Canadian Drug Expert Committee
Final Recommendation – Plain Language Version

ALITRETINOIN
(Toctino – Basilea Medical Ltd.)
Indication: Eczema, Severe Refractory Chronic Hand

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that Toctino 30 mg, which is also called alitretinoin, be listed for the treatment of severe chronic hand eczema refractory to (has not improved enough with) high-potency topical (used on the skin) corticosteroids, if all of the following criteria are met:

- a reduced price
- not enough improvement after using high-potency topical corticosteroids for at least eight weeks
- prescribed by a dermatologist.

Reasons for the Recommendation:

1. In one medical study of patients with severe hand eczema who had not improved enough with topical corticosteroids, the percentage of patients who reached a physician global assessment (PGA) of "clear" or "almost clear" was greater for Toctino 30 mg compared with placebo (a capsule containing no active medication).
2. Toctino 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 Toctino improved quality of life in the abovementioned study. As a result, it was difficult to know whether the manufacturer's estimate of the cost-effectiveness of Toctino was correct.
3. The Committee considered that the lack of an exact and widely accepted definition of severe chronic hand eczema, and the potential for Toctino to harm an unborn baby or to be used in conditions for which it has not been approved by Health Canada, were important reasons for Toctino to only be prescribed by a dermatologist.

Background:
Toctino belongs to a group of drugs called retinoids, which are related to vitamin A. Toctino is believed to modify the immune system and have an anti-inflammatory effect on the eczematous lesions by reducing the production of some substances responsible for inflammation, thereby reducing and helping to clear eczema. Health Canada has approved Toctino for treatment of severe chronic hand eczema refractory to high-potency topical corticosteroids in adults. Toctino

should only be prescribed by doctors who understand how to use retinoids and the risk to an unborn child (when used by women of child-bearing age).

Toctino is available as 10 mg and 30 mg capsules, which are taken by mouth. The Health Canada–approved dosage range is 10 mg to 30 mg once daily, with a recommended starting dose of 30 mg once daily; the dose may be lowered to 10 mg once daily if patients have unacceptable side effects. The product monograph states that a treatment course of Toctino may be given for 12 to 24 weeks, depending on results. Stopping treatment at 12 weeks should be considered for patients who still have severe disease after the first 12 weeks of treatment.

Summary of CDEC Considerations:
To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Toctino and a review of economic information prepared by the manufacturer of Toctino. Also, CDEC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated or who might use the drug.

Clinical Trials
The review included one medical study of 1,032 adults with severe hand eczema who had not improved enough with topical corticosteroid treatment (treated for at least eight weeks within the previous six months). In the study (also called the BACH study), patients were given either Toctino 10 mg, Toctino 30 mg, or placebo, once daily for 12 to 24 weeks. Topical treatments, except for moisturizing creams, were not allowed during the study. Patients who had enough improvement at 12 weeks, based on the PGA, stopped treatment at this time. Patients who had not improved enough at 12 weeks continued treatment to 24 weeks. Patients were followed for up to 24 weeks after finishing the treatment; this included a four-week-long assessment of safety.

[Confidential information about this study, including how frequently patients stopped participating in the study and their reasons for stopping participation, was removed at the manufacturer's request.]

Outcomes
Outcomes were defined in advance 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 main purpose of the BACH study was to measure the proportion of patients who improved (disease severity considered "clear" or "almost clear" based on the PGA) at end of treatment (week 12 or week 24).

The PGA used in the BACH study included five categories: patients' disease severity was categorized as clear, almost clear, mild, moderate, or severe, based on the intensity and percent of hand involvement.

The mTLSS measures seven symptoms (redness, scaling, thickening and/or hardening, blister formation, swelling, cracking, and itching and/or pain) on a three-point scale, with higher numbers meaning greater severity. CDR found no reports describing the usefulness of the mTLSS for comparing eczema treatments, or the smallest difference in the mTLSS scale that would make an important difference for patients.

[Confidential information about the scales used to measure work-life effects and quality of life was removed at the manufacturer's request.]

Results

Efficacy or Effectiveness

- The percentage of patients who reached a PGA of clear or almost clear at end of treatment was higher for patients on either Toctino 10 mg (28%) or Toctino 30 mg (48%) than those on placebo (17%). *[Confidential information about additional analysis of this outcome was removed at the manufacturer's request.]* PaGA measurements showed similar results to the PGA results.
- The average improvement (compared with study start) in the mTLSS, at both 12 and 24 weeks, was greater for both Toctino 10 mg and Toctino 30 mg than placebo.
- *[Confidential results about work-life effects and quality of life were removed at the manufacturer's request.]*

Harms (Safety and Tolerability)

- More patients on Toctino 30 mg (9.3%) than on Toctino 10 mg (5.3%) and placebo (5.4%) stopped taking part during the study because of side effects; however, when these differences were looked at using statistics, there was no real difference between the groups.
- The percentage of patients with a serious side effect was higher for both Toctino 10 mg (4.1%) and Toctino 30 mg (2.7%) than placebo (1.5%). When these differences were looked at using statistics, there was no real difference between the groups. However, the above comparisons are complicated because the average duration of treatment differed between the three groups.
- The most common side effect was headache, reported in 20% of patients receiving Toctino 30 mg and 6% of patients receiving placebo.
- The treatment groups had about the same percentage of patients reporting depression and there were no differences between the treatment groups in side effects related to the amount of fats and cholesterol in the blood, or abnormal liver enzymes.

Cost and Cost-Effectiveness

The manufacturer submitted economic information to compare Toctino with cyclosporine for the treatment of severe chronic hand eczema in adults who did not improve enough with the use of high-strength topical corticosteroids, to evaluate the health benefit.

In its economic evaluation, the manufacturer used PGA results from the BACH study and a later follow-up study called BAP0091. Information about the effectiveness of cyclosporine came from a small (12 patients), low-quality study. As there are no studies comparing Toctino with cyclosporine in patients with severe chronic hand eczema, the manufacturer used the results of treatment groups from two different studies to make the comparison. PGA results were used to estimate changes in quality of life for patients.

CDR noted a number of potential issues regarding the manufacturer's submission, including whether confidence could be placed in the estimates of quality of life changes derived from PGA changes. Further, cyclosporine is not indicated for chronic hand eczema in Canada. A further economic analysis comparing Toctino with supportive care (the effect estimated by placebo) showed that Toctino was less cost-effective than when compared with cyclosporine.

At doses of 10 mg or 30 mg, Toctino 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 that responded to the CDR Call for Patient Input:

- Patients desired treatments that would decrease discomfort (pain, itching, stinging, and burning) and would 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 understood that some patients may have difficulty getting to see a dermatologist (due to long wait times or need to travel some distance). However, the Committee noted that the requirement of a prescription by a dermatologist was appropriate given the severity of the condition, the potential for harm to an unborn baby, and the potential for Toctino to be used for conditions not approved by Health Canada.
- The Committee noted that Toctino is the only medication 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 Toctino was removed at the manufacturer's request, as it was related to additional confidential analysis of the PGA.]*
- The Committee discussed the risk of harm to the unborn fetus that can occur with the use of Toctino and emphasized the importance of always using the Toctino Pregnancy Prevention Program, as described 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

About this Document
The information contained within this plain language version of the Canadian Drug Expert Committee (CDEC) Recommendation about this drug is based on the information found within the corresponding technical version of the CDEC Recommendation.

In making its recommendation, CDEC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the CDR Drug Database on the CADTH website (www.cadth.ca).

Background on CDEC
CDEC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The committee is made up of drug evaluation experts and public members. CDEC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CDEC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

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

The manufacturer has reviewed this document and has requested the deletion of confidential information.