Calcipotriol

Section: 13. Dermatological medicines > 13.4. Dermatological medicines > Medicines affecting skin differentiation and proliferation

EMLc ATC codes: D05AX02

Indication	Psoriasis of unspecified type ICD11 code: EA90.Z
INN	Calcipotriol
Medicine type	Chemical agent
List type	Core
Formulations	**Local > Topical > Cream:** 50 µg per mL (0.005%) **Local > Topical > Lotion:** 50 µg per mL (0.005%) **Local > Topical > Ointment:** 50 µg per mL (0.005%)
EML status history	First added in 2021 (TRS 1035)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	calcitriol (ATC codes: D05AX03) tacalcitol (ATC codes: D05AX04)
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Calcipotriol
DrugBank	Calcipotriol

Expert Committee recommendation

The Expert Committee noted that psoriasis is painful and disabling disease with a significant global burden and variable prevalence in different populations. The 2014 World Health Assembly resolution on psoriasis recognized the public health impact of psoriasis and the need for integrated management approaches. Severe forms of the disease are often treated using systemic therapies, but these can produce considerable toxicity and need careful monitoring. Topical treatment, such as calcipotriol, can be a valuable alternative, particularly for moderate disease. The Committee noted that topical calcipotriol is more effective than placebo but not as effective as topical corticosteroids (e.g. betamethasone), a class of medicines that has been included in the EML since the first list was published. However, calcipotriol may be useful in patients who cannot tolerate corticosteroids or when toxicity associated with prolonged corticosteroid exposure becomes a problem. Calcipotriol has a favourable safety profile compared with topical corticosteroids due to low systemic absorption. It is easy to use, widely available and suitable for use in both adults and children. The Expert Committee noted that, although there is limited evidence on the efficacy of calcipotriol for scalp psoriasis, it may be an appropriate alternative to prolonged topical use of corticosteroids on the scalp. Lotion formulations may provide greater patient acceptability for scalp application. Therefore, the Expert Committee recommended the inclusion of calcipotriol on the core list of the EML and EMLc for the treatment of moderate forms of psoriasis.

Background

Calcipotriol has not been previously considered for inclusion on the EML and EMLc. The EML and EMLc currently

include betamethasone valerate and hydrocortisone acetate cream or ointment, 5% coal tar solution and 5% salicylic acid solution for the treatment of psoriasis.

Public health relevance

Psoriasis affects people around the world, but its prevalence varies considerably, ranging from 0.09% in the United Republic of Tanzania to over 10% in Norway (1). At least 60 million people are estimated to be affected worldwide (2,3). Psoriasis varies in morphology, distribution, severity and course. The condition can first occur at any age: it has been reported in newborns and in elderly people. The most common age at onset for the first occurrence of psoriasis ranges from 15 to 20 years, followed by 55 to 60 years (1,4). The most common form of psoriasis is plaque psoriasis in which sharply defined, round/oval or nummular (coin-sized) plaques may be seen. This form accounts for 80–90% of cases of psoriasis (1). People with psoriasis have a lower quality of life than healthy people without the condition, and similar to, or worse than, people with other chronic diseases (4,5).

Benefits

Systematic reviews A 2013 Cochrane systematic review of 177 studies (34 808 participants) compared the effectiveness, tolerability and safety of topical treatment for chronic plaque psoriasis versus placebo, and of vitamin D analogues with other topical treatments (6). Vitamin D analogues versus placebo Twenty trials of vitamin D analogues (10 using calcipotriol, six using calcitriol and two using tacalcitol) for body psoriasis included 3771 participants. Primary efficacy outcomes included: investigator's assessment of overall global improvement or investigator's global assessment of disease severity (IAGI/IGA); total severity scores; psoriasis area and severity index (PASI); patient assessment of overall global improvement or patient global assessment of disease severity (PAGI/PGA); and a combined endpoint of these four measures. Pooled results (standardized mean difference (SMD), 95% confidence interval (CI)) for all treatments combined, and for calcipotriol, calcitriol and tacalcitol are presented in Table 7. Table 7. Efficacy of vitamin D analogues compared with placebo in treatment of psoriasis: pooled results of 20 trials Vitamin D analogues versus potent topical corticosteroids Eight studies (2655 participants) reported efficacy data for three vitamin D analogues (calcipotriol, calcitriol and tacalcitol) versus potent corticosteroids (betamethasone dipropionate, betamethasone valerate, desoximetasone, diflorasone diacetate and fluocinonide). Overall, no statistically significant difference was found between vitamin D analogues and potent corticosteroids for the primary efficacy outcomes. The SMD across all six treatment comparisons for IAGI was 0.17 (95% CI –0.04 to 0.37). For the outcome of IAGI/IGA, one study showed that calcipotriol was significantly better than fluocinonide (SMD – 0.58, 95% CI –0.99 to –0.18). Calcipotriol was significantly less effective than both diflorasone diacetate 0.05% ointment (SMD 0.27, 95% CI 0.02 to 0.52) and betamethasone dipropionate (SMD 0.43, 95% CI 0.28 to 0.58). No statistically significant differences were observed between calcipotriol and betamethasone valerate, calcitriol and betamethasone dipropionate, or calcitriol and betamethasone valerate. Comparisons of different vitamin D analogues Three trials (498 participants) contributed IAGI/IGA data for comparisons of different vitamin D analogues. The analysis found a significant difference in favour of calcipotriol versus tacalcitol (SMD –0.47, 95% CI –0.73 to –0.21), but not versus calcitriol (SMD 0.00, 95% CI –0.25 to 0.25) or maxacalcitol (SMD 0.43, 95% CI –0.12 to 0.98). Vitamin D analogues versus other treatments For the outcome of IAGI/IGA, twice-daily calcipotriol was significantly more effective than coal tar polytherapy (SMD –0.59, 95% CI –0.87 to –0.31), and once-daily vitamin D analogue application was significantly less effective than a twice-daily application (SMD –0.24, 95% CI –0.38 to –0.09). No significant differences were observed between twice-daily application of calcipotriol and other comparators, including coal tar monotherapy, betamethasone dipropionate + salicylic acid, and topical tacrolimus. Other comparative studies A randomized, double-blind study compared calcipotriol with betamethasone valerate treatment over 6 weeks in 409 participants with psoriasis (7). Efficacy was assessed using the PASI at 2, 4 and 6 weeks. Reduction of PASI was statistically significant at all time points for both treatments, and there were no significant between-treatment differences. After 6 weeks of treatment, the mean PASI reduction was 5.50 for calcipotriol and 5.32 for betamethasone. Calcipotriol produced more local irritation. Another study compared the safety and tolerability of calcipotriol cream with betamethasone 17-valerate cream in treating plaque-type psoriasis in a multicentre, double-blind, parallel-group study (8). The mean percentage reduction in PASI from baseline to end of treatment was 47.8% in the

calcipotriol group and 45.4% in the betamethasone group. The reduction from baseline was highly significant in both groups, but the difference between the groups was not significant. A study of 106 patients with chronic plaque psoriasis compared twice-daily calcipotriol with once-daily dithranol cream (short-contact regimen) (9). The mean percentage reduction in PASI from baseline to end of treatment was 57.0% in the calcipotriol group and 63.6% in the dithranol group, with no statistically significant difference between groups. Efficacy of vitamin D analogues in children with psoriasis A multicentre, prospective, open-label study evaluated the efficacy and safety of twice-daily topical calcipotriol for up to 8 weeks in 58 children with psoriasis (10). A statistically significant reduction in mean PASI scores was observed from the start to end of treatment. Marked improvement or clearance was reported in 65% of participants (investigator-assessed) and 62% of participants (patient-assessed). No significant alterations in serum ionized calcium levels or other biochemical or haematological parameters were seen over the course of treatment. A multicentre, prospective, double-blind, parallel-group study evaluated the efficacy and safety of calcipotriol in 77 children (2–14 years old) with stable psoriasis involving less than 30% of the body surface (11). Participants were assigned to receive calcipotriol twice daily for 8 weeks or placebo. Both treatment groups showed significant improvement in PASI from baseline to the end of treatment, and the difference between the groups was not statistically significant. No serious adverse effects, in particular relating to calcium and bone metabolism, were reported.

Harms

Local skin irritation is estimated to occur in up to 20% of patients using topical vitamin D analogues. This is a clinical problem when treatment is applied to the face and therefore calcipotriol and other agents are not used for facial psoriasis. Systemic hypercalcaemia has also been reported. Calcipotriol use has not been commonly associated with clinically significant hypercalcemia, possibly because it is rapidly metabolized after topical application. The cases where it has been recorded are generally single raised values in studies using vitamin D analogues over 52 weeks (12–14). A study involving hospitalized patients with severe and extensive psoriasis receiving up to 360 g of calcipotriol (50 micrograms/g) ointment a week found treatment did not affect bone turnover, but five out of 16 patients developed hypercalcaemia with a reduction in serum parathyroid hormone levels; this returned to normal within 2 days of stopping the treatment (15). The above-mentioned Cochrane review analysed the adverse effects recorded in the included studies (6). Eleven studies evaluated local or systemic adverse events associated with calcipotriol, or both. The rate of withdrawal due to local adverse events ranged from 4% to 14%, and the rate of adverse events ranged from 20% to 41%. The larger trials reported higher adverse events rates (weighted mean: 36%). In a 52-week study, facial irritation affected 30% of participants in the early stages of the trial, but the incidence declined over time. The incidence of systemic adverse events was less common, with five out of eight studies reporting no significant effects. Four studies evaluated both local and systemic adverse events associated with tacalcitol. The rate of withdrawal due to local adverse events ranged from 0% to 6%, and the rate of adverse events ranged from 10% to 21%. Three studies found no systemic adverse events. One study found that over half of participants with psoriasis affecting 10–20% of their body surface area exceeded the recommended daily dose of 5 g/day (up to 13 g daily). However, no effect on calcium homeostasis was reported. Systemic adverse events were identified in over half of participants in an uncontrolled study, but only 6/155 events were considered treatment-related. Three studies evaluated adverse events associated with calcitriol. One study examined the tolerability and systemic adverse events of calcitriol used as monotherapy (3 micrograms/g ointment applied twice daily) in 253 patients. Three per cent of participants withdrew due to adverse events and 15% reported local adverse events. The rate of withdrawal due to systemic adverse events was low (0.4%), but four cases of hypercalcaemia were reported. The effects of high-dose calcitriol (15 micrograms/g once daily) were tested on three groups of participants, with the quantity used proportional to the area affected. No systemic adverse events, skin irritation, or clinically relevant changes in vital signs, haematology, biochemistry, urine or electrocardiogram were observed. Studies on the use of calcipotriol in children reported low levels of local irritation in some children, but blood abnormalities, including those affecting calcium metabolism, were not observed (10,11,16). Use in pregnancy Adequate, well controlled studies of the use of calcipotriol during pregnancy are lacking. Fetal abnormalities have been reported in animal studies. It is recommended that calcipotriol be used during pregnancy only if the potential benefits justify the potential risks.

Cost / cost effectiveness

A cost–effectiveness study compared topical calcipotriol with short-contact dithranol in the treatment of mild to moderate plaque psoriasis (17). Only the costs of drug treatment to the British National Health Service were considered. Considering only drug treatment costs, calcipotriol was the more effective option and also the more costly. Over the long term, first-line treatment with calcipotriol had the highest expected cost per successful treatment at £ 164.91, compared with £ 126.25 with short-contact dithranol. The reported listed costs for calcipotriol are: £ 7.43 (30 g) in the United Kingdom of Great Britain and Northern Ireland, US$ 149–263 (60 g) in the USA, Can$ 254–282 (60 g) in Canada and € 9.70 in Italy.

WHO guidelines

WHO guidelines for the management of psoriasis are not available.

Availability

Calcipotriol is licensed for use in 97 countries worldwide.

Other considerations

The use of calcipotriol may spare the use of steroids. The application briefly described adverse events of topical corticosteroids, specifically tolerance, tachyphylaxis or diminishing therapeutic effect over time, as shown in eczema studies (18). The application also highlighted that in all environments, and particularly in warm and humid climates, misapplication of creams or ointments containing steroids to infections or infestations leads to suppression of inflammation and subsequent spread of the secondary infection (19,20), as well as allergic contact dermatitis accentuated by repeated use (21).

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