CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

OZENOXACIN 1% CREAM (OZANEX)

(Ferrer Internacional, S.A.)

Indication: The topical treatment of impetigo in patients aged two months and older.

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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.

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

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Abbreviations

CDR	CADTH Common Drug Review
ICUR	incremental cost-utility ratio
ITC	indirect treatment comparison
QALY	quality-adjusted life-year

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Ozenoxacin (Ozanex)
Study Question	What is the cost-effectiveness of ozenoxacin versus other topical antibiotics with similar Health Canada indications for the treatment of impetigo in patients two months and older?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with impetigo aged two months and older
Treatment	Ozenoxacin applied twice daily for five days
Outcome	QALYs
Comparators	• Fusidic acid • Mupirocin
Perspective	Canadian publicly health care payer
Time Horizon	14 days
Results for Base Case	• Ozenoxacin vs. fusidic acid: Dominant (ozenoxacin is associated with lower total costs and more QALYs) • Ozenoxacin vs. mupirocin: $55,792 per QALY
Key Limitations	• The model is deterministic, not probabilistic, rendering it difficult to assess parameter uncertainty and the impact on the estimated ICUR. • Oral antibiotics, deemed appropriate comparators by the clinical expert consulted by CDR for this review, were not considered. • The manufacturer assumed 30 g would be dispensed for comparators, when the recommended amount is 15 g based on clinical practice guidelines. • The model is relatively simplistic in nature and does not take into account consequences of no cure, impetigo recurrence, or resistance to treatment.
CDR Estimates	• Ozenoxacin vs. fusidic acid: $171,907 per QALY gained. • Ozenoxacin vs. mupirocin: $244,184 per QALY. • A price reduction of 28% (vs. fusidic acid) and 51% (vs. mupirocin) would be required for ozenoxacin to be cost-effective at a threshold value of $50,000 per QALY.

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

Drug	Ozenoxacin 1% cream (Ozanex)
Indication	The topical treatment of impetigo in patients aged two months and older
Reimbursement Request	As per indication
Dosage Form(s)	1% w/w topical cream administered twice daily for five days
NOC Date	01-05-2017
Manufacturer	Ferrer Internacional, S.A.

Executive Summary

Background

Ozenoxacin 1% cream is a topical non-fluorinated quinolone antibiotic indicated for the treatment of impetigo in patients aged two months or older.[1] The recommended use for ozenoxacin is the application of a thin layer of cream to affected areas twice daily for five days. It is available in 10 g tubes at $17.78 per tube, or $1.78 per gram.[2]

The manufacturer submitted a cost-utility analysis with a 14-day time horizon — conducted from a Canadian public health care payer perspective — which compared ozenoxacin to fusidic acid and mupirocin (the two topical antibiotics available in Canada). The submitted model was in the form of a decision tree with patients receiving a topical antibiotic treatment and subsequently experiencing cure or no cure based on treatment efficacy.[3] An indirect treatment comparison was used to compare the treatment efficacy of ozenoxacin to fusidic acid, while a Cochrane systematic review and CADTH Rapid Response were used to support the assumption of equal efficacy between fusidic acid and mupirocin.[4,5] The manufacturer reported that ozenoxacin is less costly and is associated with greater quality-adjusted life-years (QALYs) (dominant) compared with fusidic acid, and the incremental cost-utility ratio (ICUR) compared with mupirocin was $55,792 per QALY.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified a number of key limitations with the manufacturer's economic submission. The submitted model was deterministic (not probabilistic, as recommended by CADTH Guidelines[6]) and did not account for parameter uncertainty, making it difficult to quantify uncertainty in the overall results. The manufacturer's model is a simplistic representation of impetigo, only accounting for a single treatment, and not incorporating recurrence of infection, antibiotic resistance, or the consequences of no cure. Further, the submission did not include oral antibiotics as comparators, and as such, the cost-effectiveness of ozenoxacin in this comparison is unknown.

In addition to the aforementioned limitations that could not be addressed by CDR, the manufacturer's submission included some key assumptions that impacted the study results and could be addressed within CDR reanalyses. It was assumed ozenoxacin had a greater treatment efficacy than fusidic acid based on an indirect treatment comparison , and that the efficacies of fusidic acid and mupirocin were similar based on two previously conducted reviews in the literature.[4,5] Based on the critical appraisal by the CDR clinical review team, it

was concluded that there was insufficient evidence to suggest a statistically significant difference in cure rates between ozenoxacin and fusidic acid. The manufacturer also assumed that the time-to-cure would coincide with the last day of treatment course, assuming a five-day treatment course for ozenoxacin and seven-day treatment course for fusidic acid and mupirocin, despite no evidence to indicate how quickly resolution of symptoms would occur, or whether any discernable difference in time-to-cure exists between these treatments. Additionally, the manufacturer assumed that fusidic acid and mupirocin would be dispensed as 30 g tubes despite current clinical practice guidelines recommending 15 g tubes.[7] These assumptions increased the QALYs associated with ozenoxacin and increased costs for the comparators, leading to ICURs that favoured ozenoxacin.

In a revised base-case analysis, CDR considered equal treatment efficacy (in terms of rates of cure) among ozenoxacin and both comparators, as well as guideline-recommended amounts of fusidic acid and mupirocin dispensed (15 g). Ozenoxacin was no longer dominant compared with fusidic acid, but associated with an ICUR of $171,907, while the ICUR for ozenoxacin compared with mupirocin increased to $244,184 per QALY.

Conclusions

Based on a reanalysis considering similar clinical rates of cure among topical treatments, and given the uncertainty associated with the available information and recommended amount of comparator drug dispensed (15 g), the clinical benefit of ozenoxacin was driven by the assumption of a small advantage in the time-to-cure (five days compared with seven to 14 days), while ozenoxacin was associated with a higher drug cost. This resulted in ICURs of more than $170,000 per QALY. A price reduction of 51% and 28% for ozenoxacin would be required for the ICURs to fall to $50,000 per QALY gained versus mupirocin and fusidic acid, respectively. Where the assumption of improvement in time-to-cure is not considered valid, ozenoxacin would be similar in clinical effects to fusidic acid and mupirocin, but would be associated with higher drug costs ($1.05/g to $1.42/g).

The clinical effectiveness of ozenoxacin compared with oral antibiotics was not considered; hence the cost-effectiveness is unknown. Many oral antibiotics are significantly less expensive than ozenoxacin.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis assessing the cost-effectiveness of ozenoxacin for the treatment of impetigo compared with other topical antibiotics — fusidic acid and mupirocin — over a 14-day time horizon.[3] The manufacturer submitted a decision tree model developed in Microsoft Excel to depict the treatment of impetigo. The model structure is simplistic in design, where a patient with impetigo receives either ozenoxacin or one of the comparators, followed by a chance of cure or no cure, which is defined as a marked improvement or resolution of symptoms in impetigo-infected lesions (Figure 1).[3] The manufacturer did not consider the consequences of no cure, impetigo recurrence, or resistance to treatment, and presents a limited aspect of impetigo treatment. The model as provided by the manufacturer was not programmed for probabilistic analyses.

Data on the efficacy and safety for ozenoxacin were obtained from a single study by Gropper et al.,[8] while the relative efficacy compared with fusidic acid was obtained from a manufacturer-created indirect treatment comparison (ITC).[3] The manufacturer assumed the clinical efficacy of mupirocin was equivalent to fusidic acid based on evidence from a Cochrane systematic review (Koning et al.[5]) and a CADTH Rapid Response Report.[4]

Utility values were obtained from a number of published sources.[9-12] Utility values were obtained for the "cure" and "no cure" states, and disutility values were derived for adverse events (e.g., skin reactions and nasopharyngitis). The manufacturer assumed that a "no cure" utility value (0.913) would apply to all patients starting in the model. Patients who moved into the "no cure" branch continued to receive this utility value, while those in the "cure" branch received an improved utility value (0.920) once treatment was completed. The utility value for cure was applied for the number of days remaining in the 14-day time horizon — it was assumed that patients receiving ozenoxacin could experience a cure after five days, while patients receiving fusidic acid or mupirocin could experience cure after seven days, which were the respective treatment durations of the medications.

Patients incurred the cost for a specialist visit and the dispensed medication, with the "no cure" branch incurring additional costs for a follow-up specialist visit. Additionally, it was assumed patients were prescribed 10 g of ozenoxacin compared with 30 g of fusidic acid or mupirocin, offsetting the higher per gram cost of ozenoxacin. Costs and disutilities for treatment-related adverse events were also incorporated into the model. Results were presented in the form of incremental cost-utility ratios (ICURs) for ozenoxacin versus each of the two comparators.

Manufacturer's Base Case

In the manufacturer's base case, ozenoxacin dominated fusidic acid — ozenoxacin was associated with lower total costs (savings of $5.96) and more quality-adjusted life-years (QALYs) (a gain of 0.000049). Compared with mupirocin, ozenoxacin resulted in increased costs ($3.08) and increased QALYs (0.0000552), resulting in an ICUR of $55,792 per QALY gained.

Summary of Manufacturer's Sensitivity Analyses

Two scenario analyses were conducted, one reflecting a 15% price reduction in ozenoxacin, and a second where the price of ozenoxacin was reduced by 15% and all comparators, including ozenoxacin, had the same treatment efficacy. When compared with fusidic acid, ozenoxacin remained dominant in both scenarios, driven by the duration of treatment and the amount of topical antibiotic prescribed. When compared with mupirocin, the first scenario resulted in a reduction in the cost per QALY gained ($7,473 per QALY gained), while the second scenario resulted in a slight increase in the cost per QALY gained ($56,479).

Limitations of Manufacturer's Submission

- **Model does not account for parameter uncertainty: T**he submitted model is deterministic in nature and not programmed to run probabilistic analyses. As such, parameter uncertainty cannot be effectively explored and is not captured within the ICUR estimate. By representing model parameters, such as rates of cure or time-to-cure, as statistical distributions and sampling from them over a number of iterations, probabilistic analyses provide less biased estimates of costs and outcomes than a deterministic analysis, which uses a single point estimate for input parameters; as such, deterministic analyses can often lead to incorrect estimates of cost-effectiveness.[6] The CADTH Common Drug Review (CDR) requested a revised probabilistic model, but the manufacturer felt this would be too resource intensive given the nature of impetigo management and its short treatment duration. Given the small number of input parameters in this model, this was a straightforward request.

- **Omission of relevant comparators:** Oral antibiotics, deemed appropriate comparators by the clinical expert consulted by CDR for this review, were not considered. As such, the clinical effectiveness and cost-effectiveness of ozenoxacin relative to oral antibiotics is uncertain. Oral antibiotics are less costly than topical treatments and are a relevant treatment option for harder-to-treat patients.

- **Assumptions pertaining to the amount of drug dispensed:** The manufacturer assumed that 30 g of fusidic acid or mupirocin would be dispensed in comparison to 10 g for ozenoxacin. The *Anti-infective Guidelines for Community-acquired Infections* suggests a treatment course of five to seven days and that15 g of topical antibiotic be prescribed for fusidic acid or mupirocin.[7] This assumption increased comparator costs, which favoured ozenoxacin. It is important to note that treatment is likely to be individualized, with the treatment duration and the amount of drug dispensed based on the severity of the infection and the response to treatment.

- **Time-to-cure on treatment:** The manufacturer assumed "cure" would occur at the end of the treatment duration — five days for ozenoxacin compared with seven days for fusidic acid or mupirocin — despite a lack of comparative information on this outcome. Additionally, the deterministic nature of the model does not account for the likely variability in time-to-cure. It is unclear whether this assumed time-to-cure is a valid approach, and it is where ozenoxacin derives most of its relative benefit compared with fusidic acid and mupirocin.

- **ITC does not include all comparators:** The ITC only included a comparison between ozenoxacin and fusidic acid, omitting mupirocin. An ITC with all comparators would have

been more relevant to this submission as it would have allowed the comparison of all treatments together in one analysis rather than separate pairwise comparisons.

- **Clinical impact beyond initial course of treatment:** Due to a lack of available clinical data, the manufacturer did not take into account the consequences of no cure, impetigo recurrence, or resistance to treatment, and only represents a very limited aspect of impetigo treatment. It also does not provide much information on the cost-effectiveness of topical antibiotics beyond their initial prescription.

CADTH Common Drug Review Reanalyses

The results of the CDR reanalysis are reported in Table 2. The reanalysis addressed two of the limitations identified above which could be addressed by:

- assuming equal treatment efficacy (rates of cure) for ozenoxacin and both comparators
- assuming 15 g of drug dispensed for fusidic acid and mupirocin, reflecting clinical guidelines.

Compared with the manufacturer's results, the CDR reanalysis reported higher expected QALYs and lower expected costs for both comparators in the equal efficacy scenario, and lower costs for both comparators in the reduction in amount of comparator dispensed scenario. In the CDR base-case analysis combining both scenarios (scenario 3), ozenoxacin was no longer dominant compared with fusidic acid, with an ICUR of $171,907, while the ICUR compared with mupirocin increased to $244,184 per QALY.

Furthermore, a scenario reflecting the list price of the comparator medications in Ontario, and not an average of available public list prices, resulted in minor changes to the ICURs from the CDR base case (scenario 4).

Table 2: CADTH Common Drug Review Reanalysis of Limitations

	Scenario	Treatments	QALYs	Cost	ICUR (per QALY) Ozenoxacin vs. Comparator
	Base case, submitted by manufacturer	Ozenoxacin	0.0351340	$100.78	N/A
		Fusidic acid	0.0350851	$106.73	Dominant
		Mupirocin	0.0350789	$97.70	$55,792
1	**Equal efficacy scenario**	Ozenoxacin	0.0351340	$100.78	N/A
		Fusidic acid	0.0350933	$104.49	Dominant
		Mupirocin	0.0350871	$95.46	$113,274
2	**15 g dispensed for each comparator**	Ozenoxacin	0.0351340	$100.78	N/A
		Fusidic acid	0.0350851	$96.01	$97,293
		Mupirocin	0.0350789	$91.55	$167,164
3 (1+2)	**CDR base-case analysis**	Ozenoxacin	0.0351340	$100.78	N/A
		Fusidic acid	0.0350933	$93.77	$171,907
		Mupirocin	0.0350871	$89.31	$244,184
4	**CDR base-case analysis (scenario 3) with listed drug prices from Ontario**	Ozenoxacin	0.0351340	$100.78	N/A
		Fusidic acid	0.0350933	$94.06	$164,887
		Mupirocin	0.0350871	$88.50	$261,501

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; N/A = not applicable; QALY = quality-adjusted life-year; vs. = versus.

A price reduction analysis (Table 3) was conducted considering the CDR base case, which found that the ICUR for ozenoxacin would fall to $50,000 per QALY compared with fusidic acid and mupirocin at a price reduction of 28% and 51%, respectively.

A scenario analysis was undertaken to assess the impact of a shorter treatment duration and time-to-cure for fusidic acid and mupirocin from seven days to five days, which is a reasonable treatment duration time seen in practice, according to the clinical expert consulted by CDR for this review. Using the CDR base case (scenario 3), both fusidic acid and mupirocin dominated ozenoxacin (Table 4).

A final set of scenario analyses using the CDR base case was conducted to explore the uncertainty associated with the quantity of topical antibiotics dispensed. It was based on:

- the availability of the smallest available tube size, assuming 30 g dispensed for fusidic acid, 15 g for mupirocin, and 10 g for ozenoxacin[13]
- real-world evidence of the number of grams typically prescribed of mupirocin and fusidic acid, despite a lack of information on indication,[13] fusidic acid and mupirocin were assumed to be dispensed in 30 g quantities. Given that this quantity is twice the amount recommended in the *Anti-infective Guidelines for Community-acquired Infections*,[7] it was assumed ozenoxacin would be prescribed similarly and dispensed at 20 g.

In the scenario based on availability of tube size, ozenoxacin was dominant compared with fusidic acid, while the ICUR compared with mupirocin was $244,184. The scenario using real-world evidence to inform the amount of drug dispensed resulted in ICURs of $345,029 and $491,913 when ozenoxacin was compared with fusidic and mupirocin, respectively (Table 13).

Due to the short time horizon of the model, the incremental QALYs were very small, and the ICURs were heavily influenced by costs. In all CDR reanalyses, ozenoxacin represented a more expensive treatment option based on drug costs alone.

Table 3: CADTH Common Drug Review Reanalysis Price Reduction Scenarios

ICURs of Submitted Drug vs. Fusidic Acid (Cost per QALY)		
Price	**Base-case analysis submitted by manufacturer**	**Reanalysis by CDR (based on CDR base case)**
Submitted	Cost-savings	$171,907
10% reduction	Cost-savings	$128,283
15% reduction	Cost-savings	$106,472
20% reduction	Cost-savings	$84,660
25% reduction	Cost-savings	$62,848
30% reduction	Cost-savings	**$41,037**
40% reduction	Cost-savings	Cost-savings
50% reduction	Cost-savings	Cost-savings
60% reduction	Cost-savings	Cost-savings
70% reduction	Cost-savings	Cost-savings
ICURs of Submitted Drug vs. Mupirocin (Cost per QALY)		
Price	**Base-case analysis submitted by manufacturer**	**Reanalysis by CDR (based on CDR base case)**
Submitted	$55,792	$244,184
10% reduction	$23,579	$206,320
15% reduction	$7,473	$187,388
20% reduction	Cost-savings	$168,456
25% reduction	Cost-savings	$149,524
30% reduction	Cost-savings	$130,592
40% reduction	Cost-savings	$92,728
50% reduction	Cost-savings	**$54,864**
60% reduction	Cost-savings	$17,001
70% reduction	Cost-savings	Cost-savings

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

Table 4: CDR Scenario Analysis — Reduction in Time-to-Cure from Seven Days to Five Days for Comparators

Treatments	QALYs	Cost	ICUR (per QALY) Ozenoxacin vs. Comparator
Ozenoxacin	0.0351340	$100.78	N/A
Fusidic acid	0.0393833	$93.77	Dominated
Mupirocin	0.03937711	$89.31	Dominated

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; N/A = not applicable; QALY = quality-adjusted life-year; vs. = versus.

Issues for Consideration

- As noted by the clinical expert consulted by CDR for this review, the prescribing of topical and oral antibiotics for the treatment of impetigo varies by prescribing physician and their preferences, as well as the location and size of impetigo-infected lesions.

- The clinical expert consulted by CDR for this review also noted that the amount of topical and oral antibiotic dispensed may vary from physician to physician. Data obtained from the PharmaStat database indicates that the number of grams dispensed of fusidic acid and mupirocin varies greatly by script.

Patient Input

Patient input was received from the Canadian Skin Patient Alliance. The most commonly reported issues with impetigo are the soreness, pain, and itching due to infected lesions, symptoms that are captured in the outcome of "cure" in the manufacturer's model. With regards to current therapy, the reoccurrence of infection was a concern raised by patients, which is an outcome not captured within the economic submission due to a lack of data for both ozenoxacin and its comparators. Additionally, ease of use of treatment was another primary concern, as current topical antibiotics are messy and sticky and are difficult to apply on young children, making oral antibiotics particularly relevant comparators in such situations.

Conclusions

To account for limitations identified with the manufacturer's economic analysis, a CDR base case assuming equal treatment efficacy and 15 g of drug dispensed for fusidic acid and mupirocin was considered, resulting in an ICUR of $171,907 per QALY gained when compared with fusidic acid, and $244,184 per QALY gained when compared with mupirocin. A price reduction of 28% (versus fusidic acid) and 51% (versus mupirocin) would be required for ozenoxacin to achieve an ICUR threshold of $50,000 per QALY gained. It should be noted that the clinical benefits of ozenoxacin are small (out to five decimal places), and ozenoxacin ($1.78/g) is more expensive than the comparators ($0.36/g to $0.73/g).

CDR was unable to assess the cost-utility of ozenoxacin compared with oral antibiotics. Many oral antibiotics are significantly less expensive than ozenoxacin.

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 of Topical Antibiotics for the Treatment of Impetigo

Drug/ Comparator	Strength	Dosage Form	Price per Gram ($)	Recommended Dosage	Course of Treatment (Days)	Available Tube Size
Ozenoxacin (Ozanex)	**1%**	**Topical antibiotic**	**1.7780[a] (10 g tube = $17.78)**	**Apply a thin layer to affected area twice daily for five days**	**5**	**10 g**
Fusidic acid (fucidin 2% cream)	2%	Topical antibiotic	0.7340	Apply two to three times daily for seven to 14 days	5 to 7[b]	30 g
Fusidic acid and hydrocortisone acetate	2% / 1%	Topical antibiotic	1.3185[c]	Apply three times daily for up to 14 days	5 to 7[b], 14 max.	30 g
Mupirocin (Bactroban)	2%	Topical antibiotic cream	0.5500	Apply three times daily for up to 10 days	5 to 7[b], 10 max.	15 g, 30 g
Mupirocin (generic)	2%	Topical antibiotic ointment	0.3556	Apply three times daily for up to 10 days	5 to 7[b], 10 max.	15 g, 30 g

CDR = CADTH Common Drug Review; max= maximum.

Note: Over-the-counter topicals may also be used (e.g., Polysporin triple antibiotic ointment — polymyxin B / bacitracin zinc / gramicidin) but are generally not listed by participating public drug plans.

[a] Based on manufacturer's submission.[2]

[b] As recommended by the CDR clinical expert and in the *Anti-infective Guidelines for Community-acquired Infections*.[7]

[c] Price from Saskatchewan drug benefit.[14]

Source: Ontario Drug Benefit / Comparative Drug Index (effective April 27, 2018), unless otherwise noted.

Table 6: CDR Cost Comparison Table of Oral Antibiotics for the Treatment of Impetigo

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Price per Course ($)
Amoxicillin / clavulanic acid (Clavulin, generics)	250 mg /125 mg 500 mg /125 mg 875 mg /125 mg 25 mg and 6.25 mg/mL 50 mg and 12.5 mg/mL 200 mg and 28.5 mg/mL 400 mg and 57 mg/mL	Tab Tab Tab O/L O/L Susp Susp	0.9375 0.6673 0.5551 0.0517 0.1830 0.1499 0.2799	Adults: 500 mg/125 mg twice daily for 10 days Children: 25 mg/kg of amoxicillin twice per day for 10 days Children > 38 kg dosed as adults	Adults: 13 Children: 5 kg: 9 20 kg: 37 40 kg: 18 (O/L) or 13 (tab)
Cephalexin (generics)	250 mg 500 mg 250 mg 500 mg 25 mg/mL 50 mg/mL	Cap Cap Tab Tab Susp Susp	0.3703 0.7252 0.2250 0.4500 0.2193 0.3675	Adults: 1 g per day for up to 10 days Children: 25 mg/kg to 50 mg/kg per day every 6 hours for up to 10 days	Adults: 9 Children: 5 kg: 11 to 18 20 kg: 37 to 74 40 kg: 74 to 147
Clindamycin (generics)	150 mg 300 mg	Cap Cap	0.2217 0.4434	Adults: 150 mg every 6 hours for up to 10 days Children (> 18.2 kg and able to swallow): 6 mg/kg to 16 mg/kg per day for up to 10 days	Adults: 9 Children: 5 kg: N/A 20 kg: 2 to 5 40 kg: 4 to 10
Doxycycline	100 mg	Tab	0.5860	200 mg on day 1, 100mg thereafter, for 10 days	6
Erythromycin (Erythro Base, Erythro E-C)	250 mg 250 mg	Tab Cap	0.1865 0.2915	Adults: 1 g per day for ten days Children: 30 mg/kg to 50 mg/kg per day for ten days	Adults: 7 5 kg child: 1 to 2 20 kg child: 4 to 7 40 kg child: 9 to 15
Sulfamethoxazole / trimethoprim (generics)	400 mg / 80 mg 800 mg / 160 mg 40 mg and 8 mg/mL	Tab Tab O/L	0.1077 0.1471 0.1026	Adults: 800 mg sulfamethoxazole and 160 mg trimethoprim twice per day, for at least 5 days Children: 15 mg/kg sulfamethoxazole and 3 mg/kg trimethoprim twice per day, for at least 5 days	Adults: 1 Children: 5 kg: 1 20 kg: 7 40 kg: 15

CDR = CADTH Common Drug Review; Cap = capsule; N/A = not applicable; O/L = oral Liquid; Susp = suspension; Tab = tablet.

Source: Ontario Drug Benefit / Comparative Drug Index (effective March 1, 2018), unless otherwise noted.

Appendix 2: Summary of Key Outcomes

Table 7: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is Ozenoxacin Relative to Fusidic Acid?

Ozenoxacin vs. Fusidic Acid	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)		X				
Drug treatment costs alone		X				
Clinical outcomes			X[a]			
Quality of life		X				
Incremental CE ratio or net benefit calculation	Ozenoxacin dominates fusidic acid					

CE = cost-effectiveness; N/A = not applicable; vs. = versus.

[a] In the CADTH Common Drug Review reanalyses, the benefits in the form of incremental quality-adjusted life-years were out to five decimal places, and while relatively attractive compared with other topical antibiotics, they are small.

Table 8: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is Ozenoxacin Relative to Mupirocin?

Ozenoxacin vs. Mupirocin	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes			X[a]			
Quality of life		X				
Incremental CE ratio or net benefit calculation	$55,792 per QALY					

CE = cost-effectiveness; N/A = not applicable; QALY = quality-adjusted life-year; vs. = versus.

[a] In the CADTH Common Drug Review reanalyses, the benefits in the form of incremental QALYs were out to five decimal places, and while relatively attractive compared with other topical antibiotics, they are small.

Appendix 3: Additional Information

Table 9: 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 10: Author’s 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

☐ Other (please specify)

	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 HTA Reviews of Drug

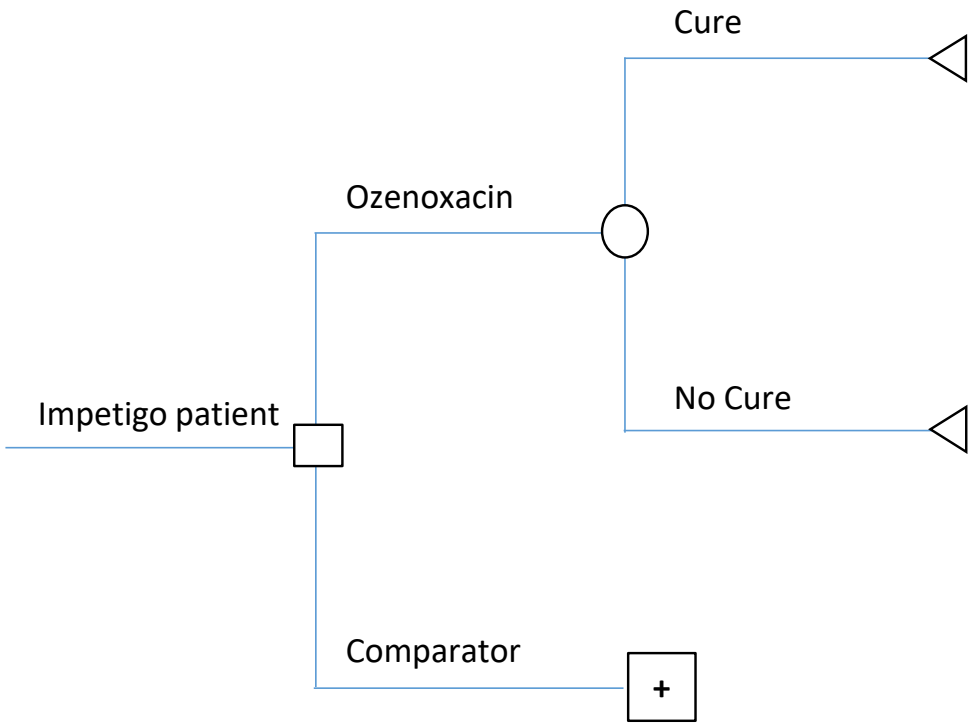
No other completed heath technology assessment reviews for ozenoxacin were identified. Ozenoxacin is currently under review with l'Institut national d'excellence en santé et en services sociaux.

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a decision tree model developed in Microsoft Excel to depict the treatment of impetigo with a topical antibiotic ointment. Within the model structure, a patient with impetigo received either the submitted medication, ozenoxacin, or one of its comparators at the decision node, followed by a chance node with the potential outcomes of "cure" or "no cure," which also serve as the terminal nodes (Figure 1). The model as provided by the manufacturer was not programmed for probabilistic analyses.

Figure 1: Manufacturer's Model Structure



Source: Manufacturer's pharmacoeconomic submission.[2]

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	Efficacy for ozenoxacin obtained from an RCT by Gropper et al., 2014.[8] Indirect treatment comparison conducted by the manufacturer compared with fusidic acid. Efficacy of other comparator, mupirocin, versus ozenoxacin was deemed equivalent with that of fusidic acid versus ozenoxacin, based on published literature (Koning et al.,[4] and Edge and Argaez[5]).	The CDR clinical reviewer critically appraised the manufacturer submitted ITC and determined that there was uncertainty around the comparative efficacy of fusidic and mupirocin, and that no statistically significant difference in cure rate was observed.
Natural history	Not applicable.	Natural history of the disease was not modelled given the simple nature of the model.
Utilities	Utility values for cure and no cure obtained from Pogany 2006[11] and Hay 2014.[10] Disutilities for AEs obtained from Riis 2016 [12] and Delea 2013.[9]	There was concern over the anchor utility value for cure, given that it was derived from a childhood cancer survivorship study. A general age-adjusted utility value for healthy individuals would have been more appropriate given the acute nature of impetigo and its assumed disutility. Despite this concern, the anchor utility value had little impact on resultant ICURs.
Resource use	Unclear, no source listed.	Resource use is appropriate.
AEs (skin reactions, nasopharyngitis)	AE rate of occurrence obtained from the following studies: Gropper 2014 [8], Morley 1998,[15] White 1989, Sutton 1992,[16] Koning 2002,[17] and Oranje 2007.[18]	Sources are appropriate.
Mortality	Not applicable.	Mortality was not included as a consequence of the disease or treatment. This is appropriate.
Costs		
Drug	Comparators drug costs obtained as an average of the provinces where the public drug program price of the drug is available.	It is generally preferable to use the price from a single province.
Administration	Visits to specialists are assumed to occur, with fees obtained from the Ontario Schedule of Benefits.[19]	Source is appropriate.
AEs	AEs were assumed to result in repeat physician visits, with costs for such a visit obtained from the Ontario Schedule of Benefits.[19]	Source is appropriate.

AE = adverse events; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; ITC = indirect treatment comparison; RCT = randomized controlled trial.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
Differential cure rates between ozenoxacin and comparators	Inappropriate. The CDR clinical review team critically appraised the manufacturer submitted ITC and determined that there was uncertainty around the comparative efficacy of ozenoxacin and fusidic acid, and that no statistically significant difference in cure rate was observed.
Five days required for cure to be observed with ozenoxacin, while comparators require seven days	Appropriate. Consultation with the CDR clinical expert indicated treatment duration may range from five to seven days. To account for a potential shorter treatment duration, a scenario analysis where the time-to-cure was five days for all comparators was assessed. When treatment duration was altered for fusidic acid and mupirocin from seven to five days within the CDR base-case analysis, ICURs for ozenoxacin compared with fusidic acid and mupirocin were $1,088,399 and $907,343 per QALY gained.
Amount of drug prescribed for comparators is assumed to be 30 g	Inappropriate. *Anti-infective Guidelines for Community-acquired Infections* recommend 15 g of mupirocin and fusidic acid to be prescribed.[7]
Resource use with no cure: A second physician visit only occurs when patient is not cured	Appropriate.
Cure utility value	Inappropriate. Utility value for cure was obtained from a childhood cancer survivorship study. A general age-adjusted utility value for healthy individuals would have been more appropriate given the acute nature of impetigo and its assumed disutility. Despite this concern, the anchor utility value had little impact on resultant ICURs.

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

Manufacturer's Results

All manufacturer results were reported in the main report.

CADTH Common Drug Review Reanalyses

Table 13: CDR Scenario Analyses — Variation in Amount of Topical Antibiotic Dispensed

	Scenario	Treatments (Amount Dispensed)	QALYs	Cost	ICUR (per QALY) Ozenoxacin vs. Comparator
A	**Amount dispensed based on tube size availability**	Ozenoxacin (10 g)	0.0351340	$100.78	N/A
		Fusidic acid (30 g)	0.0350933	$104.49	Dominant
		Mupirocin (15 g)	0.0350871	$89.31	$244,184
B	**Amount of comparators dispensed based on real-world evidence — and assumption for ozenoxacin**	Ozenoxacin (20 g)	0.0351340	$118.56	N/A
		Fusidic acid (30 g)	0.0350933	$104.49	$345,029
		Mupirocin (30 g)	0.0350871	$95.46	$491,913

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; N/A = not applicable; QALY = quality-adjusted life-year; vs. = versus.

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