CEDAC FINAL RECOMMENDATION

CALCITRIOL OINTMENT
(Silkis – Galderma Canada Inc.)
Indication: Mild-to-Moderate Plaque Psoriasis

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that calcitriol ointment not be listed.

Reasons for the Recommendation:
1. The two trials included in the CDR systematic review both reported no statistically significant difference between calcitriol and calcipotriol for the primary outcome (i.e., investigator-derived global assessment of improvement); however the comparison may not have been adequately powered in one trial. Further, there were statistically significant differences favouring calcipotriol over calcitriol for one secondary outcome in each of the two trials (i.e., Dermatological Sum Score and proportion of patients with clearance/control). The two trials were limited by a lack of double-blinding in the evaluation of subjective outcomes and data on quality of life were not reported.
2. At the submitted price, calcitriol costs more than calcipotriol.

Background:
Calcitriol ointment is indicated for topical treatment of mild-to-moderate plaque psoriasis, with up to 35% body surface involvement. Calcitriol, or 1 alpha 25-dihydroxyvitamin D3, is a topical, non-steroidal, antipsoriatic drug. It is the naturally occurring and biologically active metabolite of vitamin D3. The mechanism of action of calcitriol in the treatment of psoriasis has not been established.

Calcitriol ointment is available in a 60 g tube, at a concentration of 3 mcg per gram. The Health Canada-recommended dose of calcitriol ointment is a maximum of 30 g daily. It should be applied twice daily, and no more than 35% of the body can be treated.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by CDR: a systematic review of randomized controlled trials (RCTs) of calcitriol and a critique of the manufacturer's pharmacoeconomic evaluation.

Clinical Trials

The CDR systematic review included two single-blind, published, manufacturer sponsored, non-inferiority RCTs, the Zhu study (N = 250) and the Lahfa study (N = 125). Only trials that included a topical treatment for psoriasis as an active comparator were included in this review.

Both trials compared calcitriol 3 mcg/g ointment with calcipotriol 50 mcg/g ointment in patients with mild-to-moderate psoriasis. Patients in the Lahfa study also used clobetasol 0.05% cream for up to four weeks after entry into the trial, and those who did not achieve at least marked improvement by four weeks were removed from the trial.

The enrolled patient populations differed between the two trials. In the Lahfa study, 87% of patients reported receiving any previous therapy for psoriasis, and in the Zhu study only 3% of patients reported using any therapy for psoriasis within six months before enrolment. In the Lahfa study, the mean duration of psoriasis was approximately 17 years; in the Zhu study, disease duration was not reported.

The study design and 12-week duration of both trials did not permit long-term evaluation of the maintenance of treatment effect. Withdrawals were 8% in the Zhu study and 13% in the Lahfa study.

Outcomes

The primary outcome of both trials was the investigator's global assessment of improvement score. The Lahfa study used a seven-point scale, which has good reliability and known validity. The Zhu study used a newly developed, modified, four-point scale with unknown reliability and validity.

Other outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: disease clearance, disease severity, and disease relapse.

In the CDR systematic review, disease clearance was defined as the proportion of patients achieving an investigator global assessment of improvement score of clear or almost clear.

Disease severity was measured by the adapted Psoriasis Area Severity Index (PASI) in the Lahfa study and by the Dermatological Sum Score (DSS) in the Zhu study. For both the PASI and the DSS, lower scores indicate lesser disease severity. A minimal clinically important difference has not been established for the DSS.

Quality of life was not measured in either trial.

Results

Efficacy or Effectiveness

- In the Zhu study, calcitriol was reported to be non-inferior to calcipotriol (non-inferiority margin of –0.6) based on the modified four-point investigator global assessment score

(mean difference [MD] = 0.001, 95% confidence interval [CI]: –0.183 to 0.186). However, the minimal clinically important difference of the modified global assessment score is unknown. Investigator global assessment scores in the Lahfa study were similar between calcitriol and calcipotriol.

- In the Lahfa study, calcitriol was reported to be non-inferior to calcipotriol (non-inferiority margin of –1.01) based on differences in adapted PASI scores (MD –0.41, 95% CI: –0.96 to 0.14). The Zhu study did not report adapted PASI scores.
- In the Zhu study the Dermatological Sum Score (DSS) at 12 weeks was statistically significantly lower (less severe) for calcipotriol compared with calcitriol; 1.87 versus 2.54 respectively, P = 0.008. Further the DSS was statistically significantly lower for calcipotriol compared with calcitriol at all post-baseline visits. The Lahfa study did not report DSS.
- Based on a CDR statistical analysis, in the Lahfa study, statistically significantly fewer calcitriol patients achieved disease clearance compared with calcipotriol (49% versus 69% respectively, P = 0.03). In the Zhu study, similar proportions of patients achieved disease clearance between calcitriol and calcipotriol (30% versus 35% respectively, P = 0.37).
- Standard definitions of relapse were not applied in the two RCTs. However, in the Lahfa study, of patients who achieved at least marked improvement in the first four weeks, numerically more calcitriol patients than calcipotriol patients returned to a lesser degree of improvement by week 12, but the difference was not statistically significant (25% versus 20% respectively). Relapse while on treatment was not reported in the Zhu study and neither trial measured maintenance of response following discontinuation of therapy.

Harms (Safety and Tolerability)

- Total adverse events and withdrawals due to adverse events were similar between calcitriol and calcipotriol groups in both trials.
- Dermatological adverse events were similar between calcitriol and calcipotriol in the Lahfa study. In the Zhu study, dermatological adverse events were statistically significantly lower in the calcitriol group compared with the calcipotriol group (4% versus 11% respectively, relative risk = 0.36 (95% CI: 0.13 to 0.96). However, the majority of dermatological adverse events for both drugs were considered mild.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-effectiveness analysis comparing treatment sequences initiated with calcitriol versus calcipotriol for patients with mild-to-moderate psoriasis over a 24-week time frame. Patients in this analysis could be successfully treated, leading to treatment cessation; fail treatment, leading to a treatment switch to calcipotriol plus betamethasone; or, relapse, leading to retreatment. The manufacturer estimated treatment response rates that slightly favoured calcitriol over calcipotriol, based on an unadjusted indirect comparison.

The manufacturer assumed that calcitriol induces remission and has lower relapse rates than calcipotriol (52% versus 81% respectively). These assumptions were not supported by the CDR systematic review. When an 81% relapse rate was assumed for both drugs, the incremental cost per disease-free day gained for calcitriol compared with calcipotriol increased from $2.72 to $33.41.

Calcitriol costs $1.15 per gram while calcipotriol costs $0.75 per gram.

Other Discussion Points:

- Calcitriol is only available in ointment formulation, which limits prescribing choice compared with products that also have a cream formulation.
- The Committee discussed that corticosteroids and vitamin D derivatives used to treat mild-to-moderate psoriasis are considered to suppress psoriasis while patients are on therapy, rather than induce remission. Suppressive therapies must be continued in order to maintain disease control.
- It was noted that two double-blind, randomized, placebo-controlled trials have demonstrated that calcitriol is statistically significantly better than placebo in the treatment of mild-to-moderate psoriasis.

CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, and Dr. Yvonne Shevchuk.

Regrets:

None

Conflicts of Interest:

CEDAC members reported no conflicts of interest related to this submission.

About this Document:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.