5.12 TACROLIMUS, Ointment, 1 mg per g, 30 g, aZematop®, ARROTEX PHARMACEUTICALS PTY LTD.

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule Authority Required (STREAMLINED) listing of 0.1% tacrolimus (TAC) ointment for the treatment of moderate to severe atopic dermatitis (AD).

1.2 Listing was requested on a cost-minimisation basis compared to 1% pimecrolimus (PIM) for use in moderate AD affecting the face and eyelids only and a cost-utility basis compared to vehicle ointment (VO) for use in moderate to severe AD any part of the body, including the face and eyelids.

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

Component	Description
Population	Patients 16 years and older with moderate to severe AD affecting any part of the body, including face, neck and flexure areas, who have failed to achieve satisfactory disease control with TCS despite appropriate dose, duration and adherence.
Intervention	0.1% TAC ointment, 30g tube. Recommended for short-term and intermittent long-term treatment.
Comparator	For face and eyelids with moderate AD: 1% PIM cream For any part of the body including the face and eyelids with moderate to severe AD: VO
Outcomes	Outcomes include disease severity (signs and symptoms), EASI score, physician and patient rating of overall clinical response, and %BSA affected.
Clinical claim	In the treatment of patients with moderate AD on the face and eyelids, 0.1% TAC is superior to PIM at improving disease activity outcomes and no worse in terms of safety. In the treatment of patients with moderate to severe AD affecting any part of the body, 0.1% TAC is superior to VO and no worse in terms of safety.

Source: Table 1-1, p14 of the submission.
AD = atopic dermatitis; BSA = body surface area; EASI = Eczema Area and Severity Index; PIM = pimecrolimus; TAC = tacrolimus; TCS = topical corticosteroids; VO = vehicle ointment.

2 Background

Registration status

2.1 TAC 0.1% ointment was approved by the TGA in December 2023 for the treatment of moderate to severe AD in adults (16 years of age and above) for both flare and maintenance treatment:

- Flare treatment: Treatment of moderate to severe flares of AD in patients who are not adequately responsive to, or are intolerant of, conventional therapies such as TCS.

- Maintenance treatment: Prevention of flares and prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations who have responded to 0.1% TAC during flares.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	DPMQ	Max. qty packs	Max. qty units	№. of Rpts	Available brands
TACROLIMUS 0.1%					
Tacrolimus 0.1%, 30g ointment tube	$[redacted]	1	1	1	aZematop Arrotex Pharmaceuticals Pty Ltd

Source: Table 1-10, p 42 of the submission.
DPMQ = dispensed price for maximum quantity; max = maximum; № = number; Qty = quantity; Rpts = repeats.

Category / Program: General Schedule
Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
Restriction type: ☒Restricted benefit ☒Authority Required (STREAMLINED)
Indication: Moderate to severe atopic dermatitis
Treatment Phase: Initial therapy
Clinical criteria:
Patient must have failed to achieve satisfactory disease control with intermittent (moderate or potent) topical corticosteroid therapy, OR Patient must be considered unsuitable/contraindicated for topical corticosteroids therapy AND The condition must have been initially diagnosed more than three months prior to this treatment
Treatment Phase: Continuing intermittent therapy
Clinical criteria:
Patient must have completed and responded to up to 6 weeks' treatment using tacrolimus ointment twice daily. After 12 months' treatment, a review of the patient`s condition should be conducted by the physician and a decision taken whether or not to continue maintenance treatment.
Treatment criteria:
Must be treated by a medical practitioner; OR Must be treated by a nurse practitioner
Population criteria:
Patients with moderate to severe atopic dermatitis aged 16 years and older.
Prescribing Instructions: 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 tacrolimus treatment and reinitiate only if there is a flare of their AD. Continuing therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.

Source: Table 1-12, p 43 of the submission.

3.1 TAC 0.1% ointment is currently available in Australia as a pharmacy compounded ointment by private prescription. There were over 48,800 compounded units of 0.1% TAC sold from approximately 500 compounding pharmacies across Australia in 2024. Not all patients currently using compounded 0.1% TAC are likely to meet the proposed PBS restrictions and there is potential off label use in paediatric patients less than 16 years of age with moderate to severe AD and in all patients with mild AD, particularly as assessment of disease severity by the treating physician is subjective.

3.2 The requested DPMQ is $[redacted] per 30 g tube (AEMP = $[redacted]).

3.3 The proposed PBS indication for 0.1% TAC is aligned with the TGA approved indication and includes treatment of moderate to severe AD flares and continuing intermittent therapy (maintenance treatment) for any area of the body.

3.4 The proposed PBS population restriction is patients aged >16 years who have failed to achieve satisfactory disease control with intermittent (moderate or potent) TCS or who are considered unsuitable/contraindicated for TCS. The ESC noted that specific clinical criteria defining who was unsuitable for or contraindicated for TCS were not provided in the proposed restrictions. The ESC noted that the 1% PIM PBS listing, albeit for intermittent treatment of the face and eyelids, included a criterion which states that "Patient must have 1 or more of the 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." The ESC noted that the 1% PIM PBS listing for also defines failure to achieve satisfactory disease control with intermittent TCS therapy as (i) failure of the facial skin to clear despite at least 2 weeks of topical hydrocortisone 1% applied every day; or (ii) failure of the facial skin to clear despite at least 1 week of a moderate or potent TCS applied every day; or (iii) clearing of the facial 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 facial skin with at least 1 week of a moderate or potent TCS applied every day, but almost immediate and significant flare in facial disease (within 48 hours) upon stopping TCS, occurring on at least 2 consecutive occasions. Further, the ESC recalled that during consideration of 2% crisaborole ointment, it had advised that the criteria for defining failure of TCS needed to be more specific; however, noted that 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 (paragraph 3.3, crisaborole public summary document [PSD], November 2020 PBAC meeting).

3.5 The proposed PBS listing for continuing intermittent therapy (maintenance treatment twice weekly) restricts the eligible population to patients that have completed and responded to up to 6 weeks initial treatment for flares of 0.1% TAC twice daily.

3.6 The proposed PBS restrictions for 0.1% TAC are for prescription by a medical practitioner and a nurse practitioner. The prescription of PBS funded 1% PIM is by a medical practitioner only.

3.7 The proposed PBS restrictions for 0.1% TAC do not provide a clinical definition of moderate to severe AD and do not include clinical criteria for assessing treatment success or treatment failure based on clinical outcome measures (such as those included in the Australasian College of Dermatologists (ACD) consensus guidance) to determine eligibility for treatment continuation. As noted above, subjectivity in the definition of disease severity might lead to the potential for use outside the requested restriction.

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

4 Population and disease

4.1 AD is an incurable chronic skin condition characterised by dry, itchy, and inflamed skin lesions that may be accompanied by oozing and blistering. The cause of AD is not well understood but has been attributed to a combination of genetic and environmental factors. The disease has a relapsing and remitting course with frequent exacerbations in clinical symptoms (flares) which usually require escalation and intensification of treatment.

4.2 Patients with AD are at increased risk of bacterial skin infections, which can result in significant morbidity and need for additional therapy. AD can significantly impact on both physical and mental health, resulting in reduced quality of life (QoL).

4.3 Management depends on the severity of AD, with AD generally classified as mild, moderate or severe. The Australasian College of Dermatologists (ACD) consensus statement defines moderate and severe AD based on treatment response as follows:[1]

- Moderate AD: Patients whose condition may not be adequately controlled by topical therapies alone. Eczema Area and Severity Index (EASI) score between 10-20, intermittent flares, some impact on QoL; however, may not require continuous therapy.
- Severe AD: Any patient whose condition does not respond adequately to optimised outpatient emollient use, avoidance of irritants and disease triggers, and standard topical anti-inflammatory therapies. EASI score >20, frequent flares, poor QoL.

4.4 The overall goal of AD treatment is to reach and maintain a state in which symptoms are absent or mild without daily activities being disturbed by AD, treatment impacts minimally on QoL, and there are no/minimal drug-related toxicities[1].

4.5 The ACD consensus statement states that the aim of AD management is always to optimise topical therapies which include topical microbiome measures (e.g. bleach baths), wet wrap therapy, emollients and appropriate use of TCS and topical calcineurin inhibitors (TCI). Management of AD is by a general medical practitioner, with referral to a specialist if treatment escalation to systemic therapy is required to treat flares that cannot be adequately managed with topical therapies. Systemic therapies for the treatment of AD include phototherapy, systemic corticosteroids, systemic antimicrobial agents, and other systemic therapies such as dupilumab and upadacitinib.

4.6 In the submission, the positioning of TCI in the proposed treatment algorithm is as a second line (2L) therapy after TCS treatment failure, despite appropriate dose and duration of and adherence to an appropriate TCS trial (usually of approximately 2 to 4 weeks duration) as defined by the ACD guidance[1]. The ACD quantitative definition of

[1] The Australasian College of Dermatologists. Consensus statement: Management of atopic dermatitis in adults. 2021; Available from: https://www.dermcoll.edu.au/fellows/statements-guidelines-resources/.

treatment failure is a Dermatology Life Quality Index (DLQI) score of ≥6 points and a Physicians Global Assessment (PGA)[2] has either not improved or improved by less than 2 points from a baseline of PGA ≥3. These criteria were not included in the proposed restrictions.

4.7 If a patient has a contraindication to use of TCS, a TCI would be used as a first line (1L) therapy. The submission noted that research conducted by the sponsor indicated that contraindications to use of TCS are rare and therefore it is anticipated that this subpopulation of adults with moderate to severe AD would be small.

4.8 TAC 0.1% ointment is a TCI. The immunomodulatory activity of 0.1% TAC is due to suppression of calcineurin activity. In the cytoplasm of the target cells, TCIs bind to an intracellular protein macrophilin-12. TAC has a 3-fold greater affinity for macrophilin-12 than PIM. TCIs are associated with minimal systemic absorption, with no evidence of systemic accumulation in pharmacokinetic studies[3].

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

5 Comparator

5.1 The submission nominated two comparators, standard of care in the form of vehicle ointment (VO) and 1% PIM cream.

5.2 Vehicle ointment (VO) was the nominated comparator for treatment of moderate to severe AD affecting any part of the body, and severe AD affecting the face and eyelids only. VO was the nominated comparator for short-term treatment of flares and long-term intermittent proactive maintenance treatment for prevention of flares.

5.3 The ESC noted that VO may not be an optimal comparator for initial flare treatment in patients who have failed to achieve disease control with intermittent TCS use as these patients would be unlikely to use non-medicated topical moisturisers and emollients alone to manage a flare. The ESC considered that these patients may continue treatment with moderate to high potency TCS applied with increasing frequency to the affected areas in an effort to control their AD which increases the risk of AEs such as skin atrophy, and infections.

5.4 Further, the ESC noted that the submission stated that TCSs were not considered a relevant comparator to 0.1% TAC in the submission because 0.1% TAC is indicated for as a 2L therapy for patients who are not adequately responsive to or are intolerant of

[2] DLQI = Dermatology Life Quality Index: ten questions which ask about symptoms, feelings, daily activities, leisure, work, school, personal relationships, and treatment in the previous week. Questions are scored from 0 to 3 ([0] not at all, [1] a little, [2] a lot or [3] very much). The total overall maximum score is 30 ranging from 0 (no impact on quality of life) to 30 (maximum impairment). PGA = physician's global assessment: How is the patient's atopic dermatitis today? ([0] Clear, [1] Almost clear, [2] Mild, [3] Moderate, [4] Severe).

[3] Krueger GG, Eichenfield L, et al. Pharmacokinetics of tacrolimus following topical application of tacrolimus ointment in adult and pediatric patients with moderate to severe atopic dermatitis. *J Drugs Dermatol*. 2007 Feb;6(2):185-93.

conventional therapies such as TCS. However, the submission described 0.1% TAC as a "steroid-sparing" therapy which implies that TCS could be substituted intermittently by 0.1% TAC to achieve adequate control of AD following failure of TCS treatment. The Pre-Sub-Committee Response (PSCR) stated that the submission targets patients whose AD cannot safely or effectively be managed with TCS and in whom TCS no longer represent a clinically acceptable alternative.

5.5 The ESC did consider that VO would be a suitable comparator for initial flare treatment in patients who are contraindicated to TCS.

5.6 The ESC noted that VO may be a more acceptable comparator to 0.1% TAC for long-term proactive maintenance treatment. Use of VO in this context would be representative of current standard of care where VO is used as a maintenance therapy and AD flares occurring during maintenance treatment are managed with a short-term medicated topical treatment, such as a TCS of appropriate potency or use of a TCI.

5.7 The pre-PBAC response stated that the submission specifically targets adults whose AD cannot be safely or effectively managed with TCS due to inadequate response, poor tolerability or clinical contraindications. Therefore, the pre-PBAC response stated that TCSs are not an appropriate comparator. Further, the pre-PBAC response reiterated that 0.1% TAC is not positioned as a first-line replacement for TCS, rather as an alternative for patients in whom TCSs are no longer suitable.

5.8 Systemic therapies could be substituted by 0.1% TAC in some circumstances. When severe AD is refractory to topical therapy, clinicians can prescribe PBS-listed systemic therapies (phototherapy, a short-term systemic corticosteroid or a long-term systemic therapy such as dupilumab or upadacitinib). Systemic therapies were not considered relevant comparators in the submission as the proposed use of PBS-listed 0.1% TAC was prior to use of systemic therapies. However, the PBS-listing of 0.1% TAC could delay treatment escalation to PBS-listed systemic therapy by increasing control of AD flares or preventing disease progression to chronic severe AD.

5.9 The ESC considered that the nomination of PIM 1% ointment as the comparator for treatment of moderate AD flares affecting the face and eyelids was reasonable. PIM 1% ointment was considered by PBAC at the July 2006 meeting (pimecrolimus PSD, July 2006 PBAC meeting). Both TCS and VO were accepted comparators in the PBAC consideration of 1% PIM (pimecrolimus PSD, July 2006 PBAC meeting).

5.10 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

5.11 For the requested PBS population, the following PBS-listed medicine may be considered an alternative therapy for treatment of moderate AD affecting the face

and eyelids because it could be replaced in practice: 1% PIM. This alternative therapy may be less costly than 0.1% TAC ointment.

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 health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The health professional noted that compounded TAC ointments, which are generally accessed through the public hospital setting, are recommended to be discarded 30 days after first use, which may result in access and equity issues.

6.3 The PBAC noted the advice received from the Australasian College of Dermatologists which supported the submission, stating that there was strong evidence for the safety and efficacy of 0.1% TAC over long-term TCSs. The College also noted that the currently available compounded products are available at significant cost to patients and are associated with drug stability issues and secondary bacterial infections. The Australasian Society of Clinical Immunology and Allergy also supported the submission, stating that the PBS availability of 0.1% TAC ointment ensures equitable access. Further, it was noted that 0.1% TAC can be as effective as potent TCS and may be useful for patients where the use of TCS is inappropriate, including treatment of sensitive areas.

6.4 Eczema Support Australia expressed their strong support for the submission, noting the high cost, limited shelf life and access issues with the currently available compounded products. Eczema Support Australia also noted the need for non-steroidal anti-inflammatory options for patients who are unable to use TCSs.

Clinical trials

6.1 The submission noted that given the age of the product, the sponsor does not have access to clinical study reports of the relevant 0.1% TAC trials in AD, and that the available evidence presented in the submission was sourced from trial publications in the literature. This hampered the assessment of bias, verification and presentation of data.

6.2 Details of the trial publications presented in the submission are provided in Table 2**Error! Reference source not found.**.

Table 2: Trials and associated reports presented in the submission

Trial	Publication title	Citation
0.1% TAC vs VO		
Ruzicka (1997)	Ruzicka T, Bieber T, Schöpf E, et al. European Tacrolimus Multicenter Atopic Dermatitis Study Group. A short-term trial of tacrolimus ointment for atopic dermatitis.	*N Engl J Med*. 1997 Sep 18;337(12):816-21.
Hanifin (2001) Soter (2001) Kang (2003) Drake (2001)	Hanifin JM, Ling MR, Langley R, et al. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part I, efficacy. Soter NA, Fleischer AB Jr, Webster GF, et al. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part II, safety. Kang S, Paller A, Soter N, et al. Safe treatment of head/neck AD with tacrolimus ointment. Drake L, Prendergast M, Maher R, et al. The impact of tacrolimus ointment on health-related quality of life of adult and pediatric patients with atopic dermatitis.	*J Am Acad Dermatol*. 2001 Jan;44(1 Suppl):S28-38. *J Am Acad Dermatol*. 2001 Jan;44(1 Suppl):S39-46. *J Dermatolog Treat.* 2003 Jun;14(2):86-94. *J Am Acad Dermatol*. 2001 Jan;44(1 Suppl):S65-72.
Wollenberg (2008) Reitamo and Allsopp (2010) (NCT00480610)	Wollenberg A, Reitamo S, Atzori F, et al; European Tacrolimus Ointment Study Group. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. Reitamo and Allsopp. Treatment with twice-weekly tacrolimus ointment in patients with moderate to severe atopic dermatitis: Results from two randomised, multicentre, comparative studies;	*Allergy*. 2008 Jun;63(6):742-50. *J Dermatol Treat.* 2010; 21, 34-44.
0.1% TAC vs 1% PIM		
Paller (2005) Fleischer (2007) Abramovits (2008) (NCT00666302)	Paller AS, Lebwohl M, Fleischer AB Jr, et al; US/Canada Tacrolimus Ointment Study Group. Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: results from 3 randomized, comparative studies. Fleischer AB Jr, Abramovits W, Breneman D, Jaracz E; US/Canada tacrolimus ointment study group. Tacrolimus ointment is more effective than pimecrolimus cream in adult patients with moderate to very severe atopic dermatitis. Abramovits W, Fleischer AB Jr, Jaracz E, Breneman D. Adult patients with moderate atopic dermatitis: tacrolimus ointment versus pimecrolimus cream.	*J Am Acad Dermatol*. 2005 May;52(5):810-22. *J Dermatolog Treat*. 2007;18(3):151-7. *J Drugs Dermatol*. 2008 Dec;7(12):1153-8.
Long-term Follow-up Studies		
Hanifin (2005)	Hanifin JM, Paller AS, Eichenfield L, et al; US Tacrolimus Ointment Study Group. Efficacy and safety of tacrolimus ointment treatment for up to 4 years in patients with atopic dermatitis.	*J Am Acad Dermatol*. 2005 Aug;53(2 Suppl 2):S186-94.
Reitamo (2008) (NCT00560378)	Reitamo S, Rustin M, Harper J, et al; 0.1% Tacrolimus Ointment Long-term Follow-up Study Group. A 4-year follow-up study of atopic dermatitis therapy with 0.1% tacrolimus ointment in children and adult patients	*Br J Dermatol.* 2008 Sep;159(4):942-51.
Tan and Langley (2004)	Tan J, and Langley R. Safety and efficacy of tacrolimus ointment 0.1% (Protopic) in atopic dermatitis: a Canadian open-label multicenter study.	*J Cutan Med Surg*. 2004 Jul-Aug;8(4):213-9.
Koo (2005)	Koo JY, Fleischer AB Jr, Abramovits W, et al. Tacrolimus ointment is safe and effective in the treatment of atopic dermatitis: results in 8000 patients.	*J Am Acad Dermatol*. 2005 Aug;53(2 Suppl 2):S195-205.

Trial	Publication title	Citation
Meta-analyses		
Lax (2024)	Lax SJ, Van Vogt E, Candy B, et al. Topical anti-inflammatory treatments for eczema: network meta-analysis.	*Cochrane Database Syst Rev*. 2024 Aug 6;8(8):CD015064.
Chu (2023)	Chu DK, Chu AWL, Rayner DG, et al. Topical treatments for atopic dermatitis (eczema): Systematic review and network meta-analysis of randomized trials.	*J Allergy Clin Immunol.* 2023 Dec;152(6):1493-1519.
Pena (2023)	Pena J, Zameza PA, Pixley JN, et al. A Comparison of Topical Corticosteroids and Topical Calcineurin Inhibitors for the Treatment of Atopic Dermatitis.	*J Allergy Clin Immunol* Pract. 2023 May;11(5):1347-1359.
Abędź and Pawliczak (2019)	Abędź N, Pawliczak R. Efficacy and safety of topical calcineurin inhibitors for the treatment of atopic dermatitis: meta-analysis of randomized clinical trials.	*Postepy Dermatol Alergol*. 2019 Dec;36(6):752-759.
Cury Martins (2015)	Cury Martins J, Martins C, Aoki V, et al. Topical tacrolimus for atopic dermatitis.	*Cochrane Database Syst Rev.* 2015 Jul 1;2015(7):CD009864.
Ashcroft (2005)	Ashcroft DM, Dimmock P, Garside R, et al. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials.	*BMJ.* 2005 Mar 5;330(7490):516.

Source: Table 2-3, p50 and Table 2-4, p51 of the submission.

6.3 The key features of the included evidence are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	n/N[a]	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Treatment of moderate to severe AD flares (0.1% TAC vs VO)						
Ruzicka 1997	108/213 adults and adolescents	Phase 2, DB, MC RCT three weeks' treatment twice-daily and one-week follow-up	Uncertain	Adults and adolescents ≥13 years with moderate to severe AD	Change in Score 1[d] Change in Score 2[e]	Not used
					Overall assessment of the treated area by the investigator	Used
Hanifin 2001	421/632 adults	Two identical, DB, MC, RCT Up to 12 weeks	Low	Adults ≥16 years with moderate to severe AD	Physician's global evaluation of clinical response Treatment success[f] EASI score Total clinical scores for individual signs of AD %BSA Patient's assessment of pruritus	Not used
Soter 2001	421/631[b] adults		Low		Safety	Not used
Drake 2001	579/632 adults		Uncertain[c]		Change in DLQI score from baseline to end of treatment	Not used
Long-term maintenance treatment (0.1% TAC vs VO)						
Wollenberg 2008 (CONTROL study)	257 adults	Phase 3, MC, RCT 12 months	Low	Adults ≥16 years with mild to severe AD	Number of any flares Tacrolimus ointment use	Used
					Safety	Not used
Reitamo 2010	183 adults	*Post hoc* subgroup analysis of Wollenberg 2008	High	Adults ≥16 years with moderate to severe AD	Number of major flares[g] Number of any flares Number of patients without a major flare Number of patients without a flare Time to first major flare	Used
					Number of days of flare treatment Time to first flare Tacrolimus ointment use DLQI score Safety	Not used
Long-term extension study of Wollenberg 2008						
Hanifin 2005	408 adults	OL, NC study Up to 4 years	Uncertain	Adults ≥16 years with active AD	Safety	Not used
Treatment of moderate AD flares on the face and eyelids (0.1% TAC vs 1% PIM)						
Paller 2005	413 adults	IB, MC, three RCTs Up to 6 weeks	Uncertain	Adults ≥16 years with mild to very severe AD	Change in EASI score Success of therapy based on the IGADA Improvement in IGADA The Physician's assessment of Individual Signs %BSA affected Safety	Not used
Fleischer 2007	281 adults	*Post hoc* subgroup analysis of Paller 2005	High	Adults ≥16 years with moderate to very severe AD		

Trial	n/N[a]	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Abramovits 2008	188 adults	*Post hoc* subgroup analysis of Paller 2005	High	Adults ≥16 years with moderate AD		

Source: Table 2-5, p53 of the submission.
AD = atopic dermatitis; AE = adverse event; BSA = body surface area; DB = double blind; DCP = disease control period; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; IB = investigator-blinded; IGADA = Investigator Global Atopic Dermatitis Assessment; MC = multi-centre; NC = non-comparative; OL = open label; RCT = randomised controlled trial.
[a] n/N is number of adults receiving 0.1% TAC or VO/the total number of adults
[b] Data for one 15-year-old patient enrolled in the adult study was not included.
[c] Includes patients receiving 0.03% TAC; the number of adults in the individual treatment arms included in the QoL analysis was not stated and therefore the risk of bias was uncertain
[d] Score 1 = Change in the sum of the scores for erythema, oedema, and pruritus in the treated area from baseline to the completion of treatment
[e] Score 2 = the sum of score 1 and the scores for oozing or crusting, excoriation, and lichenification of involved skin and dryness of non-involved skin from baseline to the completion of treatment
[f] Treatment success defined as cleared or excellent improvement (90%-100% improvement) based physician's global evaluation of clinical response.
[g] Flare requiring a substantial therapeutic intervention which was defined as the use of 0.1% tacrolimus ointment for >7 days to treat an IGA of 3–5 measured on day 1 of the DE treatment period. [IGA classification: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe; 5, very severe disease]. If a patient had two such flares with <7 days separating them (with or without any type of treatment) then the episodes were combined and considered as one flare.
[h] Investigator Global Atopic Dermatitis Assessment (IGADA) is a five-point severity rating scale from [0] clear to [5] severe AD.

6.4 The key evidence was as follows:

Treatment of moderate to severe AD flares (0.1% TAC vs VO twice daily):

- One 3-week RCT of 0.1% TAC versus VO in adults with moderate to severe AD (Ruzicka, 1997)[4]
- Two identically designed 12-week RCTs in adults ≥16 years with moderate to severe AD were reported in the following publications:
  (i) efficacy outcomes for whole population (Hanifin, 2001)[5]
  (ii) safety outcomes (Soter, 2001)[6]
  (iii) efficacy in head/neck region (Kang, 2003)[7]
  (iv) analysis of QoL outcomes (Drake, 2001)[8]

[4] Ruzicka T, Bieber T, et al. A short-term trial of tacrolimus ointment for atopic dermatitis. European Tacrolimus Multicenter Atopic Dermatitis Study Group. *N Engl J Med*. 1997 Sep 18;337(12):816-21.
[5] Hanifin JM, Ling MR, et al. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part I, efficacy. *J Am Acad Dermatol*. 2001 Jan;44(1 Suppl):S28-38.
[6] Soter NA, Fleischer AB, Jr., et al. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part II, safety. *J Am Acad Dermatol.* 2001 Jan;44(1 Suppl):S39-46.
[7] Kang S, Paller A, et al. Safe treatment of head/neck AD with tacrolimus ointment. *J Dermatolog Treat*. 2003 Jun;14(2):86-94.
[8] Drake L, Prendergast M, et al. The impact of tacrolimus ointment on health-related quality of life of adult and pediatric patients with atopic dermatitis. *J Am Acad Dermatol*. 2001 Jan;44(1 Suppl):S65-72.

Long-term maintenance treatment (0.1% TAC vs VO twice weekly):

- One 12-month, RCT (CONTROL study) comparing proactive maintenance treatment with 0.1% TAC twice weekly versus VO twice weekly in adults ≥16 years with mild to severe AD was a reported in the following publications:
  (i) whole study population (Wollenberg 2008)[9]
  (ii) *post hoc* subgroup analysis in adults with moderate to severe AD (Reitamo 2010)[10]

Treatment of moderate AD flares (0.1% TAC vs 1% PIM twice daily):

- One 6-week RCT in adults ≥16 years with mild to very severe AD comparing 0.1% TAC vs 1% PIM was a reported in the following publications:
  (i) efficacy and safety for whole trial population (Paller 2005)[11]
  (ii) *post hoc* subgroup analysis of efficacy and safety in adults ≥16 years with moderate to very severe AD (Fleischer 2007)[12]
  (iii) *post hoc* subgroup analysis of efficacy and safety in adults ≥16 years with moderate AD (Abramovits 2008)[13].

6.5 The long-term safety of 0.1% TAC was based on evidence from four non-comparative extension studies. The results from six meta-analyses were also summarised and presented in the submission as additional supporting evidence assessing the relative efficacy of TCIs, in particular 0.1% TAC vs 1% PIM (Table 2).

6.6 Overall, there was a high risk of bias associated with the evidence presented in the submission. Most of the evidence comparing 0.1% TAC with VO as proactive maintenance treatment in moderate to severe AD and 0.1% TAC with 1% PIM as treatment of moderate AD flares was based on published *post hoc* subgroup analyses with small patient numbers.

6.7 Results based on graphical illustrations from published articles may depict data for non-TGA approved doses or ointment concentrations of TAC (0.03% and 0.3%) which are not being considered in this submission.

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[9] Wollenberg A, Reitamo S, et al. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. *Allergy*. 2008 Jun;63(6):742-50.

[10] Reitamo S, Allsopp R. Treatment with twice-weekly tacrolimus ointment in patients with moderate to severe atopic dermatitis: results from two randomized, multicentre, comparative studies. *J Dermatolog Treat*. 2010 Jan;21(1):34-44.

[11] Paller AS, Lebwohl M, Fleischer AB, Jr., Antaya R, Langley RG, Kirsner RS, et al. Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: results from 3 randomized, comparative studies. *J Am Acad Dermatol*. 2005 May;52(5):810-22.

[12] Fleischer AB, Jr., Abramovits W, Breneman D, Jaracz E. Tacrolimus ointment is more effective than pimecrolimus cream in adult patients with moderate to very severe atopic dermatitis. *J Dermatolog Treat*. 2007;18(3):151-7.

[13] Abramovits W, Fleischer AB, Jr., Jaracz E, Breneman D. Adult patients with moderate atopic dermatitis: tacrolimus ointment vs. pimecrolimus cream. *J Drugs Dermatol*. 2008 Dec;7(12):1153-8.

Comparative effectiveness

Treatment of moderate to severe AD flares

Ruzicka et al (1997)

6.8 In a Phase 2 double-blind RCT by Ruzicka et al (1997) comparing 0.1% TAC (n=54) versus VO (n=54) in patients with moderate to severe AD ≥13 years of age**Error! Bookmark not defined.**, the primary outcome was change from baseline to treatment completion (Week 3) in the sum of Score 1[14] (the sum of the scores for erythema, oedema, and pruritus in the treated area on a scale of 0 to 9). The secondary end point was the change from baseline in score 2 (Score 1 plus the sum of the scores for oozing or crusting, excoriation, and lichenification of involved skin and dryness of non-involved skin in the treated area).

6.9 Score 1 for 0.1% TAC vs VO in the ITT population, the median percentage reduction from base line to treatment completion (Week 3) was 83.3% vs 22.5% for the trunk and extremities (difference 60.8%; p<0.001) and 83.3% vs 25.0% for the face and neck (difference 58.3%; p<0.001).

6.10 There was a statistically significant difference in median decreases from baseline to Week 3 in the secondary outcome of Score 2 favouring 0.1% TAC over VO for trunk and extremities (71.4% vs. 21.8%, difference 49.6%; p<0.001) and for face and neck (75.0% vs. 27.3%, difference 47.7%; p-value could not be verified).

6.11 The overall assessment of the treated area by the investigator and the patient was scored as symptoms: completely resolved, markedly improved, moderately improved, slightly improved, unchanged, or worse. According to the investigators' overall assessment of the treated areas, a significantly higher proportion of patients in the 0.1% TAC arm (81.4%) versus the VO arm (9.8%) had completely resolved or markedly improved AD (p<0.001). Response to primary therapy in the first cycle of the economic model was based on this data from investigator overall assessment. Percentages reported in the submission were obtained from a digitisation of a bar chart from the study publication. The length of primary therapy in the economic model was aligned with the 3-week treatment period of the study.

Hanifin et al (2001)

6.12 Hanifin et al (2001) presented efficacy data from two identical double-blind RCTs which compared 0.1% TAC (n=209) with VO (n=212) treatment for 12 weeks (or until approximately 1 week after complete AD clearance) in adults ≥16 years with moderate to severe AD**Error! Bookmark not defined.**. The primary outcome was physician's g lobal evaluation of clinical response at the end of treatment, with success defined as 90% - 100% improvement (cleared or excellent improvement) (Table 4). Other outcomes included the physician's assessment of clinical signs of AD, the Eczema Area and Severity Index (EASI), the percent of BSA (%BSA) affected, and the patient's assessment of pruritus (itch).

6.13 Around two thirds of patients were Caucasian, and a quarter were African American. Individuals with skin of colour are more susceptible to AD development and may have more severe AD compared to Caucasians. Scoring of AD disease severity and treatment response using measures such as the EASI is more difficult for skin of colour as AD presentation and symptoms differ to that observed in Caucasians. Therefore, the accuracy of the scoring is less reliable. People with skin of colour are often underrepresented in clinical studies of AD.

Table 4: Success rates from Hanifin et al (2001) defined as ≥90% improvement based on physician's global evaluation

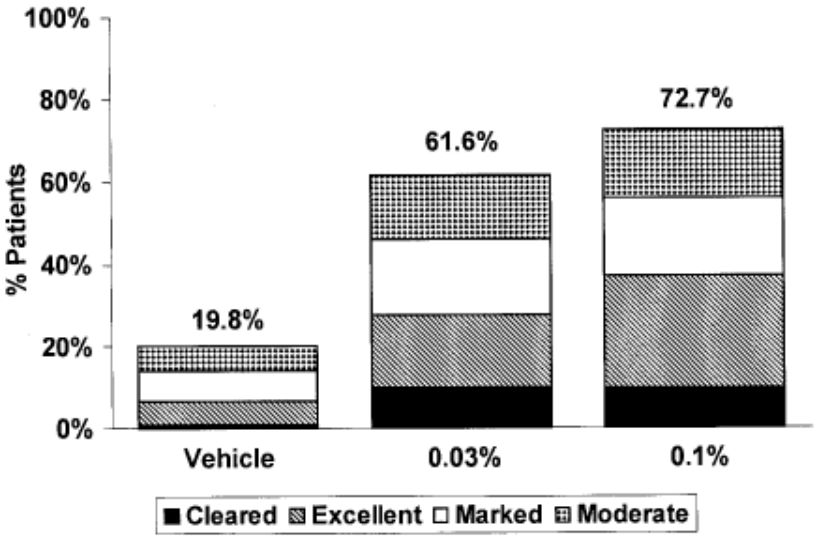
Study	Treatment group		*P* value
	0.1% TAC	VO	
Pooled data	77/209 (36.8%)	14/212 (6.6%)	<0.001
Study 1	35/99 (35.4%)	8/102 (7.8%)	<0.001
Study 2	42/110 (38.2%)	6/110 (5.5%)	<0.001

Source: Table 2-24, p82 of the submission; Hanifin et al (2001)[5]
TAC = tacrolimus; VO = vehicle ointment.

6.14 Based on pooled data from the two studies, 36.8% of patients treated with 0.1% TAC versus 6.6% treated with VO had treatment success defined as ≥90% improvement in physician's global evaluation of clinical response at the end of treatment.

6.15 Cumulative percentages of patients with improved ratings for the physician's global evaluation of clinical response differed for patients treated with 0.1% TAC vs VO are presented in Figure 1. At least a moderate improvement (≥50% improvement) in AD was observed for 72.7% and 19.8% of patients treated with 0.1% TAC and VO, respectively.

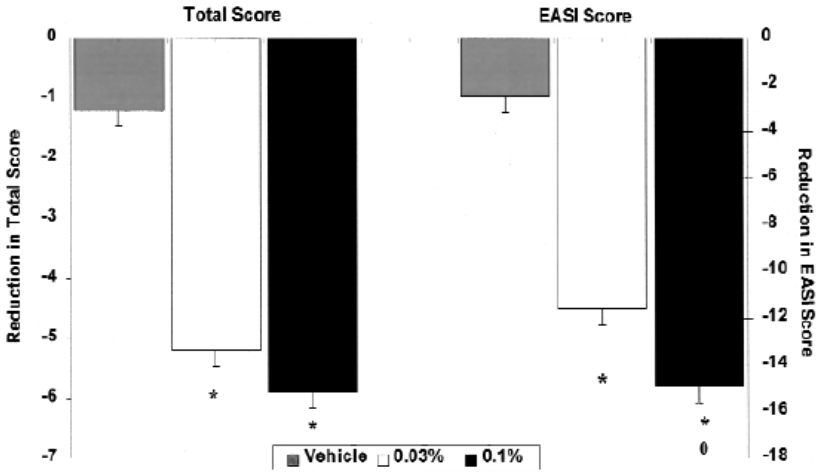
Figure 1: Cumulative percentages of patients with improvement ratings for the physician's global evaluation of clinical response (ITT)



Source: Figure 2-6, p83 of the submission.
Cleared (100% improvement, solid bars), excellent (90%-99% improvement, hatched bars), marked (75%-89% improvement, open bars), or moderate (50%-74% improvement, speckled bars).
Data for 0.03% TAC is not relevant to the submission.

6.16 Improvements in AD were significantly higher in patients treated with 0.1% TAC compared with patients treated with VO with respect to EASI scores, total and clinical scores of individual signs of AD (Figure 2), % BSA affected, and the patient's assessment of itch (p<0.001). Improvement was observed as early as 1 week after the start of treatment with 0.1% TAC.

Figure 2: Change in total clinical score for signs of AD and EASI score from baseline to the end of treatment from Hanifin et al (2001)



Source; Figure 2-7, p83 of the submission; Hanifin et al (2001)[5]
AD=atopic dermatitis; EASI=Eczema Area and Severity Index; TAC=tacrolimus ointment; VO=vehicle ointment.
VO (shaded bars) and 0.1% TAC (solid bars).
Note: Data for 0.03% TAC (open bars) are not relevant to the submission.

* Significantly greater improvement compared with VO (p <0.001).

6.17 Data published by Hanifin et al (2001) was not included in the economic model. The trial populations in Hanifen et al (2001) were not aligned with the proposed PBS population**Error! Bookmark not defined.** as there was no information to indicate that p atients had not been able to achieve satisfactory disease control with intermittent (moderate or potent) TCS therapy or were unsuitable/contraindicated for TCS. Adults that have not responded adequately to moderate or potent TCS may represent a "harder to treat population" and may also not respond as well to TCIs and other AD therapies.

Drake at al (2001)

6.18 Drake at al (2001) presented data on quality of life (QoL) outcomes from three multicentre RCTs (including the two adult RCTs by Hanifin et al 2001[5]) comparing 0.1% TAC versus VO in both adult and paediatric patients with moderate to severe AD[15]. The paediatric trial in Drake et al (2001) was not discussed in the submission; only data for the two adult studies were presented. QoL was assessed at baseline, Week 3, and Week 12 or at the end of treatment using the Dermatology Life Quality Index (DLQI) (Table 5). The DLQI contains ten items that comprise six categories used to assess the impact of the patient's skin condition during the last week. The higher the score, the more QoL is impaired. Baseline demographics and clinical severity were comparable across treatment arms for the 579 adults included in the QoL assessment using the DLQI. The number of adults included in each treatment arm was not stated in the study publication.

Table 5: Change in DLQI scores from baseline to end of treatment for adults receiving 0.1% TAC versus VO from Drake et al (2001)

DLQI scale	0.1% TAC LS Mean ± SE	VO LS Mean ± SE	*P* value VO vs 0.1% TAC
Symptoms and Feelings	–41.1 ± 1.9	–10.4 ± 1.9	0.000 [a]
Daily Activities	–28.4 ± 1.8	–6.0 ± 1.8	0.000 [a]
Leisure	–28.6 ± 1.8	–7.3 ± 1.8	0.000 [a]
Work/School	–31.8 ± 2.5	–5.7 ± 2.5	0.000 [a]
Personal Relationships	–15.1 ± 1.5	–0.6 ± 1.5	0.000 [a]
Treatment	–14.8 ± 1.9	–3.1 ± 1.9	0.000 [a]
Total score	–27.1 ± 1.4	–5.6 ± 1.4	0.000[a]

Source: Table 2-25, p87 of the submission; Drake et al (2001)[8]
DLQI = Dermatology Life Quality Index; LS Mean = Least squares mean reported from the analysis of covariance model; N = number; SE = standard error of the mean; TAC = tacrolimus ointment; VO = vehicle ointment.
[a] Differences are significantly different (analysis of covariance, $P < 0.05$).

6.19 Adults receiving 0.1% TAC experienced greater QoL improvements from baseline to end of treatment compared with VO for all seven QoL categories (p<0.001). The

[15] Drake L, Prendergast M, et al. The impact of tacrolimus ointment on health-related quality of life of adult and pediatric patients with atopic dermatitis. J Am Acad Dermatol. 2001 Jan;44(1 Suppl):S65-72.

differences were most substantial for the Symptoms and Feelings and Work/School categories.

6.20 The number of adults with QoL data from the DLQI receiving 0.1% TAC and VO included in the studies by Hanifin et al (2001) was not stated and therefore QoL outcomes observed may not be representative of all adults receiving 0.1% TAC and VO. Additionally, these patients were not aligned with the proposed PBS population and therefore benefits of 0.1% TAC in the proposed PBS population may differ from those reported by Drake et al (2001).

Maintenance treatment

Reitamo at al (2010)

6.21 Supporting evidence for proactive maintenance treatment for adults with moderate to severe AD was from a *post hoc* subgroup analysis of the CONTROL study by Reitamo at al (2010) in 183 adults ≥16 years with moderate to severe AD[16]. In total, 155 patients who achieved an investigator global assessment (IGA) of AD score of <2 with twice daily 0.1% TAC treatment during the open-label phase were randomised in the 12-month, double-blind disease control period to receive proactive maintenance treatment with either 0.1% TAC twice-weekly or VO twice-weekly (standard regimen). Patients in both study arms applied emollient daily throughout the study. If a patient experienced an AD flare, they switched to open-label twice-daily 0.1% TAC treatment for 1–6 weeks until the flare resolved, defined as an IGA≤2.

6.22 The most common reason for withdrawal in the adult study was an IGA score >2 after 6 weeks of open-label 0.1% TAC treatment (n = 19; 10.4%]; of these, 16 patients had severe AD at screening. The 6-week treatment period is applicable to the time that eligibility is assessed for maintenance treatment. There is a selection bias as most of the patients not eligible for randomisation into the disease control period had severe AD at study screening.

6.23 The population was not aligned with the proposed PBS restriction of failure to achieve satisfactory disease control with intermittent (moderate or potent) TCS or intolerance/contraindicated for TCS treatment.

6.24 The primary endpoint was the number of major flares[17] during the disease control period. Patients who experienced a flare that lasted >6 weeks were withdrawn from the study. Other efficacy endpoints included the total number of flares during the disease control period, the percentage of days of flare treatment, the time to the first flare, patients' perception of itch, QoL with the DLQI and amount of 0.1% TAC used.

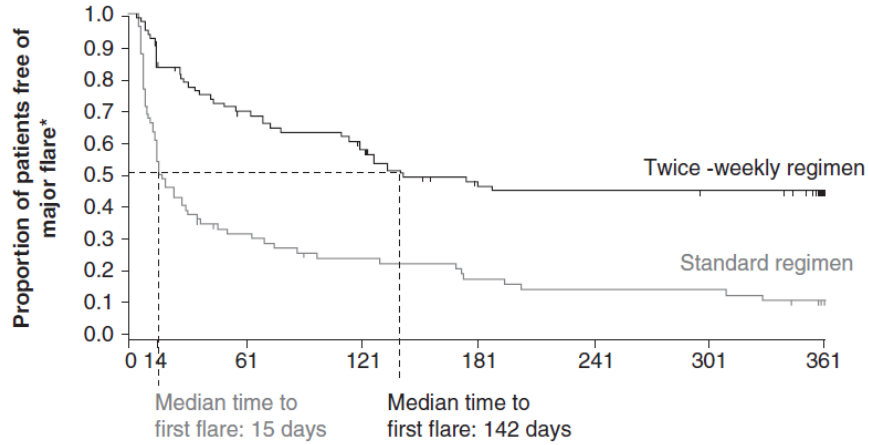
[16] Reitamo S, Allsopp R. Treatment with twice-weekly tacrolimus ointment in patients with moderate to severe atopic dermatitis: results from two randomized, multicentre, comparative studies. *J Dermatolog Treat*. 2010 Jan;21(1):34-44.

[17] Major flares were defined as disease exacerbations with an IGA >2 on day 1 of the exacerbation that required the use of twice-daily 0.1% TAC for >7 days.

6.25 A higher percentage of patients using VO (standard regimen) discontinued treatment compared with the twice-weekly TAC regimen (53.4% vs 35.0%).

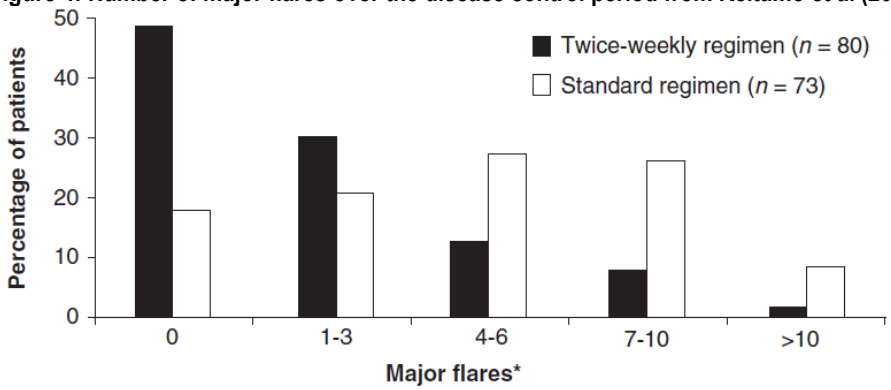
6.26 Figure 3 presents the time to first major flare and Figure 4 presents the total number of flares over the 12 month trial period from Reitamo et al (2010).

Figure 3: Time to first major flare in the disease control period from Reitamo et al (2010)



Source: Figure 2-17, p93 of the submission; Reitamo at al (2010)[10]
*Defined as disease exacerbations with IGA > 2 on day 1 of the exacerbation, that required the use of twice-daily 0.1% TAC for > 7 days.

Figure 4: Number of major flares over the disease control period from Reitamo et al (2010)



Source: Figure 2-15, p92 of the submission; Reitamo at al (2010)[10]
*Defined as disease exacerbations with IGA > 2 on day 1 of the exacerbation, that required the use of twice-daily tacrolimus ointment for > 7 days. Adjusted for length of time at risk. Values for 1, 2 or 3 flares correspond to 0.5–<1.5, 1.5–<2.5 and 2.5–<3.5 flares, etc., in the adjusted analysis.

6.27 After treatment of moderate to severe AD flares during the open-label phase, proactive maintenance treatment of skin previously affected by AD lesions with twice weekly 0.1% TAC prevented the occurrence of flares and significantly prolonged flare-free intervals compared with a standard treatment regimen in adults. Proactive maintenance treatment with 0.1% TAC increased the median time to first major flare

to 142 days compared to 15 days with the standard regimen and significantly reduced the number of major flares over the disease control period.

6.28 More than three times as many patients receiving proactive maintenance treatment with 0.1% TAC had no flares of any severity over 12 months compared with the standard regimen (42.5% vs 12.3%; P<0.001) and the percentage of days with flare treatment during the 12-month disease control period was substantially lower in patients receiving proactive maintenance treatment with 0.1% TAC at 16.2% vs 39.4% of days. The amount of 0.1% TAC used per day over 12 months was similar in the 0.1% TAC maintenance treatment versus VO treatment regimen (1.68 vs 2.2 g/day, respectively which included any 0.1% TAC used to treat AD flares during the maintenance period).

6.29 QoL was assessed using the DLQI during the 12-month disease control period. Mean total DLQI scores at baseline and Month 12 were 3.9 ± 3.5 and 3.5 ± 2.9, respectively, with twice-weekly 0.1% TAC and 5.6 ± 4.8 and 5.9 ± 5.6 with twice-weekly VO. As the proportion of patients included in the QoL analysis was not reported in the study publication, these QoL estimates may be unreliable.

Treatment of moderate AD flares on the face and eyelids

Abramovits et al (2008)

6.30 Abramovits et al (2008) presented a *post hoc* subgroup analysis of the study by Paller 2005[11] in 188 adults aged ≥16 years with moderate AD anywhere on the body including the head and neck provided supporting evidence for the comparison of 0.1% TAC (n=98) versus 1% PIM (n=90)[18]. A thin layer of the assigned study medication was applied twice daily to all affected areas for up to 6 weeks or until 1 week after the affected area(s) was completely cleared, whichever came first. At baseline, 62.2% and 64.4% patients in the 0.1% TAC and 1% PIM groups, had moderate AD affecting their head and neck. Baseline patient demographics and characteristics were balanced between treatment groups; around half of patients were Caucasian and a third were African American. The primary outcome was EASI score, and secondary outcomes reported included improvement in signs and symptoms of AD for the head and neck region, improvement in their Investigator Global Atopic Dermatitis Assessment (IGADA) score, success of therapy based on the IGADA and %BSA affected (Table 6).

6.31 As 30% of adults in the adult ITT population of the RCT had mild AD at baseline, the population was not applicable to the proposed PBS restriction or the TGA approved indication for 0.1% TAC[19]. As the clinical claim for 0.1% TAC is based on treatment of moderate AD on the face and eyelids, the *post hoc* subgroup analysis which includes

[18] Abramovits W, Fleischer AB, Jr., et al. Adult patients with moderate atopic dermatitis: tacrolimus ointment vs. pimecrolimus cream. *J Drugs Dermatol*. 2008 Dec;7(12):1153-8.

[19] Paller AS, Lebwohl M, Fleischer AB, Jr., Antaya R, Langley RG, Kirsner RS, et al. Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: results from 3 randomized, comparative studies. *J Am Acad Dermatol*. 2005 May;52(5):810-22.

adults with moderate AD anywhere on the body including the head and neck region was the most appropriate.

6.32 The 6-week treatment period corresponds to the proposed 0.1% TAC PBS restriction in which the patient must have responded to up to 6 weeks of twice-daily treatment in order to be eligible for 0.1% TAC maintenance treatment.

6.33 The population in the study did not align with the proposed PBS restriction in terms of unsatisfactory response to, or intolerance/contraindication to TCS use. Therefore, it is not possible to confirm if the treatment response in this population would be representative of treatment response in the population proposed for PBS funding.

Table 6: Outcomes observed for adults with moderate AD treated with 0.1% TAC versus 1% PIM from Abramovits et al (2008)

Outcome	Time	0.1% TAC (n=98)	1% PIM (n=90)	*P* value
Percentage improvement in EASI score from baseline, (LS mean) %	Week 1	41.7	33.8	0.05
	Week 3	53.2	42.1	0.03
	Week 6/EOS	59.0	42.8	0.01
Percentage of patients with improvement in IGADA by 1 or more grades, %	Week 1	65.3	47.8	<0.02
	Week 3	71.4	55.6	0.03
	Week 6/EOS	78.6	62.2	<0.02
Percentage of patients with success of therapy defined as clear or almost clear by IGADA score, %	Week 1	15.3	12.2	0.47
	Week 3	32.7	20.0	0.03
	Week 6/EOS	44.9	31.1	0.04
Percentage improvement in signs and symptoms of AD on the head and neck, (LS mean) %	Week 1	44.5	39.2	0.52
	Week 3	68.8	50.3	0.05
	Week 6/EOS	75.2	54.1	0.04
Percentage improvement in %BSA affected, (LS mean) %	Week 1	31.9	29.1	0.42
	Week 3	44.4	37.3	0.16
	Week 6/EOS	49.6	36.1	0.10

Source: Figure 2-30, p103; Figure 2-31, p103; Figure 2-32, p104; Figure 2-33, p105 of the submission; Abramovits et al (2008)[13]
AD = atopic dermatitis; BSA = body surface area; IGADA = Investigator Global Atopic Dermatitis Assessment; EASI = Eczema Area Severity Index; EOS = end of study; LS mean = least square mean; PIM = pimecrolimus; TAC = tacrolimus.

6.34 A significantly greater percentage mean improvement in EASI score was observed in patients with moderate AD anywhere on the body treated with 0.1% TAC vs 1% PIM at all time points assessed to Week 6.

6.35 For treatment of the head and neck region, significantly greater improvement was observed for the signs and symptoms of AD score in patients treated with 0.1% TAC versus 1% PIM group. The efficacy data reported to support the claim is for the head and neck rather than specifically for use on the face and eyelids. Whether there would be a difference in treatment response between these areas is unclear.

6.36 A significantly greater proportion of patients with moderate AD affecting their whole body treated in the 0.1% TAC group compared with the 1% PIM group had an improvement in their Investigator Global Atopic Dermatitis Assessment (IGADA) score (≥1 grades) at all time points to Week 6 or end of study (EOS). Results were similar for

treatment success (defined as clear or almost clear based on the patient's IGADA) at Week 3 and Week 6/EOS.

6.37 A significant improvement was observed at Week 3 and Week 6/EOS for all outcomes assessed except percentage improvement in %BSA where a trend towards greater improvement was observed in patients treated with 0.1% TAC. No standard errors were presented for the LS mean data, so it was not possible to assess the precision of the LS means reported.

Meta-analyses

6.38 The ESC noted that 6 meta-analyses were presented as additional supporting evidence. The ESC noted the results of the most recent Cochrane meta-analysis of topical anti-inflammatory treatments, Lax et al (2024) which included 291 studies involving TCS, TCI, PDE-4 inhibitors, JAK inhibitors and hydrocarbon receptor activators, reported that for:

- Patient reported symptoms, the most effective agents were 0.1% TAC, potent TCS and ruxolitinib, with 0.1% TAC exhibiting similar efficacy to potent TCS;
- Clinician reported outcomes, the most effective treatments were potent TCS, 0.1% TAC and ruxolitinib;
- Investigator Global Assessment, 0.1% TAC was among the most effective agents.

6.39 Overall, the meta-analysis concluded that potent TCS, JAK inhibitors and 0.1% TAC were consistently ranked as the most effective topical anti-inflammatory treatments.

Comparative harms

6.40 Safety data was reported by Soter et al (2001) for the two identical, 12-week RCTs in 631 adults ≥16 years with moderate to severe AD treated with 0.1% TAC vs VO[20]. Treatment exposure based on the median number of treatment days was lower for VO than 0.1% TAC (22 days vs 84 days). This reflected the higher discontinuation rate with VO treatment vs 0.1% TAC (68.4% vs 24.9%), mainly attributed to lack of efficacy (44.8% vs 8.6%) and AEs (12.3% vs 5.3%).

The reported 12-week incidence rates of AEs were adjusted for treatment exposure (

[20] Soter NA, Fleischer AB, Jr., et al. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part II, safety. J Am Acad Dermatol. 2001 Jan;44(1 Suppl):S39-46.

6.41 Table 7).

Table 7: Incidence of adverse events observed adjusted for treatment exposure as reported by Soter et al (2001)

Adverse Event	0.1% TAC (n = 209)	VO (n = 212)	P value
Skin burning	57.7 ± 3.52	25.8 ± 3.43	<0.001
Pruritus	46.1 ± 3.59	36.5 ± 3.70	0.062
Flu-like symptoms	30.8 ± 3.61	19.3 ± 4.06	0.034
Skin erythema	27.9 ± 3.19	19.8 ± 3.04	0.066
Headache	19.2 ± 2.99	10.7 ± 2.79	0.036
Skin infection	4.7 ± 1.65	10.6 ± 2.67	0.063
Skin tingling	7.6 ± 1.91	2.4 ± 1.04	0.015
Acne	7.1 ± 2.02	1.8 ± 1.30	0.028
Alcohol intolerance	6.9 ± 1.92	0.0 ± 0.00	<0.001
Hyperesthesia	6.5 ± 1.74	0.5 ± 0.47	0.001
Folliculitis	4.3 ± 1.50	0.5 ± 0.51	0.016
Rash	2.1 ± 1.27	0.5 ± 0.50	0.230
Sinusitis	2.2 ± 1.09	0.7 ± 0.68	0.241
Cyst	3.1 ± 1.55	0.0 ± 0.00	0.046
Myalgia	1.6 ± 0.91	0.0 ± 0.00	0.081
Back pain	1.6 ± 0.92	0.0 ± 0.00	0.081

Source: Table 2-29, p108 of the submission; Soter et al (2001)[20]
TAC = tacrolimus ointment; VO = vehicle ointment
Data expressed as rate ± standard error. Includes events with a statistically greater incidence between 0.1% TAC and the VO group, and events with an incidence of greater than 10% in any treatment group.
The adverse event incidence rate at 12 weeks was adjusted for the number of days of treatment and was calculated based on Kaplan-Meier estimates.
Alcohol intolerance = skin/facial flushing, redness, heat sensation, etc; flu-like symptoms = cold, common cold, influenza, upper respiratory infection, etc; hyperesthesia = generally localized, hypersensitive reaction, sensitive skin, skin sensitive to temperature changes, etc; skin burning = burning sensation, pain, stinging, soreness, etc; folliculitis = swollen or infected hair follicle

6.42 Patients in the 0.1% TAC arm had a significantly higher incidence ($p<0.05$) of skin burning sensation, flu-like symptoms, headache, skin tingling, acne, alcohol intolerance, hyperesthesia, folliculitis, and cysts than patients in the VO arm. Application site events were usually mild or moderate in severity and reduced in intensity within the first week of treatment, which may reflect resolution of the AD lesions. Sensations of skin burning and other application site AEs were more commonly reported by patients with severe AD or with >75% BSA affected than by patients with moderate AD or with a lower %BSA affected. The incidence of application site AEs on the head and neck was not higher than the incidence for other body regions for both 0.1% TAC and VO[5,7].

6.43 Skin infections are associated with AD due to disruption of the skin barrier. There was a higher incidence in the 0.1% TAC arm versus the VO arm of folliculitis (4.3% vs 0.5%), herpes simplex infection (3.3% vs 1.9%) and molluscum contagiosum (0.5% vs 0%). The PI for 0.1% TAC[21] states that treatment with 0.1% TAC may be associated with an increased risk of folliculitis and herpes viral infections and that in the presence of these

[21] aZematop 0.1% (tacrolimus) ointment product information. Available at: https://www.tga.gov.au/resources/artg/388172

infections, the balance of risks and benefits associated with 0.1% TAC use should be evaluated.

6.44 Skin atrophy was not observed and there were no serious treatment-related AEs attributed to 0.1% TAC during the 12-week treatment period. There were no consistent or notable differences in laboratory profiles. The tacrolimus concentrations observed in the blood were consistent with minimal absorption of 0.1% TAC through affected skin.

6.45 In the 3-week RCT reported by Ruzicka et al (1997)**Error! Bookmark not defined.**, the most frequent reason for discontinuation of 0.1% TAC treatment was a burning sensation at the application site (3 patients). Exacerbation of AD was the most frequent reason for discontinuation of VO (3 patients).

6.46 AEs observed by Hanifen et al (2005)[22] and Reitamo et al (2008)[23] during long-term follow-up of 0.1% TAC treatment of up to 4 years were comparable with that reported in short-term studies of 0.1% TAC; no new safety signals were identified.

6.47 Overall, there was no significant differences in safety between the 0.1% TAC and 1% PIM groups (p=0.19) reported by Abramovits et al (2008)[13] over the 6-week treatment period, although there was a trend towards a higher frequency of the most common AEs in the 0.1% TAC group vs the 1% PIM group. The most common AEs for 0.1% TAC vs 1% PIM were application-site reactions, burning sensation (19.4% vs 13.3%; P=0.33) and pruritis (9.2% vs 5.6%; P=0.41). Study withdrawals due to AEs were comparable (2.0% vs 2.2%).

6.48 In transplant patients, prolonged systemic exposure to intense immunosuppression following systemic administration of tacrolimus has been associated with an increased risk of developing lymphomas and skin malignancies. Patients with AD treated with 0.1% TAC did not have significant levels of systemic TAC[20]. The 0.1% TAC PI states that based on long-term studies and post market surveillance, a link between 0.1% TAC treatment and development of cancers has not been confirmed[21]. However, no definitive conclusions have been reached. The PI recommends that 0.1% TAC is used at the lowest frequency for the shortest duration necessary based on the physician's evaluation of the AD.

Benefits/harms

Treatment of moderate to severe AD flares with 0.1% TAC vs VO

6.49 On the basis of direct comparative evidence for efficacy in adults with moderate to severe AD presented by the submission:

[22] Hanifin JM, Paller AS, et al. Efficacy and safety of tacrolimus ointment treatment for up to 4 years in patients with atopic dermatitis. J Am Acad Dermatol. 2005 Aug;53(2 Suppl 2):S186-194.

[23] Reitamo S, Rustin M, et al. A 4-year follow-up study of atopic dermatitis therapy with 0.1% tacrolimus ointment in children and adult patients. Br J Dermatol. 2008 Sep;159(4):942-51.

- There was an 83% reduction in symptoms of redness, swelling and itching after 3 weeks of treatment with 0.1% TAC in comparison with approximately a 25% reduction in these symptoms when using VO. TAC 0.1% ointment is equally effective on the body and more sensitive areas such as the face and neck.
- For every 100 patients with moderate to severe AD treated with 0.1% TAC in comparison to emollient (VO) for three weeks, 71 additional patients will have their AD resolved or markedly improved.
- For every 100 patients with moderate to severe AD treated with 0.1% TAC in comparison to its emollient (VO) for 12 weeks, 53 additional patients would have a moderate or greater improvement in their AD.
- For every 100 patients treated with 0.1% TAC in comparison with emollient (VO) over 12 weeks,
  - 43 less patients would discontinue treatment due to lack of efficacy.
  - 32 additional patients would experience a burning sensation at the application site for the first few days of treatment.

Proactive maintenance treatment for moderate to severe AD with 0.1% TAC vs VO

6.50 On the basis of direct comparative evidence for efficacy in adults with moderate to severe AD presented by the submission, for every 100 patients with moderate to severe AD using proactive 0.1% TAC maintenance treatment in comparison with emollient (VO) over 12 months:

- 30 additional patients would likely not experience any AD flares;
- the time to first major flare will increase from approximately 2 weeks to approximately 20 weeks.

Treatment of moderate AD flares with 0.1% TAC vs 1% PIM

6.51 On the basis of direct comparative evidence for efficacy in adults with moderate AD on the face and neck presented by the submission:

- Adults will experience a 75% reduction in their symptoms when treated for up to 6 weeks with 0.1% TAC compared to a 54% reduction in symptoms when treated with 1% PIM.

Clinical claim

6.52 The submission presented two clinical claims:

i. The submission described 0.1% TAC ointment as superior in terms of efficacy and non-inferior in terms of safety compared with VO in the treatment of patients with moderate to severe AD affecting any part of the body.

ii. The submission described 0.1% TAC ointment as superior in terms of efficacy and non-inferior in terms of safety compared with 1% PIM in the treatment of patients with moderate AD on the face and eyelids.

6.53 Based on the evidence provided in the submission, the ESC considered that 0.1% TAC demonstrated superior efficacy and non-inferior safety versus VO for the treatment of flares, and as maintenance treatment in adults ≥16 years with moderate to severe AD. Thus, in patients who were contraindicated to TCS, the ESC considered that 0.1% TAC was superior to VO. However, as the trial populations were not completely aligned with the proposed PBS population, the ESC considered that the benefit in patients had failed to achieve satisfactory disease control with intermittent (moderate or potent) TCS therapy was uncertain.

6.54 The ESC considered that TAC 0.1% ointment demonstrated superior efficacy and non-inferior safety compared to 1% PIM for the treatment of flares in patients with moderate AD affecting the face and neck. Although no direct evidence was presented in the submission, the ESC considered that the clinical claims would also apply to moderate AD affecting the face and eyelids.

6.55 The ESC noted that there were additional issues with the evidence presented in the submission including:

- The efficacy and safety evidence were sourced from publications of pooled or combined data from several trials with limited information on the conduct of the individual studies, on the presence of selection bias in the subgroup populations and the reporting of outcomes across the studies. Concerns were raised regarding heterogeneity across the studies included in the publications, and across publications, including differences in the study population demographics and disease characteristics, measures used to assess treatment response, the clinical outcomes presented and their measurement, and the period of treatment or follow-up. This hampered an assessment of the quality of the evidence base as a whole.
- Several of the subgroup analyses were conducted in a *post hoc* manner and were not part of the original statistical analysis plan of the relevant trials. Furthermore, the majority of the TAC versus VO trials were conducted more than a decade ago, with some trials conducted more than two decades ago. The standard of care is likely to have improved substantially, e.g. the minimal use of irritants in emollients in current practice.
- The sources of the evidence in the submission did not use clinical measures recommended for the assessment of AD severity and symptoms included in the consensus statement from the ACD (e.g. SCORing Atopic Dermatitis [SCORAD], Patient Oriented Eczema Measure [POEM]). There was limited or no discussion about the disease characteristics of those adults who did not respond adequately to 0.1% TAC. Further, none of the populations enrolled in the included studies were fully aligned with the proposed PBS population in terms of prior response/intolerance to TCS treatment.
- There may be other relevant comparators such as TCS and systemic therapies but the extent of substitution by 0.1% TAC remains uncertain.

6.56 The PBAC noted that 0.1% TAC was superior in terms of efficacy and non-inferior in terms of safety compared to VO but considered that VO was not representative of standard management.

6.57 The PBAC considered that the claim that 0.1% TAC was superior in terms of efficacy compared to 1% PIM was not adequately supported by the data. On balance, the PBAC considered that 0.1% TAC was likely non-inferior to 1% PIM in terms of efficacy and safety.

Economic analysis

Cost-effectiveness analysis

6.58 The submission presented a trial-based economic evaluation based on (i) a 3-week, randomised study[24] for primary treatment (Ruzicka 1997), (ii) CONTROL[25], a direct randomised trial, that compared the effectiveness of 0.1% TAC versus VO for the treatment of mild to severe AD (Wollenberg 2008), and (iii) a *post hoc* subgroup analysis of patients with moderate to severe AD from the adult CONTROL study (Reitamo 2010)[26].

6.59 The key components of the economic evaluation are summarised in Table 8.

[24] Ruzicka T, Bieber T, Schöpf E, Rubins A, Dobozy A, Bos JD, et al. A short-term trial of tacrolimus ointment for atopic dermatitis. European Tacrolimus Multicenter Atopic Dermatitis Study Group. N Engl J Med. 1997 Sep 18;337(12):816-21.

[25] Wollenberg A, Reitamo S, Girolomoni G, Lahfa M, Ruzicka T, Healy E, et al. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. Allergy. 2008;63(7):742-50.

[26] Reitamo S, Allsopp R. Treatment with twice-weekly tacrolimus ointment in patients with moderate to severe atopic dermatitis: results from two randomized, multicentre, comparative studies. J Dermatolog Treat. 2010 Jan;21(1):34-44.

Table 8: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	0.1% TAC versus VO
Time horizon	3 weeks of primary therapy for the treatment of flares + 1 year for maintenance therapy in the base case (vs 1 year of maintenance therapy in the CONTROL study). The modelled duration of primary therapy did not consider that 0.1% TAC may be used for up to 6 weeks for the treatment of flares in the proposed PBS restriction. Further, while the proposed restriction states that continuing treatment may be given for more than a year, the economic model does not allow for an increase in duration of maintenance therapy. However, the PBAC has previously considered a time horizon of 1 year to be appropriate for AD (paragraph 6.59, crisaborole PSD, November 2018 PBAC Meeting).
Outcomes	Quality-adjusted life-years gained.
Methods used to generate results	Hybrid model: Decision tree to capture response to primary treatment + area under the curve allocation approach to capture response to maintenance treatment.
Health states	3 health states in the state transition model: Flare-free, Post-initial flare and Discontinued
Maintenance phase cycle length	Daily.
Allocation to health states	Transitions from the primary to maintenance therapy phase was based on response in the 3-week study (Ruzicka 1997). Health state allocation in the state transition model was based on time-to-event data from the *post-hoc* analysis of the adult CONTROL study (Reitamo 2010). The time-to-first major flare curve from the *post-hoc* analysis of the adult CONTROL study was utilised to calibrate time-to-first flare and time-to-discontinuation curves. Given that major flares were those that would require treatment, it may have been reasonable to utilise the time-to-first major flare curves directly in the model. Further, the relationship between patients remaining flare-free and those that discontinue treatment was not well established in the submission, and using a hazard ratio applied to the time-to-first flare curve may not represent time to treatment discontinuation.
Number of flares	Post-initial flare health state: 0.1% TAC arm = 4.10 flares, VO arm = 1.0 flare Discontinued health state: 9.51 flares across both arms. The studies used to inform the number of flares, by health state, have uncertain applicability, as the CONTROL study included patients with mild AD and the study used to inform the number of flares in the discontinued health state included children. Further, the study likely predated systemic therapies and thus, may not have captured the benefits associated with systemic therapies in these patients. Further, the rationale that patients in the vehicle arm would only have 1 flare was not well justified in the submission and is not consistent with the clinical claim that 0.1% TAC reduces the number of flares.
Health related quality of life	Utility values of 0.87 and 0.76 applied to flare-free and flare days from a published economic evaluation which made use of health-related quality-of-life (HRQoL) data collected in the adult CONTROL study [a]. The submission applied utility values of mild AD patients to flare-free days and a weighted utility value of moderate and severe AD patients to flare days. The tool used to translate the HRQoL data was not reported in the study. The study also did not provide information about the completion rate.
Subsequent treatment costs	Costs for phototherapy, UPA , DUPI and ciclosporin were applied to about 18% of patients while in the discontinued health state. The estimated use of DUPI was based on a survey of patients that aimed at understanding TCS use and from a study of 85 patients in Australia for ciclosporin. The use of UPA was calculated based on the market share of DUPI and UPA. Phototherapy use was based on primary research conducted by the Sponsor. The basis for the distribution of use of systemic therapies in the discontinued health state remains uncertain. Phototherapy costs were applied to each flare for patients in the discontinued health state which may not be appropriate as it is unclear whether phototherapy is given as maintenance therapy or as continuous treatment. Further, the study used to estimate the use of DUPI may not be applicable to the proposed setting.

Source: tabulated during the evaluation, from Table 3-1, p128 of the evaluation and the "Attachment 2 Tacrolimus final model 06March2025" workbook included in the submission.

AD = atopic dermatitis; DUPI = dupilumab; HRQoL = health-related quality of life; TAC = tacrolimus; TCS = topical corticosteroid; UPA = upadacitinib; VO = vehicle ointment

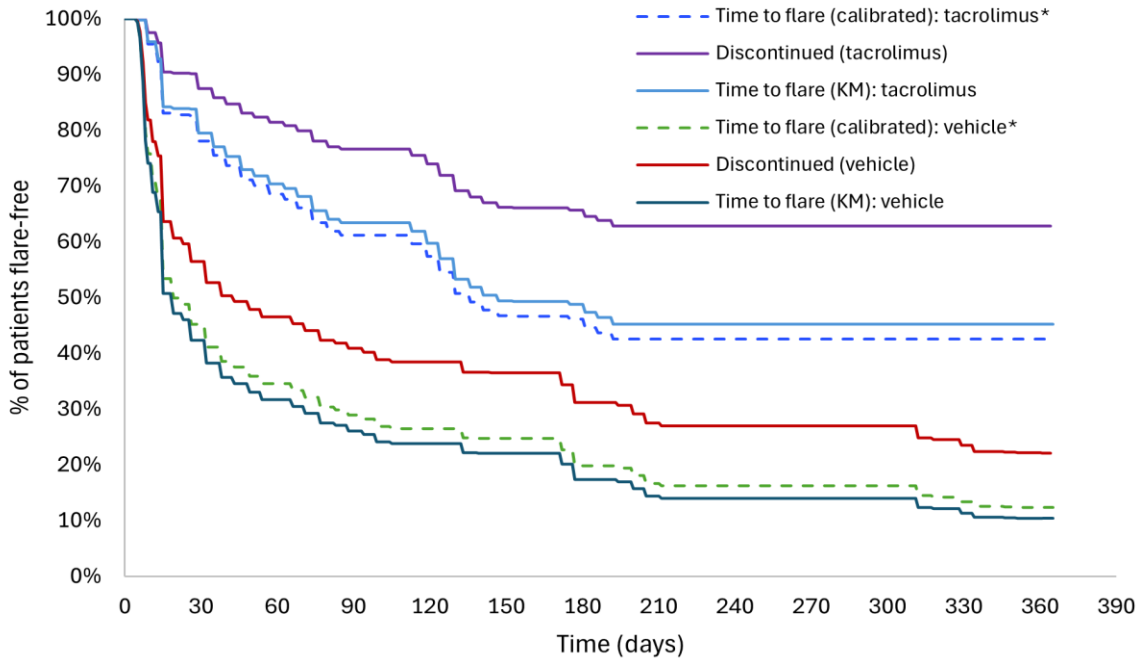
[a] Healy E, Bentley A, Fidler C, Chambers C. Cost-effectiveness of tacrolimus ointment in adults and children with moderate and severe atopic dermatitis: twice-weekly maintenance treatment vs. standard twice-daily reactive treatment of exacerbations from a third-party payer (U.K. National Health Service) perspective. British Journal of Dermatology. 2011;164(2):387-95.

6.60 The submission adopted a hybrid decision-tree and area under the curve state transition model. The decision tree was utilised to capture response to primary therapy over a period of 3 weeks, with patients who responded to primary therapy entering the flare-free health state and those that did not respond to primary therapy entering the discontinued health state of the state transition model.

6.61 A time horizon of 21 days for primary therapy and 1 year for maintenance treatment was modelled in the base case analysis. Primary therapy can be given for up to 6 weeks in clinical practice. While the model allows for an increase in the duration of primary therapy, the response to primary therapy was based on a 3-week study. The PSCR acknowledged that no six-week responder data exist. One year of maintenance treatment was consistent with the adult CONTROL study.

6.62 In patients who received maintenance therapy, subsequent health state allocation was based on the time-to-first major flare data from the *post-hoc* analysis of the adult CONTROL study. Hazard ratios , based on the proportion of patients that were flare-free or remained on treatment at the end of the study period, were calculated to generate time-to-first flare (from reported time-to-first major flare data) and time-to-discontinuation curves for each treatment arms. Hazard ratios of 1.078 and 0.924 for time-to-first flare curves and of 0.54 and 0.72 for time-to-discontinuation curves were applied in the to the 0.1% TAC and VO arms, respectively. The assumption that the Post-flare health state represents patients subsequent to a flare of any severity was not justified in the submission and appears inconsistent with the definition of flares applied to estimate costs and outcomes (i.e. flares which require substantial therapeutic intervention). The relationship between the patients remaining flare-free at the end of the study and that of treatment discontinuation was also not well established in the submission, and it may not be reasonable to assume that these follow the same shape over time. The calibrated time-to-first flare and time-to-discontinuation curves for the 0.1% TAC and VO arms are presented in Figure 5.

Figure 5: Time-to-event curves for both treatment arms



Source: constructed during the evaluation, from Sheet 'Maintenance TTE estimate' of the "Attachment 2 Tacrolimus final model 06March2025" Workbook provided in the submission.
KM = Kaplan-Meier
* indicates curves utilised in the base case analysis.

6.63 The proportion of patients in the post-initial flare health state of the model was calculated as the difference between the time-to-first flare and time-to-discontinuation curves. The submission assumed that patients who transition to the post-initial flare health state (i.e. maintenance treatment) in the 0.1% TAC arm would experience 4.10 flares on transition into the health state, with each flare lasting 16.11 days. While the duration of flares was reasonable, the mean number of flares could not be verified from data from the CONTROL study. However, CONTROL included mild AD patients and thus, the number of flares reported may not be applicable to the proposed target population. It may be more informative to utilise the number of major flares reported in the *post-hoc* analysis of the CONTROL study that was restricted to moderate and severe AD patients. The submission assumed that patients in the VO arm would experience 1 flare only on transition to the post-initial flare health state. The ESC noted that the rationale behind this assumption was not clear.

6.64 The submission assumed that patients in the discontinued health state, across both treatment arms, would experience 9.51 flares, with each flare lasting 15.20 days. This was sourced from a study of 2,002 patients with moderate and severe AD in 8

countries[27]. The applicability of this study remains uncertain as it included paediatric patients. While number of flares was reported by severity, it did not report number of flares by age and severity, or extent of systemic therapy use.

6.65 Based on the mean number of flares, flare days per flare and health state membership, the submission calculated the number of flare and flare-free days for patients on maintenance treatment and in the discontinued health state across both treatment arms. Health-state independent utility weights of 0.87 and 0.76, converted to per cycle utility weights of 0.0024 and 0.0021, were applied to flare-free and flare-days in all health states (and responders and non-responders, respectively, in the primary phase of the model assuming response occurred mid-way through the phase). Utility weights were sourced from a published economic evaluation which made use of health-related quality-of-life (HRQoL) data collected in the adult CONTROL study[28]. The submission applied the utility value of patients with mild AD to flare-free days and a weighted utility value (based on the split of moderate and severe AD patients in CONTROL) of patients with moderate and severe AD to flare days. The PSCR stated that the application of a utility value, based on mild AD, to flare-free days and a weighted utility, based on moderate to severe AD, to flare days mirrored clinical reality in which patients without flares are classified as having mild AD, whereas those with a flare returns the patient to moderate or severe status. The submission did not state the tool utilised to translate the HRQoL data, nor did it provide information about the completion rate in the study. Alternate values (0.85 and 0.78 for flare-free and flare days, respectively), from a study[29] that made use of HRQoL data from CONTROL and UK tariffs for EQ-5D and SF-6D responses to estimate the utility changes associated with TAC use, significantly increase the ICER. The ESC noted that while it may be reasonable to apply utility values for mild AD to flare-free days and a weighted utility value of moderate and severe AD to flare days, the source studies were associated with uncertainty.

6.66 Treatment costs associated with 0.1% TAC were estimated based on the average use per day observed in the adult CONTROL study for treatment of primary therapy/flares and maintenance treatment, that is, 3.88 g per day for flare treatment and 1.23 g per day for maintenance treatment. Based on the proposed DPMQ of $[redacted] per 30 g ointment tube, a cost per gram of $2.45 was applied to flare and flare-free days while patients were on treatment with 0.1% TAC.

[27] Zuberbier T, Orlow SJ, Paller AS, Taïeb A, Allen R, Hernanz-Hermosa JM, et al. Patient perspectives on the management of atopic dermatitis. J Allergy Clin Immunol. 2006 Jul;118(1):226-32.

[28] Healy E, Bentley A, Fidler C, Chambers C. Cost-effectiveness of tacrolimus ointment in adults and children with moderate and severe atopic dermatitis: twice-weekly maintenance treatment vs. standard twice-daily reactive treatment of exacerbations from a third party payer (U.K. National Health Service) perspective. British Journal of Dermatology. 2011;164(2):387-95.

[29] Poole CD, Chambers C, Sidhu MK, Currie CJ. Health-related utility among adults with atopic dermatitis treated with 0·1% tacrolimus ointment as maintenance therapy over the long term: findings from the Protopic® CONTROL study. British Journal of Dermatology. 2009;161(6):1335-40.

6.67 Costs associated with disease management were accrued daily based on assumed healthcare resource utilisation per flare and flare-free day. The submission assumed a higher resource utilisation for patients experiencing flare days, in both treatment arms and for patients on or off treatment.

6.68 Subsequent treatment costs for phototherapy, dupilumab, upadacitinib and ciclosporin were included for 4%, 9%, 1.9% and 2.4%, respectively, of patients that were in the discontinued health state. While inclusion of subsequent therapies was reasonable, ciclosporin, dupilumab and upadacitinib are currently listed for treatment of severe AD only. It was unclear whether patients discontinued TAC due to treatment success, inadequate response to treatment or due to worsening of disease symptoms. Further, the ESC noted that the distribution of the subsequent therapies in the discontinued health state remains uncertain, with the PBAC noting low uptake rates of 3.5 to 5% in eligible patients (Table 5, dupilumab PSD, November 2020 PBAC Meeting). Additionally, the ESC noted that costs for dupilumab and upadacitinib were estimated based on the assumption that patients would undergo one year of treatment. However, approximately 60% and 70% of patients respond to initial treatment with dupilumab and upadacitinib, respectively (Table 19, dupilumab PSD, March 2020 PBAC Meeting and Table 16, upadacitinib PSD, July 2021 PBAC Meeting). When response to initial treatment is considered, the number of scripts per patient per year reduces to 10.08 and 9.38 (compared to the base case of 13.50 and 13.05 scripts) for dupilumab and upadacitinib, respectively. The PSCR stated that PBS data indicates that 92% of patients who receive a PBS-funded biologic have previously received PBS-funded topical therapies; further, the data indicated that the mean length of treatment with was 1.7 years. Phototherapy costs were applied per flare to patients in the discontinued health state, based on a treatment schedule of 3 sessions a week, for 10 weeks. It is unclear whether patients would require phototherapy on occurrence of each flare as phototherapy may be administered intermittently or continuously as maintenance treatment. Although the PSCR stated that a conservative assumption was made that phototherapy would be restricted to flare management only, the ESC noted that the assumption that phototherapy would be required for each flare (assuming 9.51 flares per year) remained unjustified. The pre-PBAC response stated that when all phototherapy costs were removed, the ICER remained dominant, demonstrating that 0.1% TAC was cost-effective even under unfavourable assumptions.

6.69 The key drivers of the economic model are summarised in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact Revised base case: Dominant.
Proportion of patients treated with dupilumab as subsequent therapy	Applied to 9% of patients in the discontinued health state.	High, favours tacrolimus. The extent of use of dupilumab is uncertain with the PBAC noting low uptake rates of 3.5 to 5% in eligible patients (Table 5, dupilumab PSD, November 2020 PBAC Meeting). Reducing the use of dupilumab in the discontinued health state reduces the costs of subsequent therapies, thereby, reducing the incremental cost savings associated with the listing of tacrolimus.
Use of dupilumab and upadacitinib as subsequent therapy	Costs for one year of treatment were applied in patients who uptake treatment.	High, favours tacrolimus. The submission did not consider response to initial treatment in the base case analysis. PSDs suggest that 40% and 30% of patients did not respond to initial treatment for dupilumab and upadacitinib, respectively (Table 19, dupilumab PSD, March 2020 PBAC Meeting and Table 16, upadacitinib PSD, July 2021 PBAC Meeting).
Phototherapy costs	Applied to 4% of patients, to each flare, in the discontinued health state.	High, favours tacrolimus. Exclusion of phototherapy costs reduces the incremental cost savings estimated with the listing of tacrolimus.
Number of flares in the discontinued health state	9.51 flares per year, applied to patients in the discontinued health state.	Uncertain, may favour tacrolimus. Since the costs and outcomes in the vehicle arm are driven by the discontinued health state, and the number of flares applied were sourced from an external study, this remains uncertain.

Source: tabulated during the evaluation
PBAC = Pharmaceutical Benefits Advisory Committee; PSD = public summary document.

6.70 The results of the economic evaluation are presented in Table 10.

Table 10: Results of the economic evaluation

Component	Proposed medicine	Comparator	Increment
Costs	*$[redacted]*	*$3,759.92*	*-$[redacted]*
QALYs	0.885	0.869	0.016
Incremental cost/QALY gained			**Dominant**

Source: Table 7, p11 of the executive summary.
QALY = quality-adjusted life year
Note: Ciclosporin costs were corrected during the evaluation

6.71 The disaggregated costs and outcomes of the economic analysis are presented in Table 11.

Table 11: Disaggregated summary of cost impacts and health outcomes

Resource item	Tacrolimus	Vehicle	Increment	% of total increment
Number of flares				
Post-initial flare health state	1.92	0.09	1.83	-
Discontinued health state	4.06	9.16	-5.11	
Time in health state (days)				
Flare-free health state	158.01	9.07	148.93	
Post-initial flare health state	51.07	3.89	47.19	
Discontinued health state	155.92	352.04	-196.12	
Costs				
Drug costs	$[redacted]	-	$[redacted]	-[redacted]%
Subsequent treatments	$1,364.91	$3,081.70	-$1,716.80	[redacted]%
Disease management	$625.43	$678.22	-$52.79	[redacted]%
Total cost	**$[redacted]**	**$3,759.92**	**-$[redacted]**	**100%**
Outcomes				
Primary therapy QALYs	0.046	0.044	0.002	13.5%
Maintenance treatment QALYs	0.487	0.030	0.457	2794.8%
Discontinued treatment QALYs	0.352	0.795	-0.443	-2708.6%
Total QALYs	**0.885**	**0.869**	**0.016**	**100%**

Source: tabulated during the evaluation, from Table 3-12, pp150-151 of the submission and Sheet 'Results' of the "Attachment 2 Tacrolimus final model 06March2025" workbook included in the submission.
QALYs = quality-adjusted life years

6.72 The ESC noted that the main driver of the incremental cost savings were the costs associated with subsequent treatments following discontinuation of vehicle or TAC treatment. Some issues regarding the inclusion of systemic therapies in the discontinued health state were noted during the evaluation (paragraph 6.68). Thus, the ESC considered that the offsets associated with subsequent treatment may be overestimated in the base case analysis.

6.73 The results of key sensitivity analyses presented in the submission and around areas of uncertainty identified during the evaluation are summarised in Table 12.

Table 12: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Revised base case	**-$[redacted]**	**0.016**	**Dominant**
Number of flares in the post-initial flare health state (base case: 4.10 - tacrolimus arm, 1 - vehicle arm)			
• 4.19 and 6.58 [a]	-$[redacted]	0.018	Dominant
% of patients that discontinue treatment in the vehicle arm at one-year (base case: 90%)			
• 50%	-$[redacted]	0.015	Dominant
Time-to-event distribution			
• Linear interpolation	-$[redacted]	0.017	Dominant
Utility values (base case: flare-free days = 0.87; flare days = 0.76)			
• Flare-free days = 0.85	-$[redacted]	0.014	Dominant
• Flare days = 0.78	-$[redacted]	0.013	Dominant
• Flare-free days = 0.85; flare days = 0.78 [b] (#1)	-$[redacted]	0.011	Dominant
Number of flare days (16.11 post-initial flare health state; 15.20 days discontinued health state)			
• 11.9 days across both health states [c]	-$[redacted]	0.014	Dominant
Number of flares in the discontinued health state (base case = 9.51)			
• 7	$[redacted]	0.010	$[redacted][1]
• 5	$[redacted]	0.006	$[redacted][2]
• 3	$[redacted]	0.001	$[redacted][3]
Tacrolimus use per day (base case: 1.23 g maintenance, 3.88 g flare)			
• 0.48 g maintenance, 1.68 g flare [d]	-$[redacted]	0.016	Dominant
• 1.68 g (maintenance and flare) [e] (#2)	-$[redacted]	0.016	Dominant
Costs			
• Exclusion of phototherapy costs (#3)	-$[redacted]	0.016	Dominant
• Applying systemic therapies costs to only severe AD patients (43% of those in discontinued health state) (#4)	$[redacted]	0.016	$[redacted][4]
• Adjusting DUPI and UPA use for response to initial treatment (10.06 and 9.38 scripts per patient per year) (#5)	-$[redacted]	0.016	Dominant
• Reducing % of use of dupilumab (3.5%) (#6)	-$[redacted]	0.016	Dominant
• Reducing % of use of dupilumab (5%) (#7)	-$[redacted]	0.016	Dominant
• Healthcare resource utilisation (based on DUPI submission to NICE)	-$[redacted]	0.016	Dominant
• Healthcare resource utilisation (PBAC multiplier)	-$[redacted]	0.016	Dominant
• Using the cost-minimised price for TAC ($54.60: calculated at AEMP level)	-$[redacted]	0.016	Dominant
• Using the cost-minimised price for TAC ($68.06: calculated at DPMQ level)	-$[redacted]	0.016	Dominant
Multivariate analyses			
• #1, #2	-$[redacted]	0.011	Dominant
• #1, #2, #3	-$[redacted]	0.011	Dominant
• #1, #2, #3, #4	$[redacted]	0.011	$[redacted][2]
• #1, #2, #3, #4, #5	$[redacted]	0.011	$[redacted][5]
• #1, #2, #3, #4, #5, #6	$[redacted]	0.011	$[redacted][6]
• #1, #2, #3, #4, #5, #7	$[redacted]	0.011	$[redacted][6]
• #1, #2, #4, #5, #6	$[redacted]	0.011	$[redacted][2]
• #1, #2, #4, #5, #7	$[redacted]	0.011	$[redacted][7]

Source: tabulated during evaluation, from the "Attachment 2 Tacrolimus final model 06March2025" workbook included in the submission.
AD = atopic dermatitis ; DUPI = dupilumab; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life year ; UPA = upadacitinib

[a] Based on the number of major flares reported in the *post-hoc* analysis of CONTROL (Reitamo 2010).
[b] Based on a study that utilised HRQoL data from CONTROL and applied UK tariffs (Poole 2009).
[c] Sourced from the "Attachment 9 – Primary Research Report" provided in the submission.
[d] Based on the average use per day reported in the *post-hoc* analysis of CONTROL.
[e] *Corrected as per publication*
The redacted values correspond to the following ranges:
[1] *$5,000 to < $15,000*
[2] *$25,000 to < $35,000*
[3] *$355,000 to < $455,000*
[4] *$0 to < $5,000*
[5] *$35,000 to < $45,000*
[6] *$55,000 to < $75,000*
[7] *$15,000 to < $25,000*

6.74 The ICER was sensitive to the proportion of patients that discontinued treatment after primary therapy, the utility values applied to flare and flare-free days, the number of flare days per flare assumed, the average use of 0.1% TAC per day, the number of flares in the discontinued health state and the proportion of patients that received systemic therapies in the discontinued health state. However, generally the conclusion of cost savings, based on published prices for dupilumab and upadacitinib, did not change. When cumulative changes, such as using alternate utility values, average use of 0.1% TAC per day, excluding phototherapy costs, restricting systemic therapies to severe AD patients and reducing the use and uptake of dupilumab and upadacitinib, are made to the model, 0.1% TAC is associated with additional costs.

Cost-minimisation analysis

6.75 The submission presented a cost-minimisation approach (CMA) of 0.1% TAC versus 1% PIM for the treatment of moderate AD on the face and eyelids. The CMA was based on a claim of superior efficacy and non-inferior safety of 0.1% TAC compared to 1% PIM based on a comparison of the effectiveness and safety profiles of 0.1% TAC and 1% PIM over a period of 6 weeks in paediatric and adult patients with AD. The key assumptions and components of the CMA presented in the submission are shown in Table 13.

Table 13: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Effectiveness is assumed to be superior.
Therapeutic claim: safety	Safety is assumed to be non-inferior.
Evidence base	Direct comparison of tacrolimus and pimecrolimus in 3, multicentre, randomised studies.
Equi-effective doses	1 g of 0.1% tacrolimus = 1 g of 1% pimecrolimus.
Direct medicine costs	Costs per patient per course of acute therapy, 1 g of tacrolimus compared to 1 g of pimecrolimus.
Other costs or cost offsets	No difference in adverse events and healthcare resource utilisation was assumed.

Source: Table 3-16, p157 of the submission.

6.76 The submission established the equi-effective doses as follows:

1 g of 0.1% TAC = 1 g of 1% PIM.

6.77 The studies utilised (Paller 2005[30], Abramovits 2008[31]) to establish the equi-effective doses of 0.1% TAC and 1% PIM for the treatment of AD did not report the average use per day for the face and neck regions. Although the submission noted that identical application of 0.1% TAC and 1.0% PIM was undertaken in the studies, there was uncertainty regarding the amount of ointment that may be required for the treatment of flares on the face and eyelids. Further, the proposed restriction and TGA indication for 0.1% TAC is not separated by the area of body under consideration (face/eyelids or rest of the body). This suggests that patients could use 0.1% TAC as maintenance treatment, i.e., twice daily for treatment of flares and twice weekly as maintenance, on all lesions on the face/neck and the rest of the body. Since there is no evidence for the use of 0.1% TAC compared to 1% PIM as maintenance treatment (after clearing of lesions/flares) on the face and eyelids, the equi-effective doses established in the submission may be reasonable only for treatment flares.

6.78 The submission did not present any additional costs or cost offsets associated with 0.1% TAC owing to the claim of non-inferior safety and similar safety profiles for 0.1% TAC and 1% PIM established by the subgroup analysis.

6.79 The results of the CMA using the AEMP of 1% PIM are presented in Table 14.

Table 14: Results of the cost-minimisation approach (based on AEMP and equi-effective doses)

Component	Tacrolimus	Pimecrolimus
Pimecrolimus AEMP	-	$19.13
Cost per gram	$1.28	$1.28 [a]
Cost per tube (DPMQ)	$54.60 for 30 g	$34.03 for 15 g
Cost per tube (AEMP)	**$38.26 for 30 g**	**$19.13 for 15 g**
Difference in AEMP	$19.13	

Source: tabulated during evaluation.
AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity
[a] Cost per gram of pimecrolimus, based on the AEMP for a 15 g tube.

6.80 Of note, the proposed price of 0.1% TAC utilised in the cost-utility analysis (DPMQ: $[redacted]), is higher than the cost-minimised price calculated during the evaluation (DPMQ: $54.60). The ESC noted that the submission inappropriately did not propose a weighted price according to the expected use in moderate AD on the face and eyelids versus rest of body moderate to severe AD and that, at the proposed DPMQ, 0.1% TAC would be associated with a higher cost per gram than 1% PIM. Although the PSCR stated that a weighted price would be difficult to calculate as clinician estimates of grams of ointment applied to the face and eyelids versus the body vary widely, the pre-PBAC response stated that if 80% of 0.1% TAC use was assumed to be for the body,

[30] Paller AS, Lebwohl M, Fleischer AB, Antaya R, Langley RG, Kirsner RS, et al. Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: Results from 3 randomized, comparative studies. Journal of the American Academy of Dermatology. 2005 2005/05/01/;52(5):810-22.

[31] Abramovits W, Fleischer AB, Jr., Jaracz E, Breneman D. Adult patients with moderate atopic dermatitis: tacrolimus ointment versus pimecrolimus cream. J Drugs Dermatol. 2008 Dec;7(12):1153-8.

with 20% for the face and eyelids, this would result in an AEMP for 0.1% TAC of $52.34 (DPMQ: $69.74).

6.81 While equivalence on a per gram basis may be reasonable for the treatment of flares, due to the differences in pack sizes between 0.1% TAC and 1% PIM, the CMA assumes that patients would otherwise use two tubes of 1% PIM.

Drug cost/patient/year

6.82 The drug cost/patient/year for 0.1% TAC is presented in Table 15. The financial estimates utilised the average use per day reported in the *post-hoc* analysis of the CONTROL study for estimation of treatment costs. This assumed that all patients would receive treatment in Year 1, with 65% of patients continuing treatment in each subsequent year. This resulted in a higher cost per year in the financial analysis and longer duration of treatment compared to the economic analysis.

Table 15: Drug cost per year for tacrolimus

	Trial dose and duration	Economic model	Financial estimates
Mean dose			
Flare days	1.68 g	3.88 g	1.68 g
Flare-free days		1.23 g	
Number of flare days for patients on treatment with tacrolimus			
Flare days – primary therapy	NA	21	NA
Flare days – maintenance therapy		30.92	
Flare free days		178.16	
Mean treatment duration	386 days [a]	230.08 [b]	2.64 years [c]
Cost for primary treatment	NA	$ [redacted]	NA
Cost for maintenance treatment		$ [redacted]	
Cost/patient/year	**$** [redacted]	**$** [redacted]	**$** [redacted]
Number of scripts per patient	20	14.02	20

Source: tabulated during the evaluation, from Table 3-11, p150 of the submission, the "Attachment 2 Tacrolimus final model 06March2025" and "Attachment 3 – Azematop BIM" workbooks included in the submission.

[a] Based on 21 days of primary therapy in Ruzicka and 365 days of maintenance therapy in CONTROL.

[b] 21 days of primary therapy and 209.08 days of maintenance therapy.

[c] Truncated mean, assuming 65% of patients will continue treatment each year.

Estimated PBS usage & financial implications

6.83 This submission was not considered by DUSC. The submission adopted a combined epidemiological and market share approach to estimate the use and financial impact of 0.1% TAC. The epidemiological approach estimated the net costs associated with 0.1% TAC for patients with moderate to severe AD on their body and severe AD on their face or eyelids whereas the market share approach estimated the net costs associated with patients with moderate AD on their face or eyelids.

6.84 Key components of the financial analyses are presented in Table 16.

Table 16: Key inputs for the financial estimates

Data	Value/Source	Comment
Eligible population and treatment utilisation for epidemiological approach		
Prevalence of AD	6.3%. Chidwick et al.[32]	This prevalence rate was for all Australians (not only for those aged 16 years and over).
Distribution of AD severity	Mild: 70%, moderate: 20% and severe: 10%. Beiber et al.[33]	Based on European data.
Location of AD	Face/eyelids: 25%, Body: 75% Szefler et al.[34]	No evidence was provided in the cited source to substantiate that 25% of patients would have AD on their eyelids, though the proportion with AD on their eyelids or face would be higher than the proportion on eyelids alone.
Proportion with history of TCS treatment	92%. DUPI DUSC report	-
Proportion who fail or are contraindicated to TCS	30%. Augustin et al.[35]	The applied proportion differed to what was reported in the study (40.8%).
Uptake rate	From [redacted]% in Year 1 (based on the average proportion of moderate to severe AD patients not meeting their treatment goals in Augustin et al.[35]) to [redacted]% in Year 6 (assumed).	-
Treatment discontinuation rate.	0% for patients in their first year of treatment. 35% for patients in Year 2+ of treatment based on 35% of TAC patients who discontinued treatment within 12 months of treatment in the *post hoc* analysis of the trial.[26]	It may not be reasonable to assume that all patients would complete their first year of 0.1% TAC treatment, and the assumption of ongoing treatment was not supported by the clinical or economic evidence.
0.1% TAC scripts per patient per year	20 based on an average use of 1.68 g of 0.1% TAC per day, each 30 g tube lasts approximately 18 days.	While this was consistent with the CUA, it is uncertain whether patients with AD on their face or eyelids would use the same amount of 0.1% TAC as patients with AD on their body.
Proportion of patients who do not receive further systemic therapy	65% based on treatment satisfaction rates reported for 0.1% TAC in a single arm non comparative study Reitamo et al.[36]	This could not be verified from the cited source (which reported 75% for all patients enrolled and 72% for patients aged over 16 years).[36] The PBAC considered that satisfaction with 0.1% TAC does not directly translate to avoiding the use of systemic therapies.

[32] Chidwick K, et al. Prevalence, incidence and management of atopic dermatitis in Australian general practice using routinely collected data from MedicineInsight. Australas J Dermatol. 2020;61(3):e319-e27.
[33] Bieber T, Straeter B. Off-label prescriptions for atopic dermatitis in Europe. Allergy. 2015;70(1):6-11.
[34] Szefler SJ, et al. Pediatric allergy: principles and practice: Elsevier Health Sciences; 2015.
[35] Augustin M, et al. Real-World Treatment Patterns and Treatment Benefits among Adult Patients with Atopic Dermatitis: Results from the Atopic Dermatitis Patient Satisfaction and Unmet Need Survey. Acta Derm Venereol. 2022;102:adv00830.
[36] Reitamo S, Rustin M, Harper J, Kalimo K, Rubins A, Cambazard F, et al. A 4-year follow-up study of atopic dermatitis therapy with 0·1% tacrolimus ointment in children and adult patients. British Journal of Dermatology. 2008;159(4):942-51.

Data	Value/Source	Comment
Proportion of patients who would reduce DUPI and UPA use among those who do not receive further systemic therapy	DUPI use (9%) based on a survey of eczema patients conducted by Barta et al.[37]. UPA use (2%) was based on the ratio of UPA versus DUPI patients (3,339/15,886) outlined in the DUPI DUSC report multiplied by the proportion of DUPI patients (9%).	The survey[37] of eczema patients with unspecified disease severity has unlikely applicability to patients expected to receive DUPI or UPA (chronic severe AD despite using topical therapy). Additionally, it is unclear whether UPA use would occur in addition or instead of DUPI use as reported in the Barta et al. study, given that UPA was expected share the market with DUPI (para 6.72, upadacitinib PSD, July 2021 PBAC Meeting).
Eligible scripts and treatment utilisation for the market share approach		
Forecasted 1% PIM scripts for patients with moderate AD on their face and eyelids	From 25,006 in Year 1 to 47,043 in Year 6. Annual growth of 1% PIM script (13.5%) based on the PIM script data over the last six years.	The submission had not linearly extrapolated 1% PIM scripts, the fixed growth rate of 13.5% per year assumes an exponential growth of scripts. However, this trend reflects the past six years of script data.
Distribution of 1% PIM scripts by disease severity.	Mild: 78%, moderate: 22% (Beiber et al.[33]) and severe: 0% (assumed).	-
Market share of 1% PIM scripts	50% in Year 1 increasing to 70% in Year 6. Sponsor assumption.	-
1% PIM to 0.1% TAC script replacement rate	2:1. 1% PIM is dispensed as a 15 g tube whereas 0.1% TAC is dispensed as a 30 g tube, assuming that two scripts of 1% PIM would be replaced with one script of 0.1% TAC.	As raised in the CMA, this may not be reasonable as the equi-effective dose of 1 g: 1g does not consider that 1% PIM is only used for flares whereas 0.1% TAC can be used for maintenance therapy.
Costs		
0.1% TAC script	$[redacted]. DPMQ based on a proposed AEMP of $[redacted] with Section 85 dispensing fees.	-
1% PIM script	$34.03. DPMQ of PBS item 8802G.	-
DUPI	$1,756. DPMQ of PBS items 12291X and 12292Y	
UPA	$1,273. DPMQ of PBS items 12828E and 12831H	

Source: Constructed during the evaluation from the "Attachment 3 - Azematop BIM" excel spreadsheet provided with the submission.
ABS = Australian Bureau of Statistics; AD = atopic dermatitis; AEMP = approved ex-manufacturer price; CMA = cost-minimisation approach; CUA = cost-utility analysis; DPMQ = dispensed price for maximum quantity; DUPI = dupilumab; DUSC = Drug Utilisation Sub Committee; PBS = Pharmaceutical Benefits Scheme; PIM = pimecrolimus; RPBS = Repatriation Pharmaceutical Benefits Scheme; TAC = tacrolimus; TCS = topical corticosteroids; UPA = upadacitinib.

6.85 The derivation of the number of 0.1% TAC scripts using the epidemiology and market share approach has been described in Table 16. The application of both these approaches assumes that patients with severe AD on their face would not currently be using 1% PIM (i.e. that the current market for 1% PIM is in mild-moderate AD only). There were some uncertainties noted during the evaluation regarding the epidemiological inputs (see Table 16).

[37] Barta K, Fonacier LS, Hart M, Lio P, Tullos K, Sheary B, Winders TA. Corticosteroid exposure and cumulative effects in patients with eczema: Results from a patient survey. Annals of Allergy, Asthma & Immunology. 2023;130(1):93-9.e10.

6.86 The estimated number of 0.1% TAC scripts and the net costs to the PBS per year are presented in Table 17.

Table 17: Estimated use and financial implications

Description	2025	2026	2027	2028	2029	2030
Epidemiology approach population (patients with moderate – severe AD on body or severe AD on face or eyelids)						
Epidemiological approach eligible population	[redacted]1	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Uptake rate (assumption)	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Prevalent patients who uptake	[redacted]3	[redacted]4	[redacted]5	[redacted]6	[redacted]6	[redacted]1
Treatment naïve patients[a]	[redacted]3	[redacted]7	[redacted]7	[redacted]7	[redacted]8	[redacted]8
Patients continuing treatment from previous years (65%[b])	0	[redacted]9	[redacted]10	[redacted]10	[redacted]10	[redacted]7
Patients on treatment per year	[redacted]3	[redacted]11	[redacted]11	[redacted]9	[redacted]10	[redacted]7
Scripts per year (20 per patient)	[redacted]12	[redacted]13	[redacted]14	[redacted]15	[redacted]16	[redacted]17
Market share approach population (moderate AD on their face or eyelids)						
Moderate AD scripts	[redacted]10	[redacted]10	[redacted]9	[redacted]9	[redacted]11	[redacted]11
Tacrolimus uptake rate	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Pimecrolimus scripts replaced	[redacted]7	[redacted]7	[redacted]10	[redacted]10	[redacted]10	[redacted]9
Tacrolimus scripts (2:1 script replacement rate)	[redacted]	[redacted]	[redacted]7	[redacted]7	[redacted]7	[redacted]7
Cost of tacrolimus to the PBS/RPBS						
Total tacrolimus scripts, revised[c]	[redacted]12	[redacted]13	[redacted]14	[redacted]15	[redacted]16	[redacted]17
Costs to the PBS/RPBS, revised[c,d]	$[redacted]18	$[redacted]19	$[redacted]19	$[redacted]20	$[redacted]20	$[redacted]22
Cost savings due to reduction of use of other medicines						
Cost savings due to substitution of pimecrolimus[e]	-$[redacted]23	-$[redacted]23	-$[redacted]23	-$[redacted]23	-$[redacted]23	-$[redacted]23
Cost savings due to avoided dupilumab use[f]	-$[redacted]24	-$[redacted]25	-$[redacted]18	-$[redacted]18	-$[redacted]20	-$[redacted]21
Cost savings due to avoided upadacitinib use[g]	-$[redacted]22	-$[redacted]23	-$[redacted]23	-$[redacted]23	-$[redacted]23	-$[redacted]23
Total cost savings	-$[redacted]26	-$[redacted]24	-$[redacted]25	-$[redacted]18	-$[redacted]19	-$[redacted]21
Net financial impact, revised[c]	-$[redacted]20	-$[redacted]21	-$[redacted]21	-$[redacted]21	-$[redacted]27	-$[redacted]27

Source: Constructed during the evaluation from the "Attachment 3 - Azematop BIM" excel spreadsheet provided with the submission.
AD = atopic dermatitis; CMA = cost-minimisation approach; DPMQ = dispensed price for maximum quantity; PBS = Pharmaceutical Benefits Scheme; PI = Product Information; RPBS = Repatriation Pharmaceutical Benefits Scheme.

[a] Patients who uptake 0.1% TAC in current year minus those who uptake in previous years.

[b] 65% applied to patients who have up taken treatment in previous years.

[c] The submission had erroneously double counted the number of market share scripts. This was corrected during the evaluation.

[d] Assuming each script of 0.1 TAC costs $[redacted] minus a weighted patient copayment of $26.09 per script (based on 2024 pimecrolimus PBS utilisation data by beneficiary type).

[e] Each 1% PIM script replaced by 0.1% TAC was assumed to cost $34.03 minus the patient copayment of $26.09 per script.

[f] The submission assumed that 6% (65% × 9%) of 0.1% TAC patients on treatment from the epidemiological approach population would not need to progress to dupilumab treatment). Each dupilumab script was based on the published DPMQ of $1,755.66 (PBS items 12291X and 12292Y) minus the patient copayment ($26.09 per script). Each patient was assumed to have 13.50 scripts per year, based on the fortnightly dosing frequency outlined in the PI.

[g] The submission assumed that 1% (65% × 2%) of 0.1% TAC patients on treatment from the epidemiological approach population would not need to progress to upadacitinib treatment. Each upadacitinib script was based on the published DPMQ of $1,149.97 (PBS items 12828E and 12831H) minus the patient copayment ($26.09 per script). Each patient was assumed to have 13.04 scripts per year, based daily administration of one tablet (as pe the PI) and each script contains 28 tablets.

The redacted values correspond to the following ranges:

[1] 90,000 to < 100,000

[2] *100,000 to < 200,000*
[3] *50,000 to < 60,000*
[4] *60,000 to < 70,000*
[5] *70,000 to < 80,000*
[6] *80,000 to < 90,000*
[7] *10,000 to < 20,000*
[8] *500 to < 5,000*
[9] *30,000 to < 40,000*
[10] *20,000 to < 30,000*
[11] *40,000 to < 50,000*
[12] *1,000,000 to < 2,000,000*
[13] *900,000 to < 1,000,000*
[14] *800,000 to < 900,000*
[15] *700,000 to < 800,000*
[16] *500,000 to < 600,000*
[17] *300,000 to < 400,000*
[18] *$50 million to < $60 million*
[19] *$40 million to < $50 million*
[20] *$30 million to < $40 million*
[21] *$20 million to < $30 million*
[22] *$10 million to < $20 million*
[23] *$0 to < $10 million*
[24] *$70 million to < $80 million*
[25] *$60 million to < $70 million*
[26] *$80 million to < $90 million*
[27] *$10 million to < $20 million*

6.87 The total cost to the PBS/RPBS of listing 0.1% TAC was estimated to be $10 million to < $20 million in Year 6, and total of $200 million to < $300 million over the first six years of listing. The net cost was estimated to be a saving of $100 million to < $200 million over the first six years of listing.

6.88 In the epidemiological approach, the submission has assumed all patients would complete a full year of 0.1% TAC treatment, followed by a 65% annual continuation rate for patients in Year 2+ of based on the *post-hoc* analysis which reported that 35% of patients had discontinued after 12 months.[26] The assumption of treatment beyond one year was not supported by the key trial evidence, nor by the economic analysis, as both were limited to 12 months of maintenance therapy. Patients who initiate treatment in the first year of listing are assumed to remain on treatment for an average of 2.64 years. Given that 0.1% TAC is indicated for intermittent use for the shortest duration necessary, the submission likely overestimated the use and cost.

6.89 In the market share approach, the submission assumed a script replacement rate of 1% PIM to 0.1% TAC of 2:1. This was consistent with the equi-effective dose applied in the CMA.

6.90 The ESC noted that the cost savings to the PBS/RPBS were driven by the assumption that, of patients derived from the epidemiological approach who were satisfied with 0.1% TAC treatment (65%),[36] 9% and 2%% of patients would avoid dupilumab or upadacitinib, respectively. The following uncertainties were noted during the evaluation:

- The number of patients assumed to have avoided dupilumab or upadacitinib treatment was uncertain as no data were presented to support this reduction. Additionally, 0.1% TAC treatment may delay, rather than replace, subsequent treatment. The PSCR stated that even if 0.1% TAC delays, rather than replaces, subsequent systemic therapy, it would still deliver substantial PBS savings due to the significantly lower annual cost of 0.1% TAC. The PBAC considered that satisfaction with 0.1% TAC does not directly translate to avoiding the use of systemic therapies.
- Use of dupilumab and upadacitinib was based on a survey of eczema patients with unspecified disease severity.[37] This source has uncertain applicability to patients in the proposed setting who are eligible for dupilumab or upadacitinib (i.e. chronic severe AD).
- The cost savings also assume patients receive continuous dupilumab or upadacitinib treatment. This may not be reasonable given that patients must meet treatment response continuing criteria to continue using dupilumab or upadacitinib. PSDs suggest that 40% and 30% of patients did not respond to initial treatment for dupilumab and upadacitinib, respectively (Table 19, dupilumab PSD, March 2020 PBAC Meeting and Table 16, upadacitinib PSD, July 2021 PBAC Meeting). The PSCR stated that PBS data for dupilumab show high persistence, supporting a full-year cost assumption.

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

7 PBAC Outcome

7.1 The PBAC recommended 0.1% tacrolimus (TAC) ointment be listed on the PBS as a General Schedule Authority Required (Streamlined) listing for the treatment of moderate to severe atopic dermatitis (AD) affecting the body, face and eyelids. The PBAC noted that the submission nominated two comparators, 1% pimecrolimus (PIM) cream for the treatment of moderately severe flares on the face and eyelids and vehicle ointment (VO) for flare and maintenance treatment of moderate to severe AD on the body and severe AD on the face and eyelids. The PBAC considered that 0.1% TAC was likely non-inferior in terms of efficacy and safety compared to 1% PIM and accepted the cost minimisation approach presented for this comparison. The PBAC did not consider VO to be an appropriate comparator. The PBAC considered standard medical management, which would include topical corticosteroid (TCS) treatments, to be a more appropriate comparator, noting that broad use of 0.1% TAC is expected and, in a substantial proportion of patients, it is likely that 0.1% TAC would be used as an alternative to moderate to high potency TCS. Noting the issues with the comparative data presented in the submission the PBAC accepted, based on the results of meta-analyses, that 0.1% TAC was likely non-inferior to standard medical management, including TCS. The PBAC therefore considered that for this comparison,

a cost minimisation approach versus TCS would be appropriate.

7.2 The PBAC noted the consumer inputs which highlighted the issues with the currently available TAC compounded products, including drug stability issues, secondary bacterial infections, the significant cost and accessibility issues. The PBAC noted that comments highlighted the need for treatment options for patients who are unable to use TCS therapies. The PBAC also considered that there was a clinical place for 0.1% TAC as an alternative to pimecrolimus for treatment of sensitive and thin skin areas such as the face and eyelids.

7.3 The PBAC noted that the requested listing was as a second line treatment of flares and as a maintenance treatment in patients who have 'failed to achieve satisfactory disease control with intermittent (moderate or potent) TCS therapy' or as a first line treatment for patients who were 'considered unsuitable/contraindicated to TCS therapy'. Noting that contraindications and adverse events to TCS are rare and, in a population suitable for topical treatments, TCS are effective when appropriate dosage and durations are used, the PBAC considered that the proposed restriction defined a relatively small proportion of patients (see paragraph 4.7). However, the PBAC considered that AD patients frequently do not receive an adequate level of standard care, including adequate use of TCS, and hence, there is a substantial risk of use of 0.1% TAC in a broad patient population. The PBAC considered the risk of broad use to be further increased because the proposed restrictions did not include definitions of satisfactory disease control or unsuitability/contraindications to TCS. However, the PBAC considered that even if these definitions were included in the restrictions, there would be a significant risk of initiation outside of the intended use due to inappropriate TCS trial(s) and/or inappropriate patient or clinician perception of unsuitability/contraindications associated with TCS. In this context, the PBAC considered including definitions of satisfactory disease control, unsuitability or contraindications to TCS in the restrictions would not be of value.

7.4 The PBAC noted that the submission nominated two comparators 1% PIM ointment for use in moderate AD on the face and eyelids only, and VO for the remaining population (moderate-severe AD on the body and severe AD on the face and eyelids). The PBAC accepted that 1% PIM was a reasonable comparator for use on the face and eyelids. However, the PBAC considered standard management, which would include TCS, to be the appropriate main comparator for the remaining population, noting that broad use of 0.1% TAC is expected and, in a substantial proportion of patients, it is likely that 0.1% TAC would be used as an alternative to moderate to high potency TCS (see paragraph 7.3).

7.5 The PBAC noted that the clinical evidence provided in the submission was based on published data of old clinical trials (i.e. published more than 10 years ago) and relied on *post hoc* subgroup analyses. There were also concerns regarding heterogeneity and bias between and across the trials and studies (see paragraph 7.8). Further, the PBAC noted that the trials and studies presented a variety of subjective outcomes, rather

than the more commonly used Eczema Area and Severity Index (EASI).

7.6 For the treatment of AD flares on the face and eyelids, the PBAC noted that the submission presented a *post hoc* subgroup analysis of the Paller 2005 randomised trial that compared 0.1% TAC with 1% PIM. The PBAC noted that the trial population did not align with the proposed PBS population, as patients had moderate (as opposed to moderate to severe) AD, anywhere on the body, including the head and neck region, rather than specific use on the face and eyelids. Further, the PBAC noted that the population in the trial did not have unsatisfactory response, intolerance or contraindication to TCS use. The PBAC noted that for treatment of the head and neck region, patients treated with 0.1% TAC has a greater percentage improvement in the signs and symptoms of AD compared to the 1% PIM population after 6 weeks (75.2% versus 54.1%, p value = 0.04). The PBAC noted that there were no significant differences in safety between 0.1% TAC and 1% PIM.

7.7 Noting the applicability issues associated with the comparison between 0.1% TAC and 1% PIM and the proposed PBS population, the PBAC considered that on balance, the treatments were likely non-inferior in terms of efficacy and safety for the treatment of AD on the face and eyelids.

7.8 For the comparisons with VO, the PBAC noted that data were presented for the treatment of flares and as maintenance therapy. The PBAC noted that the clinical evidence presented in the submission included a broad AD population which was not restricted to patients who had failed to achieve satisfactory disease control with TCS or who were intolerant or contraindicated to TCS. The PBAC further noted that the VO comparator arms did not represent standard of care, as many treatments, including TCS, were prohibited during the trials. The PBAC noted that the data were potentially confounded by heterogeneity across the studies as there were differences in study population demographics, disease characteristics, measures used to assess treatment response, clinical outcomes presented and the period of follow-up.

7.9 Therefore, although 0.1% TAC appeared to be superior in the treatment of AD flares and as maintenance therapy compared to VO, the PBAC considered that the effectiveness of 0.1% TAC over standard management was uncertain based on the comparative evidence provided in the submission.

7.10 The PBAC noted the results of recent, large meta-analyses presented by the submission as supporting evidence. The PBAC noted that a Cochrane meta-analysis of topical anti-inflammatory treatments for eczema, Lax et al (2024), reported that 0.1% TAC exhibited similar efficacy to potent TCS and concluded that potent TCS, JAK inhibitors and 0.1% TAC were consistently ranked the most effective topical agents (see paragraphs 6.38 and 6.39). The PBAC noted that the results from Chu, 2023[38],

[38] Chu DK, Chu AWL, Rayner AD, et al. Topical treatments for atopic dermatitis (eczema): Systematic review and network meta-analysis of randomised trials. *J Allergy Clin Immunol*. 2023;152(6):1494-1519.

which also reviewed topical treatments for AD, concluded that PIM, TAC and moderate-potency TCS are among the most effective in improving and maintaining multiple AD outcomes.

7.11 The PBAC considered that the meta-analyses provided some reassurance that 0.1% TAC was likely non-inferior in terms of efficacy compared to standard medical management, which included TCS.

7.12 The PBAC accepted that 0.1% TAC was non-inferior in terms of safety compared to both TCS and 1% PIM.

7.13 The PBAC noted that the submission presented two economic analyses, a cost utility analysis comparing 0.1% TAC with VO for the treatment of flares and as maintenance therapy and a cost minimisation approach versus 1% PIM for the treatment of flares on the face and eyelids.

7.14 The PBAC considered the cost utility analysis between 0.1% TAC and VO was not informative because VO, in the clinical trials informing the model, did not reflect standard management and the outcome relied on avoidance of subsequent oral treatments and phototherapy. The PBAC noted that there was no evidence presented in the submission to support that systemic treatments would be avoided with the use of 0.1% TAC. The PBAC considered that topical and systemic treatments are likely to be used in different patient subsets, defined by a range of factors including extent of disease. Therefore, the PBAC considered the impact, if any, of 0.1% TAC on systemic therapies would be to primarily delay, rather than avoid, systemic treatments.

7.15 In the context of the expected use in a broad patient population, the PBAC considered that 0.1% TAC would be cost-effective if it was cost minimised versus the least costly PBS listed high potency TCS. The PBAC considered that the equi-effective doses could be determined by assuming a gram-for-gram equivalence.

7.16 The PBAC considered that for the proportion of use on the face and eyelids where 0.1% TAC would replace PIM, it would be appropriate for 0.1% TAC to be cost minimised versus PIM. The PBAC noted the equi-effective doses for 0.1% TAC and PIM were uncertain (see paragraph 6.77); however, in the context of this use being relatively small, accepted that the equi-effective doses were:

1 g of 0.1% TAC = 1 g of 1% PIM

7.17 The PBAC noted to calculate a weighted price for 0.1% TAC across the two cost minimisation approaches, that the estimated use for each of the populations informing the financial estimates could be used.

7.18 The PBAC noted that although the estimated cost of listing 0.1% TAC on the PBS at the proposed price was high, at approximately $200 million to < $300 million over the first 6 years, a saving to the PBS was estimated overall due to the assumption that 0.1% TAC would avoid the need for subsequent systemic therapies. The PBAC noted the

avoidance of subsequent systemic therapies was based on the assumption that satisfaction with 0.1% TAC directly translates to reduced use of subsequent systemic therapies. As noted in paragraph 6.90, the PBAC considered the impact, if any, of 0.1% TAC on systemic therapies would be to primarily delay, rather than reduce their use. The PBAC therefore considered offsets for systemic therapies should be removed from the financial estimates.

7.19 The PBAC considered the estimated use of 0.1% TAC to be overestimated due to the assumed high continuation rates (100% in Year 1 and 65% subsequently), noting that 0.1% TAC is indicated for intermittent use for the shortest duration necessary. However, countering this is the potential for broad interpretation of the restriction criteria 'satisfactory disease control' and 'unsuitable/contraindicated' in relation to prior TCS use, especially given high patient and clinician perception of risks associated with TCS. The PBAC noted the financial estimates would need to be revised to account for the cost minimisation recommendations in paragraphs 7.15 and 7.16 and the weighted price, as outlined in paragraph 7.17.

7.20 The PBAC recommended that the proposed initial and continuing restrictions for the use of 0.1% TAC should be simplified, advising that:

- the initial and continuing treatment restrictions could be combined into a single phase restriction;
- the restriction should be Authority Required (STREAMLINED); and
- the restriction should align with the TGA indication and allow use in patients aged 16 years or above.

7.21 The PBAC advised that continuing supply of tacrolimus is suitable for prescribing by nurse practitioners.

7.22 The PBAC advised that tacrolimus should not be exempt from the Early Supply Rule.

7.23 The PBAC advised that under section 101(3BA) of the *National Health Act 1953*, tacrolimus should not be treated as interchangeable on an individual patient basis with any other drug.

7.24 The PBAC noted that its recommendations were on a cost-minimisation basis and advised that, because 0.1% is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over 1% PIM or the currently listed TCS therapies, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.25 The PBAC noted that this submission was not eligible for an Independent Review, as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
TACROLIMUS						
Tacrolimus 0.1% ointment, 30 g		NEW	1	1	1	AZematop
Concept ID	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)					
	Prescriber type: ☒ Medical Practitioners ☒ Nurse Practitioners					
	Benefit type: ☒ Authority Required (STREAMLINED) [new code]					
	Administrative advice: No increase in the maximum quantity or number of units may be authorised.					
	Administrative advice: No increase in the maximum number of repeats may be authorised.					
	Restriction Summary [new1] / Treatment of Concept: [new1A]					
	Indication: Moderate to severe atopic dermatitis					
	Clinical criteria:					
	Patient must be initiating treatment with this drug, or Patient must be continuing treatment with this drug if they have demonstrated an adequate response to at least 6 weeks of treatment, applied at the recommended dosing regimen as per the approved Therapeutic Goods Administration (TGA) Product Information (PI).					
	Population criteria:					
	Patient must be at least 16 years of age.					
	Prescribing instructions: Treatment should be discontinued, and further treatment options should be considered if one of the following situations occurred: a) no signs of improvement are seen after two weeks of treatment. b) improvement is not maintained after a 3-month period of treatment (i.e. Atopic Dermatitis (AD) is not clear or almost clear). Once clearance or near clearance of AD is achieved, patients should take a break in tacrolimus treatment and reinitiate only if there is a flare of their AD.					
	Prescribing instructions: Prescribers must review the patient's condition after 12 months of treatment and regularly thereafter, to determine whether maintenance treatment should/should not be continued.					

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

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers

applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.