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CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

OZENOXACIN 1% CREAM (OZANEX — Ferrer Internacional, S.A.)
Indication: The topical treatment of impetigo in patients aged two months and older

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that ozenoxacin not be reimbursed for the treatment of impetigo.

Service Line:	CADTH Drug Reimbursement Recommendation
Version:	Final
Publication Date:	October 2018
Report Length:	7 Pages

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

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ozenoxacin not be reimbursed for the treatment of impetigo.

Reasons for the Recommendation:

1. No high quality direct evidence comparing ozenoxacin with topical antibiotics used in Canada to treat impetigo was identified. The two phase III, placebo-controlled randomized controlled trials (RCTs) of patients with impetigo identified in the systematic review (Study P-880 and Study P-881) were designed to compare ozenoxacin with vehicle (placebo).

2. The two manufacturer-submitted indirect treatment comparisons (ITCs), of ozenoxacin versus sodium fusidate and ozenoxacin versus mupirocin, had several limitations, including the availability of only one study per direct comparison in each ITC. Limitations of the ozenoxacin versus sodium fusidate ITC included the use of a post hoc end point in Study P-880, and there was a lack of information on the use of concomitant antimicrobial therapies in the other trial. The ozenoxacin verus mupirocin ITC was limited by a high risk of attrition bias and small sample size in one study, and between study heterogeneity in terms of study design and patient characteristics. Consequently, the comparative efficacy and safety of ozenoxacin versus other available topical antibiotic treatments for impetigo remains uncertain.

3. CDEC determined that the reviewed clinical trials do not provide sufficient evidence that ozenoxacin would fulfill an unmet need in the treatment of impetigo.

Discussion Points:

- CDEC noted that impetigo is frequently treated by primary care physicians and that obtaining swabs for culture and sensitivity is not common. Furthermore, local and national data regarding sensitivities to topical antibiotics are not widely available; thus, it is unclear if ozenoxacin has a role in the treatment of impetigo caused by bacteria resistant to fusidic acid and mupirocin. The committee further expressed concern regarding the possibility of promoting quinolone-resistance through the use of ozenoxacin where there is no obvious unmet need.
- CDEC discussed that the *in vitro* surveillance data suggesting increasing resistance to mupirocin and fusidic acid, provided by the manufacturer in their request for reconsideration, were primarily from hospitalized patients with skin and soft tissue infections, and thus may not be reflective of localized impetigo in the community. The extent of resistance-related treatment failure in impetigo infections treated with fusidic acid or mupirocin in the community is uncertain, and clinical evidence of the benefit of topical ozenoxacin after failure of fusidic acid or mupirocin is lacking.
- CDEC noted that the small benefits in quality-adjusted life-years (QALYs) predicted by the manufacturer in the economic model were based on assumptions regarding time-to-cure with the treatments, for which there is no comparative clinical evidence. The lack of information on duration of use was also noted. CDEC considered that in clinical practice patients' or caregivers' application of topical treatments may be based on the appearance of lesions rather than the duration of use recommended in product monographs.
- CDEC noted significant uncertainty with the manufacturer's economic evaluation, and determined that the clinical benefits were unlikely to justify the price premium of ozenoxacin ($1.78 per gram) compared with fusidic acid ($0.73 per gram) and generic mupirocin ($0.36 per gram).

Background:

Ozenoxacin has a Health Canada indication for the topical treatment of impetigo in patients aged two months and older. Ozenoxacin is a non-fluorinated quinolone available as a 1% cream. The Health Canada–approved dose is application in a thin layer to the affected area twice daily for five days.

Summary of CDEC Considerations:

The committee considered the following information prepared by CDR: a systematic review of RCTs of ozenoxacin, and a critique of the manufacturer-submitted ITC and pharmacoeconomic evaluation. It also considered input from a clinical expert with experience in treating patients with infectious disease, as well as patient group–submitted information about outcomes and issues important to patients.

Patient Input Information:

One patient group, the Canadian Skin Patient Alliance, provided input for this submission. Patient perspectives were obtained from an online survey and from online disease discussion boards. The following is a summary of key input from the perspective of the patient group:

- Children with impetigo may not be able to attend school or daycare for days to weeks (depending on the severity of their infection) and parents often need to stay home from work to provide care.
- Itching — sometimes severe enough to lead to bleeding — was the primary concern expressed by patients, although some also experienced fever and general soreness and pain. Self-consciousness about their condition and concerns about being infectious often lead to social isolation.
- Current topical treatments for impetigo were reported as time consuming to apply, as well as messy and sticky, making it difficult to apply and use on young children, particularly infants. Patients' issues with current therapies (oral and topical antibiotics) also included side effects (yeast infection, bad breath, diarrhea, and nausea), lack of efficacy, and cost.
- New therapies for impetigo are expected to be effective, with quick response time, in order to limit the potential spread of the infection to others, as well as to quickly ease the pain symptoms that have been reported.
- None of the survey respondents had experience using ozenoxacin.

Clinical Trials

The systematic review included two phase III, placebo-controlled, double-blind, parallel-group RCTs of patients with clinically diagnosed impetigo with a total affected area of 100 cm^2 or less. Both trials evaluated ozenoxacin 1% cream applied topically as a thin layer to affected areas twice a day (morning and evening) for five days. Patients in Study P-880 (N = 465) were of at least two years of age and were randomized (1:1:1) to ozenoxacin, placebo, or retapamulin. Results from the retapamulin arm were not considered as retapamulin is not currently available in Canada. Patients in Study P-881 (N = 412) were of at least two months of age and were randomized (1:1) to ozenoxacin or placebo. Neither trial included a relevant active comparator or study sites in Canada. Patients were followed for 10 to 13 days.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: clinical response, clinical success, and the need for additional therapy. The primary outcome in both trials was clinical response one to two days after the five days of treatment or "end of study treatment." Neither trial included health-related quality of life outcomes using a validated scale.

- Clinical response: Clinical response was determined according to the presence and severity of individual signs and symptoms on the Skin Infection Rating Scale (SIRS) (see below) and whether or not additional antimicrobial therapy was necessary. To achieve clinical cure at the end of study treatment in Study P-880, a SIRS score of 0 was required for exudate/pus, crusting, tissue warmth, and pain; and a score of 1 or less was required for erythema/inflammation, tissue edema, and itching. To achieve clinical cure at the end of study treatment in Study P-881, a SIRS score of 0 was required for blistering, exudate/pus, crusting, and itching/pain; and a score of 1 or less was required for erythema/inflammation. In addition, in both trials, patients must not have required additional antimicrobial therapy following the study treatment period.
- Clinical success: In Study P-881, an alternative definition of clinical efficacy, referred to as "clinical success," was also evaluated at the end of study treatment. Clinical success was defined as the total absence of treated lesions, treated lesions becoming dry

without crusts (SIRS score of 0 for exudate and crusting), or improvement (decline in size of affected area, number of lesions, or both) such that further antimicrobial therapy was not needed.

- Need for additional therapy: Antibacterial therapies taken on or after the same date as the first dose of study medication were reported as concomitant medications in both trials. Antimicrobial therapies required following the end of study treatment were also documented in Study P-881. Antimicrobial therapies included both topical and systemic therapies.
- SIRS: SIRS consists of several signs and symptoms, each rated on an ordinal scale by the investigator. The SIRS used in Study P-880 was based on seven signs or symptoms: exudate/pus, crusting, erythema/inflammation, tissue warmth, tissue edema, itching, and pain. Scores from 0 to 6 corresponded to the following symptom ratings: "absent" (0), "mild" (2), "moderate" (4), and "severe" (6). The SIRS used in Study P-881 was based on five signs or symptoms: blistering, exudate/pus, crusting, erythema/inflammation, and itching/pain. Scores of 0, 1, 2, and 3 corresponded to ratings of "absent," "mild," "moderate," and "severe," respectively. In patients with multiple affected areas at baseline, each individual sign or symptom score was determined by the highest score observed among all of the lesions. The SIRS is a non-validated scale for which a minimal clinically important difference was not identified.

Efficacy

In Study P-880, 35% of patients in the ozenoxacin arm had clinical cure at the end of study treatment compared with 19% of patients in the placebo arm, for a between-treatment difference of 15.5% (95% confidence interval [CI], 5.6% to 25.5%; *P* = 0.003) in favour of ozenoxacin. In Study P-881, 54% of patients in the ozenoxacin arm had clinical cure at the end of study treatment compared with 38% of patients in the placebo arm, for a between-treatment difference of 16.0% (95% CI, 6.3% to 25.6%; *P* = 0.001) in favour of ozenoxacin.

There was no control for type I error and all outcomes aside from the primary outcome should be considered exploratory in nature. In Study P-881, 89% of patients in the ozenoxacin arm had clinical success (the alternative definition of clinical efficacy) at the end of study treatment compared with 78% of patients in the placebo arm for a between-treatment difference of 10.4% (95% CI, 3.5% to 17.3%) in favour of ozenoxacin. The alternative definition may reflect clinical practice more accurately as it incorporates lesion severity, and number and size of lesions, as well as a greater emphasis on the decision of whether to provide additional treatment.

A greater proportion of patients in the placebo arm of Study P-881 required additional antimicrobial therapy following the study treatment course (as judged by the investigator; 10% in the ozenoxacin arm and 19% in the placebo arm). In both trials, a greater proportion of patients in the placebo arm used concomitant systemic antibiotics (3% versus 5% in Study P-880 and 5% versus 11% in Study P-881 in the ozenoxacin versus placebo arms, respectively) and topical antibiotics (9% versus 16% in Study P-880 and 8% versus 17% in Study P-881 in the ozenoxacin versus placebo arms, respectively).

There were no notable differences from the overall trial populations in clinical response within the subset of patients with a drug-resistant infection. Small sample sizes precluded analysis of differences between treatment arms within this subset.

Harms

In Study P-880, 5.1% of patients in the ozenoxacin arm and 6.4% of patients in the placebo arm had an adverse event (AE). In Study P-881, 3.9% of patients in the ozenoxacin arm and 3.4% of patients in the placebo arm had an AE. There were no serious AEs in either study, though in Study P-881, one patient in the ozenoxacin arm and three patients in the placebo arm withdrew due to an AE. The most common AEs were nasopharyngitis in 2.6% of patients and rash in 1.3% of patients (both in Study P-880).

Indirect Treatment Comparisons

In the manufacturer-submitted ITC of ozenoxacin versus sodium fusidate, two trials (one being Study P-880) were included, with retapamulin as a common comparator. Although the studies were similar in terms of selection criteria, patient characteristics, treatment duration, and end-point assessment, several limitations of the ITC were identified, including the availability of only one study per direct comparison, the use of a post hoc end point for Study P-880 and uncertainty regarding the use of concomitant antimicrobial therapies in the other trial. The ITC suggested no statistically significant difference in clinical success between ozenoxacin and sodium fusidate in patients with impetigo (the risk ratio for sodium fusidate versus ozenoxacin was 0.93 [95% CI, 0.83 to 1.04]).

In a second ITC provided by the manufacturer, two trials (one being Study P-880) were included to compare clinical cure between ozenoxacin and mupirocin, with placebo as a common comparator. In addition to only one study being available per direct comparison, there were differences between the trials in terms of the proportion of patients with lesions positive for *Staphylococcus aureus*, treatment timing relative to clinical assessment, and definition of clinical cure. As well, there was a high risk of attrition bias in the placebo-controlled mupirocin trial as 27% of randomized patients were excluded from the analysis. The ITC suggested no statistically significant difference in clinical cure between ozenoxacin and mupirocin in patients with impetigo (with a risk ratio for mupirocin versus ozenoxacin of 1.08 [95% CI, 0.54 to 2.16]). Another approach taken by the manufacturer to estimate the comparative efficacy of ozenoxacin versus mupirocin was based on a naive comparison between the results of the ITC of ozenoxacin versus sodium fusidate, as well as the results of a meta-analysis of four RCTs comparing mupirocin with fusidic acid — this approach is not methodologically sound.

Cost and Cost-Effectiveness

Ozenoxacin 1% cream is a topical antibiotic indicated for the treatment of impetigo in patients aged two months or older. It is available in 10 g tubes at $17.78 per tube or $1.78 per gram.

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. An ITC 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. The manufacturer reported that ozenoxacin is less costly and associated with greater QALYs (dominant) compared with fusidic acid, and the incremental cost-utility ratio (ICUR) compared with mupirocin was $55,792 per QALY.

CDR identified the following key limitations with the manufacturer's submitted economic analysis:

- The submitted model was deterministic (not probabilistic, as recommended by CADTH Guidelines) and did not account for parameter uncertainty in the model, making it difficult to quantify uncertainty in the overall results.
- Oral antibiotics were not included as comparators within the manufacturer's submission, yet were deemed to be relevant comparators by the clinical expert consulted by CDR.
- The manufacturer assumed that fusidic acid and mupirocin would be dispensed as 30 g tubes despite current clinical practice guidelines and the clinical expert consulted by CDR recommending dispensing as 15 g.
- A difference in time-to-cure for ozenoxacin (five days) and its comparators (seven days) was assumed, despite insufficient clinical evidence.
- The CDR clinical review determined there was insufficient evidence from the manufacturer's ITC to support its assumption of a significant difference in the cure rate between ozenoxacin and its comparators.

Based on a CDR reanalysis considering similar clinical rates of cure among topical treatments, given the uncertainty associated with available information, and the recommended amount of comparator drug dispensed (15g), the clinical benefit of ozenoxacin was driven by the assumption of a small advantage in the time-to-cure (e.g., 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 for ozenoxacin when compared with fusidic acid or mupirocin. 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.

June 20, 2018 Meeting

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

None

Conflicts of Interest:

None

October 17, 2018 Meeting

CDEC Members:

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

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None.