

**5.03 CRISABOROLE,  
Ointment containing crisaborole  
20 mg per g, 60 g,  
Staquis<sup>®</sup>,  
Pfizer Australia Pty Ltd**

**1 Purpose of Application**

- 1.1 The submission requested a Section 85, Streamlined Authority listing for crisaborole for the treatment of mild to moderate atopic dermatitis in patients at least 2 years old who are contraindicated, have failed to achieve satisfactory disease control, or are intolerant to TCS. The PBAC has not previously considered crisaborole.
- 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 submission**

Component	Description
Population	Patients aged ≥2 years with mild to moderate atopic dermatitis who are contraindicated, have failed to achieve satisfactory disease control, 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 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, pp4-5 of the submission

- 1.3 There were inconsistencies in the definition of the target population between the clinical issue addressed by the submission, clinical management algorithm and the proposed PBS listing. The target population described in the clinical issue and clinical management algorithm included patients who were contraindicated to and who were failing TCS as well as those who were intolerant due to adverse effects and ‘steroid phobia’ whereas the requested PBS restriction limited use to those who were contraindicated to TCS and those who did not achieve symptom resolution with corticosteroids.
- 1.4 The target population described below refers to the broader definition of those who were contraindicated/failing/intolerant to TCS.

**2 Requested listing**

- 2.1 Suggestions and additions proposed by the Secretariat are in italics and strikethrough is used for deletions.

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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 ointment 2%, 60 grams	1	2	\$ [REDACTED]	Staquis Pfizer
<b>Category/Program:</b>	Section 85			
<b>Episodicity:</b>	Chronic			
<b>Severity:</b>	Mild to moderate			
<b>PBS Indication:</b>	Mild to moderate atopic dermatitis			
<b>Restriction:</b>	Streamlined Authority			
<b>Clinical criteria:</b>	Patient must have failed to achieve satisfactory disease control with topical corticosteroids, OR Patient must have 1 or more of following contraindications to topical corticosteroids: (i) perioral dermatitis; (ii) periorbital dermatitis; (iii) rosacea; (iv) epidermal atrophy; (v) dermal atrophy; (vi) allergy to topical corticosteroids; (vii) cataracts; (viii) glaucoma; (ix) raised intraocular pressure			
<b>Population criteria:</b>	Patient must be aged $\geq 2$ years			
<b>Prescriber Instructions</b>	Failure to achieve satisfactory disease control with <del>intermittent</del> topical corticosteroid therapy is manifest by: (i) failure of the skin to clear despite at least 2 weeks of topical hydrocortisone 1% applied every day; or (ii) failure of the skin to clear despite at least 1 week of a moderate or potent topical corticosteroid applied every day; or (iii) clearing of the skin with at least 2 weeks of topical hydrocortisone 1% applied every day, but almost immediate and significant flare in facial disease (within 48 hours) upon stopping topical corticosteroids, occurring on at least 2 consecutive occasions; or (iv) clearing of the skin with at least 1 week of a moderate or potent topical corticosteroid applied every day, but almost immediate and significant flare in facial disease (within 48 hours) upon stopping topical corticosteroids, occurring on at least 2 consecutive occasions.  <i>Details of the contraindication must be documented in the patient's medical records when treatment is initiated.</i>			

- 2.2 The submission inadequately justified the proposed quantity and repeats, particularly given the submission positioned crisaborole as a chronic, ongoing therapy. The submission did not clearly describe the proposed use of crisaborole in terms of treatment initiation, treatment discontinuation and optimal duration of therapy. The proposed listing is for chronic use for an indeterminate period of time, which may not be appropriate given the lack of efficacy data beyond 4 weeks. The ESC noted that the requested quantity is either only sufficient for 4 weeks based on the key clinical trials or would give 2 years supply based on US market data suggesting an average of [REDACTED] tubes per patient per year. The ESC considered that the appropriate maximum quantity and repeats was not clear.
- 2.3 The proposed restriction was based on merging the current restrictions under the pimecrolimus listing for patients who are contraindicated to TCS, and patients who are failing to achieve satisfactory disease control with intermittent corticosteroid therapy. Key differences between the crisaborole and pimecrolimus restrictions include an annual limit for pimecrolimus scripts and no limits for crisaborole scripts,

and the age range for pimecrolimus is from at least 3 months old whereas crisaborole is indicated in patients who are at least 2 years old.

- 2.4 The submission did not adequately justify the use of clinical criteria from the existing pimecrolimus listing to define the PBS population. Although these definitions were previously considered acceptable by the PBAC for pimecrolimus, this was in the context of use on the face and eyelids only which is considered a more sensitive area where use of higher potencies and longer duration of corticosteroid use is inadvisable (pimecrolimus PSD, July 2006). These definitions are less likely to be applicable to other areas of the body. The ESC considered that merging the restrictions for pimecrolimus was not appropriate as the definitions of contraindication and lack of disease control for pimecrolimus use on the face and eyelids are not applicable to crisaborole use on the whole body.
- 2.5 The clinical data and requested TGA indication were for the broader population with mild to moderate disease. No data were provided in support of restricting treatment to the subgroup of patients who are contraindicated to, or failing TCS. The ESC considered that restricting the requested population in this way was not sufficiently justified.
- 2.6 The proposed restriction was narrower than the target population described in the clinical issue and clinical algorithm which includes patients who are intolerant to TCS. The ESC noted that the proposed restriction did not include patients who are intolerant to TCS, which may include patients who express 'steroid phobia'.
- 2.7 Satisfactory disease control as defined in the restriction appears to be based on symptom resolution only, which does not capture patients who have improvement but not complete clearance of symptoms, and patients who are not achieving disease clearance due to non-compliance to TCS. The submission suggested that a significant proportion of patients, caregivers and health practitioners express 'steroid phobia', which may affect their compliance to TCS treatment.
- 2.8 There is potential for use of crisaborole outside the requested restriction, particularly in younger patients (<2 years) and those with severe disease.

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

### **3 Background**

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

- 3.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration the TGA delegate's overview was available. This document noted that the delegate considered that sufficient data and justification have been provided to support the registration of crisaborole on quality, safety and efficacy grounds for the treatment of patients with mild to moderate atopic dermatitis.

The requested TGA indication is for topical treatment of mild to moderate atopic

dermatitis in patients 2 years of age and older.

*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 submission positioned crisaborole as a first-line therapy in patients who are contraindicated to TCS. No data were provided for crisaborole in this subgroup of patients. The population who are contraindicated to topical corticosteroids, particularly in the whole of body, was not explicitly defined in the submission.
- 4.3 The submission positioned crisaborole as a second-line therapy in patients who have failed or are intolerant to TCS. This population was poorly defined in the submission and appears to be broadly based on concepts of 'steroid phobia', limitations of use (duration and potency) of topical corticosteroids in sensitive areas and skin thinning/atrophy associated with long-term use of TCS. TCS are likely to remain a treatment option for most patients, particularly in less sensitive areas of the body.
- 4.4 While the submission claimed that the target population has greater clinical need due to limited treatment options, the broader population with mild to moderate atopic dermatitis may also benefit from treatment with crisaborole. The submission did not adequately justify the exclusion of these patients from subsidised treatment given the clinical evidence included patients with atopic dermatitis without regard to contraindication to or failure of TCS.
- 4.5 The proposed clinical management algorithm did not clearly define the role of crisaborole as long-term maintenance therapy. Recent guidelines have positioned crisaborole in the second-line setting as an alternative to topical calcineurin inhibitors or in combination with weak TCS for acute flare-ups in mild disease only (UpToDate – Atopic Dermatitis June 2018). Other guidelines have suggested that the role of crisaborole is unclear given the lack of comparative data versus established therapies (European consensus guidelines 2018). The ESC considered that the role of crisaborole as either intermittent treatment for flares and/or maintenance to prevent flares was unclear and this has implications for the frequency of use and amount required. The ESC also noted that the clinical management algorithm presented was inaccurate as intolerance to TCS is not included in the criteria for pimecrolimus, so these patients would not be eligible for treatment with pimecrolimus.

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

## 5 Comparator

- 5.1 The submission nominated pimecrolimus as the comparator for use on the face and eyelids. The submission argued that pimecrolimus is the only PBS-listed treatment for atopic dermatitis (face and eyelids only) in patients who are contraindicated to or who have failed TCS. This was reasonable although there are other relevant comparators such as tacrolimus (0.03% or 0.1%) ointment that may be available via the Special Access Scheme (SAS) or through a compounding pharmacy. The ESC considered that pimecrolimus was an appropriate comparator for use on the face and eyelids.
- 5.2 For use on the rest of the body, the submission nominated standard management as the comparator. The submission claimed that there are no other PBS-listed treatments for other regions of the body in the target population, and therefore standard management, defined as the use of moisturisers, emollients and non-irritant cleansers, was the appropriate comparator. While this may be reasonable for patients contraindicated to TCS, standard management for the remainder of the target population who are intolerant to or failing to achieve satisfactory disease control is still likely to include treatments for symptom management including TCS at varying dose regimens (e.g. short-term intermittent use). There is a wide range of formulations and potencies of TCS available on the PBS. The ESC considered that the comparator of standard care was reasonable for patients contraindicated to TCS, though this population is likely to be relatively small. The ESC considered that TCS would be an appropriate comparator for patients 'intolerant' to TCS or failing to achieve satisfactory disease control with TCS. The ESC noted that the Pre-Sub-Committee Response (PSCR, p1) did not address this comparator issue but stated that prior TCS treatment had been received by approximately 40% of patients in the pivotal trials. The pre-PBAC response (p1) claimed that those patients intolerant to or having failed to achieve satisfactory disease control with TCS would not continue treatment with TCS.
- 5.3 The PBAC previously considered that TCS were also appropriate comparators when considering pimecrolimus for treatment in patients contraindicated to or those failing intermittent TCS. The listing was recommended on a cost-effectiveness basis given the submission's claim of superior efficacy and similar toxicity compared to the vehicle cream, and inferior efficacy but less toxicity versus TCS (pimecrolimus PSD July 2006).

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

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies in adult and paediatric populations and discussed the natural history of the disease, noting the current unmet need and disease impacts on the quality of life for patients who don't respond to or can't tolerate the treatments currently available.

The clinician also addressed other matters in response to the Committee’s questions, particularly on how the drug would be used in practice; the clinician stated that crisaborole would be used as sole therapy, as was used in the clinical trials, and it will likely be used intermittently for flares for 2–3 weeks at a time. The PBAC noted the submission did not assess the cost-effectiveness of intermittent treatment of disease flares.

### Consumer comments

6.2 The PBAC noted and welcomed the input from two organisations: the Eczema Association of Australasia and Hands to Hold, 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 difficulty in finding treatments that are safe and effective. The comments noted that crisaborole offers hope to patients who have few other treatment options and has the benefit of being able to be used long term.

### Clinical trials

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

- Direct comparison of crisaborole versus ointment vehicle based on two head-to-head randomised trials (AD-301, AD-302); and
- Indirect comparison of crisaborole (AD-301, AD-302) versus pimecrolimus (Barba 2003, Breuer 2004, Trials B305 and B307, Trial 0316, Leung 2009) using ointment vehicle/cream vehicle as the common reference.

6.4 The submission excluded a large body of evidence for pimecrolimus that addressed its use in long-term maintenance therapy (e.g. treatment of flares, as a steroid-sparing agent) and combination use with TCS on the basis that these trials did not have outcomes data that matched the crisaborole trials. Trials comparing pimecrolimus with other established treatments such as tacrolimus or TCS were also excluded as there was no common reference arm for the indirect comparison. The limited selection of short-term, vehicle-controlled trials may be less informative in terms of the comparative efficacy and safety of pimecrolimus.

6.5 Details of the trials presented in the submission are provided in the table below.

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

Trial ID	Protocol title/ Publication title	Publication citation
<b>Crisaborole trials</b>		
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  Itch, 3:e13

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Trial ID	Protocol title/ Publication title	Publication citation
	Yosipovitch G, Simpson EL, Bushmakin AG et al (2018). Assessment of pruritus in atopic dermatitis: validation of the Severity of Pruritus Scale (SPS) 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 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 Yosipovitch G, Simpson EL, Bushmakin AG et al (2018). Assessment of pruritus in atopic dermatitis: validation of the Severity of Pruritus Scale (SPS) 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	Journal of the American Academy of Dermatology, 75(3):494-503 Itch, 3:e12 Itch, 3:e13 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 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	Journal of the American Academy of Dermatology, 77:641-649 Internal study report
<b>Pimecrolimus trials</b>		
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
Breuer 2004	Breuer K, Braeutigam B, Kappa A et al (2004). Influence of pimecrolimus cream 1% on different morphological signs of eczema in infants with atopic dermatitis Kaufmann R, Fölster-Holst R, Höger P et al (2004). Onset of action of pimecrolimus cream 1% in the treatment of atopic eczema in infants Staab D, Kaufmann R, Bräutigam M et al (2005). Treatment of infants with atopic eczema with pimecrolimus cream 1% improves parents' quality of life: a multicenter, randomized trial	Dermatology, 209:314-320 Journal of allergy and clinical immunology, 114(5):1183-1188 Pediatric allergy and immunology, 16(6):527-533.
Leung 2009	Leung DY, Hanifin JM, Pariser DM et al (2009). Effects of pimecrolimus cream 1% in the treatment of patients with atopic dermatitis who demonstrate a clinical insensitivity to topical corticosteroids: a randomized, multicentre vehicle-controlled trial	British Journal of Dermatology, 161(2):435-443
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 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 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	Journal of the American Academy of Dermatology, 46(4):495-504 Pediatric dermatology, 25(3):301-307 Pediatrics, 110(6):1133-1136

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Trial ID	Protocol title/ Publication title	Publication citation
Trial 0316	Ho VC, Gupta A, Kaufmann R, Todd G et al (2003). Safety and efficacy of nonsteroid pimecrolimus cream 1% in the treatment of atopic dermatitis in infants	Journal of Pediatrics, 142:155-162

Source: Table 2.2-1, pp43-45 and Table 2.2-1, pp94-95 of the submission

Note: Published conference abstracts for the identified trials were not included in this table

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

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Crisaborole vs. ointment vehicle</b>						
AD-301 <sup>a</sup>	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	Not used
AD-302 <sup>a</sup>	764	MC, DB, R, VC 29 days	Low	≥2 years old with mild to moderate AD		Not used
Meta-analysis	1527	Included ISGA outcomes from the crisaborole and ointment vehicle arms in Trials AD-301 and AD-302				ISGA 0 or 1 with ≥2-grade improvement; ISGA 0 or 1
<b>Pimecrolimus vs. cream vehicle</b>						
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
Breuer 2004	190	MC, DB, R, VC 4 weeks	Unclear	3-23 months old with mild to very severe AD	EASI score, IGA 0 or 1, SCORAD	Not used
Trial B305 <sup>b</sup>	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 <sup>b</sup>	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
Trial 0316	186	MC, DB, R, VC 6 weeks	Low	3-23 months 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: Table 2.3-1, pp48-49 and Table 2.3-1, pp96-97 of the submission

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; R, randomised; SCORAD, SCORing Atopic Dermatitis; VC, vehicle-controlled

<sup>a</sup> Identical study designs

<sup>b</sup> Identical study designs

6.7 There was limited information reported for the Barba 2003 trial which was only available in an abstract.

6.8 In the Breuer 2004 trial, patients could be switched to open-label pimecrolimus after 2 weeks of the double-blind phase if they achieved total disease clearance or did not show any improvement. The potential risk of bias for Week 4 results was unclear as the number of patients who switched treatments was not reported in the publication.

- 6.9 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).
- 6.10 The ESC noted that the PSCR (p1) presented results of extension study AD-303 to support long-term intermittent efficacy of crisaborole. The ESC noted that study AD-303 was a single arm, open-label study that was not designed to measure efficacy.
- 6.11 The ESC considered that the crisaborole trials had a reasonably low risk of bias but that there was uncertainty in the pimecrolimus trials due to the limited details available.

### Comparative efficacy

- 6.12 The submission claimed that the vehicle in the crisaborole trials has a therapeutic benefit, therefore crisaborole is likely to have a greater treatment effect when compared to placebo. No data were provided on the magnitude of treatment effect associated with the vehicle versus placebo or proprietary emollients.
- 6.13 The primary endpoint of the crisaborole trials 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) are summarised in the table below.

**Table 4: 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 <sup>a</sup>
Logistic regression multiple imputation	29.1%	22.0%	0.038 <sup>b</sup>
Repeated measures logistic regression model	28.3%	21.2%	0.039
Logistic regression multiple imputation (using Day 29 observed data only)	30.0%	23.5%	0.070
Last observation carried forward	32.2%	23.8%	0.014
Trial AD-302	Crisaborole N=513	Ointment vehicle N=250	p-value
MCMC multiple imputation	31.4%	18.0%	<0.001 <sup>a</sup>
Logistic regression multiple imputation	26.5%	14.2%	<0.001 <sup>b</sup>
Repeated measures logistic regression model	31.8%	18.7%	<0.001
Logistic regression multiple imputation (using Day 29 observed data only)	27.8%	15.9%	<0.001
Last observation carried forward	30.6%	17.6%	<0.001

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

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

<sup>b</sup> 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.

- 6.14 A statistically significantly higher proportion of patients treated with crisaborole achieved an ISGA score of 0 or 1 and  $\geq 2$ -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 submission. The differences between the methods of imputation were unclear due to limited documentation. The ESC noted that the results differed based on the imputation method. The PSCR (p4) only provided additional detail in regard to the handling of missing data for the primary outcome in the pivotal trials for 3 of the 5 methods used (Markov Chain Monte Carlo, repeated measures logistic regression, logistic regression using Day 29 observations only). In particular, the response did not adequately address the differences in results using logistic regression multiple imputation which reported lower estimates compared to the primary analysis.
- 6.15 Outcomes based on investigator-assessed global assessments of disease severity appeared more subjective than commonly used clinical tools such as Eczema Area and Severity Index (EASI) or SCORing Atopic Dermatitis (SCORAD) that use more objective scoring methods based on severity of symptoms, affected regions and disease involvement. The clinical importance of results based on ISGA was unclear. The PBAC has previously considered outcomes based on the EASI score (pimecrolimus PSD, July 2006). The pre-PBAC response referred to several publications supporting the validity and reliability of the ISGA<sup>1,2</sup>.
- 6.16 Results from Trial AD-301 failed to achieve the submission's nominated minimal clinically important difference (MCID) of 10% difference in the primary outcome (crude difference of approximately 7%) whereas results from Trial AD-302 achieved the nominated MCID (crude difference of approximately 13%). The clinical importance of an MCID from a sample size calculation for this outcome was unclear.
- 6.17 Results of the meta-analysis of Trials AD-301 and AD-302 based on the primary endpoint of ISGA score of 0 or 1 at Day 29 with a minimum 2-grade improvement from baseline are presented in the table below.

**Table 5: ISGA score of 0 or 1 with  $\geq 2$ -grade improvement at 4 weeks from baseline in the crisaborole vehicle-controlled trials**

Trial	Crisaborole	Vehicle ointment	Odds ratio (95% CI)	Risk ratio (95% CI)	Risk difference (95% CI)
AD-301	165/503 (32.8%)	65/256 (25.4%)	<b>1.43 (1.02, 2.01)</b>	<b>1.29 (1.01, 1.65)</b>	<b>0.07 (0.01, 0.14)</b>
AD-302	161/513 (31.4%)	45/250 (18.0%)	<b>2.08 (1.44, 3.02)</b>	<b>1.74 (1.30, 2.34)</b>	<b>0.13 (0.07, 0.20)</b>
Meta-analysis of trials			<b>1.71 (1.19, 2.47)</b>	<b>1.48 (1.11, 1.99)</b>	<b>0.11 (0.05, 0.16)</b>
Heterogeneity, I <sup>2</sup>			53%	39%	58%

Source: Table 2.6-1, p87 of the submission

<sup>1</sup> Božek A and Reich A. Assessment of intra- and inter-rater reliability of three methods for measuring atopic dermatitis severity: EASI, Objective SCORAD, and IGA. *Dermatology*, May 12, 2017

<sup>2</sup> Cappelleri JC, Gerber RA, Bushmakina AG *et al.* Evaluation of treatment effects on the Investigator's Static Global Assessment: Longitudinal analysis of 2 phase 3 studies of the phosphodiesterase 4 inhibitor crisaborole ointment, 2% in patients 2 years and older with mild to moderate atopic dermatitis. Presented at the EADV 2018 Annual Meeting; September 12-16; Paris, France.

Abbreviation: CI, confidence interval; ISGA, Investigator’s Static Global Assessment (5-point scale)

Note: The number of patients in each arm appeared to be calculated using estimated proportions with model-based imputation for missing values.

- 6.18 The results from the meta-analysis suggest that a higher proportion of patients treated with crisaborole achieved an ISGA score of 0 or 1 with a minimum 2-grade improvement from baseline (approximately 11%) across both trials compared to patients treated with the ointment vehicle. These results should be interpreted with caution given uncertainties noted with the absolute proportions in individual trial results that appeared dependent on the method of imputation used. The meta-analysis suggests there was moderate heterogeneity between the trials ( $I^2= 39\text{-}58\%$ ), the reasons for which were not explored in the submission.
- 6.19 Overall the ESC considered that crisaborole showed only a small benefit over the vehicle and that this benefit may not be clinically significant.
- 6.20 Key results for the secondary endpoint of the crisaborole trials are presented in the table below. Meta-analysed results of this outcome are presented with results for the indirect comparison with pimecrolimus in Table 8.

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

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

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

<sup>a</sup> 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

- 6.21 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.
- 6.22 In both trials, changes in quality of life measures (Dermatology Quality of Life Index, Dermatitis Family Impact) were generally greater in the crisaborole arm compared with placebo, however, the statistical significance of these results were not assessed.
- 6.23 It was unclear whether trial results from the broader atopic dermatitis population are directly applicable to the target population who are contraindicated to, intolerant to or who are failing TCS. No subgroup analyses were presented in the submission. In both trials, descriptive results for pre-specified analyses by sex, race and ethnicity

remained in favour of crisaborole. However, there was no observable difference between the crisaborole and vehicle arms in the subgroup of patients who were 18 years and older, suggesting that treatment effects may vary with age. The ESC considered that the patient population in the trial was not representative of the population in the requested listing. The Pre-Sub-Committee Response (PSCR, p1) presented a post-hoc subgroup analysis of patients achieving ISGA clear or almost clear with a 2-point reduction by prior treatment. The PSCR claimed that this showed that crisaborole was efficacious regardless of prior use of TCS, however the full data were not provided.

- 6.24 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 (TCS 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.
- 6.25 Key outcomes reported in the pimecrolimus versus cream vehicle trials are summarised in the table below. Results based on Investigator's Global Assessment (IGA), scored on a 6-point severity scale ranging from clear (0), almost clear (1), mild (2), moderate (3), severe (4) and very severe (5), were used for the indirect comparison with pimecrolimus in Table 8.

Table 7: Results for atopic dermatitis disease severity outcomes from Barba 2003 (3 weeks), Breuer 2004 (4 weeks) and 6-week outcomes from Trial B305, Trial B306, Trial 0316 and Leung 2009.

Trial	Facial IGA score 0 or 1	IGA score 0 or 1	EASI	SCORAD	Pruritus	Good or complete control
<b>Barba 2003 (3 weeks)</b>						
Pimecrolimus (n=76)	75%	31%	Mean % -66.7%	-	No or minimal 90%	91%
Cream vehicle (n=38)	31%	23%	+23%		46%	49%
	p=0.0004	p=0.0037	p=0.0001		p<0.0001	p<0.0001
<b>Breuer 2004 (4 weeks)</b>						
Pimecrolimus (n=129)	-	53.5%	Mean % -71.5%	-55.2%	-	-
Cream vehicle (n=66)		10.6%	+19.4%	+1.1%		
		p<0.001	p<0.001	p=0.002		
<b>Trial B305 (6 weeks)</b>						
Pimecrolimus (n=130)	-	37.7%	NR <sup>a</sup>	-	Absent or mild 50%	-
Cream vehicle (n=68)		16.2%			32.4%	
		p=0.02			p<0.02	
<b>Trial B307 (6 weeks)</b>						
Pimecrolimus (n=137)	-	32.1%	NR <sup>a</sup>	-	Absent or mild 62.8%	-
Cream vehicle (n=68)		20.6%			35.3%	
		p=0.076			p<0.001	
<b>Trial 0316 (6 weeks)</b>						
Pimecrolimus (n=123)	-	54.5%	Median % -81.6%	-	Absent or mild 69.9%	71.5%
Cream vehicle (n=63)		23.8%	-25.0%		36.5%	27.0%
		p<0.001			p<0.001	p<0.001
<b>Leung 2009 (6 weeks)</b>						
Pimecrolimus (n=46)	-	11%	Mean % (SD) +1.8 (81.3)	-	Absent or mild 30%	-
Cream vehicle (n=26)		0%	+26.9 (99.8)		23%	

Source: Table 2.5-1, p106 of the submission; Table 305-6, p9, Table 305-9, p12, Table 307-6, p17, Table 307-9, p19 of Elidel (ASM 981, pimecrolimus) Cream 1% FDA statistical review

Abbreviations: EASI, Eczema Area & Severity Index; IGA, Investigator's Global Assessment; SCORAD, SCORing Atopic Dermatitis Index; SD, standard deviation

<sup>a</sup> Individual trial results were not available. An analysis of pooled data (Trials B05 and B307) was reported in Eichenfield 2002 publication suggesting a statistically significant difference in mean percentage change in EASI score when comparing pimecrolimus with vehicle (-45% vs -1%, p<0.001).

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

6.26 Overall, a higher proportion of patients treated with pimecrolimus achieved clear or almost clear disease in the included trials. Results were statistically significant in all trials except for the Leung 2009 study. Patients treated with pimecrolimus experienced greater percentage reductions in EASI score compared with its vehicle. More patients receiving pimecrolimus were reported as having absent or mild pruritus compared with its vehicle.

6.27 The indirect comparison of crisaborole and pimecrolimus based on outcomes of IGA/ISGA score of 0 or 1 (with no requirement for a ≥2-grade improvement from baseline ) reported in the trials at varying time points (3 weeks, 4 weeks and 6 weeks from baseline) are presented in the table below.

Table 8: Summary of results of the indirect comparison for ISGA/IGA score of 0 or 1

Trial ID	Patients, n/N (%)		OR (95% CI)	RR (95% CI)	RD (95% CI)
	Intervention	Common reference			
<b>Crisaborole versus ointment vehicle</b>					
AD-301	260/503 (51.7%)	104/256 (40.6%)	<b>1.56 (1.15, 2.12)</b>	<b>1.27 (1.07, 1.51)</b>	<b>0.11 (0.04, 0.18)</b>
AD-302	249/513 (48.5%)	74/250 (29.7%)	<b>2.24 (1.63, 3.10)</b>	<b>1.64 (1.33, 2.02)</b>	<b>0.19 (0.12, 0.26)</b>
Pooled	509/1016 (50.1%)	178/506 (35.2%)	-	-	-
Meta-analysis of trials Heterogeneity			<b>1.87 (1.31, 2.66)</b> <i>I</i> <sup>2</sup> = 61%	<b>1.43 (1.12, 1.84)</b> <i>I</i> <sup>2</sup> = 71%	<b>0.15 (0.07, 0.23)</b> <i>I</i> <sup>2</sup> = 56%
<b>Pimecrolimus versus cream vehicle</b>					
Barba 2003 <sup>a</sup>	24/76 (31%)	9/38 (23%)	1.49 (0.61, 3.62)	1.33 (0.69, 2.58)	0.08 (-0.09, 0.25)
Breuer 2004	69/129 (53.5%)	7/66 (10.6%)	<b>9.69 (4.12, 22.83)</b>	<b>5.04 (2.46, 10.35)</b>	<b>0.43 (0.32, 0.54)</b>
<i>Trial B305</i>	<i>49/130 (37.7%)</i>	<i>11/68 (16.2%)</i>	<b>3.13 (1.50, 6.55)</b>	<b>2.33 (1.30, 4.18)</b>	<b>0.22 (0.09, 0.34)</b>
<i>Trial B307</i>	<i>44/137 (32.1%)</i>	<i>14/68 (20.6%)</i>	1.82 (0.92, 3.63)	1.56 (0.92, 2.64)	0.12 (-0.01, 0.24)
Trial 0316	67/123 (54.5%)	15/63 (23.8%)	<b>3.83 (1.94, 7.56)</b>	<b>2.29 (1.43, 3.36)</b>	<b>0.31 (0.17, 0.44)</b>
Leung 2009	5/46 (11%)	0/26 (0%)	7.02 (0.37, 132.31)	6.32 (0.36, 109.91)	0.11 (0.00, 0.21)
Pooled	258/641 (38.7%)	56/329 (17.0%)	-	-	-
Meta-analysis of trials Heterogeneity			<b>3.22 (1.83, 5.67)</b> <i>I</i> <sup>2</sup> = 60%	<b>2.22 (1.51, 3.26)</b> <i>I</i> <sup>2</sup> = 50%	<b>0.21 (0.10, 0.33)</b> <i>I</i> <sup>2</sup> = 80%
<b>Indirect comparison of crisaborole vs. pimecrolimus</b>			0.58 (0.30, 1.13)	0.64 (0.41, 1.02)	-0.06 (-0.20, 0.08)

Source: Table 2.6-1, p110 of the submission; Table 305-6, p9 and Table 307-6, p17 of Elidel (ASM 981, pimecrolimus) Cream 1% FDA statistical review

Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; ISGA, Investigator's Static Global Assessment; OR, odds ratio; RD, risk difference; RR, relative risk

<sup>a</sup> The numbers of patients were calculated in the submission from the proportion of patients in each arm and then rounded

*Italicised results were calculated during the evaluation*

- 6.28 When comparing crisaborole with its vehicle, results from the meta-analysis suggest a higher proportion of patients treated with crisaborole achieved clear or almost clear disease at 4 weeks from baseline (approximately 15%) compared to patients receiving its vehicle. These results should be interpreted with caution given substantial heterogeneity between the trials (*I*<sup>2</sup>=56-71%) which was not explored in the submission.
- 6.29 The meta-analysis of the pimecrolimus trials indicated that a higher proportion of patients treated with pimecrolimus achieved an IGA score of 0 or 1 (by around 22%) compared to patients treated with vehicle. The results should be interpreted with caution given substantial statistical (*I*<sup>2</sup> = 82%) and clinical heterogeneity between the included trials with respect to differing age groups, baseline disease severity, treatment durations and trial designs based on different primary endpoints and/or objectives.
- 6.30 The submission assumed that the IGA and ISGA outcomes which are based on different scales of severity (6-point versus 5-point respectively) were sufficiently interchangeable for the indirect comparison. However, the correlation between these scales was uncertain. The PSCR noted that the majority of patients in the two pimecrolimus trials and all patients in the crisaborole trials had mild to moderate

disease and therefore the additional IGA score of 5 (very severe disease) was not relevant to the comparison. The ESC noted that there are also differences in the wording of the less severe IGA/ISGA score categories (0-4) that may have resulted in different categorisation of patients between the trials.

- 6.31 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 submission noted that numerical differences in the results appeared to favour pimecrolimus. The indirect comparison may not be informative due to 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 ESC noted the major transitivity issues with the indirect comparison were:
- the differences in vehicle response (35% vs 17% for crisaborole and pimecrolimus respectively);
  - the assumption that scores of 1 or 2 on ISGA were equivalent to scores of 1 or 2 on the IGA; and
  - the high clinical and statistical heterogeneity in the pimecrolimus trials.
- 6.32 The submission claimed that crisaborole was non-inferior to pimecrolimus based on the lower bound of the 95% confidence interval of risk difference between treatments that did not exceed -25% (RD -0.06, 95% CI: -0.20, 0.08). The nominated non-inferiority margin did not appear reasonable given it exceeds the estimated difference for both treatments compared with their vehicles (15% and 20% for crisaborole and pimecrolimus respectively). In addition, the non-inferiority margin was based on a nominated MCID with uncertain clinical importance. The ESC noted that the indirect comparison favoured pimecrolimus, with the lower bound of the confidence interval being -20%. The ESC noted that the non-inferiority margin was larger than the benefits seen with either treatment and was 2.5 times the MCID used to claim superiority over standard management. The ESC considered that the results of the indirect comparison did not exclude the possibility that pimecrolimus was superior to crisaborole.

### **Comparative harms**

- 6.33 No safety data were provided comparing crisaborole with standard management. However, the vehicle ointment for crisaborole may be a reasonable proxy for emollients given similarities in the ingredients used in the vehicle and those typically used in ointment-based emollients.
- 6.34 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.

- 6.35 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 submission 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***

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

### ***Clinical claim***

- 6.37 The submission described crisaborole as superior in terms of efficacy and non-inferior in terms of safety compared with standard management. This claim was inadequately supported given the uncertain clinical importance of investigator-assessed global outcomes, lack of data for chronic disease management, lack of comparative data with well-established treatments used in standard management and concerns with the applicability of the broader trial population to the PBS population. The magnitude of benefit associated with crisaborole compared with its vehicle appeared small and only just exceeded the MCID proposed. The safety data suggest that crisaborole was associated with more application site burning or stinging compared with its vehicle. The ESC considered that the clinical claim of superior efficacy and non-inferior safety versus standard management was not reasonable based on 4-week data of crisaborole versus its ointment vehicle, which showed only a small benefit over the vehicle. The ESC noted that the benefit for crisaborole over vehicle alone may not be clinically significant and the patient population in the trial was not representative of the population in the requested listing. There were no available long-term efficacy data, comparative data versus well-established treatments, or data on use in combination therapy for crisaborole. The pre-PBAC response stated that there are data to support sustained efficacy of crisaborole when used intermittently over 48 weeks from study AD-303. Only safety outcomes from this study were provided in the submission.

- 6.38 The submission described crisaborole as non-inferior in terms of efficacy and safety compared with pimecrolimus. This claim may not be reasonable given the concerns with the robustness of the indirect comparison due to issues with heterogeneity and exchangeability of the trials, the unknown clinical importance and exchangeability of investigator-assessed global outcomes based on different severity scales and a nominated non-inferiority margin that may not be reasonable (margin exceeds treatment benefits compared to vehicle). The ESC considered that the clinical claim of non-inferior efficacy versus pimecrolimus based on the indirect comparison was not reasonable given major concerns with heterogeneity and exchangeability of the trials and assumed interchangeability of IGA/ISGA outcomes using different scales. The nominated non-inferiority margin did not appear reasonable given the margin exceeds the benefits associated with each treatment compared to their vehicles. The ESC considered that the results of the indirect comparison did not exclude the possibility that pimecrolimus was superior to crisaborole. The ESC considered that pimecrolimus and crisaborole are likely to have similar adverse event profiles.
- 6.39 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 non-inferior comparative effectiveness compared with pimecrolimus was not adequately supported by the data.
- 6.40 The PBAC considered that the claim of non-inferior comparative safety compared with standard management was not adequately supported by the data as the results of the indirect comparison did not exclude the possibility that pimecrolimus was superior to crisaborole in terms of efficacy. The PBAC considered that the claim of non-inferior comparative safety compared with pimecrolimus was likely to be reasonable but was supported by limited data.

### **Economic analysis**

- 6.41 The submission presented a cost-minimisation analysis for the comparison of crisaborole versus pimecrolimus for use on the face and eyelids and a cost-effectiveness analysis versus standard management for use on the rest of the body. The ESC considered that the cost-minimisation analysis was not reasonable given that the clinical claim of non-inferiority to pimecrolimus was inadequately supported. The ESC considered that the cost-utility analysis was not reasonable due to the inappropriate comparator and the inadequate support for the clinical claim of superiority. A weighted dispensed price for crisaborole based on usage in separate areas of the body is summarised in the table below.

**Table 9: Calculation of weighted DPMQ for crisaborole**

	Face and eyelids	Rest of body
Proposed DPMQ	\$ [REDACTED]	\$ [REDACTED]
BSA distribution	9%	91%
<b>Weighted DPMQ</b>	\$ [REDACTED]	

Source: Table 3.4-1, p162 of the submission  
 Abbreviation: BSA, body surface area

- 6.42 The submission used the ‘rule of nines’ to determine the weightings of the DPMQ for the face or eyelids and the remainder of the body. The rule assumes the total body surface area comprises 9% for the head and neck, each arm, the front and back of each leg, the four trunk quadrants; and 1% for the genital area and is used in the SCORAD index to calculate extent of disease. Estimates of body surface area based on this rule may not be reliable given dermatology studies of assessment tools have noted concerns with its accuracy in practice due to wide inter-observer variations (Charman et al 1999, Tripodi 2003).
- 6.43 The ESC considered that the estimated price for crisaborole was not appropriately weighted using an assumed distribution of total body surface area (9% face and eyelids and 91% in the rest of the body) which may not correlate with areas affected by the disease (i.e. treatable areas). The mean percent treatable body surface area in patients using crisaborole in the whole of body in the trials was around 18%. The distribution of affected areas between the face and eyelids versus the rest of the body was unknown.
- 6.44 The cost-minimisation analysis for crisaborole versus pimecrolimus is presented in the table below. The cost-minimisation analysis should have been conducted using ex-manufacturer prices due to the differences in fees and mark-ups associated with the different total script numbers between treatments.

**Table 10: Results of the cost-minimisation analysis**

Component	Crisaborole	Pimecrolimus
<b>DPMQ</b>		
Cost per script	\$ [REDACTED]	\$31.44 <sup>a</sup>
Amount of drug per script	60 g	15 g
Cost per gram		\$ [REDACTED]
Total cost per 60 g	\$ [REDACTED]	\$125.76
<b>AEMP</b>		
AEMP cost per script	\$ [REDACTED]	\$18.93 <sup>a</sup>
Amount of drug per script	60 g	15 g
Cost per gram (AEMP)		\$ [REDACTED]
Total cost per 60 g (DPMQ) <sup>a</sup>	\$ [REDACTED]	\$125.76

Source: Tables 3.4-1 and 3.4-2, p161 of the submission

<sup>a</sup> Based on 1 June 2018 PBS price

*Italicised values were calculated during the evaluation*

- 6.45 The cost-minimisation analysis was conducted in the submission assuming crisaborole is equivalent to pimecrolimus on a per gram basis based on product information dosing frequencies. The submission stated that 4 tubes of pimecrolimus supplied in a 15 g tube would be required to supply the same quantity as crisaborole which is supplied in a 60 g tube. This approach implicitly assumes that crisaborole is equivalent to pimecrolimus on a per gram basis. This was inappropriate as the submission did not account for differences in amounts required depending on circumstances of use. Pimecrolimus is recommended for short-term intermittent therapy for up to 6 weeks whereas the requested restriction for crisaborole indicates that crisaborole is for chronic use. The optimal duration of therapy for crisaborole was unclear, with available data based on acute disease management only over 4 weeks. The ESC noted

that there was no data provided in the submission or PSCR to support the equi-effective doses proposed in the submission. The ESC considered that the assumption of equivalence for crisaborole and pimecrolimus on a per gram basis was not appropriate and was unlikely to reflect actual use of the treatments.

- 6.46 During the evaluation, an estimated price for crisaborole was calculated using the AEMP for pimecrolimus and the assumed equi-effective doses in the submission. This estimate was lower than the proposed price calculated using the DPMQ for pimecrolimus. The ESC noted that although this was the appropriate method for calculation of the prices, the price is unlikely to be appropriate due to uncertainty in the equi-effective doses.
- 6.47 No additional costs or cost-offsets were claimed in the submission. This was appropriate.
- 6.48 The table below is a summary of the cost-effectiveness analysis of crisaborole versus standard management (using the ointment vehicle as a proxy). There was inadequate justification for a modelled cost-effectiveness analysis over 5 years given the clinical data were limited to 29 days for acute disease management only. A trial-based analysis may be more appropriate. The ESC considered a one-year model (as was used in NICE HTA & Kuznik et al 2017 and ICER review 2017), including intermittent treatment of disease flares, would have been a more informative model structure.

**Table 11: Key components of the economic evaluation**

Component	Description
Type of analysis	Cost-utility analysis
Methods used to generate results	Markov cohort model (with half-cycle correction for all consequences and disease management costs only)
Time horizon	5 years
Cycle length	29 days
Discounting	5% for costs and outcomes, applied annually
Population	AD-301 and AD-302 trial populations; patients aged 2 years and above with mild to moderate atopic dermatitis
Health states	Clear/almost clear (ISGA 0 or 1), mild (ISGA 2), moderate (ISGA 3), severe (ISGA 4), dead
Outcomes	Quality-adjusted life years
Transition probabilities	<p>Transition probabilities in the first 29-day cycle were derived from the primary and secondary endpoints (ISGA score of 0 or 1 with/without <math>\geq 2</math>-grade improvement) in Trials AD-301 and AD-302 (29 day trial durations).</p> <p>In Cycles 2-12 (first year of treatment), the submission assumed that the likelihood of patients moving to less severe health states was progressively decreased in each subsequent cycle by 50% compared to the preceding cycle. From Cycle 13 (start of year 2) to the end of the model, all patients remained in the health states they were in at the end of Cycle 12 (year 1 of treatment).</p> <p>In all cycles, the submission also assumed that patients can only remain in the state in which they began the cycle or transition to a better state (i.e. no patients get worse over the model lifetime).</p> <p>Transition probabilities to death were based on Australian age-specific death rates in 2016 for the general population.</p>
Software package	Excel 2010

Source: Table 3.1-1, p132 of the submission

Abbreviation: ISGA, Investigator's Static Global Assessment

6.49 All patients start in either the mild or moderate disease health states. In each 29-day cycle up to model cycle 12 (first year of treatment), patients can remain in the health state in which they began that cycle, move to a less severe health state or die. Patients who enter the clear/almost clear health state can only remain in that state or die. From model cycle 13 (start of year 2), patients can only remain in the health state in which they began that cycle or die. In the base case analysis, no patients occupied the severe health state. Patients in all health states except clear/almost clear and dead accrued ongoing chronic costs and consequences associated with mild to moderate disease. The model assumed that patients in the crisaborole arm received ongoing treatment over the model lifetime regardless of disease status whereas patients in the vehicle arm received no active treatments. The model does not allow for treatment discontinuation.

6.50 Key drivers of the economic model are summarised in the table below.

**Table 12: Key drivers of the model**

Description	Method/Value	Impact
Treatment costs	Based on the proposed DPMQ for crisaborole of \$ [redacted] per 60 g tube. The cost per 60 g tube was applied once every 8 cycles based on an assumed annual utilisation of [redacted] g ([redacted] tubes per year). The assumption was inadequately supported by US claims data provided in the submission that were highly uncertain due to exclusion of many groups of patients from the analysis (e.g. excluding patients with intermittent use of crisaborole) and misinterpretation of the results ([redacted] claims does not directly translate to [redacted] tubes). Supportive data based on another analysis of US health insurance claims data were also uncertain due to significant data loss with only 4% of the population remaining at the end of the 12-month analysis period. US claims data may not be generalisable to the Australian setting as US health insurance providers typically have different restrictions in terms of eligibility and quantity dispensed. The assumed utilisation amounts to approximately [redacted] g per 29-day model cycle which was inconsistent with crisaborole trials reporting an average of 170 g used over 4 weeks.	High, favours crisaborole
Time horizon	5 years. This was inconsistent with the majority of published economic models that used 1-year time horizons to evaluate interventions for atopic dermatitis.	High, favours crisaborole
Extrapolation of treatment effect	In Cycles 2 to 12, the submission assumed that the likelihood of patients moving to less severe health states was progressively decreased in each subsequent cycle by 50% compared to the preceding cycle. No data were provided in support of this assumption. In Cycles 13 to 63 of the 5-year model, the submission assumed that patients could only remain in the health states in which they started each cycle (i.e. they could not get any better or worse). The submission stated that this was due to maintenance of treatment benefit, consistent with continuous treatment with crisaborole over the modelled time horizon. No data were provided in support of this assumption which does not appear to reflect the underlying nature of a relapsing-remitting disease. This assumption was also inconsistent with trial data suggesting a small percentage of patients who had mild to moderate disease at baseline had severe disease at the end of the trial.	High, favours crisaborole

Source: compiled during the evaluation

6.51 The ESC considered that the model structure did not reflect the clinical reality of a chronic disease with intermittent acute phases. The main areas of concern were:

- the model structure did not capture all relevant health states as it did not include responder and non-responder health states;
- it was inappropriate to assume that all patients receive treatment regardless of symptoms;

- the model assumed no transition of patients to worse health states and the structure did not allow adequate assessment of the impact of the absence of transitions to worse health states; and
- it was inappropriate to assume that the incremental benefit in year 1 was maintained over the remaining 4 years of the 5 year model as this structure ignores the intermittent nature of AD, is inconsistent with trial data in which a small proportion of patients ended the trial in severe health states and favours the intervention.

6.52 The modelled circumstances of use (treatment duration, frequency of use) of crisaborole were unlikely to reflect clinical practice. All patients in the crisaborole arm continued to receive the same treatment cost at fixed intervals in the model regardless of symptoms and disease severity (e.g. patients who were in the clear/almost clear health state were attributed the same drug cost as patients who remained in the moderate health state). The PSCR (p5) suggested that treatment costs assumed in the model were based on average consumption over a period of time, during which flares occurred. The ESC noted this focus on treatment cost does not reflect the applicability of treatment benefits. In clinical practice, treatment initiation, discontinuation and amount used would be dependent on the presence/absence of symptoms and disease severity. The ESC considered that the major translation issues for the model were:

- the time horizon of 5 years despite no comparative evidence for longer than 29 days. The extrapolation of treatment effect beyond the first 29-day cycle was based on unsupported assumptions and treatment effects beyond the first year that appeared clinically implausible (e.g. patients could not get better or worse);
- the target population is narrower than the trial population;
- the requested setting was for chronic use whereas the data provided is in the acute setting. The PSCR (p1) referred to study AD-303 as evidence of the effectiveness of long term intermittent crisaborole use, however this study focussed on safety, was a single arm, open-label study that was not designed to measure efficacy and was not used in the modelled evaluation;
- trial-based treatment benefits using 170 g over 4 weeks were not applicable to the modelled population assumed to be using ■ g per year; and
- baseline disease severity was assumed to be the same across all age groups.

6.53 The submission used separate utility values for children (2-18 years) and adults (≥18 years). Estimates were derived using the averages of published utility values that were mapped to each health state in the model. This approach was inappropriate given duplication of data across studies (primarily driven by lower estimates from one study), differences in sampled populations (general population versus patient-derived preferences), methods (mapped utilities, standard gamble utilities, multi-attribute utility instruments) and different severity definitions. These differences resulted in widely varying utility estimates for some health states (e.g. moderate disease ranges

from 0.69-0.88). The ESC noted that the utility values obtained from the literature may have limited applicability to health states based on ISGA score.

6.54 The costing data used to inform disease management costs in the model were based on older, out-dated data from an outpatient survey (Su et al 1997) that may not represent current clinical practice and/or current health resource costs. Mean estimates from the study may not be reliable given the relatively small sample size (n=48) and substantial variability as indicated by wide standard deviations in the results.

6.55 The results of the economic evaluation are summarised in the table below.

**Table 13: Results of the economic evaluation**

Component	Crisaborole	Vehicle	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	4.124	4.070	0.0532
<b>Incremental cost per quality-adjusted life year</b>			<b>\$ [REDACTED]</b>

Source: Section 3.8, pp154-156 of the submission

Abbreviation: QALY, quality-adjusted life year

6.56 In patients with mild to moderate atopic dermatitis who are contraindicated to, intolerant to or failing to achieve satisfactory disease control with TCS, treatment with crisaborole was associated with an incremental cost per QALY gained of less than \$15,000 per QALY compared to its vehicle.

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

**Table 14: Results of sensitivity analyses**

Analyses	Incremental cost	Incremental QALY	ICER
<b>Base case</b>	\$ [REDACTED]	0.0532	\$ [REDACTED]
Time horizon (base case: 5 years, 63 cycles)			
29 days (1 cycle)	\$ [REDACTED]	0.0005	\$ [REDACTED]
1 year (12 cycles)	\$ [REDACTED]	0.0177	\$ [REDACTED]
2 years (25 cycles)	\$ [REDACTED]	0.0232	\$ [REDACTED]
10 years (126 cycles)	\$ [REDACTED]	1.2792	\$ [REDACTED]
Transition probabilities (base case: In each cycle, patients can only remain in the same disease severity or transition upwards to a better health state)			
In each cycle, 5% of patients transition to a more severe state	\$ [REDACTED]	0.0716	\$ [REDACTED]
Crisaborole treatment costs (base case: 1 x 60 g tube every 8 cycles)			
3 x 60 g tubes every 8 cycles	\$ [REDACTED]	0.0532	\$ [REDACTED]
[REDACTED] g in each cycle (average of [REDACTED] g over [REDACTED] cycles)	\$ [REDACTED]	0.0532	\$ [REDACTED]
1 x 60 g tube in each cycle	\$ [REDACTED]	0.0532	\$ [REDACTED]
3 x 60 g tubes in each cycle	\$ [REDACTED]	0.0532	\$ [REDACTED]
<b>Multivariate analysis</b>			
3 x 60 g crisaborole in Cycle 1, time horizon of 29 days	\$ [REDACTED]	0.0005	\$ [REDACTED]

Source: Table 3.9-2, p158 of the submission

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

*Italicised analyses were conducted during the evaluation*

6.58 The results were highly sensitive to the costs of treatment with crisaborole and extrapolation of treatment benefits beyond the clinical trial data. Sensitivity analyses based on the trial duration of 1 cycle (29 days) increased the ICER to more than

\$200,000 per QALY and varying the amount of crisaborole to 3 x 60 g tubes in each model cycle as in the trial increased the ICER to more than \$200,000 per QALY. Multivariate analysis based on the trial duration and amount of crisaborole used on the trial increased the ICER to substantially more than \$200,000 per QALY. The model structure did not allow for testing of intermittent use for the treatment of disease flares.

- 6.59 The ESC considered that the time horizon of one year, consistent with published literature in the area, would be more appropriate as the base case. The use of a one-year time horizon results in an ICER of less than \$15,000 per QALY. The ESC noted that the application of drug costs to the model every 8 cycles rather than an average cost per cycle resulted in anomalies in the ICER over different time horizons and considered that it would be preferable to have applied an average cost per cycle. For example, due to the application of costs every 8 cycles the ICER for 8 cycles is substantially higher (\$15,000 - \$45,000 per QALY) than the ICER for 12 cycles (less than \$15,000 per QALY).
- 6.60 The sensitivity analysis suggests that the model was insensitive to the change that allowed 5% of patients to transition to a more severe state in each cycle. However, the implementation of transitions to more severe states may not be appropriate as it resulted in clinically implausible outcomes (e.g. no patients are clear of disease and the majority have severe disease at Year 5). The impact of assumed transition probabilities used in the base case (i.e. patients cannot transition to a worse state) could not be adequately assessed with sensitivity analyses due to the structure of the economic model.

### ***Drug cost/patient/course***

- 6.61 Based on the proposed weighted DPMQ for crisaborole for use on the whole body including face and eyelids, the estimated drug cost per patient per year was \$ [REDACTED] (using a DPMQ of \$ [REDACTED] per gram and assuming [REDACTED] grams per patient per year as per US claims data). This estimate was highly uncertain and was inconsistent with usage reported in the trials. Based on trial data, the estimated drug cost for crisaborole per patient per 4 weeks was \$ [REDACTED] (mean dose of 170 g).
- 6.62 Based on use on the face and eyelids only, the estimated drug cost for pimecrolimus per patient per year was \$125.76 (using a DPMQ of \$31.44 per 15 gram script and assuming a maximum of 60 grams as per the annual limit under PBS restrictions).

### ***Estimated PBS usage & financial implications***

- 6.63 This submission was considered by DUSC. The submission used a mixed epidemiological and market share approach to estimate the utilisation and financial implications of listing crisaborole.
- 6.64 The estimated eligible population and budget impact of listing crisaborole is summarised in the table below.

**Table 15: Estimated utilisation and cost of crisaborole**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	████	████	████	████	████	████
Number of scripts dispensed <sup>a</sup>	████	████	████	████	████	████
<b>Estimated financial implications of crisaborole</b>						
Cost to PBS/RPBS	\$████	\$████	\$████	\$████	\$████	\$████
Co-payments	\$████	\$████	\$████	\$████	\$████	\$████
Cost to PBS/RPBS less co-payments	\$████	\$████	\$████	\$████	\$████	\$████
<b>Estimated financial implications for pimecrolimus</b>						
Cost to PBS/RPBS	\$████	\$████	\$████	\$████	\$████	\$████
Co-payments	\$████	\$████	\$████	\$████	\$████	\$████
Cost to PBS/RPBS less co-payments	\$████	\$████	\$████	\$████	\$████	\$████
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$████	\$████	\$████	\$████	\$████	\$████

Source: Table 4.2-1, Table 4.2-2, p176; Table 4.2-3, Table 4.2-4, Table 4.2-5, p177; Table 4.2-11, pp180-181; Table 4.2-12, p181; Table 4.2-13, pp181-182 of the submission; Table 4.4-1, p186 of the submission.

Abbreviations: AD, atopic dermatitis; DPMQ, dispensed price for maximum quantity; pt, patient; TCS, topical corticosteroids; yr, year

6.65 Treatment costs associated with crisaborole may be substantially underestimated based on the assumed use of █████ scripts (████ g) per patient per year. The assumption was based on US claims data that may not be generalisable to the Australian setting. The assumed usage was inconsistent with trial data suggesting approximately 3 x 60 g tubes were required for 4 weeks of therapy. The pre-PBAC response presented an alternative approach in which the number of tubes per patient per year was calculated using the other 3 time points in the US data (90, 180 and 270 days). Based on these estimates the number of tubes per patient per year ranged from █████ to █████, with an average of █████.

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

- The evidence used to guide the estimates was very limited. The estimated eligible population was highly uncertain as it was largely derived using mid-point estimates from a sponsor-commissioned study. The estimates in this study were wide-ranging and varied according to age and disease severity.
- The submission did not consider additional uptake of crisaborole from the private prescription market for pimecrolimus or over-the-counter topical corticosteroids. The size of this market and circumstances of use (e.g. amounts dispensed) is unknown.

- There is also potential for use of crisaborole outside the requested restriction, particularly in younger patients (under 2 years of age), those with severe disease and as first-line therapy in those not contraindicated to topical corticosteroids. DUSC advised that a disinclination for patients and/or prescribers towards the use of steroids may contribute to use outside of the requested restriction in the first line setting.
  - The estimated utilisation of crisaborole was highly uncertain as it was based on market penetration rates for pimecrolimus. The crisaborole market is unlikely to mimic utilisation rates of pimecrolimus, given existing restrictions that do not apply to crisaborole (face and eyelids only, annual limit of 4 scripts).
  - The submission did not adequately justify restricting the patient population to those who are contraindicated to, intolerant to, or failing topical corticosteroids given the clinical data and requested TGA indication were for the broader population with mild to moderate disease.
  - Analysis of the 10% Medicare sample data to derive the market penetration rates and number of patients contraindicated to topical corticosteroids was poorly detailed and not fit for purpose.
  - Treatment costs associated with crisaborole may be substantially underestimated based on an assumed use of use of [REDACTED] scripts ([REDACTED] g) per patient per year. The assumed usage was inconsistent with trial data suggesting approximately 3 x 60 g tubes were required for 4 weeks of therapy. DUSC advised that this assumption was poorly justified and created the potential for usage well above the base case estimates.
- 6.67 Based on the estimates presented, at year 6 the estimated number of patients was 100,000-200,000 and the net cost to the PBS would be \$20-\$30 million. As noted by DUSC it is likely that these estimates are significantly underestimated.
- 6.68 The pre-PBAC response commented that the sponsor assumes that, should crisaborole be PBS-listed, a risk-share agreement would be in place to manage leakage. No details of a proposed risk-share arrangement were provided.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of crisaborole for the treatment of mild to moderate atopic dermatitis due to the omission of a relevant comparator, uncertainty regarding the appropriate place in therapy, uncertain comparative efficacy and highly uncertain cost effectiveness.
- 7.2 The PBAC noted that the proposed listing is for chronic use for an indeterminate period of time, which it considered may not be appropriate given the lack of efficacy data beyond 4 weeks. The PBAC considered that the restriction should address the use of crisaborole in terms of initiation, discontinuation and optimal duration of therapy. The PBAC agreed with ESC that the maximum quantity and number of repeats was inadequately justified and the appropriate amount remains unclear. The PBAC noted

the proposed restriction was based on merging the two existing restrictions for pimecrolimus, however the PBAC considered that this was not appropriate due to differences in the use of these drugs such as the annual limit, age range and restriction to use on the face and eyelids for pimecrolimus.

- 7.3 The PBAC noted that the proposed listing is narrower than the requested TGA indication in that it was limited to patients who are contraindicated, have failed to achieve satisfactory disease control, or are intolerant to TCS. The PBAC considered that this restriction was not consistent with the clinical data and was not adequately justified. The PBAC noted that the concept of intolerance to TCS was not addressed in the proposed restriction and remained open to interpretation.
- 7.4 The PBAC considered that the appropriate clinical place for crisaborole was not clearly defined in the submission and was not consistent in the relevant clinical guidelines. The PBAC noted that the data presented in the submission was limited to 4 weeks of acute treatment, but it was assumed that long-term intermittent use was likely and the clinician presenting the sponsor hearing indicated that treatment would usually be intermittent for flares lasting two to three weeks. The pre-PBAC response (p2) claimed that data from Study AD-303 support the effectiveness of long-term intermittent use of crisaborole, however only safety data for study AD-303 were included in the submission. The PBAC noted that 2018 European consensus guidelines comment that the role of crisaborole is unclear given the lack of comparative data versus established therapies, while other guidelines position crisaborole as an alternative to TCIs or in combination with weak TCS for acute flare-ups in mild disease (UpToDate – Atopic Dermatitis June 2018).
- 7.5 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 for the rest of the body the comparator of standard management was appropriate for the small number of patients who are contraindicated to TCS; for patients with intolerance to TCS or who have failed to achieve satisfactory control with TCS, some degree of continuing TCS use is likely for symptom management, and TCS should be included as a comparator. The PBAC noted that this was consistent with its previous consideration of pimecrolimus (pimecrolimus PSD July 2006) in which the PBAC considered that TCS were also appropriate comparators for treatment in patients contraindicated to or those failing intermittent TCS.
- 7.6 The PBAC noted that the evidence presented for the comparison of crisaborole with standard management was based on two 4 week RCTs versus vehicle alone (AD-301 and AD-302). The PBAC noted that these trials had limited applicability to the proposed listing as they reflected acute use over 4 weeks only, no data were provided for the subgroup of patients included in the proposed restriction, the clinical importance of the primary endpoint ISGA was uncertain and there was a lack of comparative data with well-established treatments used in standard management. The PBAC also noted that the meta-analysis of the crisaborole trials was problematic as there was heterogeneity between the two crisaborole trials, the statistical

significance of the results appeared sensitive to the method of imputation used and the magnitude of benefit associated with crisaborole over its vehicle appeared modest and only just exceeded the MCID proposed. The PBAC considered that overall the claim of superior comparative effectiveness compared with standard management was not adequately supported by the data.

- 7.7 The PBAC noted that the evidence presented for the comparison with pimecrolimus was based on an indirect comparison using ointment vehicle/cream vehicle as the common reference. The PBAC noted that a large body of evidence for pimecrolimus was excluded based on differences in treatment duration, comparison with active treatments and combination use with TCS. The PBAC also noted that there were 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 agreed with ESC 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.
- 7.8 The PBAC noted that no safety data were provided comparing crisaborole with standard management but that the vehicle ointment may be a reasonable proxy. The PBAC noted that crisaborole was associated with more frequent application site disorders than its vehicle and considered that the claim of non-inferior comparative safety compared with standard management was not adequately supported by the data. The PBAC noted that no formal comparison of safety between crisaborole and pimecrolimus was possible and considered that the claim of non-inferior comparative safety compared with pimecrolimus was likely to be reasonable but was supported by limited data.
- 7.9 The PBAC considered that the cost-effectiveness of crisaborole compared with standard management was highly uncertain as the analysis did not include a relevant comparator and the model did not reflect the likely use in practice, or capture all relevant health states, and extrapolation of the treatment benefit was based on unsupported assumptions which appeared clinically implausible. The PBAC noted that usage costs in the model also appeared substantially underestimated and did not reflect use in the trial on which the treatment benefit was based.
- 7.10 The PBAC agreed with ESC that the cost-minimisation analysis was not reasonable given that the clinical claim of non-inferiority to pimecrolimus was inadequately supported. The PBAC also agreed with the ESC that 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. The PBAC also agreed with ESC 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.

- 7.11 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. 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.
- 7.12 The PBAC 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 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.
- 7.13 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 Context for Decision**

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

## **9 Sponsor’s Comment**

Pfizer Australia is pleased that the PBAC acknowledged the unmet need that exists for patients with atopic dermatitis and is committed to working with the PBAC to enable reimbursed access to crisaborole.