WHO Expert Committee on the Selection and Use of Essential Medicines: Application for inclusion of calcipotriol (calcipotriene) on the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc) for the indication of psoriasis

International League of Dermatological Societies,

General items

1. Summary statement of the proposal for inclusion, change or deletion

This application is made in support of the inclusion of the Vitamin D analogue, calcipotriol, as a treatment for psoriasis in the WHO Model List of Essential Medicines for adults (EML) and children (EMLc) (Section 13.4 Medicines affecting skin differentiation and proliferation). This proposal is being made because there are currently no topical alternatives to the use of topical corticosteroids for the treatment of psoriasis. Psoriasis is a disease which is increasingly recognised as a disabling skin disease of world wide distribution. As a result it has been the subject of a World Health Assembly resolution (67.9 https://apps.who.int/gb/ebwha/pdf_files/WHA67-REC1/A67_2014_REC1-en.pdf#page=25). This highlighted:

- The urgent need to pursue multilateral efforts to promote and improve human health, providing access to treatment and health care education;
- that psoriasis is a chronic, noncommunicable, painful, disfiguring, and disabling disease for which there is no cure;
- that in addition to the pain, itching and bleeding caused by psoriasis, many affected individuals around the world experience social and work-related stigma and discrimination;
- and that too many people in the world suffer needlessly from psoriasis due to incorrect or delayed diagnosis, inadequate treatment options and insufficient access to care;

The purpose of the proposed inclusion on the EML as an anti-psoriatic is based on the need to provide a wider choice of treatment options for patients and, in particular, in those for whom corticosteroid therapy has either failed or is not indicated. It is also important that use of corticosteroids on the skin is subject to accepted practice procedures and that those treating the disease have more than one practical therapeutic option for the commonest forms of psoriasis This will increase the range of available therapies and meet the expressed concern about poor access to adequate treatments for this condition

Effective treatment of patients with psoriasis with calcipotriol has been reported in many different clinical environments from individual patients to institutions and in different age groups. There have been a number of clinical trials where it has been found to have clinical efficacy in different type of psoriasis. However, the principle target would be plaque-type psoriasis (see below) which is the form seen in 80% of patients with the skin condition.

At present psoriasis is often treated with topical agents such as corticosteroids, using medium to high potency formulations. Other medications such as anthralin (dithranol) are less commonly used because of the difficulties in effective application and side effects such as higher level of skin irritancy. Dithranol is particular difficult to apply outside outpatient treatment centres under supervision which limits access in many regions. Likewise, the other alternative therapy on the EML 5% coal tar is used much less frequently as it involves access to a bath for adequate application through immersion. This is impractical in many parts of the world. Other oral medicines such as methotrexate or ciclosporin are not indicated for many patients with psoriasis as these are used for generalised or widespread plaque type psoriasis and other forms of severe disease as well as psoriasis complicated by arthropathy. The vitamin D analogues such as calcipotriol, as well as potent topical corticosteroids, are preferred for psoriasis of moderate extent, such as mild to moderate plaque-type psoriasis or flexural psoriasis, the commonest pattern of psoriasis.

A listing of calcipotriol on the EML for the proposed indication would widen access to appropriate medications for the treatment of psoriasis and provide an effective alternative for the many patients with mild to moderate forms of this chronic condition who comprise the majority of cases.

2. Name of the WHO technical department and focal point supporting the application

Not specified

3. Name of organizations consulted and/or supporting the application

The International League of Dermatology Societies (ILDS). Roderick Hay (UK), Olivier Chosidow (France), Luigi Naldi (Italy), Claire Fuller (UK) , Christopher Griffiths (UK) and Lars French (Switzerland).

4. International Nonproprietary Name (INN) and anatomical therapeutic chemical (ATC) code of the medicine

INN: Calcipotriol

ATC Code: D05AX02 Other antipsoriatics for topical use

ICD-11 code: EA90.Z Psoriasis of unspecified type

5. Dose forms and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths

5.1 Calcipotriol is formulated as a) an ointment and b) a liquid

The formulations of calcipotriol are based on concentrations of 50 microgram/ml . This strength is suitable for both adult and paediatric use

5.1 Medicines affecting skin differentiation and proliferation	
calcipotriol	**Cream or ointment:** 0.005% **Lotion:** 0.005%

6. Whether listing is requested as an individual medicine or as a representative of a pharmacological class

The request for inclusion in the WHO Essential Medicine List is as a representative of a pharmacological class on the core list. Calcipotriol also known as calcipotriene is the most widely available medication in this group. Other members described below are tacalcitol and calcitriol. The square box unrestricted definition is requested

7 Treatment details, public health relevance and evidence appraisal and synthesis

7.1 *Pharmacology and mode of action of calcipotriol in psoriasis*

Calcipotriol (calcipotriene) is the most widely used member of a class of anti-psoriatic agents that

includes tacalcitol and calcitriol, known as Vitamin D3 analogues because of their close structural similarity to Vitamin D and their ability to bind to vitamin D receptor sites. They are used for the treatment of the skin disease, psoriasis, and are only minimally absorbed after application to the skin. Approximately 6% (± 3%, SD) of the applied dose of radiolabelled calcipotriol ointment is absorbed systemically when the ointment is applied topically to psoriasis plaques; about 5% (± 2.6%, SD) is absorbed when applied to normal skin . For the liquid formulation approximately 1% of the applied dose is systemically absorbed [1].
Clinical studies using radiolabelled calcipotriol ointment showed that much of the active substance absorbed is converted to inactive metabolites within 24 hours following topical application to psoriasis plaques and normal skin. In animal studies, calcipotriol is rapidly metabolized in the liver following systemic uptake and converted to inactive metabolites.

Elimination:
Only small amounts (< 1%) of radiolabelled calcipotriol can be recovered in the urine and faeces following topical application of this medication in patients with psoriasis [1]

Mode of action
Calcipotriol inhibits keratinocyte proliferation via the Vitamin D receptor without any evidence of cytotoxicity and it induces terminal differentiation of keratinocytes, a reversal of the abnormal keratinocyte change seen in psoriasis. [2] Calcipotriol exhibits a vitamin D–like effect by competing for the cellular receptors for calcitriol, a biologically active metabolite of vitamin D. These calcitriol receptors have been identified on keratinocytes of both normal and psoriatic skin
Calcipotriol also has an immunoregulatory role that involves the skin immune system and elicits decreases in keratinocyte expression of markers of activation [3] Calcipotriol may also reduce the release of cytokines from different T cell types and may also trigger a down-regulation of cell adhesion molecules (CAMs) that mediate the passage of activated T-lymphocytes in the dermis and in the epidermis.

7.2 Treatment details (requirements for diagnosis, treatment and monitoring)

7.2.1 Psoriasis treatment

Proposed therapeutic dosage regimen and duration of treatment

Calcipotriol is applied directly to lesion of psoriasis on the skin. The ointment is indicated for the treatment of mild to moderate plaque psoriasis, the commonest form of the disease. Calcipotriol is used on affected or lesional skin once or twice daily. Improvement of the lesions is usually seen within 4 weeks up to a maximum of 12 weeks. Practical aspects of the use of the medication involve applying enough medication to cover affected area(s) of skin and rubbing in gently and completely avoiding the use of occlusive dressing. At these levels and durations of treatment Calcipotriol does not lead to increased serum calcium levels. Studies do not indicate any modification of this regimen in children.

Calcipotriol or related analogues is indicated as a drug of choice for plaque type psoriasis in all countries where its use are is supported by national or society guidelines eg NICE [4], American Academy of Dermatology [5], Germany [6]

*7.1.2 Diagnostic tests***:** Diagnosis of psoriasis is based on a clinical diagnosis which takes

into account the morphology and appearance of lesions, their distribution and the present of other related features such as changes on the nails. In cases of doubt the diagnosis of psoriasis can be confirmed by biopsy and histopathology.

7.1.3 Monitoring Calcipotriol cream and ointment also may be used in the treatment of extensive or severe chronic plaque psoriasis. However, its use in this type of psoriasis is generally not recommended because of increased risk of hypercalcemia, secondary to excessive absorption of the medication when there is extensive skin involvement. One study involving hospitalised patients with severe and extensive psoriasis receiving calcipotriol receiving up to 360 gm of calcipotriol (50 micrograms/gm) ointment per week had no effect on bone turnover but 5/16 became hypercalcaemic with reduction in parathyroid hormone levels in serum. [7] . These reverted to normal within 2 days of stopping treatment

If calcipotriol is to be used for severe extensive psoriasis, it is necessary to monitor the serum and urinary calcium levels at regular intervals.

Psoriasis, of scalp (treatment)—Calcipotriol topical solution is indicated to treat chronic, moderately severe psoriasis of the scalp. This involves preparing scalp before application by combing and removing scaly debris, parting hair for easy access to scalp lesions; applying medication only to visible lesions; rubbing it in gently and completely; not applying on acute psoriatic eruptions.

8 Information supporting the public health relevance

8.1.1 Psoriasis - Epidemiological information on disease burden

Psoriasis has a worldwide distribution, but its prevalence varies considerably. In the USA, approximately 2% of the population is affected [8,9,10]. High rates of psoriasis have also been reported in island populations. The prevalence of psoriasis is lower in other regions and certain ethnic groups such as native Americans. Data from the Global Burden of Disease study have also contributed to the assessment [11] and as part of a new global analysis, the basis for the creation of a psoriasis atlas, it is estimated that at least 60 million people worldwide are affected [12] A family history of psoriasis is common and so genetic influences are thought to play a major role in the expression of disease. which is multigenic. Seven major psoriasis susceptibility loci have been reported; the major one PSORS1 is located at 6p21. Psoriasis can present at any age and has been reported at birth and in older people of advanced age. But the mean age of onset for the first presentation of psoriasis can range from 15 to 20 years of age, with a second peak occurring at 55–60 years.

Psoriasis is a papulosquamous disease with variable morphology from small papules to large scaly plaques, distribution, severity, and course [8,9]. The lesions of psoriasis are distinct from other entities and are classically very well circumscribed, circular, red papules or plaques with a dry scale. In addition, the lesions are typically distributed symmetrically on the scalp, elbows, knees, lumbosacral area, and in the body folds. Psoriasis may also develop at any site of trauma or injury, known as Koebner's phenomenon. If psoriasis is progressive or uncontrolled, it can result in a generalised exfoliative rash known as erythroderma. Further, psoriasis may have a variable course presenting as chronic, stable plaques or it may present acutely, with rapid progression and widespread skin involvement.

Psoriasis may be symptomatic with patients complaining of intense pruritus or burning. The severity of psoriasis, which is important in determining appropriate therapies may be assessed by classifying cases on the basis of their extent into mild, moderate or severe but increasingly by using a specific scoring tool , the Psoriasis Area and Severity Index or PASI

CLINICAL TYPES OF PSORIASIS

Plaque psoriasis

The commonest form of psoriasis is plaque psoriasis in which patients may have sharply circumscribed, round-oval, or nummular (coin-sized) plaques. This form accounts for 80-90% of cases of psoriasis. The amount of scaling varies among patients and even at different sites on a given patient. In acute inflammatory or exanthematic psoriasis, scaling can be minimal and erythema may be the predominant clinical sign.

Guttate psoriasis

In guttate psoriasis there is an acute onset of very large numbers of small, 2–10 mm diameter lesions of psoriasis. It is estimated that up to 12% of psoriasis experience this form of the disease at some stage even if they subsequently continue with the commoner plaque type rash These small lesions are usually distributed in a centripetal fashion (limbs rather than trunk) although guttate lesions can also involve the head and limbs. Often guttate psoriasis occurs shortly after an acute group B haemolytic streptococcal infection of the throat and can be the presenting episode of psoriasis in children or, occasionally, adults.

Flexural (inverse) psoriasis

Psoriasis affecting the flexures such as the inframammary, perineal, and axillary fold areas. The lesions in these sites appear as red, shiny, well demarcated plaques and are occasionally confused with candida, intertrigo, and dermatophyte infections.

Erythroderma

Total or subtotal involvement of the skin by active psoriasis is known as erythroderma and may take one of two forms. Firstly, chronic plaque psoriasis may gradually progress as plaques become confluent and extensive. Secondly, erythroderma may be a manifestation of unstable psoriasis precipitated by infection, drugs, or withdrawal of corticosteroids. Erythroderma may lead to complications including hypothermia and metabolic changes including hypoalbuminaemia, and anaemia due to loss of iron, vitamin B12, and folate. It is fortunately rare accounting for less than 1-2% of all cases of psoriasis.

Pustular psoriasis

Generalised pustular psoriasis is very rare and a form of active, unstable disease. Precipitants include withdrawal of systemic or potent topical corticosteroids and infections. The patient is often febrile with sore inflamed skin covered with sterile pustules. Patients with generalised pustular psoriasis are frequently admitted to the hospital because of their unstable condition.

A more localised pustular form, palmoplantar pustulosis, presents with similar sterile pustules on a background of erythema and scaling confined to the palms and/or soles

8.1.2 Impact of psoriasis.

Patients with psoriasis have a reduce quality of life similar to, or worse than, those with other chronic diseases [8,13], including ischaemic heart disease, inflammatory bowel and diabetes. Patients with psoriasis feel stigmatised by the condition and this has an impact on disability leading to depression and, in some individuals, suicidal thoughts in more than 5% of patients. More broadly worry and anxiety occur in at least a third of patients with psoriasis and difficulties in interpersonal relations have a significant impact on all aspects of the patient's daily life as well as the implementation of their treatment. There are a number of different severity assessment scales employed in clinical practice of which the most often used is the Psoriasis Area and Severity Index or PASI scale. Another key scoring measure used to assess the effect of the disease on Quality of Life is the Dermatology Life Quality Index or DLQI. These are very helpful and validated measures for assessing the effect of treatment in patients with psoriasis.

8.2 Assessment of current use

The treatment of psoriasis is largely governed by a number of factors such as site of rash, its extent as well as the general health of the patient and the presence of complications such as arthritis. However in published national and international guidelines such as those from the USA, European Dermatology Forum, UK (www.nice.org.uk) and many other countries the first line of treatment for most forms of psoriasis is the application of creams or medications by topical route. These include topical corticosteroids, usually of the potent or highly potent types. However the other major group of widely used topical antipsoriatic drugs are the Vitamin D analogues [14,15,16] . The three main medicines in this group are calcipotriol (calcipotriene), calcitiol, and tacalcitol. This report relates to one of these calcipotriol as this is the most widely used but the clinical and pharmacological data on these others are analogous.

Their main indication is the commonest variant of psoriasis, plaque type psoriasis which is the presenting form in more than 80% of cases. In addition, they can also be used in the flexural, scalp and guttate forms. Calcipotriol and other Vitamin D analogues may also be used in combination with a potent topical corticosteroid (already listed in the EML). Dithranol and coal tar containing products are other alternative medicines as are the topical retinoid tazarotene and topical calcineurin inhibitors such as tacrolimus or pimecrolimus. For widespread and more serious forms of psoriasis such as generalised or pustular psoriasis as well as psoriasis accompanied by arthritis oral treatment such as methotrexate, ciclosporin and acitretin are used. For widespread plaque infection light exposure using light wavelengths within the UVB range are also used. Increasingly biological therapies such as TNF-a inhibitors or IL-12 or IL17 antagonists are used. But these are costly although very effective

However as one of the two main treatments for psoriasis that affects the majority of patients this report concerns Calcipotriol as representative of the Vitamin D analogues

8.3.Target population(s)

Key target populations are patients of all ages with plaque type psoriasis, as well as flexural and guttate forms of psoriasis who require topical therapy on clinical grounds

8.4 Likely impact of treatment on the disease

Psoriasis is a chronic disease where there are intermittent episodes where the rash appears. Treatment is given during active phases of the disease. Cure is not possible but topical therapies provide a high degree of symptomatic relief. Retreatment in the event of a relapse is normal clinical practice

9. Review of benefits: summary of comparative effectiveness in a variety of clinical settings

9.1 Identification of clinical evidence

Systematic review - Cochrane Review papers [17] Plaque psoriasis https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005028.pub3/full?contentLanguage=en

In this section the application addresses the clinical evidence, including the summaries of the available data and estimates of comparative effectiveness

The evidence in this analysis was based on a review of 177 studies in plaque-type or limited psoriasis, which, in total, included 34,808 people. Studies were typically about 7 weeks' long, but this ranged from 1 week to 52 weeks. Vitamin D products such as calcipotriol were found to work better than placebo (the base cream or ointment). Some studies compared vitamin D products directly with potent or very potent corticosteroids. These products had similar effects when applied to the body, but corticosteroids worked better than vitamin D for scalp psoriasis. Vitamin D products generally performed better than coal tar, but studies found conflicting results when comparing vitamin D with dithranol. There were no differences in systemic side effects between these agents and placebo. Vitamin D antagonists produced skin irritation in some patients.

9.1.1 Vitamin D antagonists versus placebo

The analysis included eight vitamin D analogues for body psoriasis. Twenty trials with 3771 participants reported data on 7 of these treatments. Thirteen trials were between-patient design, and 7 were within-patient studies. Three studies used calcipotriol. Treatment duration ranged from 4 weeks to 12 weeks. The pooled Standardised Mean Differences (SMD) based on primary efficacy outcomes - investigator's assessment of overall global improvement and Disease Severity, total severity scores or Psoriasis Area and Severity Index (PASI) as well as patient assessment of overall global improvement - across all treatments was -0.95 (95% CI -1.17 to -0.74; I^2 statistic = 89.0%). There was considerable variation between treatments, so pooling was removed across subgroups. Six Vitamin D analogue treatments were significantly more effective than placebo, with the effect size ranging from -0.67 (becocalcidiol twice daily) to -1.66 (paricalcitol once daily). There was considerable between-study variation in the IAGI (Investigator's Assessment of Overall Global Improvement) SMD (Standard Mean Difference) for calcitriol. The pooled effect was -1.03 (95% CI -1.71 to -0.36), but this ranged from -0.26 (95% CI -0.99 to 0.47) to (P) to -3.11 (95% CI -3.57 to -2.66) [18,19]

9.1.2 Vitamin D antagonist versus potent topical corticosteroids

This comparison included eight vitamin D analogue versus potent corticosteroid comparisons for psoriasis of the body. Eight studies with 2655 participants reported IAGI data for 6 of the 8 intervention-comparator contrasts. Seven trials were between-patient design, and one was a within-patient study [20]. Treatment duration ranged from three to eight weeks. Overall, there was no statistically significant difference between vitamin D analogues and potent corticosteroids: The SMD across all 6 treatments for IAGI was 0.17 (95% CI -0.04 to 0.37; I^2 statistic = 83.4%). In the light of the high level of heterogeneity and inconsistency across treatments = the Cochrane group removed pooling. Vitamin D analogues performed statistically significantly better than one potent corticosteroid. [21]. The SMD for calcipotriol against fluocinonide 0.05% ointment was -0.58 (95% CI -0.99 to -0.18; I^2 statistic = NA). Calcipotriol was statistically 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; I^2 statistic = 50.3%). But there were no statistically significant differences between calcipotriol and betamethasone valerate, calcitriol and betamethasone dipropionate, or calcitriol and betamethasone valerate.

9.1.2.1 Comment on corticosteroid use

While topical corticosteroid therapy is known, and also supported by the evidence above, to be a useful and effective medicine for the treatment of mild to moderate psoriasis there are factors relating to topical steroid use that support the addition of alternative topical therapies on the EML. Topical corticosteroids are subject to tolerance or tachyphylaxis or diminishing therapeutic effect over time, risk of suppressing infection on the skin, allergic contact dermatitis and skin changes such as bruising, skin thinning and the formation of striae. These are related to prolonged use. This is discussed under 11.2.1

9.1.3 Vitamin D alone or in combination versus other vitamin D analogues

The Cochrane review identified three intervention-comparator contrasts in this comparison: calcipotriol versus calcitriol, calcipotriol versus tacalcitol, and calcipotriol versus maxacalcitol for body psoriasis. Three trials involving 498 participants contributed IAGI data for all 3 intervention-comparator contrasts (one trial for each contrast). Two trials were between-patient, and one was within-patient in design [22]. Treatment duration ranged from 8 to 12 weeks. The SMD for the IAGI was -0.06 (95% CI -0.51 to 0.38; I^2 statistic = 82.2%). The presence of substantial heterogeneity reflects differences in the findings from the two intervention-comparator contrasts underlying this statistic. The analysis found a statistically significant difference in favour of calcipotriol in the analysis against tacalcitol (SMD -0.47; 95% CI -0.73 to -0.21), but there was no significant difference relative to calcitriol (SMD 0.00; 95% CI -0.25 to 0.25) or between calcipotriol and maxacalcitol (SMD 0.43; 95% CI -0.12 to 0.98).

9.1.4 Vitamin D analogues versus other treatments

According to the investigator's global assessment, twice-daily calcipotriol was significantly more effective than coal tar polytherapy (SMD -0.59; 95% CI -0.87 to -0.31; I^2 statistic = 0%). Once-daily vitamin D analogue was significantly less effective than a twice-daily application (SMD -0.24; 95% CI -0.38 to -0.09; I^2 statistic = 0%) [17].

9.1.5 Flexural/facial psoriasis: placebo-controlled trials

Two between-patient studies contributed IAGI data from 457 study participants on 2 of the 5 intervention-comparator contrasts. Trial duration ranged from six to eight weeks. Both showed significant clinical improvements with calcipotriol [17].

9.1.6 Scalp psoriasis: placebo-controlled trials

Eight treatments for scalp psoriasis that were assessed using the IAGI scale were significantly more effective than placebo [17].

Vitamin D for scalp psoriasis was significantly less effective than potent steroids, either alone or in combination with vitamin D. Specifically, calcipotriol was less effective than three comparator treatments: betamethasone dipropionate (SMD 0.48; 95% CI 0.32 to 0.64; I^2 statistic = 60.4%), betamethasone valerate (SMD 0.37; 95% CI 0.20 to 0.55; I^2 statistic = 0%), and combination treatment with calcipotriol and betamethasone dipropionate (SMD 0.64; 95% CI 0.44 to 0.84; I^2 statistic = 82.3%). Combination treatment (calcipotriol/betamethasone dipropionate) was significantly more effective than betamethasone dipropionate alone (SMD -0.18; 95% CI -0.26 to -0.10; I^2 statistic = 0%). The efficacy of calcipotriol and coal tar polytherapy was similar: SMD -0.24 (95% CI -0.73 to 0.25; I^2 statistic = 91.1%).

9.2 Quality of life comparisons using SF-36

The SF-36 is a generic short-form health survey with 36 questions covering physical and mental health. The study by Van de Kerkhof 2006 [23] compared calcipotriol and dithranol administered in a day-care setting. The study found no significant difference in quality of life, either for the Skindex-29 or for the SF-36.

9.3 Other study examples of calcipotriol in psoriasis

9.3.1 Placebo controlled studies

In a right/left comparative, double-blind study, treatment with calcipotriol ointment (50 micrograms/gm) twice daily and placebo was given for 4 weeks [24]. The preferred treatment was continued blinded for another 4 weeks. Efficacy, as measured by the Psoriasis Area and Severity Index and by the investigator's and patient's global assessment, and safety were assessed every 2 weeks. The mean Psoriasis Area and Severity Index fell in 4 weeks from 14.2 to 6.3 with calcipotriol and from 14.1 to 9.2 with placebo ($p < 0.001$; 95% confidence interval for difference: 1.78-->3.94). Local side effects were equally common with calcipotriol and placebo. The mean serum calcium remained unchanged. The investigators concluded that calcipotriol was a safe and effective treatment

9.4.2 Comparative studies versus topical corticosteroids or dithranol in plaque type psoriasis

Looking at specific studies a 1992 study [25] used a randomized, double-blind comparison over 6 weeks in 409 patients. Efficacy was assessed using the Psoriasis Area and Severity Index (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. At the completion of 6 weeks of treatment, the mean PASI reduction was 5.50 for calcipotriol and 5.32 for betamethasone. Analysis of patient assessment at 6 weeks showed clearance or marked improvement in 61.2% of the calcipotriol patients and 50.5% with betamethasone. Calcipotriol produced more local side effects of irritation. A further 1997 study [26] compared safety and tolerability of calcipotriol cream with betamethasone 17-valerate cream in the treatment of plaque-type psoriasis in a multicentre double-blind, parallel group study. The severity of psoriasis was assessed using the PASI at baseline and after 4 and 8 weeks of treatment. The mean percentage reduction of 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. But there was a difference in the reduction in thickness of the lesions in favour of calcipotriol.

A comparative study of 106 patients with chronic plaque psoriasis included 54 receiving calcipotriol ointment twice daily and 52 dithranol cream once daily (short contact regimen) [27] . Patients were treated at the day-care centre, using the care instruction principle of daily visits during the first week and twice-weekly visits subsequently for up to 12 weeks. This study showed that calcipotriol is as efficacious as dithranol when used in a day-care setting (noninferiority test). The mean percentage reduction in Psoriasis Area and Severity Index from baseline to end of treatment was 57.0% in the calcipotriol group vs. 63.6% in the dithranol group. However, the two-sided test for superiority indicated no statistically significant difference between the treatment group.

9.4.3. Efficacy and safety of Vitamin D antagonists in children with psoriasis.

Studies of the use of vitamin D antagonists on children have ben fewer. However, these include the study by Darley and co-workers [28]. They showed that over an 8 week period calcipotriol was effective in improving the clinical disease state in 58 children by improving the PASI score from a mean of 6.1 at the start of the study to 2.7 at the end. Marked improvement or clearance were seen in 89% of children treated. There was no significant alteration in serum ionized calcium levels or other biochemical or haematological parameters over the course of treatment and local irritation occurred in 7. In a further trial, an 8-week, double-blind, parallel group study was conducted in 77 children. Response to treatment was assessed by means of the Psoriasis Area and Severity Index (PASI) as well as the investigators' scoring of redness and scaliness as well as the area involved. The children were 2 to 14 years of age and had stable psoriasis, involving less than 30% of the body surface. Forty-three children were assigned to receive calcipotriol ointment and 34 to receive placebo. Both treatment groups (calcipotriol and placebo) showed significant improvement in PASI from baseline to the end of treatment, and the difference was not statistically significant. But calcipotriol ointment was statistically significantly more effective than its vehicle in terms of the investigator's overall assessment and reduction in redness and scaliness. No serious side effects, in particular including those relating to calcium and bone metabolism, were recorded [29]. A smaller study of calcipotriol in

12 children also showed few adverse events – one child reported irritation - or blood abnormalities given for 4-6 weeks in 12 children from 4-12. Signs of psoriasis resolved after 4 weeks in nine patients and after 6 weeks in two patients [30]

Overall evidence of efficacy:

- Calcipotriol and related Vitamin D antagonists are highly effective for the treatment of plaque type psoriasis and is as efficacious as potent topical corticosteroids and other alternative topical agents.
- While Calcipotriol is effective in individual patients with psoriasis in plaque type lesions. It is less effective than potent topical corticosteroids for psoriasis of the scalp
- While calcipotriol is effective in cases of generalised psoriasis because of the wide body area involved an oral therapy is preferred. Use of calcipotriol of an alternative Vitamin D antagonist in such cases should be accompanied by monitoring of serum calcium levels

10. Review of harms and toxicity: summary of evidence on safety

This section includes estimates of exposure, a description of adverse events with a summary of the available data and comparative safety against comparators and identification of variations in safety that may relate to health systems

1O.1 Summary of studies and description of adverse effects or reactions (Cochrane review)

The Cochrane review [17] critically analysed the adverse reactions recorded in the studies. Eleven studies evaluated local (N = 7) or systemic (N = 8) adverse effects associated with calcipotriol, or both. The rate of withdrawals due to local adverse events ranged from 4% to 14% and the rate of adverse events ranged between 20% and 41%; larger trials reported higher rates (weighted mean: 36%). In one 52-week facial irritation affected 30% of participants in the early stages of the trial, but the incidence declined over time. The incidence of systemic effects was less common: 5/8 studies found no significant effects.

Four studies evaluated both local and systemic adverse effects associated with tacalcitol. The rate of withdrawals due to local adverse events ranged from 0% to 6%, and the rate of adverse events ranged between 10% and 21%. Three studies found no systemic effects. One study found that over half of study participants with psoriasis affecting 10% to 20% of their body surface area exceeded the recommended daily dose of 5 g/day (up to 13 g daily), but there was no effect on calcium homeostasis. Systemic effects were identified in over half enrolled participants in one study, but only 6/155 events were considered to be treatment-related in this uncontrolled study.

10.2 Specific studies and descriptions of adverse events

Three studies looked at adverse events associated with calcitriol [31, 32, 33]. One study examined the tolerability and systemic effects of calcitriol used as monotherapy (3 mcg/g ointment applied twice daily, as per licence) [32]. Three per cent of participants withdrew due to adverse events, and 15% reported local adverse events. The withdrawal rate due to systemic effects was low (0.4%), but 4 cases of hypercalcaemia were reported (N = 253). Mean daily use of calcitriol in this trial was 6 g (range = 1 to 24 g). In one study [20], participants who had responded to treatment with clobetasol spray then received 8 weeks of maintenance treatment with calcitriol 3 mcg/g ointment twice daily. Around 15% (35/235) of participants reported burning or stinging at the end of treatment. Wishart 1994 [33] tested the effects of high-dose calcitriol (15 mcg/g once-daily) on 3 groups of participants, with the quantity used proportional to the area affected The trial recruited participants with psoriasis affecting up to 30% of the body surface area. Mean daily drug use ranged from 74 to 306 mcg. The study did not observe any systemic adverse events, skin irritation, or 'clinically relevant' changes in vital signs, haematology, biochemistry, urine, or electrocardiograms.

Generally, these overviews support the view that there are two main issues with Vitamin D analogues. Skin irritation is estimated to occur in up to 20% of patients; this is a clinical problem when applied to the face and therefore calcipotriol and other analogues are not use for facial psoriasis. Calcitriol does not give rise to sensitisation, and when compared to its vehicle and white petrolatum it has demonstrated no potential photoallergic contact sensitization or phototoxicity

The second issue is hypercalcemia. Calcipotriol use has not been commonly associated with clinically significant hypercalcemia, possibly because it is rapidly metabolized after topical application. Theses case where it has been recorded are generally single raised values. Studies have used evaluations over a 52 week period [34,35,36]). A further detailed analysis of calcium metabolism in patients receiving with calcipotriol using a maximum topical dose of calcitriol (3µg/g) ointment, allowing for application on up to 35-percent BSA twice daily for 21 days, examined use in patients with plaque type psoriasis [37] . A subset of 152 patients from these studies underwent extensive laboratory testing for a number of measures that assessed calcium homeostasis. Laboratory values included serum total calcium, albumin-adjusted calcium, 24-hour urinary calcium, phosphorus, creatinine clearance, and urinary calcium to creatinine ratio. Topical calcitriol did not significantly alter the mean values of any of these laboratory measurements. None of the serum calcium values exceeded levels of 10 percent above the upper limit of normal, and all but one of the results were less than five percent above the upper limit of normal.

The studies of the use of calcipotriol in children reported previously [28,29,30] specifically examined the safety and tolerability of the medicine and showed a low level of irritation reported by some children but there were no blood abnormalities including those affecting calcium metabolism in those treated

10.2.1

Topical corticosteroids are subject to tolerance or tachyphylaxis or diminishing therapeutic effect over time, although the best evidence comes from studies of eczema [38]. In all environments and particularly in warm and humid climates, misapplication of steroid-containing creams or ointments to infections or infestations leads to suppression of

inflammation and subsequent spread of the secondary infection [39, 40] A third disadvantage is that occasionally there is allergic contact dermatitis due to application of corticosteroids to the skin. While this is not common it is accentuated by repeated use [41]. Contact allergy to topically applied steroid creams is associated with the steroid moiety rather than additives such as preservatives and is usually proved by testing against tixocortol pivolate followed by more detailed analyses. Long term application of potent corticosteroid to the skin may also result in adverse effects such as thinning of the skin and the formation of striae or stretch marks [42].

While recognising the therapeutic value of steroids, it is therefore a recommendation by dermatologists and promulgated in national treatment guidelines such as those issued by NICE that alternatives to topical corticosteroids should be available for treatment of patients with psoriasis [43].

10.3 Variations in safety related to health systems and patient factors

Routine monitoring of blood calcium levels is not recommended in patients receiving calcipotriol except in special circumstances, for instance if there is an underlying medical condition that may predispose to hypercalcemia. The maximum recommended dose of calcitriol ointment should not exceed more than 200g per week. There are no geographic related implications in usage.

Calcitriol ointment should also not be used for oral, ophthalmic, or intravaginal use. It has not been studied in pregnant or breast-feeding women. Although this is not based on evidence-based studies NICE guidelines advise using with caution in pregnancy and also that it should not be used in patients with severe hepatic impairment [44]

11. Summary of available data on comparative cost and cost effectiveness

11.1 *Listed costs:*

Calcipotriol 30 G £7.43 (BNF)

USA 60 G $149.34 – 262.82 (Drugs.com)

Canada 60 G $254.15 – 281.95 (Pharmacy Checker)

Italy 30G 9.7 Eur (Pharma compass)

11.2 *Cost effectiveness*

The only published cost effectiveness study compared topical calcipotriol TC with short contact dithranol (SCD) [45]. The authors used as inputs in the models, the success and relapse rates of TC and SCD. Success rate was defined as the proportion of patients who experienced a marked improvement or clearing of lesions based on the following 5-point patient-related scale. Only NHS costs of the drug treatment were considered. Costs of physician visits and dispensing fees were excluded as being common to both interventions. While TC was the more effective option it was

also more costly. (96.03 £ at 2000 values). The incremental cost per success was 577.50 £ using a 12-week course of calcipotriol compared with short-contact dithranol. Over the long term, first-line treatment with calcipotriol still had the highest expected cost per successful treatment (164.91 £), but the incremental cost using this strategy was 38.66 £ compared with short-contact dithranol. The study did not take into account additional costs associated with dithranol such as staining of skin and clothing and treating irritation or burning. Because of the latter dithranol, is now seldom used in clinical practice.

12. **Summary of regulatory status**

Calcipotriol is licensed for use on psoriasis by the EMA, FDA (calcipotriene) and Ministry of Health, Labor and Welfare (MHLW) in Japan. In 2013 it had been licensed for use in 97 countries

13. Availabiity of pharmacopeal standards

Calcipotriol (calcipotriene) is listed in the British, US and European Pharmacopeas

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