

**5.06 CLOBETASOL PROPIONATE,
Cream containing clobetasol propionate
500 micrograms per g, 30 g,
Ointment containing clobetasol propionate
500 micrograms per g, 30 g,
Xobet[®],
Arrotex Pharmaceuticals Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested a Restricted Benefit listing for clobetasol propionate 0.05% cream and ointment for the treatment of severe or resistant corticosteroid-responsive dermatoses in adults.
- 1.2 Listing was requested on the basis of a cost-minimisation approach versus betamethasone dipropionate 0.05% cream and ointment.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Corticosteroid-responsive dermatoses.
Intervention	Clobetasol propionate 0.05% 30g cream and ointment
Comparator	Betamethasone dipropionate 0.05% cream and ointment
Outcomes	Disease severity (signs and symptoms), physician and patient rating of overall clinical response.
Clinical claim	In patients with corticosteroid-responsive dermatoses, clobetasol propionate is non-inferior in terms of efficacy and non-inferior in terms of safety when compared to betamethasone dipropionate.

Source: Table 2, p5 of the submission.

2 Background

Registration status

- 2.1 Clobetasol propionate ointment and cream 0.05% were TGA registered on 20 December 2023 for short term treatment of resistant or severe inflammatory and pruritic manifestations of steroid responsive dermatoses, including psoriasis (excluding widespread plaque psoriasis), recalcitrant dermatoses, lichen sclerosis/planus and discoid lupus erythematosus in adults.
- 2.2 The submission included the Delegate’s Overview and ACM Minutes. The Delegate raised questions about the quality of the evidence in the TGA dossier and the overall risk: benefit balance of the product. The ACM considered the product to have an overall positive risk benefit profile but noted that use should be for less than 2 weeks especially given that high doses (7 gm/day) had been shown to be associated with

hypothalamic-pituitary axis (HPA) suppression. The Product Information (PI) document states that the maximum weekly dose should not exceed 14 gm/week.

Previous PBAC consideration

- 2.3 The PBAC has not previously considered clobetasol propionate ointment or cream. In November 2013 the PBAC considered and recommended listing of clobetasol propionate shampoo (500 mcg/mL) for the treatment of scalp psoriasis not adequately controlled with a vitamin D analogue *or* high potency topical corticosteroid (TCS).
- 2.4 The submission for clobetasol propionate shampoo for scalp psoriasis nominated and PBAC accepted as the comparator betamethasone dipropionate + calcipotriol (a vitamin D analogue). PBAC accepted the claim that clobetasol propionate was non-inferior to betamethasone dipropionate + calcipotriol based on an indirect treatment comparison using data from two randomised trials of clobetasol propionate vs calcipotriol (total N = 181) and three randomised trials of betamethasone dipropionate + calcipotriol vs calcipotriol (total N = 1979).
- 2.5 The PBAC had expressed concern that because clobetasol propionate shampoo was the first very-high potency TCS there was potential for use beyond the proposed restriction.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CLOBETASOL PROPIONATE					
Clobetasol propionate, 0.05% cream, 30g	\$20.84	1	1	1	Xobet
Clobetasol propionate, 0.05% ointment, 30g	\$20.84	1	1	1	Xobet

Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Restricted benefit
Indication: Corticosteroid-responsive dermatoses
Treatment Phase: [blank]
Clinical criteria: [blank]
Treatment criteria:
Must be treated by a medical practitioner; OR
Must be treated by a nurse practitioner
Population criteria:
Patient must be 18 years or older
Prescribing Instructions: 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 1.11. p 35 of the submission.

- 3.1 The submission proposed that continuing treatment should be permitted. This is not consistent with the PI, which states that a maximum of 2 weeks continuous treatment is recommended and that if ongoing treatment is required a less potent TCS should be used. The Pre-Sub-Committee Response (PSCR) stated that the sponsor was amenable to the restriction to a two-week treatment period (1 x 30 g tube) by removing the repeat. The PSCR also acknowledged it may therefore be appropriate to remove the provision for nurse practitioner prescribing, which was requested for continuing therapy. The ESC considered a maximum quantity of one and nil repeats was reasonable and suggested also adding an administrative advice or caution to the listing to the effect of 'Treatment should be limited to a maximum of 15 g per week'. The ESC considered these restriction and listing changes appropriate for managing potential adverse events. The ESC agreed with removing nurse practitioner prescribing.
- 3.2 The proposed treatment algorithm implied, consistent with the PI, that it is appropriate to start treatment with a lower potency corticosteroid, including betamethasone dipropionate, and use clobetasol propionate only in patients unresponsive to first-line treatment. The proposed restriction does not require treatment with a less potent TCS to have been ineffective, although the submission states, in line with the PI, that "[c]lobetasol propionate should only be used once treatment resistance to less potent corticosteroids has been confirmed". The PSCR proposed an additional clinical criterion specifying a patient must have previously failed treatment on a lower potency TCS be added to the restriction. The ESC supported this addition to the restriction.
- 3.3 Betamethasone dipropionate, betamethasone valerate and mometasone furoate have multiple listings with varying maximum quantities based on the area of skin affected. For clobetasol propionate "[the] submission does not propose PBS listings using the [body surface area] criteria since clobetasol dipropionate [sic] is a very potent TCS and is not recommended for wide-spread use". This has important implications for the estimates of the extent of replacement by PBS-listed clobetasol propionate of large volume preparations of betamethasone dipropionate and compounded clobetasol propionate, which are, presumably, used by patients requiring treatment of large areas of skin.
- 3.4 The proposed treatment algorithm excluded use in widespread plaque psoriasis, consistent with the approved indication. The submission stated that clobetasol propionate was not intended for use in any condition affecting large areas of skin to limit adverse effects from systemic absorption, and for that reason PBS listings allowing increased maximum quantities for patients with widespread dermatoses would not be requested.
- 3.5 In general, very-high potency TCS should be discontinued once the condition is controlled. Some conditions, such as atopic dermatitis, typically have a relapsing course and may require either repeated short courses or maintenance treatment at a

reduced frequency of application - e.g., twice weekly.¹ The algorithm does not address either use. The evaluation suggested adding to the proposed restriction a limit on the frequency of 2-week courses of clobetasol propionate.

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

4 Population and disease

- 4.1 The term “corticosteroid-responsive dermatoses” covers a very large number of conditions of heterogeneous aetiology and pathogenesis. For many of these conditions the only evidence of corticosteroid responsiveness is expert opinion, and there is no complete or authoritative list of corticosteroid-responsive dermatoses.
- 4.2 Clobetasol propionate is a topical corticosteroid (TCS), a glucocorticoid which is effective when applied to the skin. Glucocorticoids have complex anti-inflammatory effects, but their mechanism of action in skin diseases is poorly understood and may not be the same in all conditions for which they are used.
- 4.3 TCS are classified in potency groups according to their ability to cause vasoconstriction in the skin, and clobetasol propionate is in the highest potency group (referred to as very-high potency or super-potent TCS).² Potency is related to bioavailability; pharmacodynamic differences among TCS are possible but have not been identified. For most TCS, potency does not increase when the concentration of active ingredient is increased in the same vehicle.³
- 4.4 There is consensus that some conditions respond well to lower potency TCS, while others respond less well and should be treated with medium potency TCS, while others again require high or very-high potency TCS, but there is no consensus on which conditions require high-potency TCS.
- 4.5 TCS can cause adverse effects on the skin to which they are applied. This is most likely when high or very-high potency TCS are inappropriately used on thin skin, such as on the face, groin or axillae.
- 4.6 Systemic absorption of TCS can cause typical glucocorticoid systemic adverse effects, and this risk is greater with more potent TCS with higher bioavailability, with application to larger areas of skin or for longer periods, and in children, who absorb more of the dose applied to the skin. Use of TCS is associated with an increased risk of

¹ Schmitt J, von Kobyletzki L, Svensson A, Apfelbacher C. Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials. *Br J Dermatol* 2011; 164:415-428.

² Clobetasol butyrate is a moderate strength TCS (Class 2 in Australia) and listed on Schedule 3.

³ <https://www.uptodate.com/contents/topical-corticosteroids-use-and-adverse-effects>, accessed 5 August, 2024.

type 2 diabetes mellitus.⁴ Hypothalamic-pituitary axis (HPA) suppression is common after use of TCS,⁵ and has been observed with clobetasol propionate after one week of use at recommended doses. The risk of HPA suppression is the reason the PI gives for allowing only small areas of skin to be treated with clobetasol propionate.⁶ Long-term use of more than the recommended dose of clobetasol propionate has been reported to cause adverse events associated with large doses of systemic corticosteroids, including osteonecrosis and systemic immunosuppression.⁷

- 4.7 Use of high-potency (but not low or moderate potency) TCS during pregnancy is probably associated with low infant birth weight, especially when the cumulative dose is relatively large (> 300 g).⁸
- 4.8 The rationale for the proposed PBS listing of clobetasol was primarily stated to be for equity of access for patients who currently pay out of pocket for private scripts. Its proposed place in therapy was unclear.
- 4.9 One reason for this was that the submission made a claim of non-inferiority vs betamethasone dipropionate, but the rationale for listing and the treatment algorithm presented implied a claim of superiority. The submission stated that a significant reason for proposing listing of clobetasol propionate was that access to clobetasol for patients not responding to PBS-listed betamethasone dipropionate requires large out-of-pocket payments for compounded clobetasol propionate, which is inequitable for lower-income patients and those with limited access to compounding pharmacies. However, unavailability of clobetasol propionate as a PBS benefit is not inequitable if clobetasol propionate is non-inferior to betamethasone dipropionate.
- 4.10 The proposed treatment algorithm is inconsistent at several points with the proposed restriction and with the text of the submission.
- 4.11 The algorithm did not suggest that clobetasol may be used as first-line treatment in severe cases, although the text of the submission did, on the ground that a “severe manifestation of a skin condition may be most appropriately treated with a higher potency TCS, regardless the specific conditions general responsiveness to TCS”. “Severity” was not defined and might refer to a condition affecting a large area of skin,

⁴ Phan K, Smith SD. Topical corticosteroids and risk of diabetes mellitus: systematic review and meta-analysis. *J Dermatolog Treat* 2021; 32:345-349.

⁵ HPA suppression as an effect of TCS use is described as “extremely rare” by Aung and Aung (*AJGP* 2021; 50:651-655), but a systematic review and meta-analysis found HPA suppression in 4.8% (95% CI = 1.1, 18.5) of patients using topical steroids in 15 studies. Broersen LHA, Pereira AM, Jorgensen JOL, Dekkers OM. Adrenal insufficiency in corticosteroids use: Systematic review and meta-analysis. *J Clin Endocrinol Metab* 2015; 100:2171-2180.

⁶ Xobet PI, 4.4, p3.

⁷ Xobet PI, 4.4, p3.

⁸ Chi CC, Wang SH, Wojnarowska F, Kirtschig G, Davies E, Bennett C. Safety of topical corticosteroids in pregnancy. *Cochrane Database Syst Rev* 2015:CD007346. The pooled relative risk (95% CI) for low birth weight in 4 cohort studies (N = 47,651) of women using high to very-high potency TCS was 1.58 (0.96, 2.58) and in 3 studies (N = 55,713) of women using mild to moderate potency TCS was 0.90 (0.74, 1.09).

for which clobetasol propionate would not be appropriate. It is not clear whether the claim that severe cases of conditions ordinarily sensitive to low or medium potency TCS require a high-potency TCS is a claim about bioavailability or pharmacodynamic effect, and in either case no evidence to support it was presented.

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

5 Comparator

- 5.1 The submission nominated betamethasone dipropionate 0.05% and betamethasone dipropionate OV 0.05% as the most appropriate comparators, with mometasone furoate 0.1% as a secondary comparator. Four high-potency TCS were PBS-listed (betamethasone dipropionate, mometasone furoate 0.1%, betamethasone valerate 0.02-0.05%, and methylprednisolone aceponate 0.1%). Of these, betamethasone dipropionate was the most widely used, and is to that extent a reasonable choice as comparator.
- 5.2 The “optimised vehicle” (OV) preparation referred to by the submission is betamethasone dipropionate dissolved in ethylene glycol or propylene glycol, which increases absorption of the betamethasone to create a very-high potency preparation. This preparation was not available on the PBS and was much more expensive than the standard preparation of betamethasone dipropionate.
- 5.3 For most of the common conditions for which clobetasol propionate might be used, changing from a high-potency to a very-high potency TCS was not the only treatment option, and a number of other treatments could be comparators for clobetasol in specific conditions. The algorithms presented by the submission acknowledge this in the case of psoriasis, where the combination of TCS and calcipotriol was included, but not in other cases, such as atopic dermatitis. In most of these cases, such as betamethasone + calcipotriol for psoriasis and topical calcineurin inhibitors for atopic dermatitis, the alternative therapies were significantly more expensive than betamethasone dipropionate.
- 5.4 For a population consistent with the approved PI for clobetasol propionate, the following PBS-listed medicines may also be considered alternative therapies because they could be replaced in practice: mometasone furoate; betamethasone valerate; methylprednisolone aceponate. However, for a population consistent with the proposed restriction, any low or medium potency TCS could also be an alternative therapy.
- 5.5 If the response to a high-potency TCS is inadequate, increased penetration and effect can be achieved by occlusion. This is particularly convenient for some areas where the submission suggests that a very-high potency TCS has a role, such as the soles of the

feet. Occlusion can be achieved with readily available, cheap materials,⁹ and could also be considered as an alternative therapy in combination with TCS.

- 5.6 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.
- 5.7 The PSCR argued that there was currently no Class IV/very potent TCS available on the PBS, and patients requiring stronger treatment for resistant dermatoses were privately paying for treatments or escalating to therapies that are more costly than TCS on the PBS, including systemic treatments and biologics. The ESC considered other treatments, including other high potency TCS, topical calcineurin inhibitors and combination TCS + calcipotriol/vitamin D analogues could be considered comparators, however noted these other treatments were either of similar cost or more expensive than betamethasone dipropionate (if a gram-for-gram equivalence is assumed). Thus, the proposed cost-minimisation approach to betamethasone dipropionate was conservative.

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 the Australasian College of Dermatologists which supported the listing, and stated the listing of clobetasol cream and ointment would provide specialist dermatologists with an additional option when treating complex and/or chronic cases of dermatoses.

Clinical studies and trials

- 6.3 The submission was based on the results of a literature search for studies comparing clobetasol propionate with betamethasone dipropionate (including betamethasone dipropionate in ethylene glycol = optimised vehicle = OV) or comparing clobetasol propionate with mometasone furoate.
- 6.4 Details of the trials presented in the submission are provided in Table 2. Although the search strategy was adequate, the direct comparative trials identified were of poor

⁹ Xobet PI, 4.2, p2.

quality (see para 6.7 below) with a high risk of bias. The submission did not include the latest published systematic review.

- 6.5 The key features of the included trials are shown in Table 3. The submission described the details of the trials and noted that ‘due to the historical nature of these studies, there is minimal detail provided for some key study factors.’
- 6.6 There is an updated version of the Mason systematic review of treatments for psoriasis.¹⁰ The updated version includes results from a number of trials of clobetasol propionate vs placebo and of betamethasone dipropionate and valerate vs placebo which were not included in the version of the review discussed in the submission. The evaluation presented data from the updated version.

¹⁰ Mason AR, Mason J, Cork M, Dooley G, Hancock H. Topical treatments for chronic plaque psoriasis. Cochrane Database of Systematic Reviews 2013, Issue 3. Art. No.: CD005028.

Table 2: Trials and reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Voigtlander, 1977	Voigtlander V. A clinical comparison of betamethasone 17,21-dipropionate and clobetasol propionate creams in dermatology.	<i>J Int Med Res</i> 1977; 5:128-131.
Yawalkar, 1991	Yawalkar SJ, Schwerzmann L. Double-blind, comparative clinical trials with halobetasol propionate cream in patients with atopic dermatitis.	<i>J Am Acad Dermatol</i> 1991; 25:1163-6.
Katz, 1987	Katz HI, Hien NT, Prawer SE, Mastbaum LI, Mooney JJ, Samson CR. Superpotent topical steroid treatment of psoriasis vulgaris: Clinical efficacy and adrenal function.	<i>J Am Acad Dermatol</i> 1987; 16:804-11.
Jacobson, 1986	Jacobson C, Cornell RC, Savin RC. A comparison of clobetasol propionate 0.05 percent ointment and an optimized betamethasone dipropionate 0.05 percent ointment in the treatment of psoriasis.	<i>Therapeutics for the Clinician Cutis</i> 1986; 37:213-20.
Mauracher, 1983	Mauracher E, Blum G, Kropfli P, Kung D, Suter H. Betamethasone dipropionate glycol ointment versus clobetasol propionate ointment: A multicentre trial in patients with resistant psoriasis and atopic dermatitis.	<i>Acta Therapeutica</i> 1983; 9:197-207.
Gip, 1984	Gip L, Hamfelt A. Studies on the efficacy and adrenal effects of Diprolene® ointment 0.05 percent and Dermovate® ointment 0.05 percent in patients with psoriasis or other resistant dermatoses.	<i>Therapeutics for the Clinician Cutis</i> 1984; 33:215-23.
Verdich, 1985	Verdich J, Karlsmark T. Betamethasone dipropionate cream for the treatment of psoriasis: A double-blind comparison with clobetasol propionate cream.	<i>Dermatologica</i> 1985; 170:152-5.
Goh, 1999	Goh CL, Lim JT, Leow YH, Ang CB, Kohar YM. The therapeutic efficacy of mometasone furoate cream 0.1% applied once daily vs clobetasol propionate cream 0.05% applied twice daily in chronic eczema.	<i>Singapore Med J</i> 1999; 40:341-4.
Virgili, 2014	Virgili A, Borghi A, Toni G, Minghetti S, Corazza M. First randomized trial on clobetasol propionate and mometasone furoate in the treatment of vulvar lichen sclerosis: Results of efficacy and tolerability.	<i>Br J Dermatol</i> 2014; 171:388-96.
Corazza, 2016	Corazza M, Borghi A, Minghetti S, Toni G, Virgili A. Clobetasol propionate vs mometasone furoate in 1-year proactive maintenance therapy of vulvar lichen sclerosis: Results from a comparative trial.	<i>J Eur Acad Derm Ven</i> 2016; 30:956-961.
Murina, 2015	Murina F, Rehman S, Di Francesco S, Mantegazza V, Felice R, Bianco V. Vulvar lichen sclerosis: A comparison of the short-term topical application of clobetasol dipropionate 0.05% versus mometasone furoate 0.1%.	<i>J Low Genit Tract Dis</i> 2015;19:149-51
Mason, 2002	Mason J, Mason AR, Cork MJ. Topical preparations for the treatment of psoriasis: A systematic review.	<i>Brit J Derm</i> 2002; 146: 351-364.
Pergialotis, 2020	Pergialotis V, Bellos I, Biliou EC, Varnava P, Mitsopoulou D, Doumouchtsis SK. An arm-based network meta-analysis on treatments for vulvar lichen sclerosis and a call for development of core outcome sets.	<i>Am J Obstet Gynecol</i> 2020; 222:542-50.

Source: Table 2-3, pp41-42 of the submission.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Conclusion
Clobetasol vs betamethasone						
Voigtlander, 1977	36, 35 male, 15-76 years; dropouts replaced and not reported	R, DB but methods not stated; 3 wk, B (18) vs C (18); dose not stated	High	18 contact dermatitis; remainder 6 conditions affecting small numbers each; all had prior TCS use, but which TCS and whether adherent not reported	Clinician's assessment	No difference B vs C
Yawalkar, 1991	248, 15-89 years; 264 randomised but 16 excluded for "protocol violations"	Two separate trials: C vs halobetasol (N = 131) and B vs halobetasol (N = 117); R, DB but methods not fully described; 2 wk, dose 120g in 2 wk but not stated if it was all used	High	Acute severe atopic dermatitis affecting < 20% BSA	Clinician's assessment	No difference H vs C, H vs B
Clobetasol vs betamethasone OV						
Katz, 1987	40, but dropouts were not accounted for; 18-62 years	R, DB but methods not stated; 3 wk; C (20) vs Bov (20); dose 7g/day	High	Psoriasis of at least moderate severity	Clinician's assessment	No difference C vs Bov
Jacobson, 1986	130, 19-83 years, but 124 completed 2 wk treatment and 91 completed 4 wk follow-up; dropouts not accounted for	R, DB but methods not stated; 2 wk treatment then 2 wk untreated; C vs Bov on opposite sides of the body; dose 25g in 2wk	High	Psoriasis moderate to severe and approximately symmetrical, but face, groin, axillae, peri-anal area not treated	Clinician's assessment	C better
Mauracher, 1983	101, 15-90 years; dropouts replaced but not reported	R, DB, but methods inadequately described; 2wk; C vs Bov; dose 7g/day	High	Psoriasis (N = 57, C = 30, Bov 27) or atopic dermatitis (N = 44, C = 21, Bov = 23) "refractory" to prior TCS but which TCS and whether adherent not reported; results for both conditions reported together	Clinician's and patient's assessment	Bov better by both clinician and patient assessment
Gip, 1984	81, 10-87 years;	R, DB but methods not stated; 2 studies, of 2 wk (N = 61) and 3 wk (N = 20) duration, C vs Bov in both; dose 7g/day	High	Dermatosis resistant to prior TCS but which TCS and whether adherent not reported; psoriasis 58, atopic dermatitis 17, eczema 6; data reported only for psoriasis	Clinician's assessment	No difference
Verdich, 1985	68, 62 completed but dropouts not accounted for; ages not stated	DB but method not stated; not stated to be R; 2 wk; C vs Bov; dose up to 7g/day	High	Psoriasis	Clinician's assessment	No difference
Clobetasol vs mometasone						

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Conclusion
Goh, 1999 ¹	60; 58 completed but dropouts not reported; 16-85 years	R but method not stated; OL; outcome assessment blinded but method not stated; 3wk; C vs M opposite sides of body	High	Eczema	Clinician assessment	C better
Virgili, 2014	54; 3 dropouts "lost to follow-up"; mean age 64 years.	R, OL; 12 wk; C (27) vs M (27); treatment 5 days per week for 4 wk then alternative days for 4 wk then twice weekly for 4 wk	High	Vulvar lichen sclerosus	Clinician assessment	No difference
Corazza, 2016	48; 4 dropouts, not accounted for; extended follow-up of Virgili	OL; 52wk, twice weekly use of treatment assigned in Virgili	High	Vulvar lichen sclerosus	Clinician and patient assessment of relapse	No difference for either clinician or patient
Murina, 2015	96	Retrospective case series, non-consecutive, 47 C, 49 M; 4wk daily treatment then twice weekly for 4wk	High	Vulvar lichen sclerosus	Patient reports of itching, burning, dyspareunia	No difference

¹ This study was not provided in the dossier. Data are from the submission.

Source: constructed during the evaluation.

B = betamethasone; Bov = betamethasone optimised vehicle; C = clobetasol; DB = double blind; H = halobetasol; M = mometasone; OL = open label; R = randomised; TCS = topical corticosteroid.

Comparative effectiveness

6.7 The evidence obtained from the head-to-head trials is generally of poor quality.

6.8 The trials have major methodological shortcomings:

- no or inadequate descriptions of the methods of randomisation and blinding, or open label trials, in the context of clinician assessment as the outcome measure;
- inadequate description of eligibility criteria and the risk of selection bias;
- inappropriate management and lack of reporting of dropouts;
- the lack of sample size calculations from which the significance of a finding of no difference between treatments could be assessed.

6.9 Most of the trials presented compared clobetasol to betamethasone OV, which is not the PBS listed product.

6.10 The patients in the trials were not representative of the spectrum of patients eligible under the proposed restriction, because many had disease that was severe or resistant to prior TCS. The PSCR agreed to the inclusion of an additional clinical criteria specifying failed treatment on a lower potency TCS being added to the restriction.

6.11 The patients in several of the trials may have used large amounts of clobetasol propionate (7 g per day) and therefore had much more extensive disease than can be

treated with clobetasol using the maximum approved dose (14 g per week). However, the actual dose used was not clear. Even allowing for the inadequate design and conduct of these trials, they do not support the use of 7 g per day as basis for determining an equi-effective dose. Three of four did not use the nominated comparator, and only one clearly used 7 g per day — and it found betamethasone dipropionate OV to be superior to clobetasol propionate. The PSCR supported the use of clobetasol propionate in a manner consistent with dosing requirements outlined in the PI and was amenable to equi-effective doses derived on that basis.

- 6.12 The outcomes of the trials were not standardised or sufficiently similar to allow for a pooled statistical analysis.
- 6.13 Given the limitations of the trials, estimation of a comparative effect size for clobetasol propionate vs betamethasone dipropionate was not possible.

Table 4: Trials used to support CMA

Trial	Design, N	Comparator	Dose	Outcomes	Comments
Jacobson, 1986.	R, DB 131	Betamethasone dipropionate OV	25 g tubes labelled “left” and “right”, one of each study treatment, to be applied to lesions on opposite sides of the trunk and extremities twice daily. Not stated whether 25gm dose was for 2 weeks.	Clinician assessment at day 14	Methods of randomisation and blinding not described. Wrong comparator, inadequate information on dose, unequal effectiveness.
Mauracher, 1983.	R, DB 101	Betamethasone dipropionate OV	Apply 3.5gm medication to affected area bd	Clinical assessment at day 14	Intervention formulation and comparator formulation different, did not show equal effectiveness
Verdich 1985.	DB 68	Betamethasone dipropionate OV	Maximum dose 7g daily for 14 days- whether this was actual dose used is not stated	Clinical assessment day 14	May not have been randomised, wrong comparator, uncertain dose
Yawalkar, 1991.	2 trials Total 264	1) Halobetasol propionate 2) Halobetasol propionate vs betamethasone dipropionate	4 tubes of 30gm for 14 days	Clinical assessment at day 14	Wrong comparator, unknown dose

Source: constructed during the evaluation from the published papers. DB= double blind; R=randomised

- 6.14 Results from the Cochrane review of treatments for psoriasis (Mason, 2013) are shown in Table 5.

Table 5: Results of a systematic review and meta-analysis of treatment for psoriasis (Mason, 2013).

	Betamethasone dipropionate once daily vs placebo	Betamethasone dipropionate twice daily vs placebo	Betamethasone valerate vs placebo	Mometasone furoate vs placebo	Clobetasol propionate vs placebo
Combined end point (IAGI and/or TSS and/or PASI and/or PAGI)					
Number of studies (number of patients)	3 (832)	4 (537)	2 (96)	1 (95)	7 (1016)
Standardised Mean Difference (95% CI)	-0.89 (-0.96, -0.64)	-1.35 (-1.56, -1.15)	-1.33 (-1.78, -0.89)	-0.75 (-1.17, -0.34)	-1.65 (-2.10, -1.20)
IAGI					
Number of studies (number of patients)	2 (739)	4 (387)	1 (74)	1 (95)	4 (471)
Standardised Mean Difference (95% CI)	-0.81 (-0.98, -0.64)	-1.35 (-1.56, -1.15)	-1.41 (-1.92, -0.90)	-0.75 (-1.17, -0.34)	-1.89 (-2.53, -1.24)
PASI					
Number of studies (number of patients)	2 (739)	1 (419)	NA	NA	NA
Standardised Mean Difference (95% CI)	-0.79 (-1.44, -0.14)	-1.21 (-1.44, -0.97)	NA	NA	NA
TSS					
Number of studies (number of patients)	1 (93)	1 (33)	1 (22)	1 (95)	3 (545)
Standardised Mean Difference (95% CI)	-0.74 (-1.16, -0.32)	-0.77 (-1.48, -0.06)	-1.09 (-2.0, -0.18)	-1.12 (-1.55, -0.68)	-1.35 (-1.80, -0.89)
Local adverse events					
Number of studies (number of patients)	2 (756)	2 (454)	NA	1 (120)	6 (845)
Risk difference (95% CI)	-0.10, -0.15, -0.04)	-0.05 (-0.12, 0.03)	NA	-0.10 (-0.23, 0.02)	0.00 (-0.03, 0.03)
Systemic adverse events					
Number of studies (number of patients)	NA	1 (419)	NA	1 (120)	3 (480)
Risk difference (95% CI)	NA	0.0 (-0.01, 0.01)	NA	0.0 (-0.03, 0.03)	-0.01 (-0.02, 0.01)

Source: Mason AR, Mason J, Cork M, Dooley G, Hancock H. Topical treatments for chronic plaque psoriasis. Cochrane Database of Systematic Reviews 2013, Issue 3. Art. No.: CD005028.

IAGI = Investigator Assessment of Global Improvement; NA = not applicable; PAGI = Patient Assessment of Global Improvement; PASI = Psoriasis Area Severity Index; TSS = Total Severity Score

6.15 The meta-analysis is consistent with the claim that for the treatment of psoriasis, clobetasol is non-inferior in efficacy to betamethasone dipropionate used twice daily or to betamethasone valerate. However, the evaluation considered as it was of limited applicability to the requested listing because the indication was different, using it as a basis for an assessment of dose equivalence was highly uncertain and likely not appropriate.

6.16 The submission presented results from a network meta-analysis of treatments for vulvar lichen sclerosus, but the publication was not included in the submission files. Clobetasol propionate and topical calcineurin inhibitors were the most effective treatments of those evaluated, but there were no studies of other TCS in the analysis.

Comparative harms

- 6.17 Most of the head-to-head trials included in the submission did not systematically report adverse events. The lack of reporting of dropouts was also problematic in relation to adverse events.
- 6.18 The updated Cochrane review was consistent with the claim that clobetasol is non-inferior in safety to the other TCS studied. However, important systemic adverse events such as HPA suppression will be under-estimated without specific testing, and the trials included in the review relied on spontaneous adverse event reporting.
- 6.19 The submission noted that “ACM was of the view that there is adequate data to support the short-term use of Xobet and that the PI adequately addresses long term safety concerns”. However, the submission-proposed restriction and the doses and durations of treatment used in the economic analysis (see paragraphs 6.24 - 6.31) were not consistent with the PI and would raise serious concerns about long-term safety. The PSCR and pre-PBAC response supported restriction amendments to ensure short-term use and mitigation of adverse events (see paragraphs 3.1 and 3.2).
- 6.20 The long-term safety concerns referred to are predictable consequences of systemic absorption: “reversible adrenal suppression with the potential for glucocorticosteroid insufficiency, manifestations of Cushing’s syndrome, hyperglycaemia, and glucosuria in some patients [...] osteonecrosis, serious infections (including necrotizing fasciitis), and systemic immunosuppression (sometimes resulting in Kaposi’s sarcoma lesions) have been reported with long-term use of clobetasol propionate beyond the recommended doses” [...] “cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR)” (Xobet PI, 4.4, pp3-4).
- 6.21 Potency of TCS is related to bioavailability, and, therefore, greater topical potency is associated with greater systemic absorption and a greater risk of systemic adverse events.

Benefits/harms

- 6.22 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

Clinical claim

- 6.23 The submission described clobetasol propionate as non-inferior in terms of effectiveness compared to betamethasone dipropionate. Although the available evidence was of poor quality, on balance, the ESC considered the non-inferiority claim was reasonable.
- 6.24 The submission described clobetasol propionate as non-inferior in terms of safety compared to betamethasone dipropionate. This claim could not be assessed on the basis of the head-to-head evidence presented. Taking the available evidence as a whole, it is likely that more frequent and more severe systemic adverse events will

occur with very-high potency TCS than with TCS of lower potency. The ESC advised that restricting use to 14 days and a max of 15 g/week may help limit this.

- 6.25 The PBAC considered that whilst the supporting trial evidence was generally poor and lacking in relevant detail, when considering the totality of the evidence including the systematic review presented, the claims of non-inferior comparative effectiveness were on balance, likely to be reasonable.
- 6.26 The PBAC considered that the claim of non-inferior comparative safety to betamethasone dipropionate was likely to be reasonable in the context of short-term use only.

Economic analysis

- 6.27 The submission presented a cost-minimisation approach. The key components are shown in Table 6.

Table 6: Key components and assumptions of the cost-minimisation approach

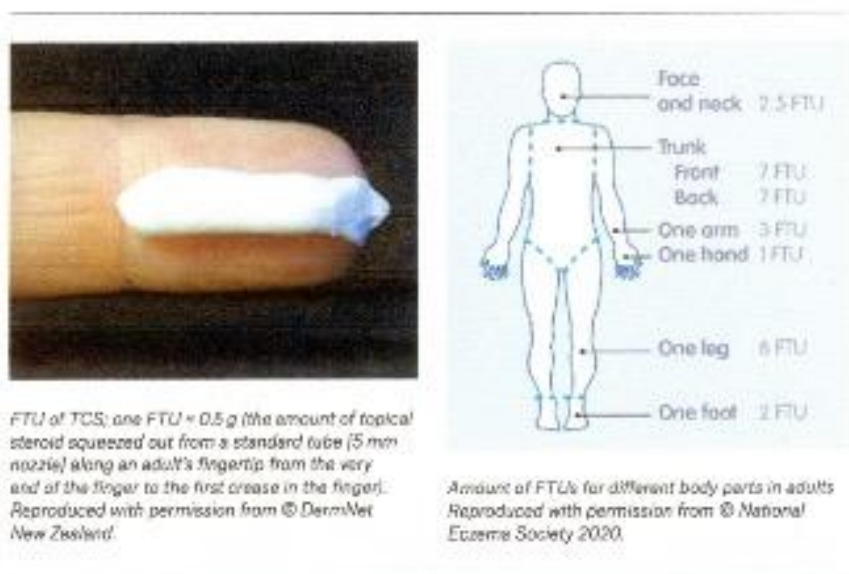
Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented, effectiveness is assumed to be non-inferior to betamethasone dipropionate
Therapeutic claim: safety	Based on evidence presented, safety is assumed to be non-inferior to betamethasone dipropionate
Evidence base	Direct comparison of proposed medicine and main comparator based on 4 randomised trials: Jacobson 1986, Maracher 1983, Verdich 1985, Yawalker 1991
Equi-effective doses	Daily dose for acute treatment (14 days duration): 7 g betamethasone dipropionate = 7 g clobetasol propionate PSCR updated this: Gram-for-gram of betamethasone dipropionate with clobetasol
Direct medicine costs	betamethasone dipropionate 15 g tube AEMP = \$3.65 clobetasol propionate 30 g tube AEMP = \$7.30
Other costs or cost offsets	none

Source: Table 3.1, p 102 of the submission.

- 6.28 The equi-effective doses were estimated by the submission as clobetasol propionate 7 g daily over 14 days and betamethasone dipropionate 7 g daily over 14 days, based on 4 the randomised trials (Jacobson 1986, Mauracher 1983, Verdich 1985, Yawalker 1991) described in Table 4. The submission calculated that over 2 weeks, the daily dosage for clobetasol propionate is 0.23 x tube 30 g (= 7 g daily) and for betamethasone dipropionate is 0.47 x tube 15 g (= 7 g daily).
- 6.29 The evaluation and ESC considered there are fundamental problems with this estimate of dose equivalence as it exceeds the maximum dose recommended in the PI: 14 g/week for 2 weeks, equivalent to 2 gm/day, which is specified for safety reasons. Patients who require larger amounts of medication because they have more extensive disease should not be treated with clobetasol.
- 6.30 Secondly, although the trials referenced as the basis for the estimate of a daily dose of 7 gm/day refer to that dose in some, only one of the trials state the actual dose delivered (Mauracher 1983) and the products used in that trial may or may not have been the same as that listed or proposed for listing on the PBS.

- 6.31 Further, the estimate of the equi-effective dose as 7 g per day is inappropriate because the concept of an equi-effective dose is difficult to apply to TCS, since the amount used depends only on the area of skin affected. Applying more cream or ointment to the same area of skin is not more effective, and different diseases do not require more or less liberal application. The possible use of 7 g per day in several of the trials submitted means only that patients in those trials had larger areas of affected skin than can be treated with clobetasol using the maximum approved dose (14 g per week).
- 6.32 To avoid both over-liberal and over-sparing application, a standard approach is to give patients instructions for how to apply TCS in terms of finger-tip units (FTU); Figure 1.
- 6.33 Equi-effectiveness of clobetasol and betamethasone means that the same number of FTU will treat the same amount of affected skin for the same duration, up to the maximum for clobetasol of 30 g = 60 FTU over 14 days.
- 6.34 Clobetasol 30 g = 60 FTU \approx 4 FTU per day for 14 days. For a patient requiring 4 FTU per day (e.g., treating both hands twice daily), 30 g of clobetasol would be equi-effective to 30 g betamethasone dipropionate. However, a patient with disease affecting one hand and applying clobetasol twice daily would use 28 FTU over 2 weeks. For that patient clobetasol 30 g would be equi-effective with betamethasone 15 g (= 30 FTU).
- 6.35 Given the safety concerns, patients requiring more than 4 FTU per day for 14 days should not be treated with clobetasol and the submission accepts this. It is therefore unclear what the indication and justification are for presentations such as compounded 50 g, 60 g and 100 g clobetasol. The evaluation and ESC considered it would be inappropriate for patients currently using large amounts of clobetasol to switch to multiple prescriptions for PBS-listed clobetasol 30 g, and the PBS listing of clobetasol cream/ointment should reflect appropriate use as outlined in the PI.

Figure 1: Fingertip units



Source: Aung T, Aung ST. Selection of an effective topical corticosteroid. AJGP 2021; 50:651-655.

6.36 No additional costs were included in the CMA. The results of the cost minimisation approach as presented in the submission are shown in Table 7.

Table 7: Cost minimisation analysis of betamethasone dipropionate 15g cream/ointment vs clobetasol propionate 30 g cream/ointment

Medicine	Daily dose (g)	Mean DOT (days)	Daily drug cost (AEMP)	Treatment course drug cost (AEMP)*	Max qty units	Pack size (days cover)	AEMP per pack
Clobetasol propionate 30 g	7	14	\$1.70	\$23.85	1	4.3	\$7.30
Betamethasone dipropionate 15 g	7	14	\$1.70	\$23.85	1	2.1	\$3.65

Source: Table 3.3, p 105 of the submission. AEMP, approved ex-manufacturer price; DOT, duration of therapy; g, gram.

6.37 The ESC considered that, whilst there were numerous factors that impact how to consider the equi-effective doses, given the dosing requirements outlined in the PI, the most appropriate equi-effective dose was likely to be clobetasol propionate 2 g daily = 2 g daily betamethasone dipropionate (given as 4 finger-tip units/FTU). These equi-effective doses result in the same AEMP per pack as the submission base case CMA (\$7.30 per pack). The ESC noted the PSCR accepted an approach based on a gram-for-gram equivalence of clobetasol and betamethasone dipropionate, and that such an approach does not materially alter the cost minimised price per pack of clobetasol.

Drug/ cost/patient/course

6.38 The drug cost per course patient might depend on the area affected and the duration of use. However, using the maximum dose of clobetasol propionate (14 g per week) over 2 weeks, one 30 g pack at proposed DPMQ of \$20.84 would be sufficient.

Estimated PBS usage & financial implications

6.39 This submission was not considered by DUSC.

6.40 For context, the submission presented an overview of the PBS utilisation of class III topical steroids. The summary utilisation information is reproduced below in Table 9.

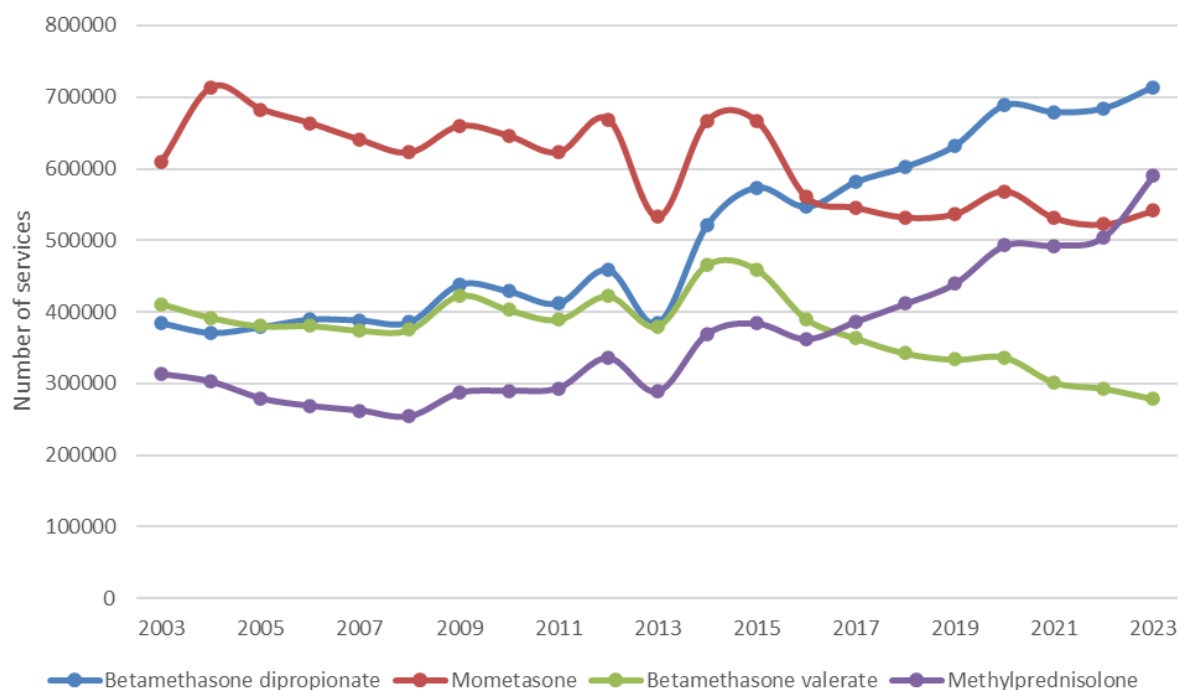
Table 9: PBS utilisation and benefit of class III topical corticosteroids listed on the PBS for the calendar year 2023 for all ages and restrictions

Medicine	PBS Item Codes	Total PBS services	Total benefit
Betamethasone dipropionate	10795E, 10800K, 10801L, 10802M, 10813D, 10816G, 10820L, 10821M, 10823P, 10824Q, 1115Q, 1119X	713,913	\$13,675,085
Mometasone	10791Y, 10792B, 10793C, 10804P, 10805Q, 10809X, 10812C, 10814E, 10815F, 10818J, 10819K, 10826T, 10827W, 10828X, 1913Q, 1915T, 4342M, 4343N, 8043H	541,354	\$8,898,306
Betamethasone valerate	10794D, 10799J, 10807T, 10808W, 10810Y, 2812B, 2813C, 4131K, 4132L	278,579	\$5,274,385
Methylprednisolone	10830B, 10833E, 10834F, 10835G, 10836H, 10838K, 10839L, 10840M, 10842P, 10843Q, 10844R, 10845T, 10846W, 10848Y, 10851D, 10852E, 10853F, 10855H, 10856J, 8054X, 8055Y, 8128T	590,143	\$11,413,559
Total		2,123,989	\$39,261,335

Source: Table 1.3, p19 of the submission.

6.41 The submission also presented a description of trends in use over time for these services. This is shown in Figure 2.

Figure 2: Class III TCS PBS services (2003-2023) for all ages and restrictions



Source: Figure 1.2, p20 of the submission.

6.42 The submission presented estimates of use and financial impact for the listing of clobetasol propionate based on a mixed private market and PBS market share approach. The assumptions used in the analyses were:

- Clobetasol propionate listing would replace use of less potent products earlier in the treatment algorithm, in line with the PBAC comments for clobetasol propionate shampoo (clobetasol propionate shampoo public summary document, PBAC Meeting November 2013, p8). This would also imply that switching from mometasone products might occur, which was not included in the estimates, on the grounds that mometasone is Schedule 3.
- The markets affected would be the current private markets for clobetasol propionate, betamethasone dipropionate OV and betamethasone dipropionate 50 g as well as the PBS market for betamethasone dipropionate 15 g;
- There would be no substitution of clobetasol propionate for mometasone furoate or the combination betamethasone dipropionate gel + calcipotriol product due to use for psoriasis rather than dermatoses. This assumption may not be reasonable as clobetasol may be used for psoriasis.

6.43 The submission assumed that patients would switch from the following preparations obtained with private scripts:

- compounded clobetasol 15 g, 30 g, 50 g, 60 g and 100 g cream or ointment;
- betamethasone dipropionate OV 30 g ointment;
- betamethasone dipropionate 50 g cream or ointment.

6.44 The submission used utilisation data from the PBS, Intellipharm for compounding pharmacies and IMS/IQVIA data for private scripts as the sources for estimating the current market size and growth. Data sources are listed in Table 10.

Table 10: Data sources used in the utilisation and financial estimates

Data	Source	Evaluation comment
Utilisation data sources		
Drug prices, quantities, item codes, indication, clinical setting	PBS online	Reasonable.
PBS/RPBS utilisation data	PBS and RPBS utilisation statistics. Accessed from http://medicarestatistics.humanservices.gov.au/ in May 2024.	Reasonable.
Dispensed volumes of compounded clobetasol propionate 30 g, 50 g and 100 g (available via private script) between May-2023 – Apr-2024.	Commissioned utilisation data: Intellipharm data for 425 compounding pharmacies (sourced May 2024). Assumes all patients will switch to PBS listed clobetasol propionate.	Sample is based on approximately half of the total of compounding pharmacies. Adjusted for different quantities to equate to 30 g quantity proposed for listing. Sample of pharmacies may not be representative. Use of 100 g compounded clobetasol accounts of 16% of the estimate of private scripts. This should not be replaced by 30 g PBS listed clobetasol due to safety concerns.
Dispensed volumes of betamethasone dipropionate OV and betamethasone dipropionate 50 g tubes (available via private script) between 2020 – 2024.	Commissioned utilisation data: IMS®/IQVIA® for 6,217 retail pharmacies (sourced May 2024). Assumes 70% of patients will switch to PBS listed clobetasol propionate.	Data suggests slight decline in use – Figure 4.1, p116 of the submission.
Proportion of patients <18, pregnant or breastfeeding	Chidwick et al. 2020 Australian longitudinal study (2017 – 2018) on patients with atopic dermatitis.	May be reasonable.

Source: Table 4.1, p109 of the submission.

- 6.45 During the evaluation, errors were identified in multiple tables in Section 4 of the submission. Corrected tables were provided by the sponsor and these corrected figures are used in tables below where the respective sources are cited.
- 6.46 The estimates of substitution from the private market are listed in Table 11. The submissions differentiated the proportion of patients eligible in each treatment group from the proposed uptake rate to calculate the net substitution rate. The assumptions for uptake rates are uncertain. The estimates of substitution from large volume clobetasol preparations may not occur if the PBS listing restricts supply to the safe maximum dose as recommended in the PI - one 30 g tube.

Table 11: Values used in utilisation estimates

Parameter	value	Source and assumptions	Evaluation comment
Net substitution from substitution of PBS listed betamethasone dipropionate	Yr 1: 10% Yr 2: 12% Yr 3: 27% Yr 4: 36% Yr 5: 41% Yr 6: 50%	Based on uptake rate of clobetasol propionate shampoo in first 6 years of PBS listing and assumptions about long-term vs short-term use	Probably reasonable although may not take account of difference in maximum duration of use
Net substitution rate from compounded clobetasol propionate (private script)	Yr 1: 67% Yr 2: 75% Yr 3: 87% Yr 4: 94% Yr 5: 100% Yr 6: 100%	Assumes all patients will switch to listed product in year 1 but only 2/3 will use it in year 1.	Not clear why it is not 100% from year 1 unless it is due to different strength or quantity products being used. Not clear how patients currently receiving more than 60 g will switch to PBS listed 30 g. Also assumes no market growth.
Net substitution from betamethasone dipropionate OV (private script)	Yr 1: 30% Yr 2: 51% Yr 3: 62% Yr 4: 76% Yr 5: 92% Yr 6: 92%	Assumes all patients will switch to PBS listed clobetasol propionate by year 6 except patients under 18 years or pregnant and breastfeeding women.	Does not take account of difference in maximum duration of use.
Net substitution from betamethasone dipropionate 50 g (private script)	Yr 1: 23% Yr 2: 39% Yr 3: 35% Yr 4: 47% Yr 5: 70% Yr 6: 70%	Assumes that most patients will switch to PBS listed product except those scripts dispensed by retail pharmacies in public hospitals.	Does not take account of difference in maximum duration of use.

Source: Tables 4.2, 4.3, 4.4, 4.5, pp110-112.

6.47 The total number of prescriptions substituted from the private market is shown in Table 12.

Table 12: Estimation of number of prescriptions from private market

		Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Switch from for compounded clobetasol propionate	■ ¹	■ ²	■ ²	■ ³	■ ⁴	■ ¹	■ ¹
B	Switch from betamethasone dipropionate OV	■ ⁵	■ ⁶	■ ⁷	■ ⁸	■ ³	■ ⁴	■ ⁴
C	Switch from betamethasone dipropionate 50 g	■ ⁷	■ ⁹	■ ¹⁰	■ ¹⁰	■ ¹¹	■ ¹¹	■ ¹¹
D	Annual growth rate	0%						
E	Total number of prescriptions from substitution from private market		■ ⁵	■ ⁵	■ ⁵	■ ⁵	■ ¹²	■ ¹²

Source: Tables 4.8, 4.11, 4.13, 4.1.4 pp 118-119 of the submission; BIM workbook Sheet 11. Italics Corrected estimates as provided by the sponsor during the evaluation.

The redacted values correspond to the following ranges:

¹ 90,000 to < 100,000

² 60,000 to < 70,000

³ 70,000 to < 80,000

⁴ 80,000 to < 90,000

⁵ 100,000 to < 200,000

⁶ 30,000 to < 40,000

⁷ 40,000 to < 50,000

⁸ 50,000 to < 60,000

⁹ 5,000 to < 10,000

¹⁰ 10,000 to < 20,000

¹¹ 20,000 to < 30,000

¹² 200,000 to < 300,000

6.48 For the estimate of the market share of the PBS market, the submission presented estimates based on the assumption that clobetasol propionate would replace 50% of the current market for betamethasone dipropionate following an initial uptake of 10%. The dispensed PBS-RPBS units over the period 2018-2023, is shown in Table 13.

Table 13: Dispensed PBS+RPBS betamethasone dipropionate units (2018 – 2023)

PBS restriction		restricted qty		Total
Dosage form		cream	ointment	
Item code		1115Q	1119X	
PBS + RPBS units dispensed	2018	218,217	155,283	373,500
	2019	208,167	153,751	361,918
	2020	206,937	159,961	366,898
	2021	189,064	146,662	335,726
	2022	181,890	142,257	324,147
	2023	175,268	139,555	314,823
	Total	1,179,543	897,469	2,077,012
Annual growth (5-year linear trendline, 2018 - 2023)		-5.1%	-2.6%	-4.0%
		-8,899	-3,612	-12,511

Source: Table 4.15, p 121 of the submission. PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme. Italics: corrected by the sponsor during the evaluation

6.49 The submission stated that the total volume of betamethasone dipropionate creams/ointments (restricted benefit) had been slowly decreasing over the past five years (annual growth -4.0% based on linear trendline). A higher proportion of creams were dispensed compared to ointments (cream 44% vs ointment 56% in 2023); however annual cream volumes were decreasing at a faster rate (-5.1% vs -2.6%).

6.50 The expected volume of clobetasol propionate units switched from PBS listed betamethasone dipropionate is shown in Table 14. Table 1.3 of the submission described the total of number of services for 2023 for all betamethasone formulations as 713,913 services/ \$10 million to < \$20 million. Of these, the total services in 2023 for betamethasone cream were 175,268 and for the ointment 139,555 (Sheet 2e and Table 13 table above).

Table 14: Expected volumes of clobetasol propionate units switched from PBS listed betamethasone dipropionate

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Medicine/Molecule	Form	2025	2026	2027	2028	2029	2030
Clobetasol propionate, restricted	cream	█ ¹	█ ¹	█ ²	█ ²	█ ²	█ ³
Clobetasol propionate, restricted	ointment	█ ¹	█ ¹	█ ⁴	█ ²	█ ²	█ ²
TOTAL		█ ⁴	█ ⁴	█ ³	█ ⁵	█ ⁶	█ ⁷

Source: Table 4.16, p121 of the submission. PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000

² 20,000 to < 30,000

³ 30,000 to < 40,000

⁴ 10,000 to < 20,000

⁵ 40,000 to < 50,000

⁶ 50,000 to < 60,000

⁷ 60,000 to < 70,000

6.51 The total financial implications of listing clobetasol propionate are summarised in Table 15.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	█ ¹	█ ¹	█ ¹	█ ²	█ ²	█ ²
Estimated financial implications of clobetasol propionate						
Cost to PBS/RPBS less copayments	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴
Net financial implications						
Net cost to PBS/RPBS	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³

Source: Table 4.25, p126 of the submission.

The redacted values correspond to the following ranges:

¹ 100,000 to < 200,000

² 200,000 to < 300,000

³ \$0 to < \$10 million

⁴ net cost saving

6.52 The submission also stated that that there would be an increase in Services Australia prescription processing given the switch from the private market, however the of the switch from the private market is uncertain.

6.53 The total cost to the PBS/RPBS of listing clobetasol propionate was estimated to be \$0 to < \$10 million in Year 6, and a total of \$10 million to < \$20 million in the first 6 years of listing. The net cost was due to the inclusion of costs for patients switching from the private market.

- 6.54 The submission presented several sensitivity analyses, with the following scenarios:
- Maximum substitution rate varied from betamethasone dipropionate (via PBS) from 50% to 25 – 75%.
 - Uptake from clobetasol propionate units (private script) decreased to Yr 1 40%, Yr 2 60%, Yr 3 80%, Yr 4 onwards 100%.
 - Proportion of compounding pharmacies captured for clobetasol propionate units (private script) increased from 46% to 70%.
 - Uptake from betamethasone dipropionate OV units (private script) decreased from 92% to 80%.
 - Maximum uptake from betamethasone 50 g units increased from 70% to 100%.
 - Maximum uptake from betamethasone 50 g units decreased from 70% to 50%.
 - Adjustment factor to account for various compounded clobetasol tube sizes decreased from 79% to 50%
 - Adjustment factor to account for various compounded clobetasol tube sizes increased from 79% to 100%.
- 6.55 All of these scenarios result in a net cost to government, ranging up to \$0 to < \$10 million in year 6.
- 6.56 The evaluation considered the estimates were uncertain. While there was likely to be a switch to clobetasol propionate PBS listed products from the private market, if the restriction for clobetasol was to be consistent with its PI, use would be limited to 2 weeks only and therefore the proportion of patients switching from betamethasone products, which have a 4- week limitation on use was likely to be less than proposed. In addition, patients currently receiving higher quantities of clobetasol propionate than 30 g via compounding pharmacies may not switch. But as the market size seemed to be underestimated in some of the figures for the estimates (see para 6.42) there may be more use than anticipated.
- 6.57 The ESC considered the listing and restriction changes accepted by the Sponsor in the PSCR, and noted in section 3 above, would likely limit the use of clobetasol on the PBS to use within the PI; some patients will respond to lower potency TCS before needing to be considered for clobetasol, and the limit of one 30 g pack of clobetasol means patients must be clinically re-assessed frequently and will not be able easily access a quantity of supply for extensive body surface area coverage. While the ESC considered the utilisation of clobetasol remained uncertain, the included sensitivity analyses suggest the total net cost to the PBS would not fluctuate greatly beyond that estimated in the submission base case.

Quality Use of Medicines

- 6.58 The submission presented estimates of the out-of-pocket costs to patients that would be saved by the PBS/RPBS listing and claimed that this represented an equity issue for access to medicines for some patients.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the General Schedule, Restricted Benefit listing of clobetasol propionate 0.05% cream and ointment for the treatment of corticosteroid-responsive dermatoses in patients who have inadequately responded to lower potency topical corticosteroids (TCS). The PBAC recommendation for listing was based on its assessment that the cost-effectiveness of clobetasol (in the requested forms) would be acceptable if it were cost minimised against betamethasone dipropionate cream and ointment.
- 7.2 The PBAC considered the equi-effective doses were clobetasol propionate 0.05% 1 gram = betamethasone dipropionate 0.05% 1 gram. The Committee noted that in practical terms, dosing would likely be administered in finger-tip units (FTU) of approximately 0.5 grams (see paragraph 6.37).
- 7.3 The PBAC noted the listing was supported by the Australasian College of Dermatologists, as the listing would provide specialist dermatologists an additional option when treating chronic and/or complex cases of dermatoses.
- 7.4 With respect to the requested listing and restriction, the PBAC considered:
- A Restricted Benefit listing was appropriate, consistent with betamethasone dipropionate;
 - The listing should include a maximum quantity of 1 tube/bottle with nil repeats, to provide a maximum of 2 weeks' treatment per script and the need for clinical follow-up to determine whether additional supply is appropriate, as clobetasol is intended for short-term use only;
 - The listing should include a requirement for a patients' condition to be resistant to prior treatment with to a lower potency TCS, noting this was also supported by the Sponsor and ESC (paragraph 3.2 refers);
 - The continuing therapy only advice for nurse practitioner prescribing should be removed (NP prescribing is discussed further below); and
 - The listing should include a note that clobetasol cream/ointment is intended for use on only on small areas of affected skin, with a maximum dose of 15 g per week.
- 7.5 The PBAC noted the submission proposed betamethasone dipropionate as the main comparator and considered this was reasonable for some indications, but also noted

the proposed treatment algorithm suggested it may be used after betamethasone dipropionate (with an implicit claim of superiority). The Committee also noted TCS were typically grouped by potency, with clobetasol often considered amongst the highest potency options, alongside betamethasone dipropionate in optimised vehicle (OV), which was not listed on the PBS. The Committee also considered other TCS, topical combinations, or topical calcineurin inhibitors could be comparators, and noted these were of similar cost or more expensive than betamethasone dipropionate. The Committee noted the PSCR stated that there was currently no Class IV/very potent TCS available on the PBS, and patients requiring stronger treatment for resistant dermatoses were privately paying for treatments or escalating to therapies that are more costly than TCS on the PBS, including systemic treatments and biologics. The PBAC considered betamethasone dipropionate was one of several relevant comparators, and as it represents the lowest cost alternative, was an appropriate main comparator for the non-inferiority claim.

- 7.6 The PBAC noted the submission was supported by a range of studies comparing clobetasol propionate and betamethasone dipropionate (including OV forms) or comparing clobetasol propionate and mometasone furoate. The PBAC agreed with the evaluation that overall, the quality of the evidence was generally poor, with inadequate descriptions of randomisation and blinding, or open label trials; inadequate description of eligibility criteria and the risk of selection bias; and inappropriate management and lack of reporting of dropouts. The studies used in support of the CMA had major methodological shortcomings or poor reporting of design, methods and results, with substantial variation in population, dose and the types of dermatoses being studied (see Table 4 and paragraphs 6.7 - 6.14).
- 7.7 The PBAC also noted the submission included a Cochrane systematic review and meta-analysis in psoriasis (Mason 2013). The PBAC noted the comparative effectiveness of clobetasol propionate and betamethasone dipropionate, supported by the systematic review in psoriasis, showed in most comparisons of individual trials there was no difference in outcomes between treatments, with one trial showing clobetasol propionate was superior to betamethasone dipropionate OV and one showing clobetasol propionate as inferior to betamethasone dipropionate OV, (see Table 5). The PBAC noted the applicability concerns of the evaluation, however considered the results of the meta-analysis in psoriasis tended to support the submission claim of non-inferior comparative effectiveness and although the direct evidence provided was poor, on balance, the claim of non-inferior comparative effectiveness to betamethasone dipropionate was reasonably supported by the totality of the evidence.
- 7.8 In terms of comparative safety, the PBAC noted most of the included studies did not systematically report adverse events (see paragraph 6.17). The PBAC noted the updated Cochrane review (Mason 2013) results were consistent with a claim of non-inferior comparative safety to the other TCS studied, but also noted the risk of more severe adverse events arising with longer-term use (see paragraph 6.18). Overall, the

PBAC considered that the claim of non-inferior comparative safety to betamethasone dipropionate was likely to be reasonable in the context of short-term use only, which further reinforced the Committee's view that the listing should be designed such that only a 2-week supply can be prescribed at a time without further clinical follow-up.

- 7.9 The PBAC considered a cost minimisation approach based on drug costs only with the equi-effective doses of a gram-for-gram equivalence of clobetasol propionate and betamethasone dipropionate was reasonable (see paragraph 6.37).
- 7.10 The PBAC noted the utilisation and financial estimates estimated a cost to the PBS of approximately \$0 to < \$10 million in year one, up to approximately \$0 to < \$10 million in year six (Table 15). The Committee considered a small net cost to the PBS may be reasonable to account for patients switching from private market to PBS-subsidised supply, however considered that with restriction changes limiting use to 2 weeks supply and use only after failure of other TCS, the total cost to the PBS was likely to be less than estimated in the submission.
- 7.11 The PBAC considered the Early Supply Rule should not apply to clobetasol propionate cream/ointment because it is for short term or recurrent episodic use.
- 7.12 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because clobetasol propionate is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over betamethasone dipropionate, 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.
- 7.13 The PBAC noted that this submission is 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	No. of Rpts	Available brands
CLOBETASOL					
Clobetasol propionate 0.05% cream, 30 g	NEW	1	1	0	Xobet®
Clobetasol propionate 0.05% ointment, 30 g	NEW	1	1	0	Xobet®
Restriction Summary Based on / Treatment of Concept: Based on					
Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Restricted benefit					

	Condition: Corticosteroid-responsive dermatoses
	Indication: Corticosteroid-responsive dermatoses
	Clinical criteria:
	The condition must be resistant to lower potency topical corticosteroid therapy
	Administrative advice: Treatment should be limited to a maximum of 15g per week
	Administrative advice: This preparation is only suitable for small areas of affected skin.

These restrictions 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.