

CDEC FINAL RECOMMENDATION

ALITRETINOIN

(Toctino – Basilea Medical Ltd.)

Indication: Eczema, Severe Refractory Chronic Hand

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that alitretinoin 30 mg capsules be listed for severe chronic hand eczema refractory to high potency topical corticosteroids if all of the following criteria are met:

- a reduced price
- inadequate response to a minimum eight-week trial of high-potency topical corticosteroids
- prescribed by a dermatologist.

Reasons for the Recommendation:

1. In one double-blind, randomized controlled trial (RCT) in patients with severe hand eczema refractory to topical corticosteroids, the percentage of patients achieving a physician global assessment (PGA) of “clear” or “almost clear” was statistically significantly higher for alitretinoin 30 mg compared with placebo.
2. Alitretinoin costs [*confidential price removed at manufacturer’s request*] daily for both the 10 mg and 30 mg capsules. Topical corticosteroid preparations range from \$0.04 to \$2.30 per gram. There was no evidence that alitretinoin improved quality of life in the aforementioned trial. As a consequence, there was considerable uncertainty around quality-adjusted life-year (QALY) estimation in the manufacturer’s cost-effectiveness analysis.
3. The Committee considered that the lack of a gold standard for the relevant diagnosis, the potential teratogenic harms of alitretinoin, and the potential for off-label use warranted that alitretinoin be prescribed by a dermatologist.

Background:

Alitretinoin has a Health Canada indication for the treatment of severe chronic hand eczema refractory to high-potency topical corticosteroids in adults. The product monograph states it should only be prescribed by physicians knowledgeable in the use of retinoids systemically, who understand the risk of teratogenicity in females of child-bearing potential. Alitretinoin is an immunomodulator and antiinflammatory agent. It is available as 10 mg and 30 mg oral capsules. The Health Canada-approved dosage range is 10 mg to 30 mg once daily, with a recommended

Common Drug Review

starting dose of 30 mg once daily; dose reduction to 10 mg once daily may be considered in patients with unacceptable adverse effects. The product monograph states that a treatment course of alitretinoin may be given for 12 to 24 weeks depending on response, with consideration to discontinue therapy for patients who still have severe disease after the initial 12 weeks of treatment.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind RCTs of alitretinoin, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials

The systematic review included one double-blind RCT of adults with severe hand eczema who were refractory to treatment with topical corticosteroids (minimum eight-week treatment duration in the previous six months). The BACH trial (N = 1,032) randomized patients to one of three treatments for 12 to 24 weeks; alitretinoin 10 mg, alitretinoin 30 mg, or placebo; all treatments were administered once daily. Topical treatments, excepting emollients, were disallowed for the duration of the trial. Patients deemed responders at 12 weeks, based on PGA, discontinued treatment at this time. Patients who did not respond at 12 weeks continued treatment to 24 weeks. Patients were followed for up to 24 weeks following the completion of treatment, including a four-week safety assessment period.

[Confidential information related to this study, including the frequency of non-completion and reasons for withdrawal was removed at manufacturer's request; one sentence removed.]

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: PGA, Patient Global Assessment (PaGA), modified Total Lesion Symptom Score (mTLSS), quality of life, and work-life effects. The primary outcome in the BACH trial was the proportion of responders (disease severity categorized as "clear" or "almost clear" based on the PGA) at end of treatment (week 12 or week 24).

The PGA used to assess disease severity in the BACH study was a five-category tool; patients' disease severity was classified, based on the intensity and percent area of hand involvement, as clear, almost clear, mild, moderate, or severe.

The mTLSS assessed seven symptoms (erythema, scaling, lichenification/hyperkeratosis, vesiculation, edema, fissures, and pruritis and/or pain) on a three-point scale, with higher numbers indicative of greater severity. No reports describing the validation or the minimal clinically important difference of the mTLSS used in the study were found by CDR.

[Confidential information related to the measurement of work-life effects and quality of life, and the validation of such measures, was removed at manufacturer's request; three sentences removed.]

Common Drug Review

Results

Efficacy or Effectiveness

- The percentage of patients achieving a PGA of clear or almost clear at end of treatment was statistically significantly higher for patients randomized to both alitretinoin 10 mg (28%) and alitretinoin 30 mg (48%) compared with placebo (17%). *[Confidential information related to sensitivity analysis of this outcome was removed at manufacturer's request; one sentence removed.]* PGA results were consistent with PaGA.
- The mean reduction (improvement) from baseline in the mTLSS, at both 12 and 24 weeks, was statistically significantly greater for both alitretinoin 10 mg and alitretinoin 30 mg compared with placebo.
- *[Confidential results regarding work-life effects and quality of life were removed at manufacturer's request; one sentence removed.]*

Harms (Safety and Tolerability)

- Withdrawal due to adverse events, during the treatment period, was more frequently observed in patients randomized to alitretinoin 30 mg (9.3%) compared with alitretinoin 10 mg (5.3%) and placebo (5.4%); between-treatment differences were not statistically significant.
- The percentage of patients experiencing a serious adverse event was higher for both alitretinoin 10 mg (4.1%) and alitretinoin 30 mg (2.7%), compared with placebo (1.5%); however, these differences were not statistically significant. The aforementioned between-treatment comparisons are complicated by between-treatment differences in exposure-time.
- The most commonly reported adverse event was headache, reported in 20% and 6% of patients receiving alitretinoin 30 mg and placebo, respectively.
- The frequency of depression was similar across treatment groups in the BACH study, and there were no between-treatment differences for adverse events related to lipid profiles and liver enzyme abnormalities.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing alitretinoin with cyclosporine for the treatment of severe chronic hand eczema refractory to high-potency topical corticosteroids in adults. Health states in the model were based on PGA categories: PGA "clear" or "almost clear" combined, PGA "mild" or "moderate" combined, and PGA "severe." The efficacy data for alitretinoin, in terms of PGA score, was derived from a single RCT of daily treatment with alitretinoin for 12 to 24 weeks, with follow-up for a further 24 weeks (BACH study) and a subsequent follow-up study (BAP0091). The efficacy estimates for cyclosporine were based on data from a small (n = 12) low quality study. In the absence of direct comparison studies, the manufacturer used an informal, naive, indirect treatment comparison, where results from individual treatment arms from BAP00089 and the cyclosporine study were compared. A two-stage mapping approach was used to derive utility values (PGA scores to Dermatology Life Quality Index to EQ-5D scores in patients with psoriasis). The manufacturer reports that treatment with alitretinoin compared with cyclosporine is associated with an incremental cost per QALY of \$15,452.

CDR noted a number of limitations with the manufacturer's submission. Utilities were based on a two-stage mapping approach and there was considerable uncertainty around reliability and generalizability of the estimates. Cyclosporine is not indicated for chronic hand eczema in

Common Drug Review

Canada. Efficacy data versus cyclosporine in the model is based on a naive, indirect comparison, using a small, low-quality study despite head-to-head efficacy data of alitretinoin versus supportive care (or placebo) being available from the BACH and BAP0091 studies. Based on this, CDR requested that the manufacturer submit a revised model that compares alitretinoin with supportive care (or placebo). Where more conservative utility estimates were applied, cost per QALY estimates increased in excess of \$25,000 per QALY versus cyclosporine and \$89,000 per QALY versus supportive care.

At doses of 10 mg or 30 mg, alitretinoin costs *[confidential price removed at manufacturer's request]* daily. Topical corticosteroid preparations range from \$0.04 to \$2.30 per gram.

Patient Input Information:

The following is a summary of information provided by one patient group who responded to the CDR Call for Patient Input:

- Patients indicated a desire for treatments that would reduce discomfort (pain, itching, stinging, and burning) and improve their ability to use their hands in a wide variety of daily tasks at home and in the workplace.

Other Discussion Points:

- The Committee acknowledged that access to a dermatologist could be a barrier for some patients, requiring travel and/or resulting in wait times. However, the Committee noted that the requirement of a prescription by a dermatologist would not be inappropriate based on the disease condition, potential for teratogenic harms, and potential for off-label use.
- The Committee noted that alitretinoin is the only pharmaceutical treatment approved for the treatment of chronic hand eczema refractory to potent topical corticosteroids.
- *[Information related to the Committee's assessment of the 10 mg dose of alitretinoin was removed at the manufacturer's request, as it related to confidential sensitivity analysis of PGA; one sentence removed].*
- The Committee discussed the risk of teratogenicity associated with alitretinoin and emphasized the importance of adherence to the Toctino Pregnancy Prevention Program, as detailed in the product monograph.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, Dr. James Silvius, Dr. Adil Virani.

September 21, 2011 Meeting

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None.

Common Drug Review

About this Document:

CDEC 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 CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC 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.