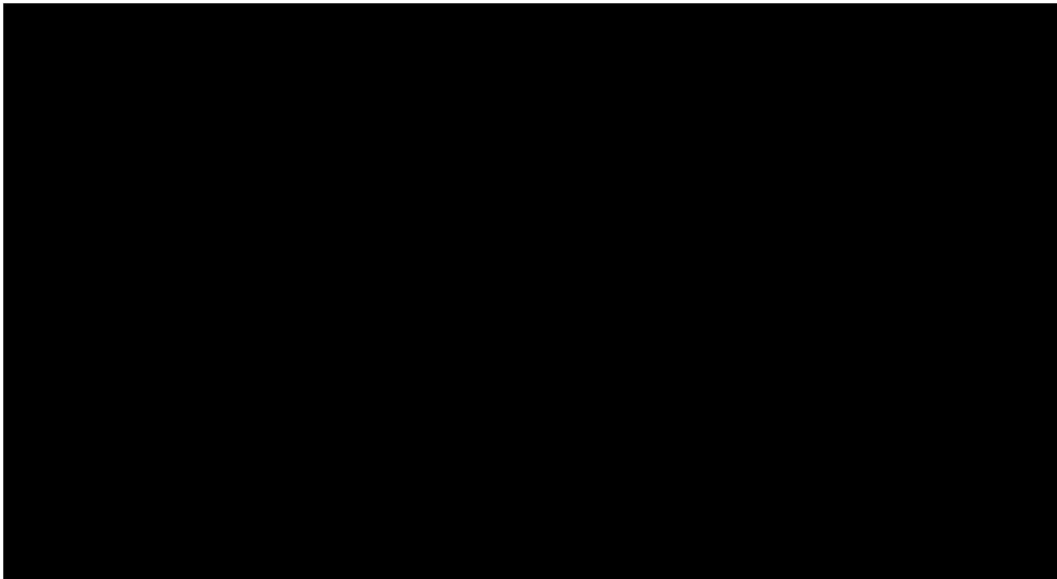


Values after first rescue treatment were set to missing. Subjects with missing EASI score at a visit were treated as a non-responder at the visit.

Source: Figure 2.5.12, p100 of the submission

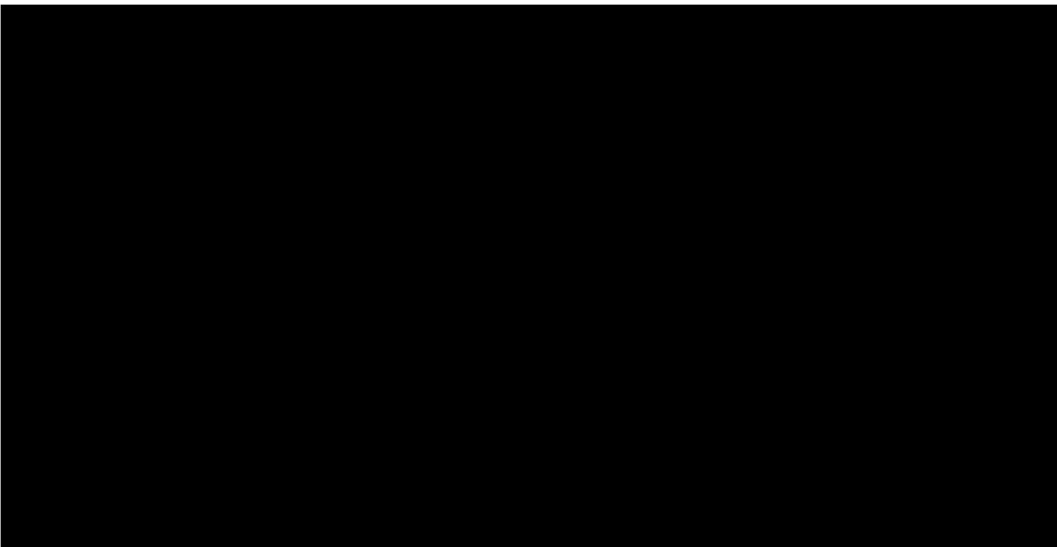
- 6.16 The proportion of patients achieving an EASI-75 response in the subgroup of patients with an IGA score of 3 or 4 (consistent with the proposed PBS population) in the individual trials and meta-analysis is presented in Figure 4 (risk difference) and Figure 5 (relative risk).
- 6.17 While no baseline characteristics of patients in the subgroups were available, it is noted that patients were stratified by IGA score in the trials.

**Figure 4: Meta-analysis results for the proportion of patients achieving an EASI-75 response at Week 16 by baseline IGA score sub-groups (FAS) – risk difference**



Source: Created during evaluation, there was an error in the results for CHRONOS presented in the submission, as results from 52 weeks were presented instead of 16 weeks. This error was corrected during the evaluation and the meta-analysis was rerun accordingly.  
Abbreviations: FAS = full analysis set

**Figure 5: Meta-analysis results for the proportion of patients achieving an EASI-75 response at Week 16 by baseline IGA score sub-groups (FAS) – relative risk**



Source: Created during evaluation  
Abbreviations: FAS = full analysis set

- 6.18 In all the trials and the meta-analysis, for the IGA 3 and IGA 4 subgroups, a statistically significantly higher proportion of patients treated with dupilumab 300mg Q2W achieved an EASI-75 response at Week 16 than patients treated with placebo.
- 6.19 The submission also conducted sub-group analyses based on prior exposure and response to CsA. These results were not relied upon in the economic evaluation as patients included in each subgroup are not entirely representative of proposed PBS population as they include patients with both moderate and severe AD.
- 6.20 The submission did not address the issue of whether patients with IGA=4 respond differently to treatment with dupilumab compared to patients with IGA=3; nor based on prior CsA exposure. A test for interaction was conducted during the evaluation to determine whether baseline severity defined by the IGA score or prior experience with CsA were treatment effect modifiers, these results are presented in Table 4.

**Table 4: Tests for interaction between subgroups**

	<b>Risk difference (95%CI) [p value]</b>	<b>Relative Risk [p value]</b>
IGA = 3 vs IGA = 4		
CAFÉ	<b>[REDACTED]</b>	<b>[REDACTED]</b>
All trials (summed n/N patients) <sup>a</sup>	<b>[REDACTED]</b>	<b>[REDACTED]</b>
Inadequate response, intolerant to or contraindicated to CsA (positive vs negative)		
All trials (summed n/N patients) <sup>a</sup>	<b>[REDACTED]</b>	<b>[REDACTED]</b>

Text in bold indicates statistically significant differences at 5%

Source: constructed during evaluation using information from Table 2.6.1, p120 and Table 2.6.2, p123 of the submission

<sup>a</sup> similar results reported when using estimate

- 6.21 There were statistically significant subgroup interactions based on relative risk with regards to baseline IGA score. Patients with a baseline IGA = 4 were relatively more likely to achieve an EASI-75 response to dupilumab 300mg Q2W treatment compared to patients with a baseline IGA = 3, however this interaction was not observed in risk difference. This applied to both those patients in the CAFÉ trial (prior CsA with an inadequate response or intolerant/contraindicated to CsA) and all trials (where prior experience with CsA was not a requirement for enrolment). The explanation for this is unclear, but it should be noted that the interaction is driven by a lower placebo response rate in patients with baseline IGA = 3 compared to patients with IGA = 4 rather than a difference in the absolute efficacy of dupilumab in the two groups of patients. The ESC considered that while conceptually, a reduction of 75% in the EASI score may have a different clinical impact in people with moderate (IGA 3) vs severe (IGA 4) disease, data were not provided to determine this. There were also no statistically significant subgroup interactions observed between patients who met the proposed CsA restriction criteria (i.e. prior CsA with an inadequate response or intolerant/contraindicated to CsA) and patients who did not (i.e. no prior CsA use and not contra-indicated to CsA). As such, there was limited evidence that supported the contention that either severity of AD or experience with CsA are treatment effect modifiers.

- 6.22 The PBAC noted the submission's request to restrict use of dupilumab to patients with IGA = 4 only and/or on the basis of prior experience with CsA and considered that the evidence appeared to demonstrate that patients with IGA = 3 and those who do not fulfil the CsA criteria specified in the requested restriction would benefit just as much from dupilumab treatment. The PSCR argued that the patients as defined by the proposed listing had the greatest unmet clinical need, and that the restriction was aligned with that of biologics for chronic plaque psoriasis. The PBAC agreed with the ESC that restricting eligibility to patients with severe AD and prior CSA exposure or contraindication was unwarrantedly narrower than the TGA indication and the trial data. The PBAC considered that restricting the use of dupilumab to patients with severe AD who are intolerant, contraindicated or non-responsive to CsA was not adequately justified.
- 6.23 There were differences in mean baseline utility both within trial (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. The PBAC considered that the comparative effectiveness of dupilumab to placebo was highly uncertain for quality of life. The PBAC noted that there was limited quality of life data extending to 52 weeks and that it was not clear whether patients who responded to treatment maintained their quality of life, or patients moved in and out of response.

### **Comparative harms**

- 6.24 Overall, across all five trials, the proportions of patients experiencing any treatment emergent adverse events (TEAEs) in the placebo and dupilumab arms were similar and not statistically significantly different. This should be interpreted with caution, as the placebo used in the trials (placebo subcutaneous injections) is not the same as the placebo/non treatment used in clinical practice.
- 6.25 Specific TEAEs with differences in frequencies between arms of note included:
- An analysis of conjunctivitis and selected eye-related disorders was pre-specified in the statistical analysis plan of CAFÉ. This analysis used a narrow customised MedDRA query (CMQ) containing five terms that included conjunctivitis which could indicate a conjunctivitis-like event which were chosen by ophthalmologists at the sponsor company. Conjunctivitis was notably more frequent in the dupilumab arms of CAFÉ than the placebo arms. This was also observed in CHRONOS and in SOLO 1. The submission claims (p115-116) that the majority of conjunctivitis events were mild to moderate in severity and were resolved at the end of the study period. This may not be reasonable as only 23/37 (62%) of patients treated with dupilumab 300mg Q2W had resolved conjunctivitis at the end of the study compared to 13/15 (87%) of patients treated with placebo who experienced conjunctivitis. The ESC noted from a recent publication (Wollenberg

et al., J Allergy Clin Immunol Pract 2018 in press) that this would not be likely to cause patients to stop treatment with dupilumab, and that patients would likely use topical treatments to resolve the conjunctivitis whilst using dupilumab long term.

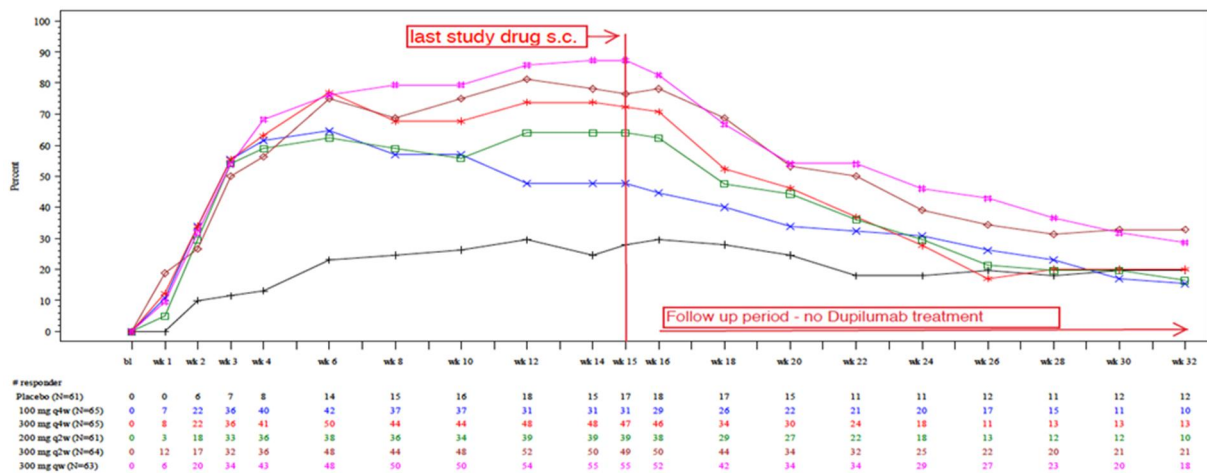
- Injection site reactions were notably higher in dupilumab arms than placebo arms across all trials, but to a lesser extent in CAFÉ and Phase IIb. It should be noted that patients in the proposed PBS population currently experience zero injection site related events as they do not receive placebo treatments.

6.26 The ESC noted there is very limited experience on the long term safety of this drug, considering it is intended for chronic use. In addition there are no data on dupilumab’s impact on live vaccines (Dupixent Product Information (PI), p5). As AD is a chronic illness, dupilumab can theoretically be used over a patient’s lifetime, thus this may impact on both AD and other long term diseases, such as asthma (Dupixent PI, p4).

6.27 The ESC noted an absence of data on the optimal duration of therapy, on when or how to withdraw therapy, or on clinical outcomes (for AD and other conditions) when therapy is withdrawn. The comparator, CsA, may cause exacerbations after withdrawal of treatment, which could potentially also occur on withdrawal of dupilumab. The ESC suggested potentially limiting the chronic listing to 12 months of treatment, until longer term safety and efficacy data are available.

6.28 The pre-PBAC response maintained that chronic (continuous) use of dupilumab was clinically appropriate and that withdrawal of dupilumab would be at the patient’s detriment, by showing a decline of EASI-50 following treatment withdrawal at week 15 in the 32 week Phase IIb dose-ranging study of dupilumab.

Figure 6: Proportion of patients with an EASI-50 over 32 weeks, with treatment withdrawal at Week 15



Source: Figure 1 of the pre-PBAC response, p2

6.29 In the pre-PBAC response, the sponsor also provided data from the SOLO-CONTINUE study, which compared patients either continuing on dupilumab or placebo treatment following 16 weeks of dupilumab treatment. Of 79 patients in the placebo

group, ■ (■■%) achieved an EASI-75 response at week 36 compared to ■/■ (■■%) of patients who continued dupilumab 300 mg Q2W dosing. The sponsor stated that patients in the placebo group had a decline in quality of life following dupilumab withdrawal. In addition the sponsor claimed that dupilumab can be withdrawn safely without an increase in TEAEs, presenting comparable safety data between placebo and dupilumab groups via the same CONTINUE study. In this study there were 81.7% and 1.2% of patients in the placebo group who experienced any TEAE and any treatment emergent serious adverse event, respectively, compared with 70.7% and 3.6% of dupilumab 300 mg Q2W patients.

- 6.30 The pre-PBAC response stated that if treatment were to be stopped and restarted, patients would be at risk of developing anti-drug-antibodies (ADAs), which is a theoretical concern for all protein biologics. The OLE study had an ADA analysis set, where at its interim analysis ■% of dupilumab-naïve patients experienced a treatment-emergent positive ADA response compared with ■% in the re-treatment group. Persistently positive ADA responses were observed in ■% of the dupilumab-naïve group versus ■% of re-treated patients. The pre-PBAC response reiterated that dupilumab should be used for ongoing treatment of chronic AD, which was in line with the TGA indication.

### **Benefits and harms**

- 6.31 A summary of the comparative benefits and harms for short term dupilumab versus placebo is presented in Table 5. Evidence on long term benefits and harms, which is more relevant to the proposed chronic use, was not available.

Table 5: Summary of comparative benefits and harms for dupilumab and placebo

<b>Benefits</b>						
<b>Dichotomous Outcome I – EASI-75 response at Week 16</b>						
Trial	Dupilumab	Placebo	RR (95% CI)	Events/100 patients*		RD, % (95% CI)
				Dupilumab	Placebo	
Meta-analysis (whole trial populations)						
CAFÉ (whole trial population)	67/107	32/108	2.11 (1.53, 2.93)	62.6	29.6	33 (20, 46)
Meta-analysis (IGA=4 subgroup); no prior CsA requirement						
CAFÉ (IGA=4 subgroup); CsA restrictions sub-group <sup>a</sup>						
<b>Harms</b>						
	Dupilumab	Placebo	RR (95% CI)	Events/100 patients*		RD (95% CI)
				Dupilumab	Placebo	
<b>Conjunctivitis</b>						
Meta-analysis (whole trial populations)						
<b>Oral herpes</b>						
Meta-analysis (whole trial populations)						
<b>Injection site reaction</b>						
Meta-analysis (whole trial populations)						
<b>Allergic conjunctivitis<sup>b</sup></b>						
Meta-analysis (whole trial populations)						
<b>Blepharitis<sup>c</sup></b>						
Meta-analysis (whole trial populations)						
<b>Allergic rhinitis<sup>d</sup></b>						
Meta-analysis (whole trial populations)						

Source: Compiled during the evaluation/

<sup>a</sup> population considered to be most representative of the proposed population

<sup>b</sup> Only reported in CAFÉ, CHRONOS and SOLO 1

<sup>c</sup> Only reported in CHRONOS

<sup>d</sup> Only reported in CAFÉ

- 6.32 On the basis of direct evidence presented by the submission, for every 100 patients treated with dupilumab in comparison to placebo over 16 weeks:
- Approximately 38 additional patients (with moderate or severe disease) would have a 75% improvement in EASI score;
  - Approximately 33 additional patients (with moderate or severe disease who have failed or been unable to tolerate previous treatment with cyclosporin) would have a 75% improvement in EASI score;
  - Approximately 36 additional patients (with severe disease) would have a 75% improvement in EASI score from baseline;
  - Approximately 42 additional patients (with severe disease who have failed or been unable to tolerate previous treatment with cyclosporin) would have a 75% improvement in EASI score from baseline. This population is most representative of those for whom listing is sought, however is based on results for subgroups of the trial populations ( $n=102$ );
  - Approximately 14 additional patients will have eye complications over 16 weeks of treatment:
    - 3 additional patients will have conjunctivitis,
    - 6 additional patients will have allergic conjunctivitis, and
    - 5 additional patients will have blepharitis;
  - Approximately 2 additional patients will have oral herpes;
  - Approximately 7 additional patients will have an injection site reaction; and
  - Approximately 6 additional patients will have allergic rhinitis.

### ***Interpretation of clinical evidence***

- 6.33 The submission claimed that dupilumab is superior in terms of efficacy to placebo (SoC) 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. The submission also claimed the safety profile of dupilumab is similar to placebo.
- 6.34 The claim of a superior clinical efficacy of dupilumab was reasonably supported by the available evidence. The CAFÉ sub-group with severe (IGA=4) AD at baseline was the most representative of the proposed PBS population. The sub-group analysis in these patients showed that a higher proportion of patients treated with dupilumab 300mg Q2W arm achieve an EASI-75 response at week 16 compared to patients treated with placebo [redacted]% vs [redacted]%. . However, it should be noted that this was a post hoc sub-group analysis and may not be sufficiently powered. The PBAC added that the CAFÉ trial was only published as an abstract and the subgroup analysis was not reported in this abstract. Moreover, the submission has not provided sufficient clinical justification for restricting treatment to patients with severe AD with baseline IGA = 4 and who have had an inadequate response or intolerance to CsA only as patients who did not fulfil these criteria appeared to derive the same magnitude of benefit from treatment with dupilumab. As such the ESC questioned the narrow

eligibility of the restriction criteria and dupilumab's proposed place in therapy after prior CsA use or intolerance.

- 6.35 The claim of a comparable safety profile with placebo is not supported by the available evidence. Patients treated with dupilumab in the included trials reported a higher incidence of conjunctivitis and injection site reactions compared to patients treated with placebo. Moreover, the placebo treatment (given via subcutaneous injection) in the clinical trials is not a true reflection of SoC (no injection) in clinical practice.
- 6.36 There is limited long-term safety and efficacy data for dupilumab treatment for AD. As such, claims of a superior clinical efficacy and inferior safety of dupilumab compared to placebo are only reasonable for up to 16 weeks of treatment. There is also limited long-term safety and efficacy data (up to 52 weeks from CHRONOS) in a broader population (i.e. patients who do not match the proposed CsA restriction criteria). As dupilumab is indicated for chronic treatment of AD in a population who are likely to be young and otherwise healthy, the ESC considered that longer term efficacy and safety data would be required to support this clinical claim in the chronic use setting. While the PSCR referred to an ongoing open label extension study that will provide 3 years of follow-up, the ESC noted that these data would not be available for another two years.
- 6.37 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.38 The PBAC considered that the claim of comparable safety was not adequately supported by the data.

### ***Economic analysis***

- 6.39 The submission used subgroup analyses from CAFÉ and CHRONOS to implement and present a stepped modelled economic evaluation. The type of economic evaluation was a cost-utility analysis (CUA) in the form of a Markov cohort model. Table 6 presents a summary of the model structure and rationale.

**Table 6: Summary of model structure and rationale**

Component	Summary
Time horizon	Five years in the model base case versus 16 weeks in a trial for a population that is most representative of the proposed PBS population (CAFÉ subgroup) and data up to 52 weeks from a trial enrolling a broader patient population (CHRONOS).
Outcomes	QALYs
Methods used to generate results	Markov cohort expected value analysis
Health states	Induction, EASI-75 responder, EASI-75 non-responder and death
Utilities	Trial based utilities. The utility values used for the responder health states in the model were highly uncertain due to low sample sizes (n=9 for placebo; n=28 for dupilumab), and due to assigning different utility values between arms despite no statistically significant differences in utility gain.
Cycle length	Three months. Inconsistent with both the induction phase (16 weeks) and continuing phase (24 weeks) proposed in the requested restriction.
Transition probabilities	Trial-based – CAFÉ subgroup up to 16 weeks for responder rates and CHRONOS (from those with response at Week 16 maintaining response at Week 52) for maintenance of response for the remainder of the time horizon.

Source: Section 3 the submission

6.40 The ESC noted that there were a number of issues with the model structure:

- the induction state was over 13 weeks in the model, compared with 16 weeks for the PBS listing;
- the model included 9 doses for the initial response period whilst the PBS restriction allows 10 doses in the initial period, therefore the model underestimated the costs for the dupilumab arm in the initial response stage;
- continuing treatment is for 13 weeks in the model (to align with 3 month cycles) whereas the proposed restriction allows continuing treatment for 24 weeks, which also resulted in underestimated costs in the dupilumab arm for the continuing stage;
- the model did not account for health gains without dupilumab treatment for patients who transition from being a non-responder to a responder. It is possible that patients would have periods of improvement without treatment (i.e. transition from non-responder to responder) due to the cyclical nature of the disease. This underestimates the health gains in the control arm in the continuing stage.

6.41 The key drivers of the model are presented in Table 7.

**Table 7: Key drivers of the model**

Description	Method/Value	Impact
Responder rates at Week 16	CAFÉ responder rate at Week 16 and 95% CIs	Moderate, use of 95% CIs around the estimate impact the base case ICER from an 8% reduction to 18% increase.
Utilities	Derived from CAFÉ, assume dupilumab responders have higher utility than placebo responders	High, favours dupilumab. If the model assumes all responders have the placebo responder utility, the base case ICER is increased by 26%.
Loss of response	Derived from CHRONOS. Base case assumes different loss of response for dupilumab and placebo.	Moderate, favours dupilumab. If placebo loss of response applied to both arms, base case ICER increases by 16%.
Time horizon	Base case of 5 years in the model. Though short, may still be considered optimistic given randomised data in the patient population of interest is limited to 16 weeks (CAFÉ).	High, favours dupilumab. A one-year time horizon results in a 42% increase in base case ICER.

Source: compiled during the evaluation

6.42 The health care resource use and costs associated with each health state in the model are presented in Table 8.

**Table 8: Health state costs applied in the model**

Resource type	Resource use per year (number of visits)		Unit cost	Resource use per year (\$)	
	Responder	Non-responder		Responder	Non-responder
Primary care visit <sup>1</sup>	4.00	11.70	\$37.05 (MBS item 23)	\$148.20	\$433.485
Dermatologist visit <sup>1</sup>	2.70	6.50	\$97.08 (MBS item 104)	\$262.116	\$631.02
Emergency room visit <sup>2</sup>	0.44	0.50	\$449.00 (NHCD, 2014-15)	\$197.56	\$224.50
Hospitalisation <sup>2</sup>	0.18	0.40	\$5,009.00 (NHCD, 2014-15)	\$901.62	\$2,003.60
Total cost (per year)				\$1,509.50	\$3,292.61
Total cost (per cycle)				\$377.38	\$823.15

Source: Table 3.6.2 (p158) of the submission

Abbreviations: NHCD = National Hospital Cost Data Collection; MBS = Medicare Benefits Schedule

<sup>1</sup>Garside et al. 2005; <sup>2</sup>Sponsor data; NHCD, 2014-15 V 2015-16

6.43 The ESC noted that the health care resource data used were not recent. The NHCD version used was not the most recent and the primary care and dermatologist source was a study of children with AD from 1997 with a small sample size of 48 patients. The source of emergency room and admissions data was from international sources and was unverifiable. The ESC questioned the absence of Australian hospitalisation data. The ESC also noted that costs of TCS or TCI were excluded as well as other costs specific to dupilumab such as GP or nurse consultations for injections, management of infections, ophthalmologist and other health service use related to other dupilumab adverse events such as injection site reactions. The pre-PBAC response argued that administration costs for dupilumab are expected to be negligible as the small number of patients requiring assistance would have their treatment administered during routine visits to their treating physicians. The pre-

PBAC response also argued that the exclusion of adverse event costs is consistent with the therapeutic conclusion on that dupilumab has a similar safety profile to placebo, however the PBAC did not consider that this conclusion was supported by the data. The PBAC noted that, in general, resource use and costs were applied without consideration of potential differences between the dupilumab and placebo groups.

6.44 The results of the stepped economic evaluation are presented in Table 9.

**Table 9: Presentation of the stepped derivation of the base case economic evaluation from the clinical study data**

Step		1	2	3	4	5	6	7
Dupilumab	Study drug costs	\$████	\$████	\$████	\$████	\$████	\$████	\$████
	Non-drug costs	\$0	\$0	\$0	\$0	\$0	\$████	\$████
	% of cohort with response	0.540	0.540	0.540	0.540			
	Years in response				████	████	████	████
	QALYs				████	████	████	████
Placebo	Study drug costs	\$0	\$0	\$0	\$0	\$0	\$0	\$0
	Non-drug costs	\$0	\$0	\$0	\$0	\$0	\$████	\$████
	% of cohort with response	0.115	0.115	0.115	0.115			
	Years in response				████	████	████	████
	QALYs				████	████	████	████
Incremental	Total costs	\$████	\$████	\$████	\$████	\$████	\$████	\$████
	% of cohort with response	0.425	0.425	0.425	0.425			
	Years in response				████	████	████	████
	QALYs				████	████	████	████
ICER	IC/Responder	\$████	\$████	\$████	\$████			
	IC/Year with response				\$████	\$████	\$████	\$████
	IC/QALY				\$████	\$████	\$████	\$████

Source: Table 3.8.1 (p160) of the submission

Abbreviations: QALY = quality-adjusted life years; IC = incremental cost

Step 1: Trial-based analysis (EASI-75 response at 16-weeks) using drug costs only

Step 2: As above, extend to 1-year

Step 3: As above, apply continuation rule at 16 weeks

Step 4: As above, apply Markov model and half cycle correction

Step 5: As above, allow for mortality, loss of response, and discounting

Step 6: As above, transform to resource utilisation costs

Step 7: As above, extrapolate to 5-years

6.45 All appropriate steps for the stepped economic analysis were included. The final step (extrapolation of the model from 1 year to 5 years) significantly reduced the ICER (by approximately \$15,000 - \$45,000 per QALY gained) due to an increase in the incremental QALY gain, and represents the most impactful step of the analysis from

when an incremental cost per QALY-gained is first generated. The implementation of the continuation rule at 16 weeks within a 1 year model (Step 3) also has a relatively big impact on results, decreasing the incremental cost per EASI-75 responder to approximately \$15,000/QALY to \$45,000/QALY.

- 6.46 The sensitivity analyses presented in the submission were limited to univariate analyses. As noted in Table 7, the key drivers of the model included inputs associated with efficacy (response and maintenance of response), utilities and the time horizon. The ESC noted that different utilities were applied to responders in each treatment group despite there being no statistically significant difference between the groups in the trial data. The very low sample sizes for the utility data (████ in the ██████████ and █████ in the ██████████) makes these values highly uncertain. The PSCR and pre-PBAC response argued that it is reasonable to expect a higher average utility across a cohort of dupilumab responders than a cohort of placebo responders based on the difference in EASI-90 response between the treatment groups (85% of responders in the dupilumab arm compared with 33% of responders in the placebo arm). However the ESC considered that it was not reasonable to use different utility values for responders in the different treatment groups given the small sample size and non-significant difference between groups. The ESC also considered that it may not be appropriate to assume that utility gains remain constant over time. Assuming no between-group difference in utility gain and using the utility gain for responders in the placebo group resulted in an increase in the ICER from \$45,000/QALY to \$105,000/QALY. The PBAC agreed with the ESC that the base case should assume the same utility for responders in both treatment groups due to the uncertainty introduced using differential utility data based on very small sample sizes.
- 6.47 The PSCR presented two additional univariate sensitivity analyses to address the uncertainty of using CHRONOS trial data in the economic model, as patients in CHRONOS were not entirely representative of the proposed PBS population. Results of these analyses are shown in the table below.
- 6.48 The first sensitivity analysis used values from the intention to treat analysis of CAFÉ, which increased the probabilities of an EASI-75 response to 62.6% and 29.6% for dupilumab and placebo respectively. This increased the ICER to \$75,000/QALY - \$105,000/QALY. This sensitivity analysis included patients with moderate and severe AD, which was broader than the proposed PBS population. The second sensitivity analysis used the CHRONOS severe AD sub-group data, which increased the ICER to \$45,000/QALY - \$75,000/QALY.

Table 10: One-way sensitivity analyses

Variable (base case)	Sensitivity analysis	Dupilumab		Placebo		Incremental		ICER
		Costs	QALYs	Costs	QALYs	Costs	QALYs	
Base case		\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Probability of EASI-75 response at 16 weeks (DUP 54%; PBO 11.5%)	CAFÉ ITT analysis (DUP 62.6%; PBO 29.6%)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Per cycle probability of maintaining EASI-75 response (DUP 93.1%; PBO 88.2%)	Data for subgroup with severe AD at baseline (DUP 92.2%; PBO 89.6%)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Table 3 of the PSCR

The redacted table shows ICERs in the range of \$45,000/QALY - \$105,000/QALY.

**Drug cost/patient/year**

6.49 \$ [REDACTED], assuming a DPMQ of \$ [REDACTED], and 13 scripts per year for continuing patients.

**Estimated PBS usage & financial implications**

6.50 This submission was considered by DUSC. The submission took a mixed epidemiological and market share approach to estimate the financial impact of dupilumab. Table 11 summarises the estimated use and financial implications as presented in the submission.

**Table 11: Estimated use and financial implications as presented in the submission**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	█	█	█	█	█	█
Number of scripts dispensed <sup>a</sup>	█	█	█	█	█	█
<b>Estimated financial implications of dupilumab</b>						
Cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Copayments	\$█	\$█	\$█	\$█	\$█	\$█
Cost to PBS/RPBS less copayments	\$█	\$█	\$█	\$█	\$█	\$█
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to {MBS/DHS/other}	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Net cost to {PBS/RPBS/MBS/DHS}	\$█	\$█	\$█	\$█	\$█	\$█

<sup>a</sup> Assuming 5.8 increasing to 6.6 scripts in Year 6 for initiating patients and 11.2 increasing to 12.7 scripts in Year 6 for continuing patients per year as estimated by the submission.

Source: Table 4.2.1 and 4.2.2 (p168-170) in the submission

6.51 The redacted table shows that over 6 years, the estimated number of patients was 10,000 – 50,000 and the net cost to the PBS would be more than \$100 million.

6.52 The estimates provided in the submission are likely to be underestimated as:

- The uptake of dupilumab was based on the uptake observed for the first bDMARDs listed for psoriasis (ranging from 0.05%-0.21% of all AD patients). The approach may not be reasonable as there are differences (i) in the nature of the conditions and treatment options; (ii) prescriber familiarity with the use of bDMARDs for the treatment of skin conditions and (iii) the method did not include response and persistence rates for the dupilumab trials. The PBAC considered that the reliance on the psoriasis market as a proxy for dupilumab uptake was not well supported and was likely to underestimate the uptake of dupilumab.
- Moreover, the submission’s own market research suggested that the eligible population (severe AD with an inadequate response to CsA) was 1.065% of all AD patients. Although this estimate is uncertain, if considered reasonable, the submission assumes that less than 5% of all eligible patients would be treated with dupilumab in Year 1 of listing, increasing to around 20% by Year 6.
- The estimates do not consider the potential for use beyond the restriction (i.e. in those with moderate AD, those aged <18 years or those using CsA).

6.53 DUSC considered the estimates presented in the submission to be uncertain and significantly underestimated. The main issues were:

- DUSC considered there is likely to be usage beyond the expectations because the uptake of dupilumab by AD patients is based on the uptake of the first biologics listed for psoriasis but the biologics market has evolved substantially since this time. Comparison with the submission's own market research on the percentage of AD patients that fulfil the restriction criteria suggested that the submission's approach may result in a substantial underestimate of dupilumab utilisation. The pre-PBAC response noted that several bDMARDs became available for psoriasis in the first years of listing, whereas dupilumab is the only bDMARD available for AD. The sponsor argued that the evolution of the biologics market is likely to be largely offset by the difference in bDMARD availability across the different indications.
- DUSC considered there is likely to be use beyond the proposed restriction for patients with moderate AD and for continued use in patients with severe AD but who do not fulfil the response criteria. DUSC considered that the base case estimates for dupilumab should be consistent with the proposed PBS criteria, response rates from the clinical trials and modelled economic evaluation, with potential for use outside of the restriction managed through a risk sharing arrangement. The pre-PBAC response argued that the utilisation in the psoriasis market reflects real world use and would therefore capture leakage outside the approved indication.

### **Quality use of medicines**

- 6.54 The submission identifies the (i) accurate use of the IGA and EASI by clinicians, (ii) correct administration of dupilumab, (iii) appropriate storage and handling of dupilumab, and (iv) comprehensive pharmacovigilance plan for dupilumab as QUM issues.

### **Financial management – risk sharing arrangements**

- 6.55 The pre-PBAC response stated that the sponsor would consider a risk share arrangement to address potential use outside of the proposed population.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of dupilumab for the treatment of severe atopic dermatitis (AD) due to uncertainty regarding the appropriate place in therapy and uncertain cost effectiveness. The PBAC did not consider that the data presented in the submission supported restricting the use of dupilumab to only severe disease.
- 7.2 The PBAC acknowledged the clinical need for a safe and effective treatment for patients with AD who do not respond to existing therapies. The PBAC noted the comments from consumers and patient support groups that emphasized the substantial impacts of AD on patients' quality of life and reflected the perceived

- efficacy and comparative safety of dupilumab. The PBAC noted the ASCIA's in-principle support for the listing of dupilumab in patients with severe AD.
- 7.3 The PBAC noted that the proposed patient population was narrower than the TGA-approved indication for dupilumab and the clinical guidelines which recommend treatment of moderate to severe AD without the requirement for prior intolerance, insufficient response or contraindication to treatment with CsA. The PSCR and pre-PBAC response maintained that these patients had the greatest unmet clinical need, and that the restriction was aligned with that of biologics for chronic plaque psoriasis. The PBAC noted that prescribers are reluctant to use CsA due to its toxicity and therefore considered that the narrow restriction proposed was not adequately justified. The PBAC requested that expert input be sought to determine if the use of dupilumab for moderate to severe disease regardless of prior CsA use would be more appropriate.
- 7.4 The PBAC noted that the majority of the clinical evidence for dupilumab didn't require failure with/contraindication/intolerance to CsA and therefore the proposed place in therapy did not align with the majority of the available clinical evidence. The PBAC noted that the evidence appeared to demonstrate that patients with IGA = 3 and those who do not fulfil the CsA criteria specified in the requested restriction would benefit equally from dupilumab treatment. 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.
- 7.5 The PBAC considered that multiple re-trials of dupilumab after inadequate response would not be appropriate, and as there are currently no other biologics for AD, proposed removal of the Initial 2 restriction. The PBAC questioned whether prescribing by clinical immunologists would be appropriate as dermatologists may be better placed to assess IGA severity and EASI response as required for continuing treatment. The PBAC noted that a grandfathering restriction was requested for patients currently in the early access program and the open label extension study as well as around 300 patients expected to be enrolled in a patient familiarisation program. The PBAC considered that it may not be reasonable to grandfather patients who had not yet commenced on the program.
- 7.6 The PBAC considered that, based on the clinical data provided, EASI-75 appears to be a valid clinical marker for AD, correlating with outcomes such as quality of life. The PBAC also noted that SCORAD may be a relevant outcome.
- 7.7 The PBAC noted that a statistically significantly higher proportion of patients treated with dupilumab 300mg Q2W achieved an EASI-75 response at Week 16 than patients treated with placebo. The PBAC noted that the long term efficacy data presented were limited but considered that there was some evidence that the effectiveness of dupilumab based on EASI-75 response at 16 weeks extended up to 52 weeks. The PBAC noted that the magnitude and direction of quality of life changes for patients

treated with dupilumab was inconsistent in the trials and was highly uncertain.

- 7.8 The PBAC considered that the claim of superior comparative efficacy against placebo was adequately supported. The claim of a comparable safety profile with placebo was not adequately supported by the available evidence as patients treated with dupilumab reported a higher incidence of conjunctivitis and injection site reactions compared to patients treated with placebo. Additionally, placebo treatment in the clinical trials was not a true reflection of SoC in clinical practice. The PBAC noted that there was a lack of long term safety and efficacy data, especially considering the chronic nature of AD.
- 7.9 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. 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. 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.
- 7.10 The PBAC noted that the base case ICER of \$45,000 - \$75,000 per QALY was relatively high. The committee recalled that the ICER of ustekinumab for psoriasis was in the range of \$15,000-\$45,000 per QALY and considered that, while not directly comparable, this provides additional context.
- 7.11 The PBAC considered that the reliance on the psoriasis market as a proxy for dupilumab uptake was not well supported and was likely underestimated. The PBAC also noted that the financial estimates did not consider the potential for use beyond the restriction (i.e. in patients with moderate AD, those aged <18 years or those without inadequate response/intolerance or contra-indication to CsA). The PBAC considered that a Risk Share Agreement may be required to address the potential for use outside the restriction.
- 7.12 The PBAC noted that any future submission for dupilumab would need to clearly identify the most appropriate place in therapy for dupilumab. The PBAC considered that it may be necessary to demonstrate that dupilumab is cost-effective in the full population relevant to the TGA indication, as reflected in the clinical trial data and consistent with clinical guidelines, as this is the population in whom dupilumab is likely to be used. Should the restriction be broadened to include patients with moderate AD, the PBAC acknowledged that the financial impact would be substantially greater at the price proposed in this submission.
- 7.13 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 welcomes the Committee's recognition of the need for a safe and effective treatment for patients with atopic dermatitis and remains committed to working with the PBAC to enable reimbursed access to dupilumab for Australian patients with atopic dermatitis.