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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

EFINACONAZOLE (JUBLIA)

(Valeant Canada LP)

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.

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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.

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Abbreviations

CDR	CADTH Common Drug Review
ICUR	incremental cost-utility ratio
KOH	potassium hydroxide
NMA	network meta-analysis
OR	odds ratio
QALY	quality-adjusted life-year

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Efinaconazole Topical Solution, 10% w/w
Study Question	Is topical efinaconazole a cost-effective alternative to no treatment for mild-to-moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *Trichophyton rubrum* and *T. mentagrophytes*?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Immunocompetent adults with of mild-to-moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *T. rubrum* and *T. mentagrophytes*
Treatment	Efinaconazole 10% w/w (8 mL bottle), followed by systemic antifungal therapy in case of no mycological cure
Outcome	Quality-adjusted life-years (QALYs)
Comparator(s)	No treatment, followed by systemic antifungal therapy in the case of no mycological cure
Perspective	Canadian public health care payer
Time Horizon	5 years
Results for Base Case	Incremental cost-utility ratio (ICUR) of $40,751 per QALY for efinaconazole (deterministic analysis) and $39,286 per QALY (probabilistic analysis)
Key Limitations	• Efinaconazole was compared with no treatment rather than the current standard of care in Canada, which is systemic therapy with oral antifungal drugs. • Relative efficacy of efinaconazole in the economic model was based on the 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 (i.e., nail of the big toe), which does not reflect the patients in the pivotal trials, who had one target toenail and a median of 3.0 additional non-target toenails affected. As a result, the quantity of efinaconazole considered in the model was underestimated, which underestimated the 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. • Efficacy evidence for efinaconazole (first-line therapy) was based on a patient population with confirmed diagnosis of onychomycosis. However, the cost of testing to identify cases with fungal infection was not included. Patients were assumed to have undergone testing at the end of efinaconazole therapy or no treatment (to check for mycological cure), and at the start and end of second-line therapy. This is not consistent with clinical practice. Also, the consequences of negative test results were not modelled at any stage. • Patients failing to achieve a mycological cure were assumed to have received oral antifungals (terbinafine or itraconazole). Costs, adverse events, and efficacy inputs for second-line treatment were weighted by the relative market shares of each oral antifungal (i.e., not limited to the onychomycosis indication), rather than incorporating each drug into the model as a separate treatment option. • Uncertainty intervals for parameters in the economic model were not based on clinical evidence but on assumptions; the resulting ICURs of probabilistic analysis were systematically lower than those based on deterministic analysis.

CDR Estimate(s)	• In the CDR base case, the number of affected toenails was changed to one great and three small toenails (consistent with the clinical trial data), the second-line therapy was assumed to be terbinafine alone, and patients were assumed not to have undergone diagnostic testing (to be consistent with clinical practice). • The CDR base-case ICUR was $169,628 per QALY when efinaconazole was compared with no treatment over a five-year time horizon. • The price of efinaconazole would need to be reduced by 62% to be considered cost-effective at a willingness to pay threshold 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 using the manufacturer's economic model, efinaconazole had higher drug costs and a lower mycological cure rate than terbinafine (as reported in manufacturer's submission), and therefore terbinafine is likely to be an attractive treatment option when compared with efinaconazole.

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Drug	efinaconazole (Jublia)
Indication	For the topical treatment of mild-to-moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *Trichophyton rubrum* and *T. mentagrophytes* in immunocompetent adult patients
Reimbursement Request	As per indication
Dosage Form	Topical solution, 10% w/w
NOC Date	October 2, 2013
Manufacturer	Valeant Canada LP

Executive Summary

Background

Efinaconazole topical solution 10% w/w (Jublia) is a triazole antifungal agent indicated for the topical treatment of mild-to-moderate onychomycosis (tinea unguium) of toenails without lunula involvement due to *Trichophyton rubrum* and *T. mentagrohytes* in immunocompetent adult patients.[1] Efinaconazole is available in 8 mL bottles at a submitted price of $89.04 per bottle. The product monograph recommends applying one drop of the solution topically to the affected toenail(s) once daily, preferably at bedtime, with a second drop applied to the affected great toenail(s). At the recommended dose, a patient with a single affected great toenail would require two bottles over 48 weeks of therapy, i.e., the duration of therapy in the manufacturer's pivotal clinical trials,[2] at a cost of $178 per patient. A patient with one affected great toenail and three smaller toenails, which is consistent with the median in the pivotal trials of four affected toenails per patient, 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. A discount rate of 1.5% was applied to costs and benefits accrued after the first year. 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 the vehicle arms in two randomized controlled trials.[2] 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 2017 Canadian publicly reimbursed market share data[3]), with efficacy based on odds ratios from a network meta-analysis.[4] 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, based on the estimates reported in a long-term observational study of systemic antifungals.[5] Half of the patients who suffered a recurrence were assumed to be re-treated with their previously successful therapy, with the exception of no-treatment patients, 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,[6] 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 completion of first- and second-line therapies and no treatment. Additional liver-monitoring costs were included for systemic antifungals.

In its deterministic base case, the manufacturer reported that efinaconazole was associated with an additional cost of $108 and 0.0027 additional quality-adjusted life-years (QALYs), compared with no treatment, resulting in an incremental cost-effectiveness ratio (ICUR) of $40,751 per QALY. The probabilistic analysis reported a slightly lower ICUR of $39,286 per QALY for efinaconazole compared with no treatment.

Summary of Identified Limitations and Key Results

CADTH identified a number of limitations in the model submitted by the manufacturer. The manufacturer compared efinaconazole with no treatment, rather than with oral antifungals, which are the current standard of therapy in Canada. The mycological cure outcome, which informs clinical efficacy parameters within the model, is of uncertain relevance to clinical practice, as it may not necessarily be associated with improvement in nail appearance, which is a key outcome for patients. Additionally, the manufacturer's assumption that patients would present with only a single affected great toenail is not consistent with the experience of patients in the pivotal clinical trials, who had a median of three additional affected toenails. Because the cost of topical treatments (efinaconazole) increases with the number of affected nails while the cost of systemic treatments does not, this assumption biases costs in favour of efinaconazole. Substantial uncertainty in the utility value used for onychomycosis, as well as with the assumption that recurrence rates would be similar for all topical and oral therapies, increases uncertainty in the results of the model. The cost of testing for onychomycosis was included for oral antifungals but not for efinaconazole, despite basing the clinical efficacy of efinaconazole on patients with a confirmed diagnosis, which biases the results in favour of efinaconazole. This bias was compounded by the inclusion of duplicate testing at the end of first-line therapy, and the initiation of second-line oral therapy. Additionally, the manufacturer did not consider the cost of testing all patients, i.e., including those with negative results who would not be eligible for efinaconazole. For second-line treatment, the manufacturer considered a treatment based on the weighted average of two systemic antifungals (terbinafine and itraconazole), where market shares were not specific to the current indication. These market share–weighted averages were applied to the costs, efficacy, adverse event rates, and recurrence rates associated with both systemic antifungals together, rather than considering the treatments individually. Finally, uncertainty intervals around parameters used to conduct probabilistic analyses[7] were not based on clinical evidence but on assumptions (primarily involving varying the mean by ± 25%). Moreover, the mean ICURs for probabilistic analyses were systematically lower than those for the deterministic analyses.

The CADTH Common Drug Review (CDR) base case addressed some of the identified limitations by assuming that: patients had four affected toenails, i.e., 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 were 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 QALYs at an additional cost of $410, resulting in an ICUR of $169,628 per QALY, over a five-year time

horizon. The probabilistic reanalysis resulted in an ICUR of $151,492 per QALY. Under the CDR base case, the price of efinaconazole would need to be reduced by 62% to be considered cost-effective at a willingness to pay threshold of $50,000 per QALY.

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

Conclusions

The model submitted by the manufacturer had a number of limitations and data-related uncertainties, some of which were addressed in the CDR reanalysis. In the CDR base case (assuming four affected toenails, no diagnostic testing, and second-line therapy of terbinafine alone), the ICUR for efinaconazole compared with no treatment is likely to be significantly higher than estimated by the manufacturer. The clinical benefit associated with efinaconazole over a five-year time horizon (0.0028 QALYs) is small, equivalent to a single extra day of perfect health. Efinaconazole is not cost-effective compared with no treatment at a willingness to pay threshold of $50,000 per QALY, unless the price of efinaconazole is reduced by 62%.

CDR noted that a more relevant comparison would be with the standard of care — oral antifungals (e.g., terbinafine and itraconazole). The drug-acquisition cost of efinaconazole is higher than that of terbinafine regardless of the number of affected toenails involved, and higher than itraconazole when three or more toenails are involved. Efinaconazole is also associated with a lower mycological cure rate than either oral antifungal. Therefore, efinaconazole is less attractive compared with oral antifungals for the treatment of onychomycosis.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis in the form of a decision-tree model, comparing topical efinaconazole with no treatment in patients with mild-to-moderate toenail onychomycosis[8] (Figure 1, Appendix 5). The perspective was that of the Canadian health care system, with a time horizon of five years. Costs and clinical outcomes (i.e., quality-adjusted life-years [QALYs]) were discounted after the first year at a rate of 1.5%. Both deterministic and probabilistic analyses were conducted, with the probabilistic analysis based on 5,000 iterations. Most parameters were assumed to vary by 25% of the mean.[8]

Upon entering the model, patients received either efinaconazole or no treatment for 52 weeks. Treatment efficacy was based on the weighted average (based on sample size) of the mycological cure rates observed in two manufacturer-conducted randomized controlled trials that compared efinaconazole with the vehicle without the active ingredient.[2,9,10] After the first year, patients who had achieved a mycological cure were assumed to remain cured for at least three full years. This assumption was based on the mean time to recurrence reported in a separate long-term observational follow-up study.[5] Patients who did not achieve a mycological cure by the end of 52 weeks were assumed to receive a three-month course of systemic treatment, which the manufacturer based on a weighted average of terbinafine and itraconazole using 2017 public claims data in Canada, excluding Quebec.[3] Mycological cure rates for the systemic antifungals were calculated by applying the odds ratio (OR) for each systemic treatment versus efinaconazole reported in a network meta-analysis (NMA) to the cure rate for efinaconazole.[4] Again, patients who were cured were assumed to remain cured for at least three full years. Patients who did not achieve a mycological cure after second-line therapy received no further treatment and continued to experience onychomycosis for the remainder of the model's time horizon. Patients who achieved a mycological cure after either first- or second-line therapy had a 16.4% risk of recurrence after three years — this was derived from the overall recurrence rate reported in the same long-term observational study of systemic antifungals for onychomycosis.[5] The model assumed that half of all patients who experienced a recurrence underwent re-treatment with the same antifungal agent with which they had previously achieved a cure. If recurrence occurred in patients who had achieved a cure with no treatment, it was assumed they were treated with systemic antifungals.

The quality of life or utility of uncured onychomycosis (including while on treatment) was based on a published study that elicited utility values from patients with onychomycosis using the time trade-off method. Patients with cured onychomycosis were assumed to have a utility value of 1.000, which is equivalent to perfect health.

The economic model included costs of the following treatment-related adverse events: application-site dermatitis for efinaconazole (based on efinaconazole clinical trials[2]), drug-drug interactions (based on a recent cost-effectiveness study[11]), and liver disorders and elevated liver enzymes for terbinafine and itraconazole (based on product monographs[12,13]). Additionally, the manufacturer assumed that patients needing a second-line systemic treatment would receive a potassium hydroxide (KOH) test and a fungal culture of a toenail sample to confirm the presence of dermatophyte fungi (indicative of onychomycosis).

However, the consequences of test outcomes (in terms of true/false-positive/negative results) were not modelled. Also, all patients were assumed to receive a KOH test and culture after completion of therapy to confirm mycological cure. Patients receiving systemic treatment (either itraconazole or terbinafine) were also assumed to require liver function monitoring at each visit, and those receiving terbinafine also had a complete blood count assessed at treatment initiation.[8,14]

Unit costs for systemic therapies and topical treatment of dermatitis were based on Ontario Drug Benefit Formulary list prices,[15] while that of efinaconazole was based on the manufacturer's submitted price. The cost of a severe drug-drug interaction was assumed to be the average cost of a hospital stay in Canada,[16] while elevated liver enzymes was associated with the cost of average ambulatory care in Ontario and a liver disorder was associated with the cost of average acute in-patient care in Ontario.[8] The cost of systemic antifungal therapy was the weighted-average cost of a three-month treatment course of terbinafine and itraconazole, with weighting based on the relative market share reimbursed by Canadian public drug plans, excluding Quebec, in 2017.[3]

Manufacturer's Base Case

In the manufacturer's deterministic base case, over a five-year time horizon, the use of efinaconazole, compared with no treatment, was associated with an incremental cost of $108 and an incremental gain of 0.0027 QALYs. As a result, efinaconazole was associated with an incremental cost-utility ratio (ICUR) of $40,751 per QALY for efinaconazole (Table 2). The manufacturer's probabilistic analysis resulted in efinaconazole being associated with a slightly lower ICUR of $39,286 per QALY. A more detailed breakdown of the undiscounted costs and associated QALYs of the deterministic analysis can be found in Table 13 in Appendix 5.

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost of Efinaconazole ($)	Total QALYs	Incremental QALYs of Efinaconazole	Incremental Cost per QALY ($)
Deterministic analysis					
No treatment	281.93	108.13	4.8346	0.0027	40,751
Efinaconazole	390.07		4.8373		
Probabilistic analysis					
No treatment	268.25	108.15	4.8352	0.0028	39,286
Efinaconazole	376.39		4.8379		

QALY = quality-adjusted life-year.

Note: Patients who did not achieve mycological cure after receiving efinaconazole or no treatment were assumed to receive second-line treatment in the form of systemic antifungal therapy. Probabilistic results presented here are the mean of 5,000 iterations; the manufacturer originally reported the median.

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted several deterministic scenario analyses to explore the impact of modelling assumptions. Reducing the time horizon to two years (from five in the main analysis) increased the ICUR associated with efinaconazole to $73,732 per QALY, while increasing the number of affected toenails to three (i.e., one great toenail and two small

toenails) increased the ICUR to $110,681 per QALY. Changing the discount rate and ignoring any disutility associated with recurrence had minimal effects on results.

Additionally, the manufacturer conducted a series of deterministic, one-way sensitivity analyses, which in most cases included varying the base-case parameters by ± 25%. These analyses included varying: the proportion of patients treated upon recurrence of the infection; the mycological cure rate associated with efinaconazole and no treatment; the health-related quality of life (utility) associated with onychomycosis; the recurrence rate after successful treatment; the proportion of patients receiving terbinafine rather than itraconazole as second-line therapy; the medical costs associated with each therapy; and the costs associated with adverse events after receiving efinaconazole or second-line therapy. Of these analyses, the ICUR was most sensitive to a change in the mycological cure rate associated with efinaconazole or no treatment, changing the utility value of onychomycosis, and varying the proportion of patients using terbinafine as the second-line therapy.

The manufacturer's model also explored the impact of changing the primary clinical outcome from mycological cure rate to "treatment success rate," defined as < 10% nail involvement, < 5% nail involvement, 0% nail involvement, and complete cure (i.e., 0% nail involvement with confirmed mycological cure). Treatment success rates for the efinaconazole and no-treatment groups were based on the two manufacturer-conducted clinical trials discussed earlier. However, comparative data on these outcomes were not available for the second-line systemic antifungals relative to efinaconazole. As a result, this scenario analysis continued to use mycological cure rate as the outcome for second-line treatment. This inconsistency of outcomes makes the analysis questionable.

Limitations of Manufacturer's Submission

- **Relevant comparison not included:** Terbinafine, a systemic antifungal indicated for the treatment of onychomycosis caused by dermatophyte fungi,[12] is the current standard of care in Canada, as stated in the manufacturer's submission[17] and confirmed by the clinical expert consulted by CADTH Common Drug Review (CDR). Terbinafine has a high cure rate for onychomycosis,[4] and is widely reimbursed by Canadian public drug plans (e.g., Alberta,[18] Ontario,[15] Saskatchewan[19]). The terbinafine indication includes *T. rubrum* and *T. mentagrophytes,* the two fungi for which efinaconazole is indicated, i.e., the terbinafine indication is broader than, but inclusive of, the efinaconazole indication.[1] Therefore, terbinafine is an important first-line comparator that was not considered by the manufacturer. Due to the inflexibility of the submitted model, CDR was unable to formally assess the cost-effectiveness of efinaconazole compared with terbinafine as first-line therapy. However, it is important to note that terbinafine is both less expensive and has a higher chance of mycological cure than efinaconazole (Table 5 and Table 10), while also requiring only three months of compliance to therapy rather than a year. Given the inflexibility of the model, it was also not possible to assess the health benefit of efinaconazole without a second-line therapy over the time horizon for which clinical data exist.
- **Appropriateness of the clinical outcome:** Clinical efficacy in the manufacturer's economic model was based on mycological cure rates, which are reported as a secondary outcome in the efinaconazole clinical trials[2] and as the only outcome in the included NMA.[4] Mycological cure, while necessary from an antifungal clinical trial perspective, is subject to a high rate of sampling error, leading to false-negative results. According to the clinical expert consulted by CDR, testing for dermatophyte fungi using a

KOH test and a fungal culture of a toenail sample is typically not performed in clinical practice. Additionally, a mycological cure without improvement in nail appearance would typically not be seen as treatment success by most patients, making this clinical outcome less relevant from a patient's perspective. While the economic model included a sensitivity analysis based on changing the clinical outcome to "complete cure" or "treatment success" (with < 10%, < 5% or 0% nail involvement), comparative data for these outcomes for the second-line antifungal treatments were not available. As a result, this sensitivity analysis continued to use mycological cure data for the second-line treatments, an approach that made the analysis inconsistent in terms of the outcomes. For this reason, the CDR base case continued to use mycological cure rate as the clinical outcome. However, exploratory analyses were conducted that assumed the ORs of success for efinaconazole compared with no treatment, and were similar across outcomes for efinaconazole compared with systemic antifungal treatments, e.g., the OR of terbinafine achieving a mycological cure compared with efinaconazole (OR = 7,83)[4] was applied as the OR of terbinafine achieving other measures of treatment success relative to efinaconazole (Table 15).

- **Number of infected toenails not consistent with the clinical trial:** The economic model submitted by the manufacturer assumed that product quantity of efinaconazole was based on onychomycosis affecting a single great nail (i.e., the target nail). While this was the minimum required nail involvement in manufacturer-conducted clinical trials,[2] patients in the clinical trials had a mean of 2.8 (median of 3) non-target nails affected in addition to the target nail. The quantity of product required to treat three or four toenails is substantially greater than the product quantity assumed in the economic model (based on two 8 mL bottles). CADTH's base-case reanalysis assumes patients have four affected toenails (one great, three small), which is consistent with the median reported in the clinical trials used as the source of the efficacy data (Table 3). This increases the expected amount of efinaconazole per patient from two bottles to five per year of therapy. CDR also explored the impact of assuming three affected toenails (as per a clinical practice guideline, involvement of up to three nails is considered mild onychomycosis),[20] and four affected nails with two of them being great toenails, in sensitivity analyses (Table 14).
- **Uncertainty in utility value associated with onychomycosis:** The utility value of the onychomycosis health state was based on a small study[6] that elicited time trade-off responses from only six patients with onychomycosis — too few to infer a statistically meaningful estimate of the mean utility value. Moreover, the mean (0.988) and median (0.997) utility values for onychomycosis state were substantially different from each other, which increases uncertainty in the results. When CDR conducted a sensitivity analysis using the median utility value (0.997) from the same study, the results had a large impact on the estimated cost-effectiveness of efinaconazole (Table 14).
- **Use of diagnostic test before treatment initiation:** The manufacturer's model included the cost of a KOH test and fungal culture for patients who required a second-line treatment with terbinafine and itraconazole (as recommended in their product monographs[12,13]), but the model assumed that this test/culture was not required before treatment with efinaconazole. While the efinaconazole product monograph[1] does not suggest that such testing is required, the efficacy data used to inform the model are from clinical trials using patients whose onychomycosis had been confirmed by these tests. If efinaconazole is used in practice without a diagnostic test (i.e., for any patient presenting with dystrophic nails), the efficacy would be expected to be lower than the estimate used in the model, which is based on the manufacturer's clinical trials. This is because many

patients in practice will have non-fungal causes for their dystrophic nails, and will therefore not benefit from efinaconazole. Because the expert consulted by CDR indicated that KOH tests and/or fungal cultures are not commonly performed in practice, and because the manufacturer's model does not include the consequences of test outcomes (e.g., true/false-negative results), the CDR base case assumed that no patient in the model would receive a KOH test or fungal culture. CDR also ran a sensitivity analysis that included a KOH test and fungal culture prior to receiving the first active treatment, if any, as well as a check for efficacy after treatment (Table 14). This approach also corrected an oversight in the manufacturer's model that had resulted in two (near-simultaneous) KOH tests and cultures performed on patients who had failed to achieve a mycological cure using efinaconazole or no treatment and who subsequently received systemic therapy.

- **Recurrence rate after treatment with efinaconazole:** In a long-term observational follow-up study of systemic antifungals by Piraccini,[5] statistically significant differences between relapse rates were found for terbinafine (11.9%) and itraconazole (35.7%). The manufacturer used the overall relapse rate from this study (16.4%) and assumed this to be the recurrence rate in patients receiving any therapy, including efinaconazole or no treatment. This estimate is unlikely to represent real-world recurrence rates for efinaconazole and no treatment, given the differences observed between systemic treatments alone. However, no data were found to inform a more likely scenario. In sensitivity analyses, CDR explored the impact of altering the relative relapse rate for both efinaconazole and no treatment to half or double that of terbinafine (Table 14).
- **Second-line therapy use based on weighted average of two products**: For second-line therapy, i.e., the treatment used in patients who failed to achieve mycological cure after efinaconazole or no treatment, the manufacturer used 2017 Canadian public plan utilization data (excluding Quebec), from IQVIA Pharmastat to estimate the proportion of patients who would receive terbinafine (87%) or itraconazole (13%). However, this assumes that the market share for each product for onychomycosis patients is the same as the overall market share for all patients using either product regardless of diagnosis. Moreover, the effectiveness of the second-line therapy is assumed to be based on a weighted average of the effectiveness of terbinafine and itraconazole, with weights based on their respective market shares that are assumed to remain constant over time. Because these assumptions are questionable, CDR assumed that terbinafine alone (the more commonly used drug), would be used as the second-line therapy (see Table 4), with itraconazole as the sole second-line drug explored in a sensitivity analysis (see Table 14).
- **Parameter uncertainty based on assumptions:** Uncertainty intervals around parameters in the economic model were not based on clinical evidence but on assumptions: generally ± 25% of the mean value. These uncertainty intervals were then used to conduct probabilistic sensitivity analyses. This limits the usefulness of the probabilistic analysis in representing the true uncertainty in model parameters. Additionally, multiple runs of both the manufacturer's model as well as the CDR reanalyses resulted in probabilistic ICURs that were systematically lower than the deterministic ICURs for the same analysis. CDR therefore reported results for both deterministic and probabilistic analyses.

CADTH Common Drug Review Reanalyses

To address the key limitations, CDR conducted the following reanalyses:

1. The number of infected toenails was assumed to be four (one great and three small toenails). This is consistent with the clinical trials of efinaconazole that provided efficacy evidence for the economic analysis.
2. Second-line therapy was assumed to be terbinafine only. This is consistent with the most commonly used systemic antifungal treatment in Canada.
3. No KOH tests or fungal cultures were conducted. This is consistent with clinical practice in Canada, where, according to the clinical expert consulted by CDR, most patients are treated empirically for onychomycosis. This also overcomes the limitation of not modelling test consequences (e.g., true/false-negative outcomes) in the manufacturer's model.
4. CDR base case (1 + 2 + 3).

The results of the CDR reanalyses are presented in Table 3. Because probabilistic ICURs were consistently lower than the deterministic ICURs, both sets of results are presented. Moreover, the uncertainty intervals around model parameters used to inform the probabilistic analysis were based on assumptions (as discussed above) rather than informed by evidence

Compared with the manufacturer's base-case results, the CDR reanalyses reported similar incremental QALYs, but higher incremental costs for efinaconazole compared with no treatment. In the deterministic analysis, efinaconazole was associated with an incremental cost of $410 and 0.0024 QALYs over the five-year time horizon, leading to an ICUR of $169,628 per QALY when compared with no treatment. The CDR probabilistic base case produced a lower ICUR of $151,492 per QALY compared with no treatment.

Table 3: CDR Deterministic Reanalysis of Limitations

	Scenario	Treatments	Deterministic Results			Probabilistic Results		
			Cost ($)	QALYs	ICUR ($ per QALY)[a]	Cost ($)	QALYs	ICUR ($ per QALY)[a]
	Base case submitted by the manufacturer	Efinaconazole	390.07	4.8373		376.39	4.8379	
		No treatment	281.93	4.8346		268.25	4.8352	
		Incremental	108.13	0.0027	40,751	108.15	0.0028	39,286
1	Assume 4 affected toenails (1 great, 3 small) as per clinical trials[2]	Efinaconazole	668.40	4.8373		652.59	4.8378	
		No treatment	281.93	4.8346		268.17	4.8350	
		Incremental	386.47	0.0027	145,646	384.42	0.0028	138,659
2	Assumes second-line systemic therapy is terbinafine only	Efinaconazole	371.71	4.8376		367.47	4.8381	
		No treatment	248.00	4.8352		251.22	4.8355	
		Incremental	123.72	0.0027	51,190	116.25	0.0026	44,334
3	Assumes patients are treated empirically for all therapies	Efinaconazole	357.90	4.8373		344.46	4.8380	
		No treatment	231.55	4.8346		216.59	4.8352	
		Incremental	126.35	0.0027	47,616	128.17	0.0027	46,670

	Scenario	Treatments	Deterministic Results			Probabilistic Results		
			Cost ($)	QALYs	ICUR ($ per QALY)[a]	Cost ($)	QALYs	ICUR ($ per QALY)[a]
4	**CADTH base-case reanalysis (1 + 2 + 3)**	Efinaconazole	630.43	4.8376		624.64	4.8379	
		No treatment	220.47	4.8352		222.90	4.8353	
		Incremental	409.96	0.0024	**169,628**	401.74	0.0027	**151,492**

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] ICUR reported as efinaconazole versus no treatment; probabilistic ICURs are the mean result of 5,000 iterations.

As noted, due to the inflexibility of the model, CDR reanalysis did not conduct a direct comparison of first-line therapy with terbinafine (an oral systemic antifungal). However, based on the data used in the economic model, it is highly likely that terbinafine, as first-line therapy, is both more effective (a mycological cure rate of 90.1% compared with 54.4% for efinaconazole) and less costly than efinaconazole, regardless of the number of nails involved (Table 10). The other indicated systemic antifungal, itraconazole, is less frequently reimbursed by public plans than terbinafine, but it is also more effective than efinaconazole (a mycological cure rate of 78.6%, Table 10), and costs less when three or more toenails require treatment due to the increased cost of efinaconazole as a topical agent when the number of affected toenails increases.

A number of sensitivity analyses were conducted to explore uncertainty in modelling assumptions, which can be found in Table 14. Those with the largest impact on the ICUR included: using the median rather than mean utility value reported in the study, which elicited utility values from six onychomycosis patients;[6] assuming that efinaconazole has a higher recurrence rate than terbinafine; and assuming that the second-line systemic therapy was itraconazole rather than terbinafine. An additional exploratory analysis was conducted to explore the impact of assuming that the ORs of treatment success between efinaconazole and no treatment, and efinaconazole and terbinafine were similar across outcomes (see Table 15).

Price-reduction scenarios were generated for both the manufacturer's results and the CADTH base case. According to the CDR base case, to be considered cost-effective at a willingness to pay threshold of $50,000 per QALY, the price of efinaconazole would need to be reduced by 62% (Table 4). Price-reduction scenarios based on the manufacturer's and CDR's probabilistic analyses can be found in Table 16.

Table 4: CDR Deterministic Reanalysis Price-Reduction Scenarios

ICURs of Efinaconazole vs. No Treatment		
Price	**Base-case analysis submitted by manufacturer ($/QALY)**	**Base Case reanalysis by CADTH ($/QALY)**
Submitted	40,751	169,628
10% reduction	33,758	150,434
20% reduction	26,765	131,239
30% reduction	19,772	112,045
40% reduction	12,779	92,850
50% reduction	5,786	73,656
60% reduction	Dominant	54,461
70% reduction	Dominant	35,267

Issues for Consideration

Patient compliance with long-term topical treatments, such as efinaconazole, is likely to be lower in the real world than is reported in randomized controlled trials, and this would lower the effectiveness of efinaconazole relative to that reported in manufacturer's clinical trials.

Patient Input

Patient input was received from the Canadian Skin Patient Alliance in collaboration with Wounds Canada. Patients indicated they were looking for a permanent cure with quick results of healthy, normal-looking nails. Eight out of nine patients who responded to an online survey conducted in 2018 indicated that they had used efinaconazole, and all eight specified that it had worked at least as well as previous therapies they had tried. One-third of responding patients indicated they had used topical treatments other than efinaconazole, one-third had tried natural health products, and one-third had used laser treatments. It was unclear whether these patients had used oral antifungal therapies. See Clinical Report, Appendix 1 for further details.

Conclusions

The model submitted by the manufacturer had a number of limitations and data-related uncertainties. Key limitations were addressed in the CDR base case by: increasing the number of infected toes to be consistent with the clinical trial, assuming no diagnostic tests assumed were conducted, and assuming that the second-line antifungal treatment was terbinafine only to reflect clinical practice in Canada. However, some key limitations could not be addressed, including the lack of an active first-line comparator, the lack of a relevant outcome from the patient's perspective, and the lack of treatment-specific recurrence data.

The CDR base case compared efinaconazole as first-line therapy for onychomycosis with no treatment (with the assumption that non-responders would be treated with a second-line systemic antifungal). The ICUR was estimated to be $169,628 per QALY. The CDR base case concluded that, to be considered cost-effective compared with no treatment, the price of efinaconazole would need to be reduced by 62%.

CDR also noted that, when considering mycological cure as the primary outcome, efinaconazole is less effective than either terbinafine or itraconazole, the two oral antifungals commonly used in clinical practice. Also, the per-course acquisition cost of efinaconazole is greater than that of terbinafine regardless of the number of toes involved, and also greater than itraconazole if three or more toes are affected.

Appendix 1: Cost Comparison

The comparators presented in Table 5 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 5: CDR Cost Comparison Table for Onychomycosis

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Daily Drug Cost ($)	Average Cost per Course ($)
Efinaconazole (Jublia)	10% w/w, 8 mL bottle	Topical solution	89.0400[a]	One drop to the affected toenail(s) once daily. A second drop should be applied onto affected big toenail(s). No removal necessary	Big toe: 0.53 Other toe: 0.27	**48 weeks** Big toe: 178 Other toe: 89 Four toes: 445
Other topical treatments						
Ciclopirox (generic)	8% w/w, 6.6 mL bottle	Topical solution	7.7433[b]	Apply with brush once daily over entire nail plate. Remove with isopropyl alcohol every 7 days	0.02[b]	**Up to 48 weeks** One toe: 8 Four toes: 15
Systemic treatments						
Itraconazole (generic)	100 mg	cap	4.2075[c]	200 mg twice daily for 7 days, followed by 21 days off. Repeat 3 times	4.21	**12 weeks (3 weeks of active therapy)** 353
Terbinafine (generic)	250 mg	tab	0.7714	250 mg once daily	0.77	**3 to 6 months** 65 to 140
Off-label systemic treatment						
Fluconazole (generic)	50 mg 100 mg 150 mg	tab tab cap	1.2904 2.2891 3.9424	150 to 450 mg weekly[d]	0.56 to 1.69	**48 weeks[d]** 189 to 568

CDR = CADTH Common Drug Review.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed September 2018) unless otherwise indicated and do not include dispensing fees. Wastage of unused medication is assumed.

[a] Manufacturer-submitted price.

[b] Wholesale price as reported by IQVIA Delta PA, September 2018; 1,080 doses per bottle assumed, as reported in Gupta (2018).[11]

[c] Saskatchewan formulary, September 2018.

[d] As cited in Gupta (2015).[4]

Appendix 2: Summary of Key Outcomes

Table 6: When Considering Only Costs, Outcomes and Quality of Life, How Attractive Is Efinaconazole Relative to No Treatment?

Efinaconazole vs. No treatment	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$169,628 per QALY[a]					

CE = cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.

[a] Based on CADTH Common Drug Review reanalyses.

Table 7: When Considering Only Costs, Outcomes and Quality of Life, How Attractive Is Efinaconazole Relative to Terbinafine[a]?

Efinaconazole vs. Terbinafine	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes				X		
Quality of life				X		
Incremental CE ratio or net benefit calculation	Not formally assessed due to lack of flexibility of the model. However, efinaconazole is more costly and less effective in terms of mycological cure rate.					

CE = cost-effectiveness; NA = not applicable.

[a] Comparison based on results from clinical studies and CADTH Common Drug Review comparison of costs.

Appendix 3: Additional Information

Table 8: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments Reviewer to provide comments if checking “no”	None		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking “poor”	None		

Table 9: Authors’ Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer

☐ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☒ De novo economic model done by a private consultant contracted by the manufacturer

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

CDR = CADTH Common Drug Review.

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

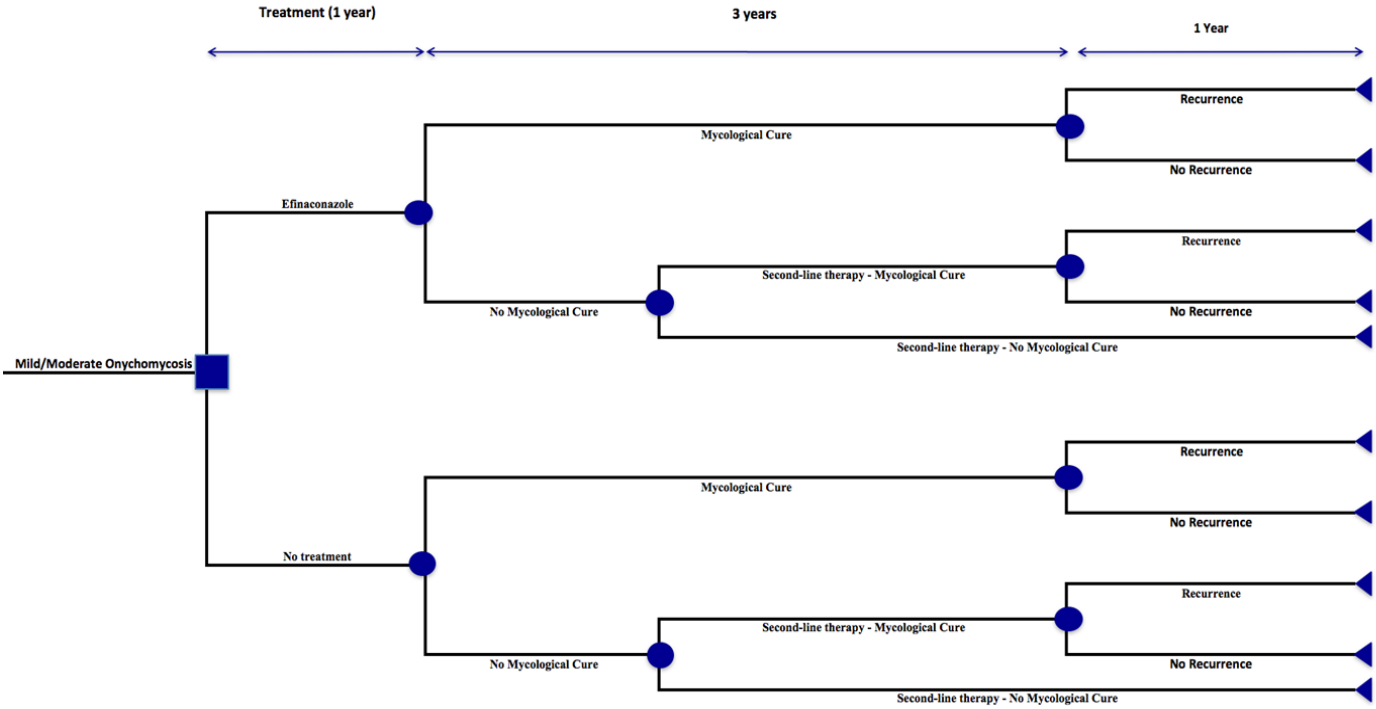
No other health and technology assessment agencies had reviewed topical efinaconazole 10% w/w at the time of this review.

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer undertook a decision-tree model comparing first-line efinaconazole with no treatment in patients with mild-to-moderate toenail onychomycosis. Decision points and accompanying timelines are illustrated in Figure 1. Outcome rates and costs associated with each branch point can be found in Table 10.

Figure 1: Manufacturer's Model Structure



Source: Manufacturer's economic submission, Figure 2.[8]

All patients entering the model initially received 52 weeks of efinaconazole or no treatment, after which 54% of efinaconazole patients and 17% of no-treatment patients had achieved a mycological cure (Table 10). Those not cured received 12 weeks of systemic antifungal therapy, with an 84% chance of successfully achieving a mycological cure. Those who did not achieve a mycological cure after these two lines of therapy remained uncured for the rest of the time horizon. Those who did achieve a cure maintained it for three years after the end of their successful therapy, after which they had a 16% chance of recurrence. Fifty per cent of those with a recurrence were assumed to receive the same treatment that had previously been successful, with the exception of those who had achieved a cure without an active treatment; these patients received systemic antifungals for their recurring onychomycosis.

Table 10: Manufacturer's Modelled Risks and Costs

Treatment	Chance/Risk	Associated Cost
Chance of mycological cure		
First-line efinaconazole	54.4%	$178.08
First-line no treatment (based on vehicle data from efinaconazole trials)	16.8%	$0
Second-line systemic antifungals (pooled average calculated from NMA OR)	83.6%	$103.33
Terbinafine (250 mg daily x 12 weeks)	90.1%	$64.80
Itraconazole (200 mg twice daily, 1 week on, 3 weeks off for 12 weeks)	78.6%	$356.26
Proportion of systemic antifungal patients using terbinafine	86.8%	NA
Recurrence rate, three years after end of successful treatment		
All treatments	16.4%	50% of patients retake previously successful treatment or systemic antifungal
Risk of adverse events		
Application-site dermatitis, efinaconazole	1.9%	$45.13
Drug-drug interaction, terbinafine and itraconazole	0.4%	$5,992.00
Liver disorder, terbinafine and itraconazole	0.008%	$14,811.00
Elevated liver enzymes, terbinafine and itraconazole	0.36%	$410.00

NA = not applicable; NMA = network meta-analysis; OR = odds ratio.

Efinaconazole was associated with a 1.9% risk of application-site dermatitis, with patients requiring two extra follow-up dermatology appointments and a prescription for a topical corticosteroid ($45.13; Table 10). Patients using a systemic antifungal had a risk of experiencing a drug interaction (assumed to result in the Canadian average cost of a standard hospital stay),[16] a liver disorder (resulting in the mean cost of a hospital stay for acute hepatic failure), or elevated liver enzymes (assumed to result in the mean ambulatory cost associated with abnormal liver function results), both sourced through the Ontario Case Costing Initiative.[8] Rates for liver disorders and elevated liver enzymes were taken from product monographs, while the rate of drug-drug interactions was taken from a 2018 cost-effectiveness study, although the method to derive this rate in the study was not reported clearly.[2] No quality-of-life decrements were associated with adverse events.

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Patients assumed to have only a single great toe involvement, using 2 bottles of efinaconazole per treatment course.	Not consistent with clinical trials, where patients had a median of 3 (mean: 2.8; range: 0 to 5) affected non-target in addition to the target toenail.[2]
Efficacy	Efficacy of efinaconazole is based on the weighted-average proportion of patients achieving mycological cure in two RCTs.	While deriving efficacy estimates for a mycological cure is acceptable, this outcome is not clinically relevant in practice, as patients are typically treated empirically (i.e., without conducting fungal tests). Mycological cure is also less important to patients than improvement in nail appearance. Finally, this outcome is not considered reliable by the clinical expert consulted by CDR, given that the result of the outcome is based on precision of sample-taking of the toenail.
Natural history	Patients who achieved a mycological cure were assumed to sustain it for three full years before there was a risk of recurrence, based on the mean reported in a long-term prospective study of patients treated with terbinafine or itraconazole.[5]	CDR found inconsistency in the mean time to relapse (3 years) between the value reported in the text of Piraccini (2009) and the mean calculated from the data table in the paper (9 years). In any case, chance of relapse would be better modelled in a Markov model, to allow for recurrent relapses. Additionally, as there was a statistically significant difference in the proportion of patients relapsing after terbinafine and itraconazole, it is not appropriate to assume all patients, including those who had achieved a cure on topical treatment or no treatment, would have the same relapse risk.
Utilities	Not having onychomycosis was assigned a utility of 1, equivalent to perfect health Taken from a dermatological utility study, Chen (2004). Onychomycosis utility weight (0.988) was based on mean time trade-off responses of 6 patients with onychomycosis.	Acceptable. Given the onychomycosis utility is based on the responses of only 6 patients, uncertainty in the value is high. Onychomycosis data in the utility study were skewed as the mean was 0.988 while the median was 0.997 — a large difference given the small incremental QALYs resulting from the model. This median value of 0.997 was tested in CADTH sensitivity analyses.
Adverse events (indicate which specific adverse events were considered in the model)	The model considered application-site dermatitis as an AE for efinaconazole with the rate from the clinical trials.[2] AEs for terbinafine and itraconazole included elevated liver enzymes and liver disorders (rates from their respective product monographs[12,13]) and drug-drug interactions, with the rate from a 2018 cost-effectiveness study.[11]	Acceptable, with the exception of the drug-drug interaction rate from Gupta (2018), the source of which is not well described.
Mortality	Not included.	Acceptable due to nature of condition.
Resource use and costs	Cost, mycological cure rates, and AE rates for systemic antifungals based on weighted average of terbinafine and itraconazole by utilization, cited by the manufacturer as from IQVIA public claims data from 2017 excluding Quebec.	Utilization data were not provided, but the proportion of terbinafine versus itraconazole was replicated by CDR through the IQVIA Pharmastat database to a close approximation and was therefore accepted as accurate. However, it is not known whether the proportions used to treat onychomycosis are similar to the overall proportion of claims made for all uses.

Data Input	Description of Data Source	Comment
Drug	Cost of efinaconazole supplied by the manufacturer. Cost of second-line therapies from ODB Formulary.	Acceptable, with the exception of the amount of product used per course for efinaconazole.
Administration	Costs of practitioner visits and lab monitoring for systemic antifungals derived from the Ontario Schedule of Benefits for Physician Services, and the Ontario Schedule of Benefits for Laboratory Services.	Sources are appropriate. However, according to the clinical expert consulted by CDR, patients in clinical practice are often treated empirically for onychomycosis, and cultures and KOH tests are typically not done regardless of treatment choice. However, by including efficacy data from trials that included only patients whose infections were confirmed (without including test costs), the manufacturer's submission is biased in favour of efinaconazole. Manufacturer's submission only included such tests for second-line therapies and also double-counted tests for some patients, i.e., those who failed their first-line therapy were tested once to assess that failure, and then again to assess starting a second-line therapy. Additionally, according to the expert consulted by CDR, patients are rarely systematically monitored as described in the terbinafine and itraconazole monographs.
AEs	Costs for application-site reactions, drug interactions, liver disorders and liver enzymes were derived from the ODB formulary, the Ontario Case Costing Initiative,[8] and the CIHI Your Health System Online Tool.[16]	Acceptable.
Health state	Patients either still had onychomycosis or were cured. Patients currently undergoing treatment, active or not, were assumed to still have onychomycosis.	Some improvement is likely to be seen prior to ending therapy. However, the conservative approach is acceptable, given the lack of utility data for varying stages of onychomycosis.

AE = adverse event; CDR = CADTH Common Drug Review; CIHI = Canadian Institute for Health Information; KOH = potassium hydroxide; ODB = Ontario Drug Benefit; QALY = quality-adjusted life-year; RCT = randomized controlled trial.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
Patients who achieve mycological cure or other treatment success outcome sustain it for at least three years	As above.
Patients assumed to have a single affected great nail	Inconsistent with manufacturer's trial data, which reported that, besides the target nail, additional non-target nails were affected. The trials reported a mean of 2.8 and median of 3 affected non-target nails. The manufacturer's assumption of one toenail significantly lowers the price of efinaconazole therapy per patient, while not changing the cost of systemic therapy, biasing the results in favour of efinaconazole.
Relapse rates are identical between all treatments	Unlikely. Piraccini (2010)[5] reported statistically significant differences between relapse rates for terbinafine (11.9%) and itraconazole (35.7%). This estimate is unlikely to represent real-world recurrence rates for efinaconazole and no treatment, given the differences observed between systemic treatments alone.
Weighted average utilization of systemic antifungals approximate use in clinical practice for onychomycosis	Weighted average data were not based on the use of terbinafine and itraconazole for onychomycosis only. Terbinafine is also indicated for fungal infections of skin and nails caused by dermatophytes[12], and itraconazole is indicated for a number of systemic fungal infections in addition to those of the skin and nails.[13] CDR reanalyses used terbinafine only in the base case and used itraconazole alone in a sensitivity analysis.
Confirmatory testing not required for efinaconazole	While the efinaconazole product monograph does not specify that confirmatory testing should be conducted prior to initiating therapy, the manufacturer is assuming a similar population by using efficacy data from clinical trials of patients whose onychomycosis had been confirmed by such tests. Requiring that confirmatory testing be done before the systemic treatments but not before efinaconazole, while assuming the same efficacy as seen in clinical trials, biases the results in favour of efinaconazole. Additionally, the manufacturer assumed that patients who had failed efinaconazole or no treatment would receive a KOH test and culture both to evaluate the efficacy of the first-line drug, and another set of KOH test and smear to judge whether a second-line drug is required. Finally, the manufacturer did not model the cost of testing patients with negative results. The CDR base-case analysis assumed all patients were treated empirically, while a sensitivity analysis assumed all patients received testing prior to active therapies, with duplicate testing removed.

CDR = CADTH Common Drug Review; KOH = potassium hydroxide.

Manufacturer's Results

See Table 2 for the manufacturer's overall results. A breakdown of undiscounted costs by decision branch can be found in Table 13.

Table 13: Cost Breakdown of Manufacturer's Deterministic Base-Case Results (Undiscounted)

Decision-Tree Path	Proportion	Drug Costs ($)	Medical Costs ($)	AE Costs ($)	Recurrence Costs ($)	Total Costs ($)	QALYs
Efinaconazole → cure → recurrence	8.91%	15.87	9.29	0.08	11.19	36.43	0.4436
Efinaconazole → cure → no recurrence	45.44%	80.92	47.35	0.38	0	128.65	2.2665
Efinaconazole → no cure → second-line → cure → recurrence	6.64%	18.68[a]	11.74	1.84	5.24	37.72	0.3303
Efinaconazole → no cure → second-line → cure → no recurrence	33.83%	95.21[a]	59.85	9.37	0	164.43	1.6866
Efinaconazole → no cure → second-line → no cure	5.18%	14.57[a]	9.16	1.43	0	25.16	0.2558
Efinaconazole TOTAL	**100%**	**225.25[a]**	**137.39**	**13.10**	**16.66**	**392.40**	**4.9827**
No treatment → cure → recurrence	2.76%	0	2.88	0	2.18	5.16	0.1375
No treatment → cure → no recurrence	14.09%	0	14.68	0	0	14.68	0.7026
No treatment → no cure → second-line → cure → recurrence	12.09%	12.49	21.39	3.25	9.96	47.09	0.6016
No treatment → no cure → second-line → cure → no recurrence	61.63%	63.68	109.03	16.54	0	189.25	3.0724
No treatment → no cure → second-line → no cure	9.43%	9.75	16.68	2.53	0	28.96	0.4659
No treatment TOTAL	**100%**	**85.92**	**164.66**	**22.32**	**12.24**	**285.13**	**4.9800**

AE = adverse event.

[a] Corrected from manufacturer's Excel file, in which the cost of the second-line therapy was left out of the decision-tree presentation. This error did not affect the manufacturer's results, as they were calculated through different input cells.

CADTH Common Drug Review Reanalyses

The main CADTH reanalyses can be found in Table 3.

To explore uncertainty in the assumptions of the CADTH base case, a series of sensitivity analyses were run, altering the utility weight assumed for onychomycosis to that of the median reported in the source study,[6] the relative recurrence rate between therapies, the choice of second-treatment, and the number and size of affected toenails (Table 14). The model was especially sensitive to choice of utility weight, which is of particular concern given the small differences in quality-adjusted life-years resulting from the model, and the high uncertainty in the utility weight given that the source study based its onychomycosis estimates on the responses of only six patients. Probabilistic results returned by the model are systematically lower than deterministic results.

Table 14: Sensitivity Analyses Around the CADTH Base Case

	Sensitivity Analysis	Treatments	Deterministic Results			Probabilistic Results		
			Cost ($)	QALYs	ICUR ($ per QALY)[a]	Cost ($)	QALYs	ICUR ($ per QALY)[a]
	CDR base case	Efinaconazole	630.43	4.8376	**169,628**	624.64	4.8379	**151,492**
		No treatment	220.47	4.8352	Reference	222.90	4.8353	Reference
1	Onychomycosis utility is median (0.997) from Chen (2004) rather than mean (0.988)	Efinaconazole	630.43	4.8502	**678,513**	624.67	4.8503	**613,104**
		No treatment	220.47	4.8496	Reference	223.06	4.8497	Reference
2	Recurrence rate for efinaconazole and no treatment is twice that of terbinafine's	Efinaconazole	652.19	4.8366	**249,919**	643.64	4.8371	**209,757**
		No treatment	221.98	4.8349	Reference	224.14	4.8351	Reference
3	Recurrence rate for efinaconazole and no treatment is half that of terbinafine's	Efinaconazole	619.55	4.8381	**144,631**	615.92	4.8385	**133,726**
		No treatment	219.71	4.8353	Reference	222.53	4.8356	Reference
4	Second-line therapy is 100% itraconazole	Efinaconazole	768.28	4.8354	**69,617**	758.13	4.8360	**60,606**
		No treatment	475.40	4.8312	Reference	483.10	4.8315	Reference
5	Second-line therapy is 100% terbinafine for 26 weeks (6 months)	Efinaconazole	666.83	4.8376	**156,846**	659.99	4.8381	**140,462**
		No treatment	287.76	4.8352	Reference	291.63	4.8355	Reference
6	Three affected toenails (1 great, 2 small)	Efinaconazole	537.65	4.8376	**131,239**	532.76	4.8380	**117,332**
		No treatment	220.47	4.8352	Reference	223.29	4.8354	Reference
7	Four affected toenails (2 great, 2 small)	Efinaconazole	723.21	4.8376	**208,017**	717.28	4.8378	**185,060**
		No treatment	220.47	4.8352	Reference	223.13	4.8351	Reference
8	Diagnosis confirmation (KOH test and fungal culture) before and after active treatment, no duplication	Efinaconazole	643.28	4.8376	**180,843**	637.79	4.8380	**162,998**
		No treatment	206.27	4.8352	Reference	208.15	4.8354	Reference
9	Monitoring costs removed	Efinaconazole	626.25	4.8376	**171,061**	620.51	4.8381	**154,474**
		No treatment	212.83	4.8352	Reference	215.14	4.8355	Reference
10	AE costs removed	Efinaconazole	616.74	4.8376	**173,759**	611.92	4.8381	**157,527**
		No treatment	196.80	4.8352	Reference	199.06	4.8355	Reference
11	AE costs doubled	Efinaconazole	644.11	4.8376	**165,498**	638.14	4.8380	**148,466**
		No treatment	244.13	4.8352	Reference	247.36	4.8354	Reference

AE = adverse event; ICUR = incremental cost-utility ratio; KOH = potassium hydroxide; QALY = quality-adjusted life-year.

[a] ICUR reported as efinaconazole versus no treatment; probabilistic ICURs are the mean result of 5,000 iterations.

Additionally, the clinical outcome of a mycological cure was used as the efficacy estimate in both the manufacturer's and CADTH's base-case analysis, and is of uncertain relevance. The efinaconazole randomized controlled trials also reported results for complete cure and treatment success with < 10% nail involvement, which the expert consulted by CADTH considered to be more relevant to both patients and clinicians. However, the network meta-analysis used to inform the efficacy of the systemic therapies included in the model only reported mycological cures. CDR attempted an exploratory analysis estimating the efficacy of terbinafine relative to efinaconazole for these other outcomes by assuming the odds ratio reported in the network meta-analysis remained consistent across outcomes. Results from this analysis can be found in Table 15, but have a high degree of uncertainty.

Table 15: Exploratory Analyses Around CDR Base Case Assuming Other Outcomes

Sensitivity Analysis	Treatments	Deterministic Results			Probabilistic Results		
		Cost ($)	QALYs	ICUR ($ per QALY)[a]	Cost ($)	QALYs	ICUR ($ per QALY)[a]
CADTH base case reanalysis (mycological cure)	Efinaconazole	649.14	4.8379	**150,536**	624.64	4.8379	**151,492**
	No treatment	250.36	4.8353	Reference	222.90	4.8353	Reference
Complete cure • **Efinaconazole: 16.6%** • **Terbinafine: 60.5%** • **No treatment: 4.4%**	Efinaconazole	669.83	4.8247	**187,718**	667.82	4.8250	**186,340**
	No treatment	235.56	4.8224	Reference	234.43	4.8227	Reference
Treatment success, 0% nail involvement • **Efinaconazole: 18.4%** • **Terbinafine: 63.5%** • **No treatment: 6.5%**	Efinaconazole	668.06	4.8261	**206,108**	666.24	4.8261	**202,207**
	No treatment	232.88	4.8240	Reference	231.99	4.8239	Reference
Treatment success, < 5% nail involvement • **Efinaconazole: 29.9%** • **Terbinafine: 76.6%** • **No treatment: 11.0%**	Efinaconazole	656.56	4.8320	**187,185**	653.74	4.8322	**184,448**
	No treatment	227.65	4.8297	Reference	226.53	4.8299	Reference
Treatment success, < 10% nail involvement • **Efinaconazole: 40.7%** • **Terbinafine: 84.1%** • **No treatment: 16.0%**	Efinaconazole	645.13	4.8352	**190,790**	641.59	4.8354	**187,288**
	No treatment	221.17	4.8330	Reference	220.10	4.8332	Reference

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: Presented probabilistic results are the mean of 5,000 iterations.

Price-reduction scenarios based on the manufacturer's and CDR's deterministic analyses are reported in Table 4, while those based on the probabilistic analyses are presented in Table 16.

Table 16: CDR Probabilistic Reanalysis Price-Reduction Scenarios

ICURs of Efinaconazole vs. No Treatment		
Price	**Base-case analysis submitted by manufacturer ($/QALY)**	**Base Case reanalysis by CADTH ($/QALY)**
Submitted	39,286	151,492
10% reduction	32,226	135,742
20% reduction	25,639	117,073
30% reduction	19,029	100,259
40% reduction	12,364	82,342
50% reduction	Dominant	65,026
60% reduction	Dominant	47,518
70% reduction	Dominant	30,161

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Note: Presented probabilistic results are the mean of 5,000 iterations.

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