Submission for Reclassification of Topical Calcipotriol

Part A

1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine

Calcipotriol

2. Proprietary name(s)

Calcipotriol is marketed in NZ as Daivonex cream, ointment and scalp application.

3. Name of company/organisation/individual requesting reclassification

Pharmacybrands Ltd, the parent company for Life, Unichem, Amcal and Care Pharmacies in New Zealand.

4. Dose form(s) and strength(s) for which a change is sought

50 µg/g cream and ointment. 50 µg/mL scalp application.

5. Pack size and other qualifications

The change is sought only for the smaller pack sizes, i.e. 30g pack sizes for cream and ointment; 30mL for scalp application.

Daivonex® is also marketed in 60mL as scalp application, and in 100g for cream and ointment.

6. Indications for which change is sought

Topical treatment of psoriasis vulgaris including plaque psoriasis in adult patients with doctor-diagnosed psoriasis.

7. Present classification of medicine

Prescription only medicine

8. Classification sought

Prescription medicine except when a maximum of 30g or 30mL is sold by a pharmacist to an adult with mild to moderate psoriasis previously diagnosed by a doctor.

9. Classification status in other countries (especially Australia, UK, USA, Canada)

To the best of our knowledge calcipotriol topical products for psoriasis are not available without prescription elsewhere, as reclassification has not been applied for in any other markets. Calcipotriol does not appear on the lists of OTC medicines in selected countries produced by The Association of the European Self-Medication Industry (AESGP).

10. Extent of usage in New Zealand and elsewhere (e.g. sales volumes) and dates of original consent to distribute

Sales volumes in New Zealand were not able to be supplied by the local distributor before the cut-off of this application. As it is fully funded on prescription and is generally considered to be first-line treatment for mild to moderate psoriasis[1], sales are likely to be greater by volume than most other psoriasis treatments.

The dates of original consent to distribute are not known, however, the New Ethicals Catalogue May 1996 lists Daivonex cream and ointment in 30g and 100g and in the same strength as currently marketed. Thus, this medicine has been available in New Zealand for over a decade. Daivonex scalp application in 30mL and 60mL is listed in the New Ethicals Catalogue May – November 2001 in the same strength as currently marketed.

11. Labelling or draft labelling for the proposed new presentation(s)

Please see attached current labelling (Appendix 1). It is envisaged that this labelling would not change.

12. Proposed warning statements if applicable

These would remain the same as the current pack insert (see Appendix 1), e.g. advising not to use more than 100g per week, not to use on the face and to wash hands after applying.

The Consumer Medicines Information for calcipotriol is available on the Medsafe website, and could be printed out for purchasers of OTC calcipotriol who have not used this before. See Appendix 2. The pharmacist would need to explain the maximum OTC of 30g/week.

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

Nil.

Part B

1. A statement of the benefits to both the consumer and to the public expected from the proposed change

Psoriasis is one of the most common skin diseases, affecting at least 1-3% of Caucasians[2]. Psoriasis is a chronic condition with remissions and relapses[2]. Psoriasis causes suffering – quality of life scores for psoriasis patients are similar to those for heart failure and cancer[3]. Psoriasis sufferers are likely to know what they have, what works for them, and will seek medical help during relapses as well as self-treat with emollients, tar preparations and salicylic acid containing products.

The benefits to psoriasis patients in making topical calcipotriol available without prescription are in increasing self-management options for them, reducing the need for making a doctor's appointment and taking time off work to see a doctor, and ensuring early treatment with a more useful agent for their condition. There is also the empowerment that comes with self-management. Vitamin D analogs are regarded as the first-line topical treatment for psoriasis patients[1], so it is appropriate, given the safety of the product, to have such a treatment available without prescription.

Currently treatments available without prescription include use of emollients, salicylic acid preparations and tar preparations, and sun-beds. Dithranol is a restricted medicine, but is unlikely to have OTC usage given the level of irritation, the requirement to manufacture in the pharmacy and the need to wash off after a specified time. Sun-beds have potential risk of skin cancer. Coal tar preparations are generally cosmetically unacceptable. Emollients are an important part of therapy but most psoriasis sufferers will need treatments additional to emollient use.

A systematic review published in the BMJ[3] reported that calcipotriol was "superior to calcitriol, coal tar, combined coal tar 5%, allantoin 2% and hydrocortisone 0.5%, short contact dithranol and tacalcitol". Topical calcipotriol was significantly more effective than potent topical steroids at 6 weeks of treatment, but not at 8 weeks. The review concluded that "calcipotriol is an effective and well tolerated treatment for mild to moderate chronic plaque psoriasis. Although skin irritation is comparatively common, this rarely requires withdrawal of calcipotriol treatment."

2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

All patients will have been previously diagnosed by a doctor with psoriasis. Pharmacists will have an algorithm to use (Appendix 3).

Pharmacists will already have seen psoriasis in their day-to-day practice, and be counselling on use of prescribed medicines, and advising on use of over-the-counter emollients and tar preparations for mild to moderate psoriasis. The classical picture of psoriasis vulgaris is generally fairly clear with symmetrical well-demarcated red scaly plaques particularly affecting the extensor aspects of the knees and elbows,

and also often affecting the scalp and the hands[2, 4]. If there is any doubt, the pharmacist will refer back to a doctor.

3. Relevant comparative data for like compounds

Vitamin D products

There are no Vitamin D analogs available for psoriasis over the counter in NZ. Topical vitamin D is a general sales medicine in NZ with no maximum strength specified. Vitamin D cream is made in NZ in a strength of 40,000IU/gram (1IU = 25ng vitamin D) with an unknown systemic absorption from this product. Daivonex, in a lower Vitamin D strength is likely to have less systemic exposure for the patient.

Oral vitamin D is unscheduled at or below 25 µg/day, above this it is prescription medicine.

Other OTC products available in NZ

Emollients, preparations containing coal tar, other tars, salicylic acid and sulphur are available without prescription and without mandatory health professional involvement, some of which have the indication of psoriasis (e.g. Coco-Scalp, Egopsoryl). Dithranol is a restricted medicine so could legally be made up by a pharmacist and supplied to a psoriasis sufferer. Dithranol is a trickier medicine to use with greater irritation including blistering.

Hydrocortisone 0.5% is available as a pharmacy only medicine, so may be purchased without health professional involvement and potentially used on psoriasis.

As noted above, calcipotriol is superior to coal tar and hydrocortisone 0.5% which are available over-the-counter.

A recent review of coal tar in dermatology showed coal tar to be second line in psoriasis, for use when first line treatments fail or pruritis is extensive[5]. The rationale for this appears to be due to poor acceptance by patients due to staining and irritation. Other documented adverse events include phototoxicity, folliculitis and contact allergy[5]. Coal tar contains carcinogens but does not appear to be linked with cancer when used dermatologically[6].

4. Local data or special considerations relating to New Zealand

There are no special considerations relating to New Zealand. The datasheet notes that excessive UV exposure should be avoided. This medicine is marketed in Australia and NZ already as a prescription medicine, so is already used in the higher UV environment. Additionally, many studies have used topical calcipotriol alongside UV treatment. The algorithm will include screening for sun-bed use, occupational UV exposure and high recreational UV exposure and exclude these people from usage. Pharmacist training material will include advice to avoid excessive sunlight.

5. Interactions with other medicines

Calcipotriol should not be used with calcium supplements or vitamin D supplements or drugs which can cause hypercalcaemia (e.g. lithium). These will be included in the algorithm, training material and patient leaflet.

6. Contraindications

I. Allergic sensitisation to any constituent of calcipotriol cream.

II. Patients with known disorders of calcium metabolism.

III. NOT FOR OPHTHALMIC USE.

Psoriasis patients will not be using this medicine in the eye, pharmacists will not advise ocular use, and the algorithm includes advice to wash hands, as does the pack insert, so the third contraindication will not be included in the algorithm. The other two are included in the algorithm and all ingredients are listed in the algorithm.

Topical calcipotriol is not licensed for use in children. Children are likely to be doctor-managed already for psoriasis and this will not change.

As safety in pregnancy has not been established, topical calcipotriol will not be recommended for OTC use in pregnancy or planned pregnancy. However, it is noted that the exposure from reasonable use of OTC calcipotriol should be lower than from unscheduled oral vitamin preparations.

7. Possible resistance

Not applicable.

8. Adverse events - nature, frequency etc.

Skin reactions are the most common adverse reactions as is expected for a topical product in psoriasis, occurring in around 15% of people[1]. Irritation is less frequent for calcipotriol than for dithranol[7]. The datasheet reports discontinuation in 2.4% of sufferers due to skin irritation[8]. The cream causes less adverse reactions than the ointment[9]. The face is particularly sensitive to calcipotriol[8]; the algorithm excludes facial use, pharmacist training material will include washing hands after application to avoid inadvertent facial and ocular application, and the pack insert advises to wash hands after use.

According to the datasheet, “Photosensitivity reactions, skin discolouration, bullous eruption, skin exfoliation, contact dermatitis and allergic reactions have been reported with topical calcipotriol therapy.” These are within the realm of reactions that have been reported with other over-the-counter medicines including those that are general sales. Drugs associated with exfoliative dermatitis, for example, include paracetamol, clotrimazole, omeprazole, ranitidine and codeine[10], all of which are available without prescription. Reviews have considered this medicine to be well tolerated[1, 3, 7]. Published papers continually state that this agent is well tolerated[1, 3, 9].

A Medline search using the MESH term psoriasis and the keyword calcipotriol revealed minimal case reports of adverse reactions. For example, one report[11] described generalised pustular psoriasis which resolved; the authors found one other case report of the same condition. Reports of hypercalcaemia were extremely rare. A Medline search (Jan 2010) with the keyword “calcipotriol” and the keywords “exfoliative dermatitis” or “erythroderma” did not reveal any published case reports of exfoliative dermatitis with calcipotriol on Medline-included publications, indicating that this is likely to be a very rare problem. Additionally, an extensive review of calcipotriol ointment by Scott et al in 2001[7] found during general clinical practice there have been isolated case reports of contact dermatitis, precipitation of generalised pustular psoriasis, photosensitivity and headaches. There was no mention in this review of case reports of other skin reactions.

The datasheet for the cream notes that “occasional hypercalcaemia has been reported, usually related to excessive (greater than 100 g/week) use”[8]. However use of up to 100g per week for one year does not generally result in changes in laboratory values[8]. One study examining effect on urine calcium excretion with topical calcipotriol[12] found no difference after 12 months’ of regular use compared with baseline of no usage. Potential for hypercalcaemia will be limited by having only the small pack sizes (maximum 30g) available without prescription, not treating patients with extensive psoriasis or greater than moderate psoriasis, and the algorithm excluding use in patients on calcium or vitamin D supplementation or with disorders potentially causing hypercalcaemia. It is noted that vitamin D topical is not scheduled and a topical preparation with stronger vitamin D activity and unknown systemic bioavailability is available in New Zealand. Oral vitamin D is prescription medicine if the dosage recommendation is more than 25µg per day, otherwise unscheduled.

Approximately 2-10% of topical calcipotriol is absorbed. Calcipotriol is much less active than naturally available $1,25(OH)_2D_3$ on calcium metabolism[8]. If 10% were absorbed, that is 5 µg available to the body for every 1g applied. Using an OTC pack of 30g in a week could result in approximately 30-150 µg calcipotriol absorbed in a week, less than the amount of Vitamin D that could be taken in an unscheduled vitamin supplement, noting of course that Vitamin D supplements are more active on calcium metabolism than calcipotriol.

The Centre for Adverse Reaction Monitoring in New Zealand have received five adverse event reports as attached (Appendix 4).

The datasheet indicates that serum calcium and renal function should be monitored at 3 monthly intervals during periods of usage of topical calcipotriol[8]. The non-prescription use of this product will only be for mild to moderate psoriasis and not for extensive areas. A maximum of 30g will be able to be supplied of cream or ointment or 30mL of scalp application and training material will advise a maximum of 30g per week usage in the non-prescription setting. In addition, for cost reasons, psoriasis sufferers will go to the doctor if they are using more than small quantities. Therefore, monitoring of serum calcium and renal function should not be required.

9. Potential for abuse or misuse.

Calcipotriol is not addictive and will not be used recreationally. Potential misuse could include overuse – however pharmacists will be well aware of this from the algorithm and training material and will notice frequent repurchasing as maximum pack size would be 30g. In addition the pack insert advises not to use more than 100g per week, the algorithm advises avoidance in extensive psoriasis, and, finally, the cost of purchasing 3 x 30g in a week (estimated over $100 retail price) would be sufficient incentive to ensure it is prescribed instead. Thus, this is considered to be highly unlikely to occur. Misuse could also include use on the face. Again this is unlikely, pharmacists will be well aware of it, it is included in the algorithm and the pack insert advises against it.

References

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