

**7.03 CRISABOROLE,
Ointment 2%, 30 g
Ointment 2%, 60 g
Staquis[®],
Pfizer Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The resubmission requested a Section 85 Streamlined Authority Required listing for crisaborole for the treatment of mild to moderate atopic dermatitis in patients aged at least 2 years who have failed to achieve satisfactory disease control with, are contraindicated or intolerant to topical corticosteroids (TCS). The PBAC previously considered crisaborole for the same indication in November 2018.
- 1.2 Listing was requested on a cost-minimisation basis compared to pimecrolimus for use on the face and eyelids and a cost-effectiveness basis compared to standard management for the rest of the body.

Table 1: Key components of the clinical issue addressed in the resubmission

Component	Description
Population	Patients aged ≥ 2 years with mild to moderate atopic dermatitis who have failed to achieve satisfactory disease control with, are contraindicated, or are intolerant to topical corticosteroids
Intervention	Crisaborole 2% ointment
Comparator	Pimecrolimus (face and eyelids) and standard management (rest of the body)
Outcomes	Improvement in signs and symptoms of atopic dermatitis
Clinical claim	Crisaborole is non-inferior in terms of efficacy and safety compared with pimecrolimus Crisaborole is superior in terms of efficacy and inferior in terms of safety compared with standard management

Source: Table 1.1.1, p4 of the resubmission

- 1.3 The commentary considered that the clinical context of the resubmission was largely unchanged compared to the November 2018 submission. The Pre-Sub-Committee-Response (PSCR) argued that the population was clearer in that the restriction included a definition of mild to moderate AD (ie. with erythematous patches and induration/papulation). The PSCR also contended that the place in clinical therapy was clearly articulated in terms of contraindication, intolerance and intermittent use of TCS.

2 Background

Registration status

- 2.1 Crisaborole was approved by the TGA on 20 February 2019 for the treatment of mild to moderate atopic dermatitis in patients aged 2 years and older.

Previous PBAC consideration

2.2 The key matters of concern from the previous November 2018 submission are summarised in the table below.

Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
<p>The PBAC considered that the comparator of pimecrolimus was appropriate for use on the face and eyelids, although tacrolimus ointment may also be a relevant comparator. The PBAC considered that TCS should be a comparator for the rest of the body (paragraph 7.5, crisaborole, PSD, November 2018 PBAC meeting).</p>	<p>No change. The resubmission nominated pimecrolimus (face and eyelids) and standard management (for rest of body) as comparators. The PSCR argued that the restriction only allows for crisaborole use where TCS would not be used, therefore TCS would not be replaced by crisaborole.</p>
<p>The PBAC considered that the proposed clinical place for crisaborole was unclear and was not consistent in published international guidelines. The PBAC noted limitations with the short-term efficacy data but assumed that long-term intermittent use was likely (paragraph 7.4, crisaborole, PSD, November 2018 PBAC meeting).</p>	<p>The place in therapy remained first-line in patients contraindicated to TCS and second-line in patients who have failed or are intolerant to TCS. Additional clarification was provided in the requested restriction regarding use alongside intermittent TCS. Additional data on long-term use was presented based on safety extension data (up to 48 weeks follow-up). The ESC considered if the restriction was applied as strictly intended, the eligible population would account for only a small proportion of AD patients.</p>
<p>The PBAC noted that the proposed listing was narrower than the requested TGA indication and inconsistent with the clinical data. The PBAC noted that the concept of intolerance to TCS was not addressed in the proposed restriction and remained open to interpretation (paragraph 7.3, crisaborole, PSD, November 2018 PBAC meeting).</p>	<p>The proposed listing is for the same target population as per the November 2018 submission (patients who are failing, contraindicated or intolerant to TCS). The proposed restriction defined intolerance as “development of atrophy of the skin, infection of the skin, contact allergy and/or systemic effects”.</p>
<p>The PBAC considered that the proposed listing for chronic use may not be appropriate (based on pimecrolimus restriction). The restriction should address the use of crisaborole in terms of initiation, discontinuation and optimal duration of therapy; the maximum quantity and number of repeats was inadequately justified; and the appropriate amount remains unclear (paragraph 7.2, crisaborole, PSD, November 2018 PBAC meeting).</p>	<p>The proposed listing in the resubmission included initial, continuing and grandfathering restrictions with stopping rules for each restriction. The resubmission also requested a smaller size tube of 30 g for the initial restriction, and the 60 g tube for the continuing and grandfathering restrictions. Restriction criteria specific to pimecrolimus were removed.</p>
<p>The PBAC considered that overall the claim of superior comparative effectiveness compared with standard management was not adequately supported and noted numerous concerns with the data presented including: limited applicability of the short-term key trials, lack of data for the requested subgroup, clinical importance of outcomes based on ISGA, lack of comparative data with well-established therapies, the robustness of the meta-analysis of the key trials, and the modest magnitude of benefit of crisaborole over its vehicle that only just exceeded the proposed MCID (paragraph 7.6, crisaborole, PSD, November 2018 PBAC meeting).</p>	<p>To address concerns regarding the lack of subgroup data for the requested restriction, the resubmission presented post-hoc subgroup analyses by prior topical corticosteroid use based on the key trials AD-301 and AD-302. To address concerns regarding the lack of long-term efficacy data for crisaborole, the resubmission presented analyses of ISGA scores over time using data from the AD-301, AD-302 trials and the open-label safety extension study AD-303. Previously only safety data were presented for study AD-303 in the submission as the CSR only reported analyses of safety. The resubmission did not nominate any MCIDs.</p>

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Matter of concern	How the resubmission addresses it
<p>The PBAC considered that the results of the indirect comparison did not exclude the possibility that pimecrolimus was superior to crisaborole in terms of efficacy and noted the following concerns with the evidence presented: the exclusion of a large body of evidence for pimecrolimus, major transitivity issues with the indirect comparison and the nominated non-inferiority margin did not appear reasonable (paragraph 7.7, crisaborole, PSD, November 2018 PBAC meeting).</p>	<p>The resubmission excluded two infant trials (Trial 0316 and Breuer 2004) from the previous indirect comparison that were not applicable to the requested PBS population. The resubmission did not nominate a non-inferiority margin.</p>
<p>The PBAC considered that the cost-minimisation analysis was not reasonable given that the clinical claim of non-inferiority to pimecrolimus was inadequately supported. The PBAC also considered that the assumption of equivalence of crisaborole and pimecrolimus on a per gram basis was not appropriate and was unlikely to reflect actual use of the treatments (paragraph 7.10, crisaborole PSD, November 2018 PBAC meeting).</p>	<p>Same approach as the November 2018 submission based on the assumption that crisaborole is equivalent to pimecrolimus on a per gram basis. The resubmission included an adjustment factor for young children in the weighting and an additional analysis for the 30 g tube (initial script).</p>
<p>The PBAC considered that the cost-effectiveness of crisaborole compared with standard management was highly uncertain due to the following concerns (paragraph 7.9, crisaborole PSD, November 2018 PBAC meeting):</p> <ul style="list-style-type: none"> • the lack of a relevant comparator; • the model did not reflect the likely use in practice, or capture all relevant health states; • the extrapolation of the treatment benefit was based on unsupported assumptions which appeared clinically implausible; and • usage costs in the model appeared substantially underestimated and did not reflect use in the trial on which the treatment benefit was based. 	<p>The resubmission presented a revised economic model for crisaborole versus standard management, with major changes to the time horizon, model structure, transition probabilities, drug costs, disease management costs and utilities.</p> <p>There was no economic evaluation comparing crisaborole with a potentially relevant comparator (topical corticosteroids, topical calcineurin inhibitors).</p>
<p>The PBAC considered the use of the 'rule of nines' in the weighting of the price was not appropriate and was unlikely to reflect actual use, though the distribution of affected areas between the face and eyelids versus the rest of the body in the crisaborole trials was unknown (paragraph 7.10, crisaborole PSD, November 2018 PBAC meeting).</p>	<p>The resubmission used a complex approach based on epidemiological data and the 'rule of nines' to calculate price weightings for the face and eyelids versus the rest of the body.</p>
<p>The PBAC noted that there was very limited evidence available to estimate the utilisation of crisaborole. The PBAC agreed with the DUSC that the estimated patient numbers presented were highly uncertain and likely to be underestimated (paragraph 7.11, crisaborole PSD, November 2018 PBAC meeting).</p>	<p>The resubmission used a revised mixed epidemiological and market share approach with updated data sources to estimate the financial impact of crisaborole. The approach to estimate utilisation was largely based on the economic evaluation of the resubmission.</p>
<p>The PBAC considered that the estimated prescription usage was highly uncertain and likely to be underestimated and that there would be a high likelihood of leakage to other types of dermatitis, infants under 2 years, and patients with 'steroid phobia'. The PBAC agreed with the sponsor that an RSA would be required to address the likelihood of leakage outside the restriction (paragraph 7.11, crisaborole PSD, November 2018 PBAC meeting).</p>	<p>The resubmission proposed initial and continuing restrictions, claiming that this would limit the use of crisaborole to patients with mild to moderate atopic dermatitis based on the description of symptoms in the clinical criteria. The sponsor also stated willingness to consider an RSA based on estimates of use. Detailed estimates were not provided.</p>

Source: compiled during the evaluation

Abbreviations: ISGA, Investigator's Static Global Assessment; MCID, minimal clinically important difference; RSA, risk sharing arrangement; PSD, public summary document

2.3 The PBAC previously considered that any resubmission would need to include TCS as a comparator, present a clearly defined population aligned with a tight restriction,

present clearly defined usage in terms of initiation, discontinuation and optimal duration of therapy aligned with an economic model that reflects the benefit and cost of this usage, and provide data to support uptake and estimated use of crisaborole in clinical practice. The PBAC previously acknowledged the important impact of treatments for AD on patient quality of life and considered that data showing improvement in quality of life measures may be a more suitable basis for demonstrating the cost-effectiveness of crisaborole compared with standard management or TCS (paragraph 7.12, crisaborole Public Summary Document (PSD), November 2018 PBAC meeting).

- 2.4 The ESC considered that there were unresolved discrepancies in the circumstances of use of crisaborole between the requested restriction, clinical evidence, economic evaluation and financial estimates.

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

3 Requested listing

- 3.1 The PSCR noted the restrictions have been revised with the intention of specifying that crisaborole should be subject to the following limitations:

- Patient has not had an adequate response to maximum tolerated doses of TCS (which may only consist of intermittent use of TCS); OR patient is intolerant to TCS; OR patient is contraindicated to TCS.
- Treatment with TCS should continue if intermittent TCS can be used; AND in these patients, crisaborole should only be used in periods in which a break in TCS treatment is necessary to avoid intolerance and problematic adverse effects (e.g. atrophy of the skin, infection of the skin, contact allergy, and/or systemic effects); AND TCS and crisaborole should not be used simultaneously on the same lesion.
- Treatment should be discontinued if an improvement is not shown after 3 months (i.e. AD is clear or almost clear), which is consistent with use of crisaborole in the extension study presented in detail in the resubmission.
- Once clearance or near clearance of AD is achieved, patients should take a break in crisaborole treatment and reinitiate only if there is a flare of their AD, which is consistent with use of crisaborole in the extension study presented in detail in the resubmission.

- 3.2 The submission's proposed listing is shown below, with preliminary additions suggested by the Secretariat in italics and deletions in strikethrough. The PBAC agreed with the ESC that the restriction would still require substantial work in order to adequately reflect the intentions described above.

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
CRISABOROLE 2% ointment, 30 grams	1	2	\$ [REDACTED]	Staquis	Pfizer Australia
CRISABOROLE 2% ointment, 60 grams	1	2	\$ [REDACTED]	Staquis	Pfizer Australia

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): <input checked="" type="checkbox"/> Authority Required –
Episodicity: Acute, intermittent or chronic
Severity: mild to moderate
Condition: Atopic dermatitis
Indication: Mild to moderate atopic dermatitis
Treatment Phase: Initiation
Clinical criteria: The condition must be patient has mild to moderate atopic dermatitis with erythematous patches and induration/papulation;
AND
Clinical criteria: Patient must have patient has not had an inadequate response to maximum tolerated doses of topical corticosteroid (TCS) including intermittent use of TCS OR Patient must be is intolerant to TCS treatment for this condition; OR Patient must be is contraindicated to TCS treatment for this condition;
AND
Treatment criteria: Treatment with TCS should continue if intermittent TCS can be used; AND In these patients crisaborole should only be used in periods where a break in TCS treatment is necessary to avoid intolerance and problematic adverse effects (e.g., atrophy of the skin, infection of the skin, contact allergy, and/or systemic effects); AND TCS and crisaborole should not be used simultaneously on the same lesion.
AND
Population criteria: Patient must be aged ≥ 2 years
AND
Prescribing Instructions: Intermittent use of TCS should continue, if required, while being treated with crisaborole for this indication. Crisaborole should not be used concomitantly with TCS, topical calcineurin inhibitors (TCI) or systemic corticosteroid; Treatment should be discontinued if improvement is not maintained after a 3 month period of treatment (i.e AD is clear or almost clear). Once clearance or near clearance of AD is achieved, patients should take a break in crisaborole treatment and reinitiate only if there is a flare of their AD.

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): <input checked="" type="checkbox"/> Authority Required –
Episodicity: Acute, intermittent or chronic
Severity: mild to moderate
Condition: Atopic dermatitis
Indication: Mild to moderate atopic dermatitis
Treatment Phase: Continuing
Clinical criteria:

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<i>Patient must have has responded to initial treatment with PBS-funded crisaborole treatment (i.e. achieved clearance or near clearance of AD)</i>
AND
Treatment criteria:
<i>Treatment with TCS should continue if intermittent TCS can be used; AND In these patients crisaborole should only be used in periods where a break in TCS treatment is necessary to avoid intolerance and problematic adverse effects (e.g., atrophy of the skin, infection of the skin, contact allergy, and/or systemic effects); AND TCS and crisaborole should not be used simultaneously on the same lesion</i>
Prescribing Instructions:
<i>Intermittent use of TCS should continue, if required, while being treated with crisaborole for this indication. Crisaborole should not be used concomitantly with TCS, topical calcineurin inhibitors (TCI) or systemic corticosteroid; Treatment should be discontinued if improvement is not maintained after a 3 month period of treatment (i.e AD is clear or almost clear). Once clearance or near clearance of AD is achieved, patients should take a break in crisaborole treatment and reinitiate only if there is a flare of their AD.</i>

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required):
<input checked="" type="checkbox"/> Authority Required –
Episodicity: Acute, intermittent or chronic
Severity: mild to moderate
Condition: Atopic dermatitis
Indication: <i>Mild to moderate atopic dermatitis</i>
Treatment Phase: Grandfather
Clinical criteria:
<i>Patient must have has responded to initial treatment with non-PBS funded crisaborole treatment (i.e. achieved clearance or near clearance of AD) prior to [PBS listing date]</i>
AND
Clinical criteria:
<i>The condition must have been Patient has mild to moderate atopic dermatitis with erythematous patches and induration/papulation at initiation of crisaborole;</i>
AND
Clinical criteria:
<i>Patient must have Patient has not had an inadequate response to maximum tolerated doses of topical corticosteroid (TCS) including intermittent use of TCS OR Patient must be is intolerant to TCS treatment for this condition; OR Patient must be is contraindicated to TCS treatment for this condition;</i>
AND
Treatment criteria:
<i>Treatment with TCS should continue if intermittent TCS can be used; AND In these patients crisaborole should only be used in periods where a break in TCS treatment is necessary to avoid intolerance and problematic adverse effects (e.g., atrophy of the skin, infection of the skin, contact allergy, and/or systemic effects); AND TCS and crisaborole should not be used simultaneously on the same lesion.</i>
AND
Population criteria:
<i>Patient must be aged ≥2 years</i>
AND

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Prescribing Instructions:

Intermittent use of TCS should continue, if required, while being treated with crisaborole for this indication.

Crisaborole should not be used concomitantly with TCS, topical calcineurin inhibitors (TCI) or systemic corticosteroid;

Treatment should be discontinued if improvement is not maintained after a 3 month period of treatment (i.e AD is clear or almost clear). Once clearance or near clearance of AD is achieved, patients should take a break in crisaborole treatment and reinstate only if there is a flare of their AD.

- 3.3 The proposed price for the 60 g tube (\$ [REDACTED]) was similar to the price proposed in the previous submission (DPMQ \$ [REDACTED]). No special pricing arrangement was proposed in the resubmission.
- 3.4 The resubmission proposed initial and continuing restrictions including stopping rules to attempt to reduce the risk of continued use in patients who are not responding to treatment with crisaborole. The proposed restriction was complex and may be difficult to implement in practice due to subjectivity in definitions of response. In general, PBS-listed topical corticosteroids do not have initial and continuing restrictions but tend to vary in restricted quantities depending on the amount required based on affected body surface area. The PSCR argued that the restriction makes it clear that only patients achieving clearance or near clearance of treated lesions are eligible for continuing treatment and that this endpoint (ISGA \leq 1) is not difficult for clinicians to ascertain.
- 3.5 There was inadequate justification provided for the differing quantities between the initial (30 g) and continuing (60 g) restrictions in the resubmission. The proposed amounts for both restrictions were inconsistent with trial data suggesting initial use of 3 x 60 g tubes over 4 weeks based on the key trials (AD-301 and AD-302) and continuing use of 2 x 60 g tubes in the extension study (AD-303) during 4-week on-treatment periods.
- 3.6 The requested quantity of repeats was also inadequately justified. The total quantity supplied for each continuing script including repeats (3 x 60 g tubes) would potentially allow for 4 weeks of continuous treatment based on average use reported in the key trials and was in excess of average use reported in the extension study (2 x 60 g tubes). In general, PBS-listed weak topical corticosteroids (e.g. hydrocortisone 1%, 30 g and 50 g preparations) are restricted to a maximum quantity of 1 tube and 1 repeat.
- 3.7 The proposed restriction in the resubmission is narrower than the approved TGA indication for the treatment of mild to moderate atopic dermatitis in patients of at least 2 years of age. The proposed subgroup was inadequately justified and inconsistent with the broader population enrolled in the key trials. It remains unclear if there are differences in terms of baseline severity or treatment response in the proposed subset compared with the broader population that were not limited by response, contraindication or intolerance to TCS.
- 3.8 The resubmission redefined satisfactory disease control (previously based on pimecrolimus restrictions), based on an adequate response to maximum tolerated doses of TCS, which may consist of intermittent use of TCS. The definition aims to

capture patients who are failing treatment despite maximum tolerated use of TCS, however, this is difficult to implement and is likely to include patients who are not achieving treatment response due to non-compliance. The previous submission indicated that a significant proportion of dermatology patients and parents express 'steroid phobia' (40-73%, p12-13 of November 2018 crisaborole submission) or are dissatisfied with topical corticosteroids. The ESC advised that patients should have had an inadequate response to TCS in addition to best usual care (including bleach baths where appropriate) and suggested wording to this effect be added to the restriction.

- 3.9 TCS failure: The ESC noted that the revised restrictions did not define "maximum tolerated doses of TCS" in terms of duration, potency, frequency or formulation of TCS and tolerance was also not defined. The ESC noted a recent survey of GPs indicated a significant number of GPs whose practice results in suboptimal amount and/or suboptimal duration of treatment (Smith et al 2017)¹. The ESC considered the criteria for defining failure of TCS need to be more specific and clearer, however the criteria will necessarily require clinical judgement and subjectivity, and as such there would remain a significant risk of leakage with regards to initiation of treatment outside the intended use in patients with an adequate trial with TCS or an inadequate response to TCS.
- 3.10 TCS intolerance: The commentary noted the population who are intolerant to TCS remains poorly defined in the resubmission and appears to be broadly based on concepts of steroid phobia and limitations associated with TCS use in sensitive areas and potential long-term TCS-related adverse events. The ESC noted that the resubmission attempted to clarify the concept of intolerance as development of atrophy of the skin, infection of the skin, contact allergy and/or systemic effects. The ESC considered that although the intention of adding these treatment criteria was reasonable, their inclusion may unhelpfully overstate the adverse effects of TCS. The ESC noted that perception of risks by a significant proportion of GPs are greater than the actual risks suggested by the evidence for TCS². The ESC considered that there is potential for misunderstanding amongst GPs that the clinical place of crisaborole is to reduce TCS use, and that re-education of primary care providers is likely to be difficult to achieve. This could result in treatment of patients with crisaborole, who are not intended for treatment under the sponsor's stated restriction, due to high perception of risk with TCS by both patients and GPs.
- 3.11 TCS contraindication: The ESC agreed with the commentary that the population who are contraindicated to topical corticosteroids, particularly in the whole of body, remains inadequately defined in the resubmission. No data were provided for crisaborole in the subgroup of patients who are contraindicated to TCS. The ESC noted

¹ Smith, Saxon D., et al. "General practitioners' knowledge about use of topical corticosteroids in paediatric atopic dermatitis in Australia." *Australian Family Physician* 46.5 (2017): 335.

² Smith, Saxon D., et al. "General practitioners' knowledge about use of topical corticosteroids in paediatric atopic dermatitis in Australia." *Australian Family Physician* 46.5 (2017): 335.

that there are a variety of contraindications for TCS as included in their PIs and it was unclear which contraindications would be applicable. The ESC considered that there would be very few patients genuinely contraindicated to TCS but not contraindicated to crisaborole.

- 3.12 There is also potential for use outside the requested restriction due to subjectivity in the definitions of disease severity, potential for use in other types of dermatitis and in younger patients (less than 2 years of age). The sponsor indicated willingness to consider a risk-sharing agreement to address the potential for leakage of use outside of the proposed restriction.
- 3.13 The ESC noted that the sponsor had attempted to address the PBAC's previous concerns regarding the restriction and welcomed the changes aimed at improving the clarity of the restriction. The ESC noted that the utilisation as intended requires first that there is appropriate use of TCS. The ESC considered there is a need to further refine the restriction in terms of ensuring that patients have received and continue to receive adequate doses and duration of treatment with corticosteroids. The ESC noted that the sponsor is willing to consider other options to clarify the intended population in the restriction, or to manage the risk of use beyond the intended population and also to determine the appropriate essential elements of the restriction (PSCR). The ESC considered that the restriction needs substantial work, and even with further refinement to restriction criteria it is likely to be difficult to ensure that patients have received and continue to receive adequate doses and duration of treatment with TCS. The Pre-PBAC response also acknowledged the potential for leakage for use outside the

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

4 Population and disease

- 4.1 Atopic dermatitis is a chronic, inflammatory skin condition that occurs predominantly in the paediatric population. The disease is characterised by dry skin, itching and skin lesions which are typically red, scaly and crusted papules (raised bumps). Symptoms may be continuous for long periods or of a relapsing-remitting nature with repeated flare-ups. Clinical presentation of atopic dermatitis is highly variable and is dependent on age, phase (chronic or acute) and disease severity.
- 4.2 The positioning of crisaborole in the resubmission was more clearly articulated, but otherwise unchanged from the previous submission.
- 4.3 The PBAC noted the NICE definitions³ of mild and moderate atopic dermatitis:

³ NICE 2007. Atopic eczema in under 12s: diagnosis and management. Quick Reference Guide December 2007. <https://www.guidelines.co.uk/skin-and-wound-care/nice-eczema-guideline/207625.article>.

- Mild: areas of dry skin, infrequent itching, little impact on everyday activities or sleep.
 - Moderate: areas of dry skin, frequent itching, redness (with or without excoriation) moderate impact on everyday activities and psychosocial wellbeing, frequently disturbed sleep.
- 4.4 The resubmission considered crisaborole, could be used alongside intermittent use of TCS. This would need to relate to periods where a break in TCS is necessary to prevent TCS-related adverse events, and concomitant use of both treatments on any lesion would be inconsistent with the intended positioning of crisaborole. There are no data available to support the efficacy and safety of crisaborole use in this setting.
- 4.5 The PBAC noted that established approaches to atopic dermatitis⁴ include:
- manage aggravating factors (e.g. contact with irritants such as soap, rough clothing, barrier ointments to manage contact with irritants)
 - Improve skin condition (e.g. use of soap substitutes, dispersible oils when bathing, emollients)
 - treat infection
 - Apply TCS, noting recurrence is more common if inflammation is undertreated, and skin atrophy is a concern but a rare adverse event as are systemic events. TCS should be applied liberally to all areas of redness until dermatitis has gone and skin is completely clear.
- The PBAC considered that these aspects of treatment were important because the proposed clinical place for crisaborole requires patients have had inadequate response to standard care, including adequate use of TCS.
- 4.6 Recent guidelines suggest that the role of crisaborole remains uncertain due to limited comparative data with established therapies for atopic dermatitis and uncertain efficacy due to the strong placebo effect noted in its key trials (UpToDate - Atopic Dermatitis June 2020).
- 4.7 The PBAC previously noted that the data presented in the submission was limited to 4 weeks of acute treatment, but assumed that long-term intermittent use was likely (paragraph 7.4, crisaborole PSD, November 2018 PBAC meeting). The clinician presenting the sponsor hearing for the November 2018 submission stated that crisaborole would be used as sole therapy, as per the clinical trials, and is likely to be used intermittently for flares for 2-3 weeks at a time (paragraph 6.1, crisaborole, PSD, November 2018 PBAC meeting).
- 4.8 The resubmission claimed that if a patient achieves disease clearance, then crisaborole can be stopped and reinitiated when the condition flares. The

⁴ eTG guidelines: Atopic dermatitis. eTG August 2020 edition.

resubmission also claimed that long-term use of crisaborole would be limited to three consecutive months without disease clearance. This appears to be based on the circumstances of use in the AD-303 open-label safety extension study, which may not be representative of clinical practice, where patients are unlikely to adopt the same on/off treatment cycles.

- 4.9 The resubmission identified a number of ongoing studies of crisaborole when used as ongoing maintenance therapy, an active-controlled trial comparing crisaborole with established therapies (hydrocortisone, pimecrolimus) and ointment vehicle, and a proof of concept study for the use of crisaborole as a steroid-sparing agent. These studies may provide some clarity on the future place in therapy for crisaborole. The ESC considered that there is a possible risk that prescribers will perceive crisaborole as a steroid sparer/alternative despite its proposed use in the resubmission, and this risk may be increased with studies being conducted with crisaborole in this setting.

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

5 Comparator

- 5.1 The resubmission nominated pimecrolimus as the comparator for use on the face and eyelids. The PBAC considered that this was appropriate, although tacrolimus ointment may also be a relevant comparator (paragraph 5.1, crisaborole, PSD, November 2018 PBAC meeting).
- 5.2 For the rest of the body, the resubmission nominated standard management as the comparator. As per the November 2018 submission, standard management was defined as the use of moisturisers, emollients and non-irritant cleansers. The resubmission argued that it is not intended for crisaborole to replace TCS use when TCS is effective, including intermittent TCS use. The ESC considered that it would be unusual for patients with mild to moderate AD to have an inadequate response to TCS when appropriate dosages and durations are used. The PBAC noted that the pre-PBAC response disagreed with this contention. The resubmission claimed that crisaborole is only intended for use in periods in between TCS use (e.g. patients who experience a flare-up of symptoms when a pause of TCS use is necessary), and therefore, standard management was the appropriate comparator.
- 5.3 In November 2018, the PBAC considered that standard management was the appropriate comparator for the small number of patients who are contraindicated to TCS. For the remaining patients who have failed to achieve satisfactory disease control with TCS or who are intolerant to TCS, the PBAC previously considered that some degree of continuing TCS use is likely for symptom management and that TCS should be included as a comparator. The PBAC also previously noted that this was consistent with its previous consideration of pimecrolimus (pimecrolimus PSD July 2006) in which TCS was considered as an appropriate comparator for treatment of patients contraindicated to or failing intermittent TCS (paragraph 7.5, crisaborole PSD, November 2018 PBAC meeting).

- 5.4 The ESC noted that the PSCR clarified that the proposed place of crisaborole in the resubmission was not as a TCS-sparing agent or to replace TCS use, and that the intent of the revised restriction was that crisaborole be used only when patients are unable to use TCS. As such the sponsor maintained that there is no intent for crisaborole to be used in place of TCS and thus TCS is not a relevant comparator. The ESC considered that although this may be reasonable, there is only a very small proportion of the AD population unable to be treated with TCS where they are used appropriately.
- 5.5 The ESC considered that despite the wording of the restriction, there is a possible risk that prescribers will perceive crisaborole as a steroid sparer/alternative. No evidence has been presented for its use in this context, although there are several ongoing trials. Appropriate use of crisaborole within the proposed restriction is predicated on appropriate use of TCS which would require significant additional resources to the re-education of the large and diverse prescriber base and patients to avoid the effects of “steroid phobia”. The PBAC considered that patients frequently do not receive an adequate level of standard care, including adequate use of TCS, despite adverse events associated with TCS being very rare. The PBAC considered that there is a considerable risk crisaborole will be used as a steroid sparer/alternative in practice, despite the intention of the restrictions proposed, in which case TCS would be a relevant comparator.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (3), health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the substantial impact on quality of life, physical and mental health outcomes associated with atopic dermatitis and the financial burden of managing the disease. The comments noted that some patients are currently able to access crisaborole but that others are not able to afford treatment. Comments also noted that crisaborole has the benefit of being able to be used long term and provides an alternative for treatment in sensitive and thin skin areas such as face and eyelids.

Clinical trials

- 6.3 The resubmission was based on the following comparisons of crisaborole and the nominated comparators:

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- Direct comparison of crisaborole versus ointment vehicle based on two head-to-head randomised trials (AD-301, AD-302). This was previously considered by the PBAC in November 2018.
 - Indirect comparison of crisaborole (AD-301, AD-302) versus pimecrolimus (Barba 2003, Trials B305 and B307, Leung 2009) using ointment vehicle/cream vehicle as the common reference. These trials were considered by the PBAC in November 2018, however, two studies of infants (Breuer 2004 and Trial 0316) that were previously included in the submission’s indirect analysis have been excluded from the comparison in the resubmission.
- 6.4 The resubmission also included the following analyses of AD-301, AD-302 and AD-303 trial data that have not previously been considered by the PBAC⁵:
- Post-hoc subgroup analyses by prior TCS use based on the key trials (AD-301, AD-302)
 - Post-hoc analyses of ISGA scores from the key trials AD-301, AD-302 and the AD-303 safety extension study.
- 6.5 The PSCR stated that the sponsor considered the data from AD-303 to be key analyses as they address a key concern of the PBAC (efficacy of intermittent use of crisaborole).
- 6.6 Details of the trials presented in the resubmission are provided in the table below.

⁵ *Note that the additional analyses described here are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Studies AD-301, AD-302 or AD-303. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

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Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Crisaborole trials		
AD-301	Paller AS, Tom WL, Lebwohl MG et al (2016). Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults	Journal of the American Academy of Dermatology, 75(3):494-503
	Yosipovitch G, Simpson EL, Tan H, et al (2018). Effect of crisaborole topical ointment, 2%, on atopic dermatitis–associated pruritus: an extended analysis of 2 phase 3 clinical trials.	Itch, 3:e12
	Yosipovitch G, Simpson EL, Bushmakin AG et al (2018). Assessment of pruritus in atopic dermatitis: validation of the Severity of Pruritus Scale (SPS)	Itch, 3:e13
	Study AD-301 (23 November 2015). A multicenter, randomized, double-blind, vehicle-controlled study of the safety and efficacy of AN2728 topical ointment, 2% in children, adolescents, and adults (ages 2 years and older) with atopic dermatitis	Internal study report
AD-302	Paller AS, Tom WL, Lebwohl MG et al (2016). Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults	Journal of the American Academy of Dermatology, 75(3):494-503
	Yosipovitch G, Simpson EL, Tan H, et al (2018). Effect of crisaborole topical ointment, 2%, on atopic dermatitis–associated pruritus: an extended analysis of 2 phase 3 clinical trials	Itch, 3:e12
	Yosipovitch G, Simpson EL, Bushmakin AG et al (2018). Assessment of pruritus in atopic dermatitis: validation of the Severity of Pruritus Scale (SPS)	Itch, 3:e13
	Study AD-302 (23 November 2015). A multicenter, randomized, double-blind, vehicle-controlled study of the safety and efficacy of AN2728 topical ointment, 2% in children, adolescents, and adults (ages 2 years and older) with atopic dermatitis	Internal study report
AD-303 extension study	Eichenfield LF, Call RS, Forsha DW et al (2017). Long term safety of crisaborole ointment 2% in children and adults with mild to moderate atopic dermatitis	Journal of the American Academy of Dermatology, 77:641-649
	Study AD-303 (24 November 2015). A multicenter, open-label study of the long-term safety of AN2728 topical ointment, 2% in the treatment of children, adolescents, and adults (Ages 2 Years and Older) with atopic dermatitis	Internal study report
Pimecrolimus trials		
Barba 2003	Barba JF (2003). Pimecrolimus cream 1% is effective, well tolerated and safe in infants/children with atopic eczema of the face. The 12th Congress of the European Academy of Dermatology and Venereology. Barcelona, Spain 15-18th October 2003.	Journal of the European Academy of Dermatology And Venereology, Abstract P2-35
Trials B305 and B307	Eichenfield LF, Lucky AW, Boguniewicz M et al (2002). Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents	Journal of the American Academy of Dermatology, 46(4):495-504
	Langley, RG, Eichenfield LF, Lucky AW et al (2008). Sustained efficacy and safety of pimecrolimus cream 1% when used long-term (up to 26 weeks) to treat children with atopic dermatitis	Pediatric dermatology, 25(3):301-307
Leung 2009	Whalley D, Huels J, McKenna SP et al (2002). The benefit of pimecrolimus (Elidel, SDZ ASM 981) on parents' quality of life in the treatment of pediatric atopic dermatitis	Pediatrics, 110(6):1133-1136
	Leung DY, Hanifin JM, Pariser DM et al (2009). Effects of pimecrolimus cream 1% in the treatment of patients with atopic dermatitis who	British Journal of Dermatology, 161(2):435-443

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Trial ID	Protocol title/ Publication title	Publication citation
	demonstrate a clinical insensitivity to topical corticosteroids: a randomized, multicentre vehicle-controlled trial	

Source: Table 2.2-1, pp38-42 and Table 2.2-1, pp86-87 of the resubmission

6.7 The key features of the included trials are summarised in the table below.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Crisaborole vs. ointment vehicle						
AD-301 ^a	763	MC, DB, R, VC 29 days	Low	≥2 years old with mild to moderate AD	ISGA 0 or 1 with ≥2-grade improvement; ISGA 0 or 1	Post-hoc analyses of ISGA scores (descriptive results only) from the key trials AD-301, AD-302 and the AD-303 safety extension study, transformed to transition probabilities ^c
AD-302 ^a	764	MC, DB, R, VC 29 days	Low	≥2 years old with mild to moderate AD		
AD-303 extension study	517	MC, OL, SA Up to 48 weeks	High	Patients who completed the AD-301 or AD-302 study	Safety only	
Meta-analysis	1527	Included ISGA outcomes from the crisaborole and ointment vehicle arms in Trials AD-301 and AD-302				
Pimecrolimus vs. cream vehicle						
Barba 2003	106	MC, DB, R, VC 3 weeks	Unclear	3 months to 18 years old with mild to moderate facial AD	Facial-IGA of 0 or 1, IGA of 0 or 1, EASI score	Not used
Trial B305 ^b	198	MC, DB, R, VC 6 weeks	Unclear	1-17 years old with mild to moderate AD	IGA 0 or 1, EASI score	Not used
Trial B307 ^b	205	MC, DB, R, VC 6 weeks	Unclear	1-17 years old with mild to moderate AD	IGA 0 or 1, EASI score	Not used
Leung 2009	73	MC, DB, R, VC 6 weeks	Low	2-50 years old with mild to moderate AD who have failed topical corticosteroids	Relationship between laboratory and clinical assessments, IGA 0 or 1	Not used

Source: compiled during the evaluation based on Table 2.2-1, pp38-42 and Table 2.2-1, pp86-87 of the resubmission

Abbreviations: AD, atopic dermatitis; DB, double blind; EASI, Eczema Area & Severity Index; IGA, Investigator's Global Assessment; ISGA, Investigator's Static Global Assessment; MC, multi-centre; OL, open label; R, randomised; SA, single arm; VC, vehicle-controlled

^a Identical study designs

^b Identical study designs

^c Note that the analyses described here are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Studies AD-301, AD-302 or AD-303. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.8 The AD-303 study was not designed to evaluate efficacy, however, disease severity based on ISGA score was assessed at 28-day intervals. The resubmission conducted post-hoc efficacy analyses using individual patient data. The ESC agreed with the commentary that results from the analyses are subject to a high risk of bias.

6.9 There was limited information reported for the Barba 2003 trial, which was only available in an abstract. The overall risk of bias was unclear.

6.10 The overall risk of bias for Trials B305 and B307 was unclear as data were only reported as a pooled analysis in the publication. During the evaluation, additional data from the

individual studies were extracted from the FDA statistical review for pimecrolimus 1% cream (2001).

Comparative effectiveness

Crisaborole trials

- 6.11 The results from the key crisaborole trials, AD-301 and AD-302 were previously considered by the PBAC in November 2018.
- 6.12 The primary and secondary endpoints of the crisaborole trials were based on Investigator’s Static Global Assessment (ISGA) scored on a 5-point severity scale ranging from clear (0), almost clear (1), mild (2), moderate (3) and severe (4). The PBAC recalled it had previously noted the clinical importance of the ISGA endpoint was uncertain (paragraph 7.6, crisaborole, PSD, November 2018 PBAC meeting) and outcomes based on ISGA appeared more subjective than commonly used clinical tools such as Eczema Area and Severity Index (EASI) or SCORing Atopic Dermatitis (SCORAD) (paragraph 6.15, crisaborole, PSD, November 2018 PBAC meeting). The PBAC noted that outcomes based on EASI and SCORAD, were not captured in the crisaborole studies.

Table 5: Results for ISGA score of clear or almost clear (0 or 1) at Day 29 with at least 2-grade improvement from baseline (ITT population)

Trial AD-301	Crisaborole N=503	Ointment vehicle N=256	p-value
MCMC multiple imputation	32.8%	25.4%	0.033 ^a
Logistic regression multiple imputation	29.1%	22.0%	0.038 ^b
Trial AD-302	Crisaborole N=513	Ointment vehicle N=250	p-value
MCMC multiple imputation	31.4%	18.0%	<0.001 ^a
Logistic regression multiple imputation	26.5%	14.2%	<0.001 ^b

Source: Table 17, p80, and Table 14.2.6, p228 of the AD-301 trial report; Table 17, p80 and Table 14.2.6, p224 of the AD-302 trial report
Abbreviation: ISGA, Investigator’s Static Global Assessment (5-point scale); MCMC, Markov Chain Monte Carlo; NR, not reported

^a The p-value from a Cochran-Mantel-Haenszel test, stratified by analysis centre. Values adjusted for multiple imputation.

^b The p-value from a logistic regression (with Firth option) test with factors of treatment group and analysis centre. Values were adjusted for multiple imputation.

Note 1: Crude number of events for each arm in the ITT population for the primary endpoint was not reported. The odds ratio was a planned outcome, however, results were not reported.

Note 2: Estimates in grey were used in the meta-analysis of the primary outcome of both trials

Table 6: Results for ISGA score of clear or almost clear (0 or 1) at Day 29 with no requirement for ≥2-grade improvement (ITT population)

Trial AD-301	Crisaborole N=503	Ointment vehicle N=256	p-value
MCMC multiple imputation	260 (51.7%)	104 (40.6%)	NR
Logistic regression multiple imputation	49.0%	37.7%	0.005 ^a
Trial AD-302	Crisaborole N=513	Ointment vehicle N=250	p-value
MCMC multiple imputation	249 (48.5%)	74 (29.7%)	NR
Logistic regression multiple imputation	45.2%	25.5%	<0.001 ^a

Source: Table 18, p83, Table 14.2.5.3.1, p202 of the AD-301 trial report; Table 18, p83 and Table 14.2.5.3.1, p198 of the AD-302 trial report
Abbreviations: ISGA, Investigator’s Static Global Assessment (5-point scale); MCMC, Markov Chain Monte Carlo; NR, not reported

^a The p-value from a logistic regression (with Firth option) test with factors of treatment group and analysis centre. Values were adjusted for multiple imputation.

Note: Estimates highlighted in grey were used in the indirect comparison of crisaborole versus pimecrolimus

- 6.13 A statistically significantly higher proportion of patients treated with crisaborole achieved an ISGA score of 0 or 1 and ≥ 2-grade improvement at 4 weeks from baseline than patients receiving the ointment vehicle. The statistical significance of results from Trial AD-301 and absolute proportion of patients achieving the endpoint in both trials appeared sensitive to the method of imputation used. Unadjusted estimates were not provided in the resubmission. The differences between the methods of imputation were unclear due to limited documentation.
- 6.14 Results for the secondary endpoint of the crisaborole trials suggest that treatment with crisaborole was associated with statistically significantly more patients achieving clear or almost clear disease (with no minimum requirement in score improvement) compared with vehicle-treated patients. The statistical significance of results based on the Markov Chain Monte Carlo imputation method was unclear due to limited documentation. The absolute proportions achieving the endpoint also varied depending on method of imputation used.
- 6.15 The key trials included scores from age-dependent dermatology-related quality of life questionnaires. The data were descriptively summarised by treatment group at each time point, as well as change from baseline (Children’s Dermatology Life Quality Index, CDLQI for subjects aged 2–15 years; Dermatology Life Quality Index, DLQI for subjects aged 16 years and older; and Dermatitis Family Impact, DFI for parents/guardians of subjects aged 2–17 years). The assessment scales included sets of 10 questions that generate a cumulative score out of 30; higher scores indicate larger (worse) impacts on quality of life.

Table 7: Results from descriptive analyses of dermatology-specific quality of life questionnaires (AD-301, AD-302 and pooled trial analyses)

Trial	Treatment arms	Baseline, mean (SD)	Day 29, mean (SD)	Change from baseline, mean (SD)	Crude difference
Children’s Dermatology Life Quality Index (CDLQI), patients aged 2-15 years					
AD-301	Crisaborole (n=393)	9.7 (6.2)	4.5 (4.8)	-5.2 (5.6)	-2.1
	Vehicle (n=199)	9.1 (6.5)	5.9 (6.0)	-3.1 (5.9)	
AD-302	Crisaborole (n=404)	9.0 (5.8)	4.8 (4.6)	-4.0 (4.9)	-1.1
	Vehicle (n=204)	8.9 (5.5)	6.0 (5.1)	-2.9 (5.0)	
Pooled trial analysis	Crisaborole (n=750)	9.3 (NR)	NR	-4.6 (NR)	-1.6 p <0.001
	Vehicle (n=355)	9.0 (NR)	NR	-3.0 (NR)	
Dermatology Life Quality Index (DLQI), patients aged ≥16 years					
AD-301	Crisaborole (n=95)	9.6 (6.4)	3.8 (4.2)	-5.5 (5.5)	-1.9
	Vehicle (n=52)	9.5 (6.5)	5.6 (5.9)	-3.6 (4.6)	
AD-302	Crisaborole (n=97)	9.7 (6.2)	4.6 (5.0)	-5.0 (5.5)	-1.6
	Vehicle (n=40)	9.1 (6.7)	5.4 (4.8)	-3.4 (4.8)	
Pooled trial analysis	Crisaborole (n=180)	9.7 (NR)	NR	-5.2 (NR)	-1.7 p=0.015
	Vehicle (n=82)	9.3 (NR)	NR	-3.5 (NR)	
Dermatitis Family Impact Questionnaire (DFI), parents/guardians/families of patients 2-17 years					
AD-301	Crisaborole (n=431)	8.5 (6.6)	4.5 (5.6)	-3.9 (5.7)	-1.2
	Vehicle (n=214)	7.5 (6.7)	4.7 (5.9)	-2.7 (5.6)	
AD-302	Crisaborole (n=431)	7.7 (6.6)	4.0 (4.8)	-3.6 (5.2)	-0.8
	Vehicle (n=217)	8.0 (5.7)	5.0 (4.5)	-2.8 (4.8)	
Pooled trial analysis	Crisaborole (n=811)	8.1 (NR)	NR	-3.7 (NR)	-1.0 p=0.003
	Vehicle (n=377)	7.8 (NR)	NR	-2.7 (NR)	

Source: Table 14.2.4.1, p191 of the AD-301 trial report; Table 14.2.4.1, p188 of the AD-302 trial report; Simpson et al (2018) publication
Abbreviation: SD, standard deviation

* Note that the results presented in Table 7 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for Studies AD-301 and AD-302. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.16 The results suggest improvement in dermatology-related quality of life scores in both treatment arms of the key trials and post-hoc analyses using pooled trial data. The publication for the pooled trial analysis nominated MCIDs for change from baseline of ≥2.5-point change for the Children’s Dermatology Life Quality Index and ≥3.3-point change for the Dermatology Life Quality Index (Simpson et al 2018). The results from both treatment arms met the nominated MCIDs.
- 6.17 There was a numerically greater change in the scores from baseline in patients treated with crisaborole compared to its vehicle. The magnitude of difference between treatment arms was smaller than the change from baseline in the individual arms. It was unclear if this was clinically important.
- 6.18 The resubmission claimed that the vehicle itself has a therapeutic benefit, therefore the difference in treatment effect due to crisaborole is likely to be higher when compared to placebo. No data were provided on the magnitude of treatment effect associated with the vehicle versus placebo.
- 6.19 AD-303 was a 48-week safety extension study following on from parent trials AD-301 and AD-302. An exploratory analysis was conducted on topical rescue medication use

(topical corticosteroids or calcineurin inhibitors) that was permitted during the study. Overall 22% of patients used rescue medication and the majority resumed treatment with crisaborole at a later date. Although efficacy was not formally assessed in this study, an additional exploratory analysis suggested that approximately 30% of patients who received crisaborole continuously for at least 12 weeks had no improvement in ISGA.

Additional analyses (not previously considered by the PBAC)⁶

- 6.20 To address concerns regarding the lack of subgroup data for the requested restriction, the resubmission presented post-hoc subgroup analyses by prior TCS use for the primary and secondary endpoints of the key trials AD-301 and AD-302. The resubmission claimed that prior TCS use was not a treatment effect modifier, therefore the clinical evidence based on the broader atopic dermatitis population was applicable to the requested subgroup. The analyses were based on patients with a history of TCS use, which may not be representative of the requested subgroup who are failing, are intolerant or contraindicated to TCS.
- 6.21 The usefulness of the analyses was limited by poor documentation, lack of patient characteristics for the subgroups and lack of interaction testing. Overall, there remains insufficient data to determine if there are differences in terms of baseline severity or treatment benefit in the proposed PBS population compared with the broader population not limited by response, contraindication or intolerance to TCS. The PSCR suggested that the study population would be motivated to participate in the study due to efficacy or safety issues with TCS. The ESC considered the population in this analysis is not the same as the proposed PBS population and suggested it is likely that the motivation to participate in the clinical studies would be broader than as specified in the restriction. The ESC considered that it was unclear how the sub-group with previous steroid use relates to the requested population (those with inadequate response to TCS, intolerant to TCS or contraindicated to TCS), and it was unclear what proportion of the sub-group could have been managed with TCS without the need for other agents.
- 6.22 To address concerns regarding the lack of long-term efficacy data for crisaborole, the resubmission presented analyses of ISGA scores over time using data from the AD-301, AD-302 trials and the AD-303 open-label safety extension study.
- 6.23 During the evaluation the presentation of these results was simplified for ease of interpretation. See also Table 2.5.7 of the submission for full results of the proportion

⁶ Note that the results presented in Paragraphs 6.20 to 6.31 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for AD-301, AD-302 or AD-303. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

of patients with ISGA scores on the day after four weeks of treatment in AD-301 and AD-302. Full results for ISGA scores at Day 29 of each 28-day treatment period in the subgroup of patients from the parent trials, AD-301 and AD-302, who subsequently enrol in the AD-303 safety extension study are shown in Table 9. The table below presents the proportion of patients with ISGA scores on the day after four weeks of treatment in the key trials.⁷

Table 8: Proportion of patients with ISGA scores at Day 29 after 4 weeks of treatment in trials AD-301 and AD-302 (ITT population)

Day 29 ISGA score, n (%)													
Crisaborole							Vehicle						
N	0	1	2	3	4	Miss.	N	0	1	2	3	4	Miss.
AD-301													
503	85 (16.9)	167 (33.2)	138 (27.4)	80 (15.9)	8 (1.6)	25 (5.0)	256	31 (12.1)	67 (26.2)	64 (25.0)	62 (24.2)	4 (1.6)	28 (10.9)
AD-302													
513	81 (15.8)	159 (31.0)	133 (25.9)	106 (20.7)	7 (1.4)	27 (5.3)	250	17 (6.8)	53 (21.2)	64 (25.6)	85 (34.0)	5 (2.0)	26 (10.4)
Pooled													
1016	166 (16.3)	326 (32.1)	271 (26.7)	186 (18.3)	15 (1.5)	52 (5.1)	506	48 (9.5)	120 (23.7)	128 (29.1)	147 (29.1)	9 (1.8)	54 (10.7)

Source: Table 2.5.7, p68 of the resubmission

Abbreviation: ISGA, Investigator's Static Global Assessment; Miss, missing

- 6.24 The results for the crisaborole arms in both trials appeared similar whereas more patients in the AD-301 vehicle arm achieved a clear/almost clear score compared to the vehicle arm of AD-302. This numerical trend was consistent with outcomes based on results from the pre-specified outcomes. Based on these results, more patients in the vehicle arm of AD-301 achieved an ISGA of 0 or 1 (38.3%) compared with the vehicle arm of AD-302 (28%). This was consistent with moderate statistical heterogeneity in the meta-analysed results of these trials, reasons for which were not explored in the resubmission.
- 6.25 There were more patients with missing data in the vehicle arms compared with the crisaborole arms, which was consistent with higher discontinuation rates for the vehicle versus crisaborole (AD-301, 12.1% vs 5.9%; AD-302, 14.8% vs 6.0%). The difference was primarily driven by subject/patient/guardian withdrawal. Specific reasons for these withdrawals were not reported.
- 6.26 The resubmission also presented the ISGA scores at Day 29 of each 28-day treatment period in the subgroup of patients from the parent trials, AD-301 and AD-302, who

⁷ Note that the results presented in Paragraphs 6.20 to 6.31 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for AD-301, AD-302 or AD-303. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

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subsequently enrol in the AD-303 safety extension study, representing the movement of patients across the symptom severity scale over time.

Table 9: Proportion of patients with ISGA scores for each cycle and ISGA scores at the end of cycle at Day 29 after each 28-day treatment cycle based on data from AD-301, AD-302 and AD-303 extension study*

ISGA at start of cycle	Patients ISGA Score at end of cycle n(%)						
	0	1	2	3	4	DC/EOS	Total
Cycle 2							
0	12 (38)	12 (38)	6 (19)	1 (3)	0 (0)	1 (3)	32
1	7 (14)	20 (41)	19 (39)	3 (6)	0 (0)	0 (0)	49
2	29 (13)	36 (17)	115 (53)	28 (13)	0 (0)	10 (5)	218
3	7 (4)	17 (9)	84 (44)	66 (34)	4 (2)	15 (8)	193
4	0 (0)	0 (0)	1 (8)	7 (58)	2 (17)	2 (17)	12
Cycle 3							
0	20 (36)	13 (24)	20 (36)	1 (2)	0 (0)	1 (2)	55
1	4 (5)	40 (47)	33 (39)	5 (6)	1 (1)	2 (2)	85
2	14 (6)	45 (20)	119 (53)	39 (17)	0 (0)	8 (4)	225
3	2 (2)	10 (10)	41 (39)	43 (41)	0 (0)	9 (9)	105
4	0 (0)	0 (0)	1 (17)	3 (50)	0 (0)	2 (33)	6
Cycle 4							
0	18 (45)	7 (18)	14 (35)	1 (3)	0 (0)	0 (0)	40
1	16 (15)	39 (36)	38 (35)	11 (10)	0 (0)	4 (4)	108
2	17 (8)	58 (27)	111 (52)	20 (9)	0 (0)	8 (4)	214
3	0 (0)	14 (15)	29 (32)	35 (38)	2 (2)	11 (12)	91
4	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	1
Cycle 5							
0	23 (45)	12 (24)	14 (27)	2 (4)	0 (0)	0 (0)	51
1	14 (12)	42 (36)	44 (37)	17 (14)	1 (1)	0 (0)	118
2	15 (8)	36 (19)	109 (56)	28 (15)	0 (0)	5 (3)	193
3	2 (3)	7 (10)	31 (46)	24 (36)	0 (0)	3 (4)	67
4	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	1 (50)	2
Cycle 6							
0	29 (54)	9 (17)	13 (24)	0 (0)	0 (0)	3 (6)	54
1	16 (16)	45 (46)	29 (30)	5 (5)	0 (0)	2 (2)	97
2	16 (8)	54 (27)	102 (51)	22 (11)	2 (1)	3 (2)	199
3	3 (4)	8 (11)	33 (46)	25 (35)	1 (1)	1 (1)	71
4	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	1
Cycle 7							
0	31 (48)	9 (14)	19 (30)	3 (5)	0 (0)	2 (3)	64
1	20 (17)	54 (47)	34 (29)	6 (5)	0 (0)	2 (2)	116
2	13 (7)	43 (24)	83 (47)	30 (17)	1 (1)	7 (4)	177
3	2 (4)	7 (13)	15 (29)	24 (46)	3 (6)	1 (2)	52

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ISGA at start of cycle	Patients ISGA Score at end of cycle n(%)						
	0	1	2	3	4	DC/EOS	Total
4	0 (0)	0 (0)	1 (25)	2 (50)	0 (0)	1 (25)	4
Cycle 8							
0	41 (62)	8 (12)	12 (18)	0 (0)	0 (0)	5 (8)	66
1	17 (15)	45 (40)	37 (33)	8 (7)	0 (0)	6 (5)	113
2	20 (13)	46 (30)	58 (38)	20 (13)	1 (1)	7 (5)	152
3	2 (3)	2 (3)	22 (34)	33 (51)	2 (3)	4 (6)	65
4	0 (0)	0 (0)	0 (0)	3 (75)	1 (25)	0 (0)	4
Cycle 9							
0	42 (53)	17 (21)	16 (20)	1 (1)	0 (0)	4 (5)	80
1	16 (16)	45 (45)	34 (34)	2 (2)	0 (0)	4 (4)	101
2	4 (3)	25 (19)	68 (53)	22 (17)	0 (0)	10 (8)	129
3	1 (2)	3 (5)	28 (44)	22 (34)	0 (0)	10 (16)	64
4	0 (0)	0 (0)	2 (50)	1 (25)	1 (25)	0 (0)	4
Cycle 10							
0	31 (49)	15 (24)	9 (14)	4 (6)	0 (0)	4 (6)	63
1	17 (19)	37 (41)	27 (30)	3 (3)	0 (0)	6 (7)	90
2	17 (11)	31 (21)	67 (45)	22 (15)	2 (1)	9 (6)	148
3	0 (0)	3 (6)	23 (48)	13 (27)	1 (2)	8 (17)	48
4	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1
Cycle 11							
0	41 (63)	8 (12)	9 (14)	3 (5)	0 (0)	4 (6)	65
1	9 (10)	39 (45)	30 (35)	3 (3)	0 (0)	5 (6)	86
2	10 (8)	20 (16)	66 (52)	17 (13)	0 (0)	13 (10)	126
3	0 (0)	4 (9)	16 (37)	17 (40)	0 (0)	6 (14)	43
4	0 (0)	1 (33)	1 (33)	1 (33)	0 (0)	0 (0)	3

Source: Table 2.5.9, p 69 of the submission

Abbreviations: ISGA, Investigator's Static Global Assessment.

Note: The study drug was administered in 4-week on-treatment periods. The investigator initiated an on-treatment period if the ISGA score was ≥ 2 . Subjects with an ISGA score of ≤ 1 entered and off-treatment period. Study drug was discontinued if there was not improvement in a subject's ISGA after 3 consecutive cycles of study drug.

A large proportion of patients discontinued at cycles 12 and 13 as this was the end of the study. The study was terminated after 271 patients completed 1 year and 396 patients completed 6 months of safety follow-up.

*Note that the results presented in Paragraphs 6.20 to 6.31 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for AD-301, AD-302 or AD-303. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.27 The resubmission acknowledged that interpretation of the data was difficult due to treatment protocols that determined on- or off-treatment periods depending on ISGA scores in the previous cycle. Overall, the data (not including end-of-study cycles 12 and 13) suggest fluctuations in cycle-to-cycle disease severity amongst those who

achieve clearance (8.4% to 20.0%), almost clear (16.9% to 27.5%), mild (32.3% to 46.2%), moderate (12.3% to 20.8%) and severe (0% to 1.2%) disease.⁸

- 6.28 The resubmission claimed the results are representative of the long-term movement of patients in terms of disease severity and can be used to inform the transition probabilities in the economic model. The PSCR also noted the following observations from this data: over 60% of patients who achieve ISGA ≤ 1 maintained response through to the next cycle; approximately 35% of patients with ISGA ≤ 1 (who were not on treatment) at the start of a cycle experienced a flare and developed ISGA ≥ 2 in a cycle; approximately 25% of patients with ISGA ≥ 2 at the start of a cycle achieved or regained response to crisaborole within one cycle. The PSCR argued that patients with ISGA ≤ 1 were likely to have discontinued because they had achieved long term symptom control, whereas patients with ISGA ≥ 2 more likely discontinued due to treatment failure and these outcomes were incorporated into the resubmission model.
- 6.29 There was potential for survivor bias over time as more patients with mild or worse disease discontinued at each cycle compared to those with clear/almost clear disease.
- 6.30 The usefulness of the post-hoc analyses was limited due to concerns with potentially high risk of bias, lack of comparative data and issues with applicability to the PBS population (circumstances of use and eligibility criteria). Treatment efficacy with crisaborole was potentially confounded due to the use of rescue medications during the study (approximately 22% of patients).
- 6.31 The PBAC agreed with the ESC that the long-term data provides some reassurance that there may be sustained effect with real-world intermittent use of crisaborole, but noted that that the analyses were limited by potential confounding and due to questionable applicability to the requested PBS population.

Indirect comparison of crisaborole and pimecrolimus

- 6.32 The pimecrolimus trials were considered by the PBAC in November 2018, however, two studies of infants (Breuer 2004 and Trial 0316) that were previously included in the submission's indirect analysis have been excluded from the comparison in the resubmission.
- 6.33 The results of the indirect comparison of crisaborole and pimecrolimus suggest no statistically significant difference between treatments in terms of the proportion of patients achieving an ISGA/IGA score of 0 or 1. The resubmission noted that numerical

⁸ Note that the results presented in Paragraphs 6.20 to 6.31 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for AD-301, AD-302 or AD-303. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

differences in the results appeared to favour pimecrolimus. However, the resubmission acknowledged substantial issues with the exchangeability of these trials, highlighted by the variance in response observed in the common reference arm of vehicle ointment/cream (0% to 40.6%) alongside other differences including the scale and definitions for the outcome of interest, age groups, baseline disease severity and treatment durations. The resubmission noted additional concerns with the wide confidence intervals that were driven by small sample sizes and high variability of results in the pimecrolimus studies. The commentary considered the indirect comparison was non-informative.

- 6.34 In November 2018, the PBAC noted major transitivity issues with the indirect comparison including: substantial clinical and statistical heterogeneity within the pimecrolimus trials and between the crisaborole and pimecrolimus trials; differences in vehicle response (35% versus 17% for crisaborole and pimecrolimus respectively), and uncertain comparability of the ISGA scale used in the crisaborole trials with the IGA scale used in the pimecrolimus. The PBAC previously considered that the nominated non-inferiority margin did not appear reasonable and the results of the indirect comparison did not exclude the possibility that pimecrolimus was superior to crisaborole in terms of efficacy (paragraph 7.7 crisaborole PSD, November 2019 PBAC meeting).
- 6.35 The resubmission did not nominate a non-inferiority margin but claimed no statistically significant difference between crisaborole and pimecrolimus. The resubmission argued that there is no evidence to support a claim of superiority of pimecrolimus versus crisaborole. Overall, the commentary considered the comparative efficacy between crisaborole and pimecrolimus remains unclear due to the lack of robustness in the analyses presented. The ESC considered that the exclusion of the two trials did not substantially impact the overall assessment of the comparison.

Comparative harms

- 6.36 The safety data in the resubmission were previously considered by the PBAC in November 2018. There were no new safety signals identified from the Periodic Safety Update Report (PSUR) covering the reporting interval 14 December 2019 through 13 June 2020.
- 6.37 The most frequently reported adverse events with crisaborole treatment were infections and infestations (nasopharyngitis, upper respiratory tract infection), general disorder and administration site conditions (application site pain, pruritus, pyrexia), respiratory, thoracic and mediastinal disorders (nasal congestion) and gastrointestinal disorders (diarrhoea, vomiting). Gastrointestinal adverse events, which have been observed with oral PDE-4 inhibitors, were reported at relatively low frequencies and were similar to vehicle-treated patients. The majority of treatment-related adverse events reported with crisaborole were associated with application site pain (burning, stinging) compared to its vehicle.

- 6.38 No safety data comparing crisaborole with standard management were provided. The PBAC previously considered that the vehicle ointment of crisaborole may be a reasonable proxy for standard management (paragraph 7.8, crisaborole PSD, November 2018 PBAC meeting). The PBAC noted that crisaborole was associated with more frequent application site disorders than its vehicle (paragraph 7.8, crisaborole PSD, November 2018 PBAC meeting).
- 6.39 No formal indirect comparison of safety between crisaborole and pimecrolimus was presented in the submission owing to the lack of detail in safety data reported in the pimecrolimus trials and differences in reporting with the crisaborole trials. Instead, the resubmission presented a brief description of safety profiles for each treatment based on a selection of studies from the included trials. Both treatments were more frequently associated with application-site disorders (e.g. burning, stinging, redness) compared with their respective vehicles.

Benefits/harms

- 6.40 On the basis of direct evidence from Trial AD-301, for every 100 patients treated with crisaborole in comparison to its ointment vehicle over 4 weeks:
- Approximately 11 additional patients with mild to moderate atopic dermatitis will achieve clear or almost clear disease.
 - Approximately 5 additional patients will experience application site burning or stinging.
- 6.41 On the basis of direct evidence from Trial AD-302, for every 100 patients treated with crisaborole in comparison to its ointment vehicle over 4 weeks:
- Approximately 19 additional patients with mild to moderate atopic dermatitis will achieve clear or almost clear disease.
 - Approximately 2 additional patients will experience application site burning or stinging.

Clinical claim

- 6.42 The PBAC previously considered that overall the claim of superior effectiveness compared with standard management was not adequately supported by the data and noted that no safety data were provided comparing crisaborole with standard management but that the vehicle ointment may be a reasonable proxy (paragraph 7.6, crisaborole, PSD, November 2018 PBAC meeting).
- 6.43 The resubmission described crisaborole as superior in terms of efficacy and inferior in terms of safety to standard management. The ESC considered that the additional data presented in the resubmission did not substantially change the evidence base due to potential differences between the study population and the PBS population.
- 6.44 The PBAC considered that the claim of superior comparative effectiveness compared with standard management was not adequately supported by the data. The PBAC considered that the claim of inferior comparative safety was reasonable.

- 6.45 The PBAC previously considered that results of the indirect comparison did not exclude the possibility that pimecrolimus was superior to crisaborole in terms of efficacy (paragraph 7.7, crisaborole PSD, November 2018 PBAC meeting). The PBAC previously noted that no formal comparison of safety between crisaborole and pimecrolimus was possible and considered that the claim of non-inferior safety compared with pimecrolimus was likely to be reasonable but was supported by limited data (paragraph 7.8, crisaborole PSD, November 2018 PBAC meeting).
- 6.46 The resubmission described crisaborole as non-inferior in terms of efficacy and safety compared with pimecrolimus. The ESC considered that the exclusion of the two trials in the resubmission did not substantially impact the overall assessment of the comparison compared with the November 2018 submission.
- 6.47 The PBAC considered that the claim of non-inferior comparative effectiveness compared with pimecrolimus was not adequately supported by the data. The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.48 The resubmission presented a cost-minimisation analysis for the comparison versus pimecrolimus for the face and eyelids, and a cost-effectiveness analysis versus standard management for the rest of the body. A weighted price for crisaborole was calculated based on an estimated distribution of use between the two areas of the body.

Cost-minimisation analysis versus pimecrolimus

- 6.49 The table below presents the results of the cost-minimisation analysis. The approach used in the resubmission was unchanged from the November 2018 submission, with an additional analysis for the 30 g formulation of crisaborole.
- 6.50 The PBAC previously considered that the cost-minimisation analysis was not reasonable given that the clinical claim of non-inferiority to pimecrolimus was inadequately supported (paragraph 7.10, crisaborole PSD, November 2018 PBAC meeting).

Table 10: Results of the cost-minimisation analysis

Component	Crisaborole	Pimecrolimus
Initial script		
AEMP	\$ [REDACTED]	\$17.98
Amount of drug	30 g	15 g
Cost per gram		\$ [REDACTED]
DPMQ	\$ [REDACTED]	\$31.35
Continuing script		
AEMP	\$ [REDACTED]	\$17.98
Amount of drug	60 g	15 g
DPMQ ^a	\$ [REDACTED]	\$31.35

Source: Table 3.4.1, p150 of the resubmission

Note. Ex-manufacturer prices based on PBS 1 August 2020 price

^a recalculated during the evaluation using estimated ex-manufacturer prices plus fees and mark-ups as of 1 August 2020.

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- 6.51 The resubmission assumed that crisaborole is equivalent to pimecrolimus on a per gram basis. The resubmission claimed that this approach was conservative as the administration of ointments is likely to spread further compared with cream-based preparations. The PBAC previously considered that the assumption of equivalence of crisaborole and pimecrolimus on a per gram basis was not appropriate and was unlikely to reflect actual use of the treatments (paragraph 7.10, crisaborole PSD, November 2018 PBAC meeting).
- 6.52 The calculated ex-manufacturer price for crisaborole was slightly lower than that in the November 2018 submission (\$██████ per 60 g) due to the reduction in the ex-manufacturer price for pimecrolimus.

Cost-effectiveness analysis versus standard management

- 6.53 The PBAC previously considered that the cost-effectiveness of crisaborole compared with standard management was highly uncertain due to the following concerns (paragraph 7.9, crisaborole PSD, November 2018 PBAC meeting):
- the lack of a relevant comparator;
 - the model did not reflect the likely use in practice, or capture all relevant health states;
 - the extrapolation of the treatment benefit was based on unsupported assumptions which appeared clinically implausible; and
 - usage costs in the model appeared substantially underestimated and did not reflect use in the trial on which the treatment benefit was based.
- 6.54 The resubmission did not present an economic evaluation comparing crisaborole with TCS or topical calcineurin inhibitors which are potentially relevant comparators.
- 6.55 Table 11 summarises the key components of the economic evaluation. There were major changes to the time horizon, model structure, transition probabilities, drug costs, disease management costs and utilities compared with the November 2018 submission.

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Table 11: Summary of key components of the economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Quality-adjusted life years
Methods used to generate results	Markov cohort model (with half-cycle correction for consequences and disease management costs only)
Time horizon	3 years
Cycle length	28 days
Treatments	Crisaborole versus standard management (using ointment vehicle as a proxy)
Health states	6 health states: ISGA 2/3 on treatment (baseline), ISGA 0/1 pause treatment, ISGA 2+ on treatment, ISGA 0/1 cease treatment, ISGA 2+ cease treatment, and dead
Transition probabilities*	<p>In Cycle 1, transition probabilities for both arms were derived from the post-hoc analyses of Day 29 ISGA scores (0 to 4 and missing) using pooled data from trials AD-301 and AD-302 (ITT population). The proportions of patients with missing data were used as the probabilities of entering the ISGA 2+ cease treatment state.</p> <p>In subsequent cycles, transition probabilities for crisaborole were based on post-hoc analyses of Day 29 ISGA scores (0-4) and discontinuations in the AD-303 extension study over 40 weeks (10 treatment periods). Study discontinuation rates were used as the probabilities of entering the ISGA 0/1 and ISGA 2+ cease treatment states.</p> <p>For subsequent cycles in standard management, transition probabilities for the ISGA 0/1 pause treatment state were assumed the same as for the crisaborole arm. Transition probabilities for the ISGA 2+ on treatment state were derived using the relative efficacy of crisaborole versus standard management in Cycle 1 applied to the transition probabilities for the crisaborole arm.</p> <p>All patients entering the ISGA 0/1 and ISGA 2+ cease treatment states were assumed to remain in those states or die.</p> <p>Background mortality was based on 2018 Australian age-specific mortality in the general population.</p> <p>98.7% of incremental QALYs and all incremental cost savings occur in the extrapolated period (beyond 4 weeks).</p>
Drug costs	Based on DPMQ \$██████ (60 g) and \$██████ (30 g). Assumed use of 30 g in the first 3 cycles, 60 g in Cycle 4 and 30 g in Cycle 5 onwards. Drug costs applied to baseline and ISGA 2+ on treatment health states.
Disease management costs (annual)	Based on published costs from an outpatient survey (Su et al 1997) adjusted for inflation to 2020 estimates: ISGA 0/1 pause treatment (\$0), ISGA 0/1 cease treatment (\$0), ISGA 2+ on treatment (\$3,162), ISGA 2+ cease treatment (\$3,162)
Utilities	<p>Based on multiple sources of published utility estimates. Estimates for moderate disease (ISGA 3) were assumed to represent the utility values for the ISGA 2+ health states.</p> <p><u>Children (2-17 years)</u> ISGA 0/1 pause treatment: 0.980, ISGA 0/1 cease treatment: 0.980, ISGA 2+ on treatment: 0.736, ISGA 2+ cease treatment: 0.736</p> <p><u>Adults (≥18 years)</u> ISGA 0/1 pause treatment: 0.929, ISGA 0/1 cease treatment: 0.929, ISGA 2+ on treatment: 0.838, ISGA 2+ cease treatment: 0.838</p>
Discounting	5% for costs and outcomes, applied annually
Software package	Excel

Source: Table 3.1.1, p116 of the resubmission

Abbreviation: ISGA, Investigator's Static Global Assessment

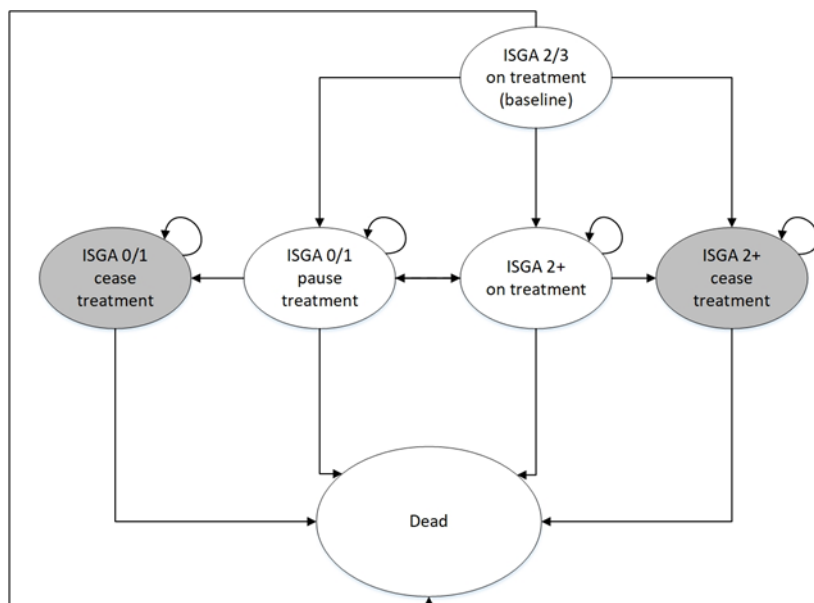
Note: ISGA is a 5-point symptom severity scale from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate) to 4 (severe)

*Note that the transition probabilities described here were derived from post-hoc analyses conducted by the applicant specifically for the

purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for AD-301, AD-302 or AD-303. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.56 The structure of the economic model is presented in the figure below.

Figure 1: Model structure



Source: constructed during the evaluation based on Section 3.2.2, p123 and Figure 3.1.1, p117 of the resubmission

Abbreviation: ISGA, Investigator's Static Global Assessment

Note: Absorbing states are highlighted in grey

- 6.57 All patients start in the mild to moderate disease (ISGA 2/3 on treatment) health state. In the first cycle, patients can achieve clear/almost clear disease and pause treatment (enter ISGA 0/1 pause treatment), have at least mild disease and stay on treatment (enter ISGA 2+ on treatment), have at least mild disease and stop treatment permanently (enter ISGA 2+ cease treatment) or die.
- 6.58 From cycle 2 onwards, patients with clear/almost clear disease who paused treatment can remain clear/almost clear of symptoms and stay in the paused treatment state, stop treatment permanently (enter ISGA 0/1 cease treatment), or have a mild to severe disease flare and reinitiate treatment (enter ISGA 2+ on treatment). Patients with at least mild disease who are on treatment (ISGA 2+ on treatment) can stay in that state, achieve clear/almost clear disease and pause treatment (enter ISGA 0/1 pause treatment) or have ongoing mild to severe disease and stop treatment permanently (enter ISGA 2+ cease treatment).
- 6.59 Patients who enter the ISGA 0/1 cease treatment or ISGA 2+ cease treatment health states state can only remain there or die. The commentary noted that this approach appeared to be based on assumptions of cure and ongoing treatment failure, which are inconsistent with the relapsing-remitting nature of the disease and the circumstances of use of treatments in practice. The PSCR noted that the submission did not claim patients are cured. The PSCR stated that patients can experience long-

term control of symptoms and may be able to discontinue treatment permanently and the model includes a long-term discontinued state to accommodate patients who do not reinitiate treatment because they are maintaining an ISGA score ≤ 1 .

6.60 The table below presents the key drivers of the model.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Extrapolation of treatment benefit	<p>Treatment benefits with crisaborole were extrapolated to 3 years based on 4-week trials of acute disease management and assumed maintenance of treatment benefit applied to changing disease status in the single-arm open-label extension study (AD-303).</p> <p>The use of background therapies was inconsistent between the key trials, extension study and as described in the proposed PBS restriction. The use of these therapies is likely to affect the magnitude of treatment benefit with crisaborole and its applicability to practice.</p> <p>It remains unclear if there are differences in terms of baseline severity or treatment response in the proposed PBS population compared with the broader population not limited by response, contraindication or intolerance to TCS.</p> <p>It was unclear whether the magnitude of treatment benefit associated with crisaborole in the model would be applicable to clinical practice, given the circumstances of use in the key trials and extension study were driven by treatment protocols that are unlikely to be observed in practice (e.g. continuous treatment for 4 weeks regardless of symptom resolution, continuous use for up to 12 weeks without any improvement).</p>	High, favours crisaborole
Model structure	<p>The construct of the model assumes that patients in the ISGA 0/1 cease treatment state have long-term control of symptoms without the need for ongoing treatment and those entering the ISGA 2+ cease treatment state have permanent failure to treatment. Patients in the ISGA 0/1 cease treatment state do not accrue further crisaborole treatment costs. The ESC noted that effects of other well-established treatments after failing crisaborole are not represented for patients in the ISGA 2+ cease treatment state. There were no data provided in support of these assumptions, which are unlikely to reflect the nature of the disease. These assumptions result in a large, ongoing benefit in favour of crisaborole.</p>	High, favours crisaborole
Time horizon	<p>3 years. This was inconsistent with the majority of published economic models that used 1-year time horizons to evaluate interventions for atopic dermatitis. The ESC previously considered a time horizon of one year, consistent with published literature, would be more appropriate as the base case (paragraph 6.59, crisaborole PSD, November 2018 PBAC meeting).</p>	High, favours crisaborole
Treatment costs	<p>The application of drug costs in the model was complex and difficult to interpret due to inconsistencies in the assumed use between initiating, reinitiating and continuing patients that were dependent on the model cycle:</p> <ul style="list-style-type: none"> • Initiating and reinitiating patients in Cycles 1 to 3 used 30 g whereas in Cycle 4 onwards, these patients were assumed to use 60 g • Continuing patients in Cycles 1 to 3 and Cycle 5 onwards used 30 g whereas in Cycle 4, these patients were assumed to use 60 g <p>The modelled treatment benefit associated with crisaborole was based on 4-week average use of 170 g in the key trials and 120 g in the extension study. These amounts were higher than treatment costs in the model that were based on assumed use of 30 g per cycle (60 g was used in one model cycle).</p>	High, favours crisaborole

Source: compiled during the evaluation

6.61 The transition probabilities in the model were derived from post-hoc analyses of Day 29 ISGA scores (0-4, missing data, study discontinuations) based on data from Trials

AD-301, AD-302 and extension study AD-303.⁹ The resubmission transformed the results into transition probabilities by collapsing the ISGA scores into two categories: ISGA 0/1 or ISGA 2+. Treatment status was assumed based on the AD-303 treatment protocol (i.e. ISGA 0/1, pause treatment and ISGA 2+, initiate/reinitiate treatment). There were concerns with the robustness of results from the post-hoc analyses, particularly with the AD-303 study, which may not be a reliable basis to derive transition probabilities.

Table 13: Non-fatal transition probabilities for Cycle 1 in the economic model*

Treatment arm	ISGA 2/3 on treatment (baseline), to:			Source
	ISGA 0/1 pause Tx	ISGA 2+ on Tx	ISGA 2+ cease Tx	
Crisaborole	48.4% [51%]	46.5% [49%]	5.1% [0%]	Probabilities based on post-hoc analyses of Day 29 ISGA scores (0 to 4 and missing) using pooled data from trials AD-301 and AD-302 (ITT population). Proportions of patients with missing data at Day 29 used as the probabilities of entering the ISGA 2+ cease treatment health state. Treatment status was assumed based on the AD-303 treatment protocol (i.e. ISGA 0/1, pause treatment and ISGA 2+, initiate/reinitiate treatment).
Standard management	33.2% [37%]	56.1% [63%]	10.7% [0%]	

* Note that the results presented in Table 13 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Studies AD-301, AD-302 or AD-303. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

⁹ Note that the analyses described here derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plans for AD-301, AD-302 or AD-303. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 14: Non-fatal transition probabilities from Cycle 2 in the economic model*

Health state	Transition probability	Source
Crisaborole		
ISGA 0/1 pause Tx	Remain in ISGA 0/1 pause Tx: 61.3%	Based on post-hoc analyses of Day 29 ISGA scores (0-4) and discontinuations in the AD-303 extension study over 40 weeks (10 treatment periods). Weighted transition probabilities based on the total number of observations over 10 treatment periods. The weighted study discontinuation rate was used as the probabilities of entering the ISGA 0/1 and ISGA 2+ cease treatment states.
	To ISGA 0/1 cease Tx: 3.6%	
	To ISGA 2+ on Tx: 35.1%	
ISGA 2+ on Tx	Remain in ISGA 2+ on Tx: 69.5%	
	To ISGA 0/1 pause Tx: 24.6%	
	To ISGA 2+ cease Tx: 5.9%	
ISGA 0/1 cease Tx	Remain in ISGA 0/1 cease Tx: 100%	Assumed
ISGA 2+ cease Tx	Remain in ISGA 0/1 cease Tx: 100%	Assumed
Standard management		
ISGA 0/1 pause Tx	Remain in ISGA 0/1 pause Tx: 61.3%	Based on post-hoc analyses of the AD-303 extension study and assumptions. Same as the crisaborole arm.
	To ISGA 0/1 cease Tx: 3.6%	
	To ISGA 2+ on Tx: 35.1%	
ISGA 0/1 cease Tx	Remain in ISGA 0/1 cease Tx: 100%	Assumed
ISGA 2+ on Tx	Remain in ISGA 2+ on Tx: 70.9%	Calculated as the complement of other transitions (100% - 16.9% - 12.3% = 70.9%).
	To ISGA 0/1 pause Tx: 16.9% [20.7%]	Based on relative difference in ISGA 0/1 pause Tx probability in Cycle 1: probability of ISGA 0/1 pause Tx in the crisaborole arm (24.6%) multiplied by the relative difference (0.686).
	To ISGA 2+ cease Tx: 12.3% [6.15%]	Based on relative difference in ISGA 2+ cease Tx probability in Cycle 1: probability of ISGA 2+ on Tx to ISGA 2+ cease Tx in the crisaborole arm (5.9%) multiplied by the relative difference (2.1).
ISGA 2+ cease Tx	Remain in ISGA 0/1 cease Tx: 100%	Assumed

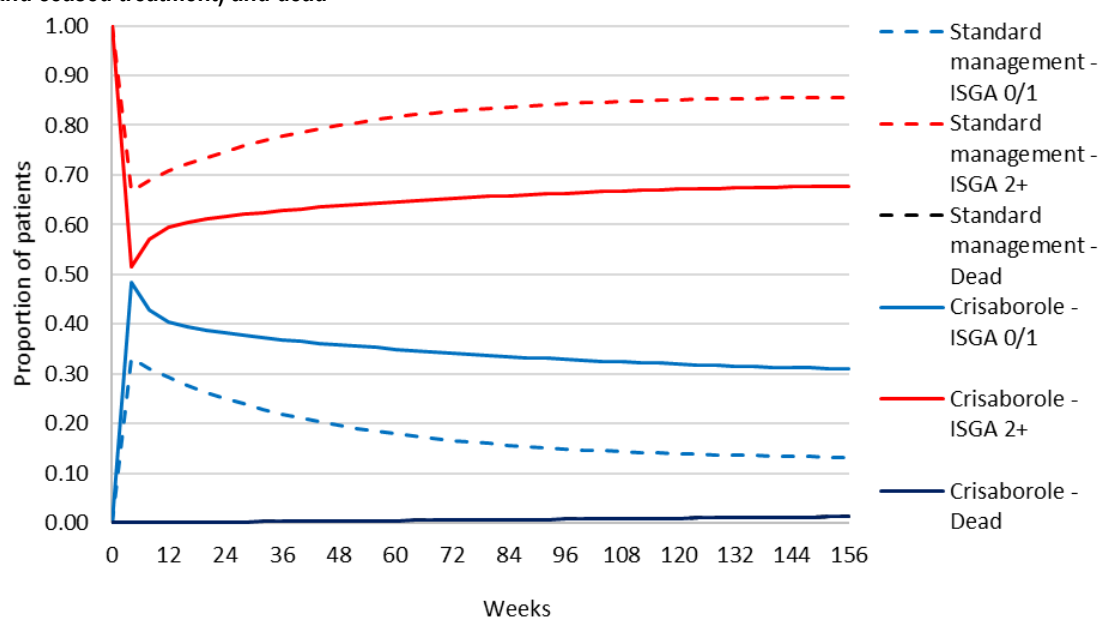
* Note that the results presented in Table 13 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for Studies AD-301, AD-302 or AD-303. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.62 The transition probabilities used in the model were highly uncertain due to assumptions made regarding missing data, discontinuation rates and efficacy in patients who cease treatment, and the relative efficacy for model cycle 2 onwards.
- 6.63 The resubmission assumed that all patients entering the ISGA 0/1 or ISGA 2+ cease treatment states either remained in those states or died. This approach assumes that patients in the ISGA 0/1 cease treatment state have long-term control of symptoms without the need for ongoing treatment and those entering the ISGA 2+ cease treatment state have permanent failure to treatment. There were no data provided in support of these assumptions. The ESC considered that the assumption that patients who discontinued from the AD-303 study ceased treatment for the remainder of the model's time horizon AND remained in the same ISGA state did not appear to be consistent with the nature of AD and was not adequately supported by the available data.
- 6.64 The estimated disease management costs for the ISGA 2+ (mild to severe) health states were highly uncertain and appeared to be overestimated due to use of data

with questionable applicability and generalisability to the model health states and population. The PBAC noted that estimated costs were primarily driven by an average of 3.4 days of hospitalisation per year, which was inconsistent with trial data suggesting a very low incidence of serious adverse events (less than 1% of patients in the key trials and 2% in the extension study). It was also unclear whether the average number of GP visits (13 per year) was representative of the population with ISGA 2+ who mostly had mild disease. The ESC considered that the disease management costs for the ISGA 2+ health states did not appear reasonable and that if data from Su et al were used, costs for patients with mild AD appear to be more representative of the population with ISGA 2+.

- 6.65 The resubmission claimed there were no quality of life data reported in the trials and therefore identified studies reporting utilities based on a literature search conducted to identify published economic evaluations for the treatment of atopic dermatitis. However, the trials reported results from age-dependent dermatology-related quality of life questionnaires suggesting improvements in quality of life scores from baseline in both arms. The clinical importance of the difference between arms was unclear.
- 6.66 The sources used to derive the utility estimates were unchanged from the previous submission. The ESC previously noted that the utility values obtained from the literature may have limited applicability to health states based on ISGA score (paragraph 6.53, crisaborole PSD, November 2018 PBAC meeting).
- 6.67 The resubmission used the calculated estimates for ISGA 3 (moderate disease) as the utility values for the ISGA 2+ health states (mild to severe disease) in the base case. This assumption was inconsistent with the trial data suggesting the majority of mild to severe patients had ISGA 2 (approximately 60-70%), a smaller proportion with ISGA 3 (approximately 25-30%) and a very small number of patients with ISGA 4 (approximately 1%).
- 6.68 The ESC noted that the utility studies are variable in method and outputs and considered that the studies by Healy (2011) and Poole (2009) appeared most robust. Utilities in Healy 2011 were 0.98, 0.69 and 0.59 in children and 0.867, 0.807 and 0.697 in adults for controlled, moderate and severe AD, respectively. Utilities reported in Poole (2009) were 0.848, 0.769 and 0.760 in mild, moderate and severe AD, respectively. The ESC considered that the difference between the ISGA 0/1 health states and the ISGA 2+ health states in the model may be higher than was reasonable.
- 6.69 Markov traces showing the proportion of patients in the ISGA 0/1 (pause and ceased treatment combined), ISGA 2+ (on and ceased treatment combined) and dead health states over the 3-year time horizon are presented in the figure below.

Figure 2: Markov traces of patients in the combined ISGA 0/1 (pause and ceased treatment), combined ISGA 2+ (on and ceased treatment) and dead



Source: Figure 3.8.2, p145 of the resubmission
Abbreviation: ISGA, Investigator's Static Global Assessment

6.70 The Markov trace shows the treatment effect of crisaborole peaked at 4 weeks, with ongoing benefits over the modelled duration. The treatment benefit appears to converge from 4 weeks to approximately 12 weeks and then increases over time. The ongoing benefits are primarily driven by the ongoing accumulation of patients in the ISGA 0/1 cease treatment and ISGA 2+ cease treatment health states.

6.71 The table below presents the results of the economic evaluation, recalculated during the evaluation to correct an error in disease management cost estimates in the resubmission.

Table 15: Results of the economic evaluation

Component	Crisaborole	Standard management	Increment
Costs	\$█	\$7,287	-\$█
QALYs	2.4246	2.3694	0.0551
Incremental cost per quality-adjusted life year			Dominant

Source: Section 3.8, p143 and the 'Crisaborole economic model' Excel workbook of the resubmission
Abbreviation: QALY, quality-adjusted life year

6.72 Based on the economic model, treatment with crisaborole was dominant compared to standard management (original estimates: incremental cost per QALY gained of \$5,000 to <\$15,000 for crisaborole versus standard management). The commentary considered the cost-effectiveness estimate should not be considered reliable given structural limitations, population and setting issues (extrapolation of treatment benefit) and parameter uncertainty.

6.73 The results of key sensitivity analyses are summarised in the table below.

Table 16: Sensitivity analyses

Univariate Analyses	Incremental cost	Incremental QALY	ICER
Corrected base case	-\$█	0.0551	Dominant
Disease management costs (corrected base case: \$3,164 per year for ISGA 2+ health states based on moderate disease)			
\$1,582 per year (base case in resubmission)	\$█	0.0551	\$█ ¹
\$1,095 per year (based on mild disease only)	\$█	0.0551	\$█ ¹
\$548 per year (50% of mild disease)	\$█	0.0551	\$█ ¹
Time horizon (base case: 3 years, 39 cycles)			
28 days (1 cycle)	\$█	0.0007	\$█ ²
168 days (6 cycles)	\$█	0.0067	\$█ ³
1 year (13 cycles)	\$█	0.0168	\$█ ¹
2 years (26 cycles)	-\$█	0.0363	Dominant
Transition probabilities as per Table 13 and 14.			
Cycle 1 transition probabilities re-estimated excluding patients with missing data at day 29; Difference in intervention and comparator cycle 2+ transition probabilities from ISGA 2+ on treatment to ISGA 0/1 pause treatment and to ISGA 2+ cease treatment reduced by 50% ^b	\$█	0.0150	\$█ ⁴
Utilities (base case children 2-17 years: ISGA 0/1 health states, 0.980; ISGA 2+ health states, 0.736 ; adults ≥18 years: ISGA 0/1 health states, 0.929; ISGA 2+ health states, 0.838)			
50% difference between ISGA 0/1 and ISGA 2+ health states (children: ISGA 0/1, 0.980; ISGA 2+, 0.858; adults: ISGA 0/1, 0.929; ISGA 2+, 0.884)	-\$█	0.0275	Dominant
75% difference between ISGA 0/1 and ISGA 2+ health states (children: ISGA 0/1, 0.980; ISGA 2+, 0.797; adults: ISGA 0/1, 0.929; ISGA 2+, 0.861)	-\$█	0.0415	Dominant
Crisaborole utilisation (base case: variable costs of \$█, \$█ or \$█ per cycle based on use of █ g or █ g)			
█ g in all cycles, \$█ per cycle	-\$█	0.0551	Dominant
█ g in all cycles, \$█ per cycle	\$█	0.0551	\$█ ¹
█ g in all cycles, \$█ per cycle	\$█	0.0551	\$█ ⁵
█ g in all cycles, \$█ per cycle	\$█	0.0551	\$█ ⁶

Source: compiled during the evaluation based on 'Crisaborole economic model' Excel workbook of the resubmission

^a The ISGA 0/1 utility value for adults was also modified to 0.939

^b For revised transition probabilities: In Cycle 1, no patients transition to the ISGA 2+ cease treatment health state, remaining transition probabilities adjusted to sum to 100% (crisaborole: to ISGA 0/1 pause treatment, 51%; to ISGA 2+ on treatment, 49%; to ISGA 2+ cease treatment, 0%; standard management: to ISGA 0/1 pause treatment, 37.2%; to ISGA 2+ on treatment, 62.8%; to ISGA 2+ cease treatment, 0%). In Cycle 2 onwards, 50% of relative treatment effect observed in Cycle 1 is assumed for transitions from ISGA 2+ on treatment to ISGA 0/1 pause treatment, and no treatment benefit assumed for transitions to ISGA 2+ cease treatment (crisaborole: to ISGA 2+ on treatment, 69.5%; to ISGA 0/1 pause treatment, 24.6%; to ISGA 2+ cease treatment, 5.9%; standard management: to ISGA 2+ on treatment, 72.9%; to ISGA 0/1 pause treatment, 21.2%; to ISGA 2+ cease treatment, 5.9%)

The redacted values correspond to the following ranges:

¹\$5,000 to <\$15,000/QALY gained

²\$75,000 to <\$95,000/QALY gained

³\$25,000 to <\$35,000/QALY gained

⁴\$45,000 to <\$55,000/QALY gained

⁵\$35,000 to <\$45,000/QALY gained

⁶\$55,000 to <\$75,000/QALY gained

6.74 The model was most sensitive to time horizon, crisaborole utilisation and alternative transition probabilities. The model was also moderately sensitive to disease management costs. The model did not appear sensitive to changes in utilities, however this may be obscured because the base case is dominant.

6.75 The structure of the economic model did not allow adequate assessment of the impacts of the long-term symptom control and failure assumptions (all patients

entering the ISGA 0/1 or 2+ cease treatment states remain in those states or die). There were no data provided in support of this assumption that is unlikely to reflect the relapsing-remitting nature of the disease.

- 6.76 Overall, the usefulness of the univariate analyses was limited due to concerns with the model structure and parameters that were driving the cost-saving scenarios. During the evaluation, multivariate analyses were conducted using alternative combinations of time horizon, crisaborole utilisation, disease management costs and utility values (summarised in the table below). Additional multivariate analyses were conducted using alternative values for transition probabilities.

Table 17: Results of multivariate sensitivity analyses

Time horizon, crisaborole utilisation and alternative transition probabilities			
Time horizon 28 days (1 cycle) and 120 g crisaborole per cycle	█	0.0007	\$ █ ¹
Time horizon 28 days (1 cycle) and 180 g crisaborole per cycle	█	0.0007	\$ █ ²
Time horizon 1 year (13 cycles) and 120 g crisaborole per cycle	█	0.0065	\$ █ ³
Time horizon 1 year (13 cycles) and 180 g crisaborole per cycle	█	0.0065	\$ █ ³
Time horizon, crisaborole utilisation, alternative transition probabilities and ISGA 2+ health state costs based on mild disease only			
Time horizon 28 days (1 cycle), 120 g crisaborole per cycle	█	0.0007	\$ █ ¹
Time horizon 28 days (1 cycle), 180 g crisaborole per cycle	█	0.0007	\$ █ ²
Time horizon 1 year (13 cycles), 120 g crisaborole per cycle	█	0.0065	\$ █ ³
Time horizon 1 year (13 cycles), 180 g crisaborole per cycle	█	0.0065	\$ █ ³
Alternative Cycle 1 and Cycle 2+ transition probabilities + ISGA 2+ health state costs based on mild disease only + alternative time horizons, crisaborole utilisations and utility values*:			
Time horizon 28 days (1 cycle), 120 g crisaborole per cycle and 50% of base case health state utility difference	█	0.0003	\$ █ ⁴
Time horizon 28 days (1 cycle), 120 g crisaborole per cycle and 75% of base case health state utility difference	█	0.0005	\$ █ ³
Time horizon 1 year (13 cycles), 120 g crisaborole per cycle and 50% of base case health state utility difference	█	0.0032	\$ █ ²
Time horizon 1 year (13 cycles), 120 g crisaborole per cycle and 75% of base case health state utility difference	█	0.0048	\$ █ ¹
Time horizon 28 days (1 cycle), 180 g crisaborole per cycle and 50% of base case health state utility difference	█	0.0003	\$ █ ⁶
Time horizon 28 days (1 cycle), 180 g crisaborole per cycle and 75% of base case health state utility difference	█	0.0005	\$ █ ⁴
Time horizon 1 year (13 cycles), 180 g crisaborole per cycle and 50% of base case health state utility difference	█	0.0032	\$ █ ⁷
Time horizon 1 year (13 cycles), 180 g crisaborole per cycle and 75% of base case health state utility difference	█	0.0048	\$ █ ²

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* 50% of base case utility difference between ISGA 0/1 and ISGA 2+ health states (children: ISGA 0/1, 0.980; ISGA 2+, 0.858; adults: ISGA 0/1, 0.929; ISGA 2+, 0.884); 75% of base case utility difference between ISGA 0/1 and ISGA 2+ health states (children: ISGA 0/1, 0.980; ISGA 2+, 0.797; adults: ISGA 0/1, 0.929; ISGA 2+, 0.861)

Source: compiled during the evaluation based on 'Crisaborole economic model' Excel workbook of the resubmission

The redacted values correspond to the following ranges:

¹\$355,000 to <\$455,000/QALY gained

²\$555,000 to <\$655,000/QALY gained

³\$455,000 to <\$555,000/QALY gained

⁴\$755,000 to <\$855,000/QALY gained

⁵\$500,000 to <\$600,000/QALY gained

⁶>\$1,055,000/QALY gained

⁷\$955,000 to <\$1,055,000/QALY gained

⁸\$255,000 to <\$355,000/QALY gained

6.77 The results were highly sensitive to the estimated use of crisaborole, extrapolation of treatment benefit beyond the key trial data and utility difference between health states in the model. The ESC noted that multivariate sensitivity analyses reflecting alternative assumptions with respect to transition probabilities (Cycle 1 transition probabilities re-estimated excluding patients with missing data at day 29; difference in intervention and comparator cycle 2+ transition probabilities from ISGA 2+ on treatment to ISGA 0/1 pause treatment and to ISGA 2+ cease treatment reduced by 50%), ISGA 2+ management costs (based on mild disease), utility values (75% of base case), crisaborole doses (120 g per cycle) and model time horizon (1 year) resulted in an ICER of \$355,000 to <\$455,000 per QALY.

Weighted price

6.78 The resubmission used a complex approach based on epidemiological data and the 'rule of nines' to calculate price weightings for the face and eyelids versus the rest of the body. The 'rule of nines' assumes head and neck represents 9% of BSA in adults and 21% in babies and young children, typically used to estimate burn size. The approach was largely revised with new data inputs compared to the November 2018 submission, however, was still dependent on the 'rule of nines' assumption and resulted in very similar price weightings as presented in the previous submission (see table below).

Table 18: Calculation of weighted DPMQ for crisaborole

	Face and eyelids	Rest of body
Initial script (30 g)		
Proposed AEMP	\$ [REDACTED]	\$ [REDACTED]
Population BSA distribution	10.3%	89.7%
Weighted AEMP		\$ [REDACTED]
Weighted DPMQ		\$ [REDACTED]
Continuing script (60 g)		
Proposed AEMP	\$ [REDACTED]	\$ [REDACTED]
Population BSA distribution	10.3%	89.7%
Weighted AEMP		\$ [REDACTED]
Weighted DPMQ		\$ [REDACTED]

Source: Table 3.1.4, p152 of the resubmission

Abbreviation: BSA, body surface area

- 6.79 The weighted DPMQ for the 60 g script was similar to the price in the November 2018 submission (\$ [REDACTED]). There was a small change to the weightings applied compared to the previous submission (face and eyelids, 9%; rest of body, 91%).
- 6.80 To derive the amount of crisaborole use substituted from pimecrolimus, the resubmission attempted to estimate age-adjusted population-based body surface area for the head and neck using measures of prevalence and the ‘rule of nines’ assumption. The PBAC previously considered the use of the ‘rule of nines’ in the weighting of the price was not appropriate and was unlikely to reflect actual use, though the distribution of affected areas between the face and eyelids versus the rest of the body in the crisaborole trials was unknown (paragraph 7.10, crisaborole PSD, November 2018 PBAC meeting). The use of topical treatments for atopic dermatitis is highly dependent on the relapsing-remitting nature of the disease, age, disease severity, number and location of affected body surface areas.
- 6.81 It was unclear whether estimates based on the broader atopic dermatitis population were applicable to the requested population with mild to moderate disease, who are failing, are intolerant or contraindicated to topical corticosteroids. There are no data available to inform the circumstances of use of crisaborole in this population.
- 6.82 The ESC agreed with the commentary that estimates in the resubmission are unlikely to reflect population-level distribution of use between crisaborole and pimecrolimus.

Drug/cost/patient/course

- 6.83 The estimated drug cost per patient per course of initial therapy (4 weeks) was \$ [REDACTED] (based on weighted DPMQ \$ [REDACTED] for 30 g tube and usage of 1 tube).
- 6.84 The estimated drug cost per patient per course of continuing therapy (4 weeks) was \$ [REDACTED] (based on weighted DPMQ \$ [REDACTED] for 60 g tube and usage of 0.5 tube) or \$ [REDACTED] (based on weighted DPMQ \$ [REDACTED] for 60 g tube and usage of 1 tube).
- 6.85 The estimated drug cost per patient per course (4 weeks) was \$ [REDACTED] based on the key trials AD-301 and AD-302 (based on DPMQ \$ [REDACTED] for 60 g tube and usage of 3 tubes) or \$ [REDACTED] based on the safety extension study AD-303 (based on DPMQ \$ [REDACTED] for 60 g and usage of 2 tubes).

- 6.86 In the November 2018 submission, the estimated drug cost per patient per year (including both initial and continuing treatment) was \$ [REDACTED] (using a DPMQ of \$ [REDACTED] per gram and assuming 96 grams per patient per year as per US claims data).
- 6.87 Based on use on the face and eyelids only, the estimated drug cost for pimecrolimus per patient was \$31.35 (using the DPMQ per 15 g script).

Estimated PBS usage & financial implications

- 6.88 This resubmission was considered by DUSC. The resubmission used a mixed epidemiological and market share approach to estimate the utilisation and financial impact of listing crisaborole, summarised in the table below.

Table 19: Estimation of number of treated patients

	Value	Year 1 ^a	Source and comment
Eligible population			
Australian population aged 2-85 years	-	25,853,194	ABS population projections from June 2021-June 2026 (3222.0 Series B, November 2018) for ages 2-85 years only. The DUSC previously considered that the exclusion of patients aged above 85 years was inadequately justified (crisaborole, DUSC advice, November 2018 PBAC meeting). This represents approximately 2% of the population.
Incidence of AD	2%	517,064	Chidwick (2020). Study of prevalence, incidence and management of atopic dermatitis (AD) in Australian general practice using data from MedicineInsight. The resubmission did not provide justification of population estimates based on newly diagnosed patients only, which did not account for a large prevalent pool of patients who are likely to be eligible for treatment. The Chidwick 2020 study provided a lifetime prevalence estimate of 16.4% based on active patients presenting to GP practices (≥3 visits over 2 years).
Mild to moderate AD	80.3%	415,202	Sponsor-commissioned market research (IQVIA report, February 2020). Online survey conducted between November 2019 and January 2020 based on responses from 126 physicians and 507 records of patients aged ≥2 years who were diagnosed with AD for at least 18 months. A weighted average of 80.3% was calculated using the number of patient records in children and adults. DUSC previously advised that mild to moderate atopic dermatitis is not consistently defined in studies used to estimate the number of patients with the disease. The previous submission estimated 90% of patients had mild to moderate disease (based on a sponsor-commissioned study using self-reported data), with a sensitivity analysis of 80%. DUSC advised that this was reasonable (crisaborole, DUSC advice, November 2018 PBAC meeting).
Prior TCS use	36%	149,473	Chidwick (2020). Based on patients with a lifetime prevalence of AD who had a prescription for topical corticosteroids within the 2-year study period (36.5%). The resubmission inappropriately applied the proportion of TCS use within a 2-year period in patients with a lifetime prevalence of AD to newly diagnosed patients. Prior TCS use (ever) in newly diagnosed patients is likely to be higher given 40% of patients with lifetime prevalence of AD did not receive any treatment within the 2 years. The resubmission did not consider use of over-the-counter topical corticosteroids.
Failed, intolerant or contraindicated to TCS	34.9%	52,166	Broeders (2016). A systematic review and meta-analysis comparing topical calcineurin inhibitors with topical corticosteroids. The resubmission assumed that 32% (complement of 68% with treatment success) of patients are failing topical corticosteroids. The rate of discontinuation due to adverse events (1.9%) and a further 1% is assumed as patients contraindicated to topical

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	Value	Year 1 ^a	Source and comment
			corticosteroids. The resubmission inappropriately assumed that complement estimates of treatment efficacy and discontinuation rates from trial data can be extrapolated to measures of prevalence in the population. There is limited evidence available to guide these estimates. The ESC considered there is only a very small proportion of the AD population unable to be treated with TCS where they are used appropriately.
Treated population			
Uptake rate	█%	█ ¹	█% (Year 1) increasing to █% (Year 6). Based on pimecrolimus uptake rates estimated in the resubmission using multiple data sources and assumptions (ABS Australian population aged 2-85 years data, incidence of AD from the Chidwick study, estimated proportion of patients with mild to moderate disease who have face and eyelid involvement based on sponsor-commissioned market data, 10% Medicare sample analysis for pimecrolimus). The DUSC previously considered the crisaborole market is unlikely to mimic utilisation rates of pimecrolimus, given existing restrictions that are not applicable to crisaborole (face and eyelids only, annual limit of 4 scripts). The DUSC also noted that the size of the private prescription market is unknown, and that there may be additional uptake from patients who are self-treating with over-the-counter topical corticosteroids (crisaborole, DUSC advice, November 2018 PBAC meeting).
Grandfathered patients	-	█ ²	Based on 50% uptake in 394 patients in 2020. Number of patients based on private script data and assumptions, and assumed use of 2 scripts per patient per year. Uptake rate was assumed. No data were provided in support of the assumptions.
Total patients	-	█ ¹	Grandfathered patients assumed to be part of treated population estimates.

Source: Table 4.2.1, p165; Table 4.2.2, p 166 of the resubmission

Abbreviations: ABS, Australian Bureau of Statistics; AD, atopic dermatitis; TCS, topical corticosteroids

^a Number of treated patients estimated at each step in Year 1 of the financial estimates.

The redacted values correspond to the following ranges:

¹10,000 to <20,000

²<500

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- 6.89 The DUSC previously considered the November 2018 estimates to be significantly underestimated due to significant concerns with the size of the eligible population, treated population estimates, potential for use outside the requested restriction, market penetration rates and treatment costs (crisaborole, DUSC advice, November 2018 PBAC meeting).
- 6.90 The approach and data sources used in the resubmission were revised compared to the November 2018 submission. However, the size of the eligible population is likely to be substantially underestimated as the estimates were based on an incident population only, not accounting for a large prevalent pool of patients likely to qualify for treatment with crisaborole.
- 6.91 In November 2018, the PBAC considered that the estimated prescription usage was highly uncertain and likely to be underestimated and that there would be a high likelihood of leakage to other types of dermatitis, infants under 2 years, and patients with 'steroid phobia' (paragraph 7.11, crisaborole PSD, November 2018 PBAC meeting). The resubmission proposed a risk-sharing arrangement to address this uncertainty, however, details of the proposed caps were not provided (see Risk-sharing Arrangements below).
- 6.92 To derive the estimated use of crisaborole, the resubmission used a complex approach based on the economic model of the resubmission to estimate time spent in the following health states over 4-week cycles: ISGA 0/1 pause treatment, ISGA 2+ on treatment, ISGA 0/1 cease treatment and ISGA 2+ cease treatment.
- 6.93 During the evaluation, the estimates of use were simplified to patient-years, in order to illustrate the number of patients and time spent in each health state over each year (i.e. dividing total patients in each health state by 12 and calculating the sum of 12 cycles for each year) (see table below).

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Table 20: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated use and cost of initial scripts						
Newly diagnosed patients starting treatment	█ ¹	█ ²	█ ²	█ ²	█ ³	█ ³
Initial scripts	█ ³	█ ⁴	█ ⁵	█ ⁵	█ ⁶	█ ⁶
Cost of initial scripts (DPMQ \$█)	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴
Estimated use and cost of continuing scripts						
Patients with ongoing ISGA 2+ for 3 months after initiation who cease treatment (21.7%) ^a	-█ ⁷	-█ ⁷	-█ ⁷	-█ ⁷	-█ ⁷	-█ ⁷
Remaining patients who are on/off treatment (patient-years)	█ ⁷	█ ²	█ ³	█ ⁴	█ ⁵	█ ⁶
- ISGA 0/1 pause treatment	█ ⁷	█ ⁷	█ ⁷	█ ¹	█ ¹	█ ¹
- ISGA 2+ on treatment	█ ⁷	█ ⁷	█ ¹	█ ¹	█ ²	█ ²
- ISGA 0/1 cease treatment	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ¹	█ ²
- ISGA 2+ cease treatment	█ ⁷	█ ⁷	█ ¹	█ ²	█ ³	█ ⁴
Continuing scripts (12 scripts /patient-year in ISGA 2+ on treatment)	█ ²	█ ³	█ ⁹	█ ¹⁰	█ ¹⁰	█ ¹⁰
Cost of continuing scripts (DPMQ \$█)	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁵	\$█ ¹⁵	\$█ ¹⁵	\$█ ¹⁶
Estimated cost of initial and continuing scripts						
Total cost to PBS/RPBS	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁵	\$█ ¹⁵	\$█ ¹⁶	\$█ ¹⁶
Patient co-pay (PBS \$6.38, RPBS \$4.90)	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴
Net cost to PBS/RPBS (DPMQ minus co-pay)	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁵	\$█ ¹⁵	\$█ ¹⁶	\$█ ¹⁶
Estimated cost offset due to use substituted from pimecrolimus						
Pimecrolimus scripts (21.8% annual growth rate)	█ ¹⁰	█ ¹⁰	█ ¹⁰	█ ¹²	█ ¹²	█ ¹³
Uptake rate	10%	15%	20%	25%	30%	35%
Total scripts substituted	█ ²	█ ³	█ ⁴	█ ⁸	█ ¹¹	█ ¹⁰
Total cost (DPMQ \$31.35)	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴
Patient co-pay (PBS \$6.26, RPBS \$4.90)	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴
Net cost offset (DPMQ minus co-pay)	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹⁴
Net cost to PBS/RPBS including cost offset	\$█¹⁴	\$█¹⁴	\$█¹⁵	\$█¹⁵	\$█¹⁵	\$█¹⁶
Previous submission (November 2018)						
Net cost to PBS/RPBS (DPMQ minus co-pay)	\$█ ¹⁵	\$█ ¹⁵	\$█ ¹⁵	\$█ ¹⁶	\$█ ¹⁶	\$█ ¹⁷
Net cost to PBS/RPBS including cost offset	\$█ ¹⁵	\$█ ¹⁵	\$█ ¹⁵	\$█ ¹⁶	\$█ ¹⁶	\$█ ¹⁷

Source: 'Crisaborole utilisation and cost model' Excel workbook of the resubmission and the November 2018 submission

Abbreviations: ISGA, Investigator's Static Global Assessment

^a Due to the distribution of initiating patients over 12 cycles, discontinuations from patients initiating in the last 2 cycles of the year are applied in the model in the following year

The redacted values correspond to the following ranges:

¹5,000 to <10,000

²10,000 to <20,000

³20,000 to <30,000

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⁴30,000 to <40,000

⁵40,000 to <50,000

⁶60,000 to <70,000

⁷500 to <5,000

⁸50,000 to <60,000

⁹80,000 to <90,000

¹⁰100,000 to <200,000

¹¹70,000 to <80,000

¹²200,000 to <300,000

¹³300,000 to <400,000

¹⁴\$0 to <\$10 million

¹⁵\$10 million to <\$20 million

¹⁶\$20 million to <\$30 million

¹⁷\$30 million to <\$40 million

6.94 The resubmission estimated a net cost to the PBS/RPBS (including cost offsets and less patient co-payments) of \$0 to <\$10 million in Year 1 of listing, increasing to \$20 to <\$30 million in Year 6, a cumulative total of \$80 to <\$90 million over 6 years.

6.95 DUSC considered the estimates presented in the submission to be significantly underestimated. DUSC considered the main issues to be:

- Use of incidence estimates only, which excludes a large prevalent pool of patients who would qualify for treatment. DUSC considered that a high uptake in the prevalent pool would be expected. The PSCR argued a low prevalent pool uptake was observed in private and international markets, however no data was provided to support this claim. DUSC noted that not accounting for the prevalent pool would lead to significant underestimates in utilisation;
- There were significant uncertainties with the estimated proportion of patients meeting the eligibility criteria. The previous submission estimated 90% of patients had mild to moderate disease, however a weighted average of 80.3% was used in the resubmission, which DUSC considered was an underestimate. DUSC previously advised that mild to moderate atopic dermatitis is not consistently defined in studies used to estimate the number of patients with the disease. DUSC considered the estimated proportion of patients who have failed, are intolerant or contraindicated to TCS (34.9%) may be under or overestimated. The size of the eligible incident population (50,000 to <60,000 in Year 1, increasing to 50,000 to <60,000 in Year 6) was substantially smaller than eligible population estimates in the previous submission (400,000 to <500,000 in Year 1, increasing to 400,000 to <500,000 in Year 6);
- There were significant uncertainties with the assumed uptake rates:
 - The market penetration is unlikely to mimic use of pimecrolimus which is restricted to the face and eyelids, an annual limit of 4 scripts and treatment limited to short-term intermittent use only.
 - The resubmission did not consider additional uptake from the private prescription market for pimecrolimus or over the counter (OTC) TCS;

- The economic model used to calculate time on treatment was complex and assumptions of the model were flawed. The commentary noted the model did not account for the relapsing and remitting nature of the disease. The pre-PBAC response claimed the model did account for the relapsing and remitting nature, as the model used outcomes from AD-303, in which patients used crisaborole intermittently;
 - The PBAC previously considered there would be a high likelihood of leakage for use outside the requested restriction, in younger patients (under 2 years of age), those with severe disease and as first-line therapy in those not contraindicated to topical steroids. DUSC considered steroid phobia may contribute to use outside of the requested restriction in the first line setting; and
 - Overall, there was very limited evidence to guide estimates. The resubmission only included one Australian GP study, commissioned market research and a poorly detailed analysis of the PBS 10% sample.
- 6.96 The evaluation noted the following additional areas of uncertainty in the utilisation/financial estimates for crisaborole:
- The estimates were largely based on the model and inputs imported from the economic evaluation, and therefore incorporate all issues of concern with the model structure and transition probabilities;
 - There was a calculation error in the resubmission for yearly estimates of patients initiating therapy, leading to a loss of 8% of the incident population each year. This error was not corrected during the evaluation due to complexities with the assumed transition probabilities and cohort model structure used in the resubmission;
 - The resubmission assumed all patients initiating treatment received 12 weeks of ongoing initial therapy regardless of treatment response (i.e. 3 initial scripts per patient). This assumption was unlikely to be representative of practice;
 - The estimated number of continuing scripts of crisaborole was based on assumed use of 12 scripts per patient-year in the ISGA 2+ on-treatment health state (i.e. 1 script of 60 g per 4-week treatment period). This assumption was inadequately justified and inconsistent with average use reported in the key trials (170 g per 4 weeks) and extension study (120 g per 4 weeks); and
 - Cost-offsets due to substitution of pimecrolimus were uncertain. The market size for pimecrolimus was estimated based on a constant growth rate that may not account for changing market dynamics over time.
- 6.97 Overall, the evaluation considered the results of the budget impact analysis should not be considered reliable due to major concerns with the approach, inputs and assumptions used in the resubmission. The evaluation identified issues with the financial estimates (assumed pathways and absorbing states in the estimates, the overall average scripts per patient, and declining year to year growth rate) which suggest that the results do not meet face validity.

- 6.98 The pre-PBAC response presented revised estimates, correcting errors in transition probabilities and calculation of prescriptions identified in the evaluation and accounting for additional patients from the prevalent population. The revised cost to the PBS/RPBS was \$10 to <\$20 million in year 1 increasing to \$30 to <\$40 million in year 4 and then decreasing again to \$20 to <\$30 million in year 6, with a total of \$100 to <\$200 million over the first 6 years.

Quality Use of Medicines

- 6.99 The Pre-PBAC response proposed that the sponsor would undertake QUM initiatives to address the potential for use of crisaborole in substitution for TCS, which is not the intent of the proposed restriction.

Financial Management – Risk Sharing Arrangements

- 6.100 In November 2018, the PBAC agreed with the sponsor (as noted in the pre-PBAC response) that a risk-sharing agreement would be required to address the likelihood of leakage outside the restriction (paragraph 7.11, crisaborole, Public Summary Document, November 2018 PBAC meeting).
- 6.101 The resubmission argued that the proposed initial and continuing restrictions limit the use of crisaborole to patients with mild to moderate atopic dermatitis based on the description of symptoms in the clinical criteria. However, the sponsor acknowledged the potential for leakage of use outside of the proposed restriction due to the degree of subjectivity in the assessment of disease severity. To address this uncertainty, the sponsor proposed a financial cap based on the following:
- the estimated number of patients with mild to moderate disease who are treated with crisaborole; and
 - the estimated rate of continued use in patients who achieve clearance or near clearance of symptoms (ISGA 0 or 1).
- 6.102 The sponsor proposed to rebate the Government for use of crisaborole in excess of these estimates. Detailed estimates for the proposed caps were not presented in the resubmission. The ESC considered there is only a very small proportion of the AD population unable to be treated with TCS where they are used appropriately. The ESC considered that additional data may be required to characterise this population accurately and the financial risk of use outside this small, intended population would need to be addressed with the RSA.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend crisaborole for mild to moderate atopic dermatitis in patients who have failed to achieve satisfactory disease control with, are contraindicated to, or intolerant to topical corticosteroids (TCS). The PBAC considered TCS are effective in patients with mild to moderate disease when used appropriately,

and hence there is a low clinical need for crisaborole. The PBAC considered that the cost-effectiveness of crisaborole remained highly uncertain. The PBAC considered that the intended population was likely to be relatively small, however there was a high risk of use in a broader population, resulting in increased financial cost.

- 7.2 The requested indication for a subset of patients who are failing, are intolerant or contraindicated to TCS is narrower than the TGA indication and clinical evidence that included a broader atopic dermatitis population. The PBAC noted that patients frequently do not receive an adequate level of standard care, including adequate use of TCS, despite adverse events associated with TCS being very rare. The PBAC considered that it would be unusual for patients with mild to moderate AD to have an inadequate response to TCS when appropriate dosages and durations are used and as such, the clinical need for crisaborole is low. The PBAC considered that there may be a clinical place for crisaborole as an alternative to pimecrolimus for treatment in sensitive and thin skin areas such as face and eyelids.
- 7.3 The PBAC noted the resubmission’s proposed changes to restrictions but considered further refinement and clarification of the intended treatment population was required in terms of defining TCS failure, intolerance and contraindication. The PBAC considered that even with changes to restriction wording there would remain a significant risk of initiation of treatment outside the intended use due to i) inadequate TCS trial or ii) inappropriately high patient or clinician perception of risks associated with TCS. The PBAC noted that use of crisaborole consistent with the proposed restriction is predicated on appropriate use of TCS, which would require significant additional resources for the re-education of the large and diverse prescriber base and patients to avoid the effects of “steroid phobia”.
- 7.4 The PBAC previously accepted pimecrolimus was the appropriate comparator for the face and eyelids (paragraph 7.5, crisaborole, PSD, November 2018 PBAC meeting). For the rest of the body, the resubmission nominated standard management as the comparator. The resubmission argued that it is not intended for crisaborole to replace TCS use when TCS is effective, including intermittent TCS use. The PBAC previously considered that TCS should also be included as a comparator (paragraph 7.5, crisaborole, PSD, November 2018 PBAC meeting). The PBAC considered that despite the intention of the resubmission and the proposed restriction, there is a substantial risk that prescribers and patients will perceive crisaborole as a steroid sparer/alternative. When used in this way, TCS would be a relevant comparator. No evidence was presented in this context, although the PBAC noted there are several ongoing trials.
- 7.5 The PBAC recalled results from the key crisaborole trials, AD-301 and AD-302 were considered at the November 2018 PBAC meeting. The PBAC recalled its previous concerns with the robustness of the meta-analysis of the key trials due to heterogeneity, uncertain statistical significance of the efficacy results in the individual trials and modest magnitude of treatment benefit over its vehicle. The PBAC also recalled it had noted the clinical importance of the ISGA endpoint was uncertain

(paragraph 7.6, crisaborole, PSD, November 2018 PBAC meeting), and outcomes based on ISGA appeared more subjective than commonly used clinical tools such as the Eczema Area and Severity Index (EASI) or SCORing Atopic Dermatitis (SCORAD) (paragraph 6.15, crisaborole, PSD, November 2018 PBAC meeting). The PBAC noted that outcomes based on EASI and SCORAD, were not captured in the crisaborole studies.

- 7.6 The PBAC noted the resubmission included the following analyses of AD-301, AD-302 and AD-303 trial data that have not previously been considered by the PBAC:
- Post-hoc subgroup analyses by prior TCS use based on the key trials (AD-301, AD-302)
 - Post-hoc analyses of ISGA scores from the key trials AD-301, AD-302 and the AD-303 safety extension study to assess efficacy with longer-term and intermittent use.
- 7.7 The PBAC considered the results based on post-hoc subgroup analyses by prior TCS use may not be generalisable to the requested population and noted there remains a lack of data specific to the subgroup who are failing, are intolerant or contraindicated to topical corticosteroids.
- 7.8 The PBAC considered the post-hoc analysis of the open-label single-arm safety extension study (up to 48 weeks) provided some reassurance of sustained benefit for real-world intermittent use of crisaborole. However, the PBAC considered these data are confounded by the potentially high risk of bias, use of outcomes not designed for efficacy assessment, applicability concerns (particularly with circumstances of use) and potential confounding due to background therapies and rescue medications.
- 7.9 The PBAC previously considered that overall the claim of superior effectiveness compared with standard management was not adequately supported by the data. The PBAC considered that the additional analyses presented in the resubmission did not substantially change this conclusion due to the limitations described in paragraphs 7.7 and 7.8. The PBAC considered that the claim of inferior comparative safety compared with standard management was reasonable.
- 7.10 The PBAC noted that the indirect comparison versus pimecrolimus considered in November 2018 was revised to exclude two studies of pimecrolimus in infants (Breuer 2004 and Trial 0316). The PBAC previously noted major transitivity issues with the indirect comparison including: substantial clinical and statistical heterogeneity within the pimecrolimus trials and between the crisaborole and pimecrolimus trials; differences in vehicle response (35% versus 17% for crisaborole and pimecrolimus respectively), and uncertain comparability of the ISGA scale used in the crisaborole trials with the IGA scale used in the pimecrolimus. The PBAC previously considered that the nominated non-inferiority margin did not appear reasonable and the results of the indirect comparison did not exclude the possibility that pimecrolimus was superior to crisaborole in terms of efficacy (paragraph 7.7 crisaborole PSD, November 2019 PBAC meeting). The PBAC considered that the exclusion of the two trials in the

resubmission did not substantially impact the overall assessment of the comparison compared with the November 2018 submission. The PBAC considered that the claim of non-inferior comparative effectiveness compared with pimecrolimus was not adequately supported by the data. The PBAC considered that the claim of non-inferior comparative safety was reasonable.

- 7.11 The PBAC noted the resubmission presented a cost-minimisation analysis versus pimecrolimus. The PBAC considered this may not be reasonable given the clinical claim of non-inferiority was inadequately supported. The PBAC also noted that no data were provided in support of the equi-effective doses proposed in the resubmission.
- 7.12 The PBAC noted that a modelled cost-effectiveness analysis versus standard management was presented in the resubmission, with a substantially revised structure and revised inputs. The PBAC considered a cost-effectiveness analysis may not be reasonable given the clinical claim of superior efficacy remained inadequately supported. Further, the resubmission did not present an economic evaluation comparing crisaborole with TCS or topical calcineurin inhibitors which are potentially relevant comparators given the high likelihood of use outside the intended population.
- 7.13 Regarding the revised model, the PBAC considered that there were a number of areas of uncertainty, the key issues being:
- The transition probabilities which were derived from post-hoc analyses of Day 29 ISGA scores using data from Trials AD-301, AD-302 and extension study AD-303, which the PBAC considered lacked robustness. There were also concerns with the assumptions used in applying these outcomes to transition probabilities in the model (see paragraphs 6.62-6.63);
 - Use of a 3 year time horizon based on 4 week trials. The PBAC considered a 1 year horizon would be more appropriate;
 - The amount of crisaborole used with the trials using 170 g per cycle or 120 g per cycle (safety extension trial) whereas the model assumed use of 30 g per cycle; and
 - The ISGA 2+ health state costs appeared overestimated as disease management costs for the ISGA 2+ health state included 3.4 hospitalisation days per year and 13 GP visits per year. The PBAC considered this was inconsistent with costs for mild to moderate disease.
- 7.14 The PBAC noted that for all multivariate analyses the ICER increased from dominant to over \$255,000 to <\$355,000 per QALY. Although the base case ICER presented in the resubmission was dominant, the PBAC considered that the ICER had a high level of uncertainty and was unacceptably high for all multivariate analyses considered.
- 7.15 The PBAC noted that the financial estimates were largely based on the model and inputs imported from the economic evaluation, and therefore incorporated the issues of concern with the model structure and transition probabilities. The PBAC considered

the intended population of patients unable to be effectively treated with TCS would be small, however the restriction as proposed in the resubmission would not limit use to this population. In this context, the PBAC considered the financial estimates presented in the submission to be highly uncertain due to the use of uncertain inputs from the economic model, limited data to support eligibility and uptake rates, and exclusion of the prevalent population. The PBAC noted the pre-PBAC response presented revised estimates to account for the prevalent population in addition to the incident population, and the cost to the PBS/RPBS increased from \$80 to <\$90 million to \$100 to <\$200 million over the first 6 years. The PBAC previously considered there would be a high likelihood of use outside the requested restriction, in younger patients (under 2 years of age), those with severe disease and as first-line therapy in those not contraindicated to TCS. The PBAC agreed with DUSC that steroid phobia may contribute to use outside of the requested restriction in the first line setting.

- 7.16 The PBAC considered that there may be a clinical place for crisaborole as an alternative to pimecrolimus for treatment in sensitive and thin skin areas such as the face and eyelids, but noted that additional data in support of non-inferiority with pimecrolimus would be required for a resubmission.
- 7.17 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 through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Pfizer is surprised at the PBAC's most recent view that there is a low clinical need for therapies to treat mild to moderate atopic dermatitis in patients who have failed to achieve satisfactory disease control with, are contraindicated to, or are intolerant to topical corticosteroids. Such a view is not consistent with the view expressed by the PBAC when it considered our previous submission, nor with advice Pfizer received from clinicians and patients. There is currently no PBS-subsidised treatment available for this population, other than for patients whose face is affected. Thus, Pfizer disagrees that topical corticosteroids are the appropriate comparator for a population

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for whom there is currently no subsidised treatment option. Pfizer believes that an appropriate risk share arrangement could have been implemented, to manage the risk of use in a broader population than intended.