CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

EFINACONAZOLE (JUBLIA — BAUSCH HEALTH, CANADA INC.)
Indication: For the topical treatment of mild to moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *Trichophyton rubrum* and *Trichophyton mentagrophytes* in immunocompetent adult patients.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that efinaconazole not be reimbursed for the topical treatment of mild- to moderate onychomycosis (tinea unguium) of toenails.

Service Line:	CADTH Drug Reimbursement Recommendation
Version:	1.0
Publication Date:	May 2019
Report Length:	7 Pages

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Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that efinaconazole not be reimbursed for the topical treatment of mild to moderate onychomycosis (tinea unguium) of toenails.

Reasons for the Recommendation

1. Several medications used to treat onychomycosis in Canada are reimbursed by the Common Drug Review (CDR)-participating drug plans, including terbinafine and itraconazole, and there is no evidence to suggest that topical efinaconazole fulfills an unmet need in treating this condition.
2. There are no randomized controlled trials (RCTs) in which efinaconazole has been compared directly with other treatments used to treat onychomycosis in Canada, and the results of an indirect treatment comparison (ITC), while having limitations, suggested that topical efinaconazole was less effective than oral terbinafine 250 mg daily and itraconazole 200 mg daily at inducing mycologic cure of onychomycosis.

Discussion Points

- The committee discussed that for patients with a medical need for treatment (such as those with diabetes or who are immunocompromised), systemic drugs are the preferred treatment. The committee further noted that the Health Canada indication for efinaconazole is specific to immunocompetent adults, and that there is limited evidence for the benefit of efinaconazole in patients with diabetes given the small percentage of patients with diabetes enrolled in the relevant trials (approximately 6%).
- The committee considered that the risk of complications as a result of not treating mild to moderate onychomycosis is low, and that patients at risk for complications of onychomycosis (e.g., secondary skin infections and sequelae) are those with severe onychomycosis, for which efinaconazole is not indicated. The committee recognized that individuals with mild to moderate onychomycosis, and/or those lacking a specific medical need may still wish to pursue treatment to improve the appearance of their nails and relieve the related distress. However, the included studies did not provide evidence that efinaconazole resulted in improved health-related quality of life, and it was noted that the lengthy duration of treatment for efinaconazole does not meet the expressed need by the patient group for a faster cure compared with current treatments. The committee further considered that the anticipated duration of treatment (i.e., 48 weeks based on the pivotal trials) may limit a patient's adherence to a full course of therapy, which could result in treatment failure, repeated physician visits, and prescriptions for additional treatment.
- The committee heard from a dermatologist experienced in treating onychomycosis that precautions related to the use of systemic antifungals, such as potential drug-drug interactions and hepatic disease, may be managed to allow for systemic antifungal treatment when treatment is warranted. The committee discussed that some patients may have a preference for topical treatments over systemic treatments, however results of the manufacturer-submitted ITC suggests that topical efinaconazole is less effective than oral terbinafine or itraconazole.

Background

Efinaconazole (Jublia) is a triazole antifungal agent that inhibits fungal lanosterol 14 alpha demethylase involved in ergosterol biosynthesis. It is indicated by Health Canada for the topical treatment of mild to moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *Trichophyton rubrum* and *Trichophyton mentagrophytes* in immunocompetent adult patients. The recommended dose is one drop applied to the affected toenail(s). A second drop should be applied onto the affected big toenail(s). It is available as a 10% w/w topical solution.

Summary of Evidence Considered by CDEC Considerations

The committee considered the following information prepared by the CADTH CDR: a systematic review of two double-blind, vehicle-controlled RCTs of efinaconazole, a manufacturer-submitted ITC, and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with toenail onychomycosis and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, the Canadian Skin Patient Alliance, in collaboration with Wounds Canada, provided input for this submission. Patient perspectives were obtained from an online survey. The following is a summary of key input from the perspective of the patient group:

- Patients reported experiencing discoloration and physical changes to their nails, including pain and pressure when wearing shoes. Patients may experience lower quality of life and reported feeling self-conscious or embarrassed, and stopping activities due to the appearance of their nails.
- Patients mentioned headaches, skin rashes, and digestive issues as common side effects of oral treatments and the belief that the oral treatments are "toxic to the liver." Topical treatments were said to cause redness in the skin around the toenail while physical or surgical treatments may be expensive. In general, topical therapy, natural health products, and laser treatment were thought to be ineffective. Patients expressed a desire for a permanent cure with quick results so they may have healthy, normal looking nails.
- The majority of patients who had experience with efinaconazole describe some success with efinaconazole used alone, or in combination with laser therapy. Most patients reported no adverse events (AEs) with treatment, although one patient reported having redness around the nail. Overall patients found efinaconazole was easy to use, or as easy to use as other treatments.

Clinical Trials

The systematic review included two identical, double-blind, vehicle-controlled RCTs of adult patients with mild to moderate distal lateral subungual onychomycosis affecting at least one great toenail (Study P3-01, N = 870 and Study P3-02, N = 785, both having a duration of 52 weeks). The trials evaluated the efficacy and safety of one to two drops of efinaconazole 10% topical solution self-applied to the affected toenail(s) once daily compared with vehicle alone for 48 weeks, without debridement. Overall, 12.3% and 14.6% efinaconazole-treated patients and 12.6% and 20.8% vehicle-treated patients discontinued Study P3-01 and Study P3-02, respectively. No active comparator trials met the review criteria.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following: health-related quality of life (HRQoL), cure (clinical, mycologic, and complete), and nail parameters (e.g., unaffected new nail growth).

- HRQoL was measured as the change from baseline in the onychomycosis quality of life questionnaire (OnyCOE-t), which is comprised of 33 items within seven individual scales. All items are transformed to a 1 to 100 scale with higher scores indicating better function. Complete cure was defined as both 0% clinical involvement of the target toenail and mycologic cure (i.e., a negative potassium hydroxide [KOH] examination and negative fungal culture of the target toenail sample).
- Treatment success or clinical efficacy was defined as a target toenail area of < 10% or ≤ 10% depending on the version of the statistical analysis plan employed.
- Complete or almost complete cure was defined as an area ≤ 5% of the affected target toenail in addition to a negative KOH examination and a negative fungal culture of the target toenail sample.
- Mycologic cure was defined as a negative KOH examination and a negative fungal culture of the target toenail sample.
- Unaffected new toenail growth was defined as the change from baseline in the healthy (unaffected) target toenail measurement in millimetres (mm) for the target toenail.

The primary outcome in both Study P3-01 and Study P3-02 was complete cure of the target toenail at 52 weeks. No data were available for the following important outcomes identified in the review protocol: pain, recurrence, and secondary complications.

Efficacy

- HRQoL was assessed as the change from baseline to Week 24 and Week 52 in the OnyCOE-t instrument; however, as it was considered to be a supportive efficacy outcome no statistical comparisons were conducted between treatment groups. As a result, it was not possible to interpret the clinical relevance of any apparent between-group differences in HRQoL.
- The proportion of patients with completed cure at week 52 in both Study P3-01 and Study P3-02 were statistically significantly higher in the efinaconazole groups (17.8% and 15.2%) compared with the vehicle-controlled groups (3.3% and 5.5%), respectively; $P < 0.001$ for both trials.
- The proportion of patients with treatment success or clinical efficacy at Week 52 were also statistically significantly higher in the efinaconazole groups (35.7% and 31.0%) compared with the vehicle-controlled groups (11.7% and 11.9%), respectively; $P < 0.001$ for both trials.
- The proportion of patients with complete or almost complete cure at Week 52 were also statistically significant in favour of efinaconazole (26.4% and 23.4%) compared with vehicle (7.0% and 7.5%); $P < 0.001$ for both trials.
- The proportion of patients with mycologic cure at Week 52 were also statistically significantly higher with efinaconazole (55.2% and 53.4%) compared with vehicle (16.8% and 16.9%); $P < 0.001$ for both trials.
- In Study P3-01, the least squares mean (LSM) standard error (SE) unaffected new toenail growth was 5.0 (0.2) mm with efinaconazole versus 1.6 (0.4) mm with vehicle; $P < 0.001$. In Study P3-02, the LSM (SE) unaffected growth was 3.8 (0.2) mm with efinaconazole versus 0.9 (0.4) mm with vehicle; $P < 0.001$.

Harms (Safety)

- Overall, the frequency of AEs was generally similar between efinaconazole and vehicle-control patients in both trials and the majority of AEs (> 96%) were mild-to-moderate in severity.
- In Study P3-01, the frequency of serious AEs was 3.8% (efinaconazole) and 2.8% (vehicle) after 52 weeks. In Study P3-02, the frequency was 3.7% and 0.5%, respectively.
- Withdrawal due to AEs occurred in 3.2% of efinaconazole-treated patients and 0.5% of vehicle-control patients in Study P3-01 and 1.9% and no patients in Study P3-02, respectively, after 52 weeks.
- Application site dermatitis occurred in 3.5% and 0.7% of efinaconazole-treated patients compared with 0% and 0.5% of vehicle-treated patients in Study P3-01 and Study P3-02, respectively. Similarly, application site vesicles occurred infrequently (2.0% and 1.2% with efinaconazole and in 0.0% of vehicle-treated patients in both trials).
- The most common reasons that led to discontinuation were AEs associated with the application site.
- [redacted].

Indirect Treatment Comparisons

- The manufacturer submitted an ITC published in 2015 that was reviewed and critically appraised by CDR. The objective of the ITC was to conduct a network meta-analysis (NMA) to compare the relative efficacy of onychomycosis treatments for the outcome of mycologic cure. The NMA included 19 RCTs that evaluated topical therapy with efinaconazole 10% solution or ciclopirox 8% nail lacquer and oral therapy with terbinafine 250 mg, itraconazole 200 mg continuous therapy, itraconazole 400 mg pulse therapy, and fluconazole 150 mg to 450 mg, in addition to other topical treatments not approved in Canada. Of note, fluconazole does not have a Health Canada-approved indication for onychomycosis. The NMA suggested that terbinafine 250 mg daily and itraconazole 200 mg daily continuous therapy were more effective than efinaconazole and that there was no statistically significant difference between efinaconazole and ciclopirox in inducing mycologic cure. Various limitations were identified with the ITC including reliance on only one outcome (mycologic cure), heterogeneity across the included trials, and other methodological issues. The results should be interpreted with caution due to differences in disease severity among patients enrolled in trials for oral drugs versus topical treatments, limited data for some treatment comparisons, and the clinical relevance of the outcome of mycologic cure, which may not be a relevant outcome due to its association with false-negative results. The manufacturer-submitted ITC did not assess comparative safety of efinaconazole versus its comparator treatments.

Cost and Cost-Effectiveness

Efinaconazole is available at a submitted price of $89.04 per 8 mL bottle. At the recommended dose, a patient with a single affected great toenail would require two bottles over 48 weeks of therapy, at a cost of $178, while a patient with one affected great toenail and three smaller toenails (consistent with the pivotal trials) would require five bottles over the 48 week period, at a cost of $445.

The manufacturer submitted a cost-utility analysis in the form of a decision tree model comparing efinaconazole as first-line therapy with no treatment in adults with mild to moderate onychomycosis. The perspective was that of a Canadian public health care payer, with a time horizon of five years. Upon entering the model, patients received either efinaconazole or no therapy for 48 weeks, with efficacy based on mycological cure rates reported for efinaconazole and vehicle treatment in two RCTs. Patients who did not achieve a cure after first-line therapy were immediately given a three month course of systemic antifungal agents (a weighted average of terbinafine and itraconazole based on publicly reimbursed market share data), with efficacy based on odds ratios from an NMA. Patients who achieved a cure on either first or second-line therapy were assumed to remain cured for three years, after which they had a risk of recurrence. Half of the patients who suffered a recurrence were assumed to be retreated with their previously successful therapy, with the exception of patients receiving no treatment, who were given systemic antifungals. Patients who were not cured after two rounds of therapy were assumed to remain untreated thereafter. The utility weight for having uncured onychomycosis was derived from a dermatological utility study, while having been cured was assumed to be equivalent to perfect health. The manufacturer also included costs for fungal testing upon initiating systemic antifungals as well as upon completion of all therapies including no treatment.

CDR identified a number of key limitations with the model submitted by the manufacturer:

- Efinaconazole was compared with no treatment rather than systemic therapy with oral antifungal drugs.
- Relative efficacy of efinaconazole in the economic model was based on mycological cure rate; however, this outcome is considered less relevant in clinical practice than complete cure or percentage nail improvement.
- Patients were assumed to have a single affected great toenail which does not reflect the patient population in the pivotal trials, where patients had one target toenail and a median of three additional non-target toenails affected. As a result, the quantity (and cost) of efinaconazole in the model was underestimated which further underestimated the incremental cost-utility ratio (ICUR).
- The utility weight used for onychomycosis is based on a small sample of six patients. Whether this is reflective more broadly of patients with this condition is highly uncertain.
- The clinical efficacy of efinaconazole was based on a population with confirmed diagnosis of onychomycosis; however, the cost of testing to confirm fungal infection was not included. Patients were assumed to undergo testing at the end of efinaconazole therapy or no treatment and at the start and end of second-line therapy. This is not consistent with clinical practice. The consequences of negative test results were not modelled.

The CDR base-case addressed some of the identified limitations by assuming that: patients had four affected toenails, that is one great and three small toenails (to be consistent with the clinical trial data); the second-line therapy was terbinafine alone (greatest market share); and, all patients are treated empirically for onychomycosis (i.e., without confirmatory testing). In the CDR base-case, efinaconazole compared with no treatment was associated with an additional benefit of 0.0024 quality-adjusted life-years (QALYs) at an additional cost of $410, resulting in an ICUR of $169,628 per QALY, over a five-year time horizon. The probabilistic re-analysis resulted in an ICUR of $151,492 per QALY. In the CDR probabilistic base-case, the price of efinaconazole would need to be reduced by 62% to be considered cost-effective at a willingness to pay of $50,000 per QALY.

CDR noted that, while a cost-utility analysis of efinaconazole versus terbinafine as a first-line therapy was not feasible because of the inflexibility of the manufacturer's economic model, efinaconazole had higher per-course drug acquisition costs and a lower mycological cure rate than terbinafine (as reported in the submitted NMA). As a result, in a population of patients who can use systemic oral antifungals, such as that modelled by the manufacturer, efinaconazole is unlikely to be a clinically or economically attractive option compared with terbinafine.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

January 16, 2019 Meeting

Regrets

None

Conflicts of Interest

None

May 15, 2019 Meeting

Regrets

Two members did not attend

Conflicts of Interest

None