CADTH

CADTH COMMON DRUG REVIEW

Clinical 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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Abbreviations

AE	adverse event
CI	confidence interval
ITC	indirect treatment comparison
ITTB	intention-to-treat bacteriological
ITTC	intention-to-treat clinical
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
PPB	per-protocol bacteriological
PPC	per-protocol clinical
RCT	randomized controlled trial
SD	standard deviation
SIRS	Skin Infection Rating Scale
SR	systematic review

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

Introduction

Impetigo, or impetigo contagiosa, is a contagious superficial skin infection that affects children in particular.[1,2] Bullous impetigo, which accounts for more than 70% of cases and is caused by *Staphylococcus aureus*, is characterized by large bullae or blisters that can rupture and leave thin, brown crusts.[1,3,4] Non-bullous impetigo is characterized by the initial appearance of thin-walled vesicles that rupture and leave honey-crusted lesions that can be painful or itchy.[1] Non-bullous impetigo is most often caused by *S. aureus*, though *Streptococcus pyogenes* may be present with or without *S. aureus*.[1] Without treatment, resolution of impetigo may occur within two to three weeks.[1,2] While the infection is considered self-limiting,[1] it can spread superficially within a patient.[4] Incidence and prevalence of impetigo are not well-established for the Canadian population. Prevalence rates estimates vary from 0.6% to 4.2% in schoolchildren in two northern Canadian indigenous communities to an age-standardized 2.5% to 2.8% in high-income North America.[5,6]

Impetigo is typically diagnosed clinically and treated with topical or oral antibiotic therapies. Topical therapies are recommended for lesions limited in size and spread while oral therapies are recommended for patients with extensive lesions, or in the case of an outbreak in order to decrease transmission.[7,8] The recommended topical therapies for impetigo available in Canada are fusidic acid 2% cream and mupirocin 2% cream.[7] Options for systemic therapy in Canada include cephalexin, clindamycin, cloxacillin, and macrolides,[7] with doxycycline and sulfamethoxazole-trimethoprim potentially useful for methicillin-resistant *S. aureus* infections.[8] While antimicrobial resistance is minimized with a topical therapy as compared with systemic therapy, mupirocin and fusidic acid resistance have been reported in Canada with a trend toward increasing resistance rates over time.[9-11]

The objective of this report is to perform a systematic review of the beneficial and harmful effects of ozenoxacin 1% cream for the topical treatment of impetigo in patients aged two months and older.

Results and Interpretation

Included Studies

This systematic review identified two published phase III, placebo-controlled, double-blind, parallel-groups randomized controlled trials (RCTs). Both trials evaluated ozenoxacin 1% cream applied topically as a thin layer to affected areas twice a day (morning and evening) for five days. Study P-110880-01 (N = 465, referred to in this report as "Study P-880") was conducted from 2012 to 2013 and randomized patients (1:1:1) to one of ozenoxacin, placebo, or retapamulin while Study P-110881-01 (N = 412, referred to in this report as "Study P-881") was conducted from 2014 to 2015 and randomized patients (1:1) to either ozenoxacin or placebo. The studies were conducted in patients with clinically diagnosed impetigo with a total affected area of 100 cm^2 or less at centres in the US, Europe, and South Africa. Study P-881 also included centres in Russia. Patients were aged two years and older in Study P-880 and two months and older in Study P-881. Results from the retapamulin group in Study P-880 are not presented in this review as retapamulin is not available in Canada.

Baseline or visit 1 coincided with the first day of the five-day course of treatment and clinical response was assessed at three subsequent visits. The primary efficacy end point in both trials was clinical cure assessed one to two days after the last day of therapy (visit 3). All other end points were secondary end points and there was no control for type I error. Clinical improvement in Study P-880 and early cure in Study P-881 were assessed on the third or fourth day of therapy (visit 2) and cumulative cure in both trials was assessed five to eight days after the last day of therapy (visit 4). At each post-baseline visit, clinical response was determined according to a set of criteria based on the presence and severity of individual signs and symptoms of the Skin Infection Rating Scale (SIRS) and whether or not additional antimicrobial therapy was necessary. While new lesions were treated, all assessments considered only the affected area identified at baseline.

The SIRS was based on seven signs or symptoms in the affected area in Study P-880 and five signs or symptoms in Study P-881 assessed by investigators blinded to treatment assignment. 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. Each sign or symptom was rated by the investigator on an ordinal scale from 0 to 6. Scores of 0, 2, 4, and 6 corresponded to the following symptom ratings, respectively: "absent," "mild," "moderate," and "severe." The version of the SIRS used in Study P-881 was based on five signs or symptoms: blistering, exudate/pus, crusting, erythema/inflammation, and itching/pain, rated on a scale from 0 to 3; with scores of 0, 1, 2, and 3 corresponding to "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 total SIRS score was determined by the sum of the individual scores for each sign or symptom, yielding a maximum total score of 42 in Study P-880 and 15 in Study P-881.

To achieve clinical cure at visit 3 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 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, patients in both trials

must not have required additional antimicrobial therapy following the study treatment period in order to achieve clinical cure.

An alternative definition of clinical response at visit 3, referred to as “clinical success,” was also evaluated in Study P-881 and was defined as the total absence of treated lesions, treated lesions becoming dry without crusts (a SIRS score of 0 for exudate and crusting), or enough improvement (a decline in size of affected area, number of lesions, or both) that further antimicrobial therapy was not needed.

In both studies, a patient was considered to have clinical improvement at visit 2 if their total SIRS score decreased by more than 10% compared with their baseline score and if they remained on study treatment. In Study P-881, a patient was considered to have early cure at visit 2 if they had clinical improvement and, according to the investigator, did not require any further antimicrobial therapy. In both trials, clinical cumulative cure at visit 4 required a total SIRS score of 0 and no further antimicrobial therapy following the study treatment period. At visit 4 in Study P-881, patients who had a non-zero SIRS total score, met the visit 3 SIRS criteria, and did not receive further antimicrobial therapy following the study treatment period were also considered to have cumulative cure.

Microbiological response was determined from culture results of microbiological samples and was based on the presence or absence of the baseline pathogen, the presence of new microorganisms, and clinical response. Patients had microbiological success at visit 2 or visit 3 if there was documented or presumed eradication of the baseline pathogen. Eradication was presumed if there was no specimen available and the patient had clinical cure, early cure, or improvement at the same visit.

Intention-to-treat and per-protocol analyses were performed for clinical end points in the entire study populations of both trials, as well as in the subset of patients in Study P-880 with an identified baseline pathogen and the subset of patients in Study P-881 with *S. aureus* or *S. pyogenes* present.

Total SIRS score and size of baseline affected area were reported in both trials, while absence of baseline lesions and appearance of new lesions were also reported in Study P-881. Antibacterial therapies taken on or after the same date as the first dose of study medication were reported under concomitant medications in both trials. Concomitant antimicrobial therapies (including both topical and systemic therapies) at visit 3 and antimicrobial therapies required at visit 3 following the study treatment course were also documented in Study P-881.

Each study employed a different version of SIRS, resulting in slightly different definitions of clinical response between the each one. SIRS is not a validated or commonly used scale, making it difficult to compare the primary end point results with other studies of impetigo treatments. A minimal clinically important difference for SIRS total score was not identified.

There were no studies directly comparing the efficacy of ozenoxacin with any of the topical or systemic antibiotics commonly recommended for the treatment of impetigo in Canada. An indirect treatment comparison (ITC) was submitted by the manufacturer to facilitate the estimation of the comparative efficacy of ozenoxacin with the topical therapies fusidic acid and mupirocin; the ITC did not include systemic therapies for impetigo. According to the clinical expert consulted for this review, systemic therapies are relevant comparators because different clinicians will have different thresholds for prescribing systemic therapies based on the extent and severity of the impetigo.

Efficacy

The clinical efficacy of ozenoxacin was demonstrated in both trials by the primary end point — clinical cure at visit 3 (Table 1).

In the primary analysis of Study P-880, 35% of patients in the ozenoxacin group had clinical cure at visit 3 compared with 19% of patients in the placebo group, for a between-treatment difference of 15.5% (95% confidence interval [CI], 5.6% to 25.5%; *P* = 0.003). In Study P-881, 54% of patients in the ozenoxacin group had clinical cure at visit 3 compared with 38% of patients in the placebo group, for a between-treatment difference of 16.0% (95% CI, 6.3% to 25.6%; *P* = 0.001). The results were consistent across all analysis sets and sensitivity analyses for missing responses. The proportion of patients with clinical cure was lower in Study P-880 overall than in Study P-881 and the discrepancy may be due to each trial using a different version of SIRS. The SIRS-based criteria for clinical cure in both studies were considered stringent by the clinical expert consulted for this review as larger affected areas take longer to heal than smaller areas, and signs and symptoms of impetigo may still be present despite apparent resolution of the infection.

The alternative definition (clinical success) used in Study P-881 resulted in a higher proportion of patients with clinical success than the primary end point of clinical cure overall, as well as a smaller between-group difference (10.4% [95% CI, 3.5% to 17.3%] difference in patients with clinical success in favour of ozenoxacin). The alternative definition may reflect clinical practice more accurately as it incorporates both lesion severity and the number and size of lesions, as opposed to severity alone. Given the uncertainty around whether patients receiving additional antimicrobial therapy during the study treatment period could still have clinical cure or clinical success at visit 3, uneven use of such therapies (10% and 19% of patients in the ozenoxacin and placebo groups, respectively) could have biased the results against ozenoxacin.

Greater proportions of patients with cumulative cure at visit 4 were also observed (differences of 12.5% [95% CI, 1.5% to 23.5%] and 10.6% [95% CI, 1.9% to 19.4%] in favour of ozenoxacin in studies P-880 and P-881, respectively). The uneven proportion of patients discontinuing Study P-881 (3% in the ozenoxacin group and 10% in the placebo group) may have biased the results against ozenoxacin at this visit. More than 80% of patients in both treatment groups in both trials had clinical early cure or improvement at visit 2 and there were no differences between treatment groups in clinical improvement in Study P-880 or early cure in Study P-881; however, the threshold for clinical improvement at visit 2 (defined by a 10% decrease in total SIRS score) was not considered to be clinically meaningful by the clinical expert, other than to confirm that the lesions were not worsening.

The difference between treatment groups in the proportion of patients with microbiological success at visit 3 was 27% (95% CI, 18% to 37%) in Study P-880 and 12.2% (95% CI, 3.6% to 20.8%) in Study P-881 in favour of ozenoxacin. Also, proportions of patients with microbiological success at visit 2 were higher in the ozenoxacin group compared with the placebo group in both trials (a difference of 35% [95% CI, 25% to 46%] in Study P-880 and 16.8% [95% CI, 6.4% to 27.2%] in Study P-881). In Study P-881, the microbiological results should be interpreted with caution as a large proportion of microbiological responses were determined by clinical response as opposed to specimen testing.

There were no notable differences from the overall study populations in clinical and microbiological response within the subset of patients from the two trials with a drug-resistant infection (65 resistant *S. aureus* infections and four resistant *S. pyogenes*

infections) or the subset of 18 patients in Study P-881 with a coinfection of *S. aureus* and *S. pyogenes* to suggest altered clinical efficacy in these populations compared with the full study population.

Measures of the symptoms of impetigo supported the results for clinical response, although there were limitations with these outcome measures. There was a trend of SIRS total score decrease with each visit and SIRS total score was lower in the ozenoxacin groups than in the placebo groups at each visit. Total affected area relative to baseline followed the same trends as SIRS total score, but measures of lesion size may not have accurately reflected clinical response because of the longer healing period for larger lesions (as aforementioned). Results from Study P-881 suggested trends toward more patients with absence of the affected area identified at baseline and less frequent development of new lesions at the end of therapy with ozenoxacin treatment.

A greater proportion of patients in the placebo group of Study P-881 required additional antimicrobial therapy at visit 3 following the study treatment course, as judged by the investigator (10% in the ozenoxacin group and 19% in the placebo group). In both trials, a greater proportion of patients used concomitant systemic antibiotics (3% versus 5% in Study P-880, and 5% versus 11% in Study P-881 in the ozenoxacin versus placebo groups, respectively) and topical antibiotics (9% versus 16% in Study P-880, and 8% versus 17% in Study P-881 in the ozenoxacin versus placebo group, respectively) at some point during their time in the study. Since more patients used concomitant antibiotic therapies in the placebo groups of both trials, results from measures of symptoms of impetigo may have been biased against ozenoxacin.

In the manufacturer's 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 in Study P-880 (reported in the publication[12]), and the lack of information on the use of concomitant antimicrobial therapies in the sodium fusidate study. The ITC suggested no statistically significant differences in clinical success between ozenoxacin and sodium fusidate in patients with impetigo (with a risk ratio for sodium fusidate versus ozenoxacin of 0.93 [95% CI, 0.83 to 1.04]).

In a second ITC provided by the manufacturer, two trials 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 *S. 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. There was 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 was used to estimate the comparative efficacy of ozenoxacin versus mupirocin 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. Given the identified limitations, the comparative efficacy of ozenoxacin with other therapies for impetigo remains uncertain.

Microbiological resistance[10] and causative species patterns[2] can vary between regions and because there were no Canadian centres included in Study P-880 or Study P-881, there is uncertainty in their generalizability to the Canadian setting. There is also a possibility that some of the patients in Study P-881 had a skin infection or condition other than impetigo as *S. aureus* or *S. pyogenes* were not identified in a large proportion of the patients. However, the study criteria reflected clinical practice as the clinical expert indicated that impetigo is typically diagnosed clinically without microbiological confirmation. There were limited numbers of patients with affected areas of 50 cm^2 and above and with SIRS total scores in the upper third of the range (particularly in Study P-880). The study population consisted mostly of study patients with lesions of mild-to-moderate severity and limited extent, reflecting the patient population likely to receive topical therapy for impetigo under Canadian guidelines.[7]

Harms

There were no serious adverse events (AEs), though one patient in the ozenoxacin group and three patients in the placebo group in Study P-881 withdrew due to an AE. The most common AEs were nasopharyngitis in four patients and rash in two patients, and skin disorders were present in only three patients or less in each treatment group (Table 1). According to the clinical expert, the safety profile was similar to that of other topical therapies for impetigo.

Potential Place in Therapy[1]

Impetigo, a superficial, contagious bacterial infection, manifests with lesions that can be popular, pustular, and erosive with crusting. It is a common skin infection in children, and can require repeated medical visits and treatment courses. Children are generally excluded from group care or school until 24 hours after therapy has started, thus affecting parental quality of life as well as that of the child. Less commonly, poststreptococcal infection complications, such as glomerulonephritis, can be observed. Although more common in warm and humid conditions, impetigo is still a common primary care issue in Canada, with increased risk in lower socioeconomic status settings.

Treatment of impetigo hastens healing and might reduce infection spread. Topical mupirocin or fusidic acid are commonly used therapeutic options, while extensive disease is usually treated with oral cloxacillin or cephalexin. Over-the-counter topical options, such as bacitracin, might also be expected to be useful; however, they may not be as effective as prescription topical drugs[13] and may induce contact dermatitis or other allergic reactions. The benefits of topical therapy for impetigo include fewer side effects and possibly less contribution to bacterial resistance. Other drugs active against the causative pathogens (the most common of which are group A streptococci and *S. aureus*) may also be used.

There is a potential benefit in adding ozenoxacin 1% cream to current treatments for impetigo as bacterial resistance may be a concern. In places where topical fusidic acid is commonly used, emergence of *S. aureus* resistance has been observed.[14] There are no Canadian data on methicillin-resistant *S. aureus* involvement in impetigo although it has been seen in a proportion of impetigo cases in some studies elsewhere.[15,16] Also, clinical microbiology labs do not ordinarily test or report resistance to topical drugs.

[1] This information is based on information provided in draft form by the clinical expert consulted by CADTH Common Drug Review reviewers for the purpose of this review.

Ozenoxacin 1% cream appears to be safe and reasonably effective, though the trials did not compare it to other therapies. However, the greater cost of this drug may be a barrier to some of the population at risk of having impetigo. Although the prescribed amount of ozenoxacin is likely sufficient to complete a single course of therapy, the amounts of fusidic acid and mupirocin dispensed are likely to suffice for more than one course should there be a recurrence. In cases where repeat treatment is necessary, the overall cost per treatment course may be reduced for fusidic acid or mupirocin, but not for ozenoxacin. Adding this to currently available options in the absence of a head-to-head trial of ozenoxacin 1% cream versus mupirocin or fusidic acid expands the options available, but as resistance to these drugs is not commonly tested or reported, choice would be guided by clinical relapse or by financial means to pay for therapy.

Conclusions

Results from the two included phase III studies showed the efficacy of ozenoxacin twice daily for five days in the treatment of impetigo. A higher proportion of patients achieved clinical cure one to two days after the end of study treatment with ozenoxacin than with the placebo in both trials. The results were supported by analyses of microbiological success, outcomes related to severity and extent of affected areas, and additional antimicrobial therapy use. Cumulative cure five to eight days after the end of the study treatment was also achieved in a greater proportion of patients with ozenoxacin treatment compared with the placebo in both trials. Clinical efficacy was not notably different in patients with drug-resistant infections. The AEs reported did not give rise to any safety concerns and the safety profile of ozenoxacin was similar to that of other topical treatments for impetigo.

Adjusted ITCs of ozenoxacin versus sodium fusidate and of ozenoxacin versus mupirocin suggested similar clinical efficacy between ozenoxacin and the topical comparators; however, the ITCs were based on only one study per direct comparison. The ITC of ozenoxacin and sodium fusidate was also limited by the use of a post hoc end point in Study P-880 and the lack of information on the use of concomitant antimicrobial therapies in the sodium fusidate study. The ITC of ozenoxacin and mupirocin was limited by a high risk of attrition bias, small sample size in one study, and differences between the studies in patient characteristics and study design. Another approach was used to compare ozenoxacin with mupirocin, in which the assumption of similar efficacy between ozenoxacin and mupirocin was based on a naive comparison between results of the ITC of ozenoxacin versus sodium fusidate and the results of a meta-analysis of four RCTs comparing mupirocin with fusidic acid — this approach is not methodologically sound. These limitations contribute uncertainty to the estimates of relative efficacy of ozenoxacin versus topical comparators and the comparative efficacy of ozenoxacin with systemic therapies for impetigo remains unknown.

Table 1: Summary of Results

	P-110880-01		P-110881-01	
Clinical efficacy	**Ozenoxacin N = 155 ITTC Set**	**Placebo N = 156 ITTC Set**	**Ozenoxacin N = 206 ITTC Set**	**Placebo N = 206 ITTC Set**
Clinical response at visit 3, n (%)				
Cure	54 (35)	30 (19)	112 (54)	78 (38)
Failure	98 (63)	120 (77)	91 (44)	121 (59)
Improvement	97 (63)	119 (76)	84 (41)	105 (51)
Failure	1 (0.6)	1 (0.6)	7 (3)	16 (8)
Unable to determine[a]	3 (2)	6 (4)	3 (2)	7 (3)
Mean difference in % of patients with cure, ozenoxacin vs. placebo (95% CI)	15.5 (5.6, 25.5) *P* = 0.003		16.0 (6.3, 25.6) *P* = 0.001	
Clinical response at visit 3 using combined SIRS and size/extent criteria, n (%)				
Success	NA	NA	183 (89)	161 (78)
Failure	NA	NA	20 (10)	41 (20)
Unable to determine[a]	NA	NA	3 (1)	4 (2)
Mean difference in % of patients with success, ozenoxacin vs. placebo (95% CI)	NA		10.4 (3.5, 17.3) *P* = 0.003[b]	
Mean total SIRS score at visit 3[c] (SD)	2.7 (2.9)	4.3 (3.9)	1.6 (2.3)	2.4 (2.9)
Change from baseline, mean (SD)	–12.4 (4.9)	–10.7 (4.8)	–6.0 (2.7)	–5.2 (3.3)
LSM difference in change[d], ozenoxacin vs. placebo (95% CI)	NR		–0.72 (–1.22, –0.23) *P* = 0.004[b]	
Mean size of affected area at visit 3 as a proportion of baseline affected area (SD)	0.304 (0.344)	0.464 (0.424)	0.196 (0.315)	0.406 (0.782)
Microbiological efficacy	**N = 154 ITTB Set**	**N = 152 ITTB Set**	**N = 125 ITTB Set**	**N = 119 ITTB Set**
Microbiological response at visit 3, n (%)				
Success	122 (79)	86 (57)	115 (92)	87 (73)
Eradication	112 (73)	74 (49)	3 (2)	0
Presumed eradication	10 (7)	12 (8)	112 (90)	87 (73)
Failure	16 (10)	55 (36)	8 (6)	20 (17)
Persistence	16 (10)	55 (36)	5 (4)	18 (15)
Presumed persistence	0	0	1 (0.8)	0
Reinfection	0	0	2 (2)	2 (2)
Presumed reinfection	0	0	0	0
Unable to determine[a]	16 (10)	11 (7)	2 (2)	12 (10)
Mean difference in % of patients with success, ozenoxacin vs. placebo (95% CI)	27 (18, 37) *P* < 0.0001[b]		12.2 (3.6, 20.8) *P* = 0.005[b]	
Safety	**N = 156 Safety Set**	**N = 156 Safety Set**	**N = 206 Safety Set**	**N = 205 Safety Set**
Patients with ≥ 1 AE, n (%)	8 (5.1)	10 (6.4)	8 (3.9)	7 (3.4)

	P-110880-01		P-110881-01	
Patients with ≥ 1 SAE, n (%)	0	0	0	0
Patients with skin and subcutaneous tissue disorders, n (%)	0	2 (1.3)	3 (1.5)	3 (1.5)

AE = adverse event; CI = confidence interval; ITTB = intention-to-treat bacteriological; ITTC = intention-to-treat clinical; LSM = least squares mean; NA = not applicable; NR = not reported; SAE = serious adverse event; SD = standard deviation; SIRS = Skin Infection Rating Scale; vs. = versus.

Note: Visit 3 occurred one to two days after the end of the five-day study treatment period.

[a] These patients were not included in calculations of mean difference.

[b] *P* value is descriptive as there was no adjustment for multiplicity.

[c] Maximum total SIRS score was 42 in Study P-110880-01 and 15 in Study P-110881-01.

[d] Analysis of covariance adjusted for baseline total SIRS score.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Introduction

Disease Prevalence and Incidence

Impetigo, or impetigo contagiosa, is a common and contagious superficial skin infection that affects children in particular.[1,2] It occurs either as a primary infection or secondary to pre-existing skin conditions such as eczema, scabies, and trauma.[2,3] Impetigo presents in one of two forms — the non-bullous form is more common than the bullous form and accounts for more than 70% of cases.[3,4]

Bullous impetigo, caused by *Staphylococcus aureus*, is characterized by large bullae or blisters up to about 2 cm in diameter that can rupture and leave thin, brown crusts.[1] The bullae usually appear on the trunk, axilla, extremities, and diaper region.[1] Systemic symptoms, which are uncommon, include fever, diarrhea, and weakness.[1,4] Non-bullous impetigo is characterized by the initial appearance of thin-walled vesicles that rupture and leave honey-crusted lesions that can be painful or itchy.[1] These lesions appear mostly on the face and extremities. Non-bullous impetigo is most often caused by *S. aureus*, though *Streptococcus pyogenes* may be present with or without *S. aureus*, especially in warm and humid climates.[1]

Without treatment, resolution of impetigo may occur within two to three weeks.[1,2] While the infection is considered self-limiting,[1] it can spread superficially within a patient.[4] Complications can arise from non-bullous impetigo, but they are rare. Complications from infections with *S. pyogenes* include guttate psoriasis, cellulitis, scarlet fever, and glomerulonephritis.[1,2] Poststreptococcal glomerulonephritis is the most serious of these complications and it is unclear whether impetigo treatment prevents its occurrence.[1,2]

The patient input submission indicates that lesions can be sore, painful, or itchy, and that fever can interfere with daily functioning and activities. Patients may feel isolated as they try to avoid spreading the infection through contact with others. Patients may also feel self-conscious about their outward appearance. There are notable impacts on families as pediatric patients may need to stay home from school and parents may miss work to provide care. Impetigo can easily spread throughout families and there is an additional burden associated with cleaning sheets, towels, and toys to limit the spread.

Impetigo is the most common skin infection in young children (two to five years old),[1,4] but its incidence and prevalence are not well-established for the Canadian population. In two northern Canadian indigenous communities, three surveys from 1984 to 1985 found prevalence rates ranging from 0.6% to 4.2% in schoolchildren.[6] Occurrence of impetigo varies worldwide and one systematic review found a median prevalence of impetigo in children of 12.3% with a range of 0.2% to 90% when various sampling methods were used.[19] Another systematic review used Bayesian meta-regression analysis to predict an age-standardized impetigo prevalence rate in high-income North America of about 2.5% to 2.8%.[5]

Standards of Therapy

The differential diagnosis of impetigo includes other blistering and rash disorders, and impetigo is typically diagnosed clinically, though an infection may be cultured if the first treatment attempt fails.[1] A systematic review of interventions for impetigo found evidence for the effectiveness of topical and oral antibiotics in treating impetigo.[2] Lesions can be treated

topically if they are limited in size and spread.[7] Oral therapies are recommended by the Anti-Infective Review Panel[7] in Canada and the Infectious Diseases Society of America[8] for patients with extensive lesions, or in the case of an outbreak to decrease transmission. Systemic therapy should also be considered for patients who are immunocompromized, have valvular heart disease, fever, or symptoms suggesting bacteremia, or who have not improved from topical therapy.[7]

The recommended topical therapies for impetigo available in Canada are fusidic acid 2% cream and mupirocin 2% cream.[7] According to the Anti-Infective Review Panel, either cream is applied two to three times a day for about five to seven days.[7,8,20,21] Options for systemic therapy in Canada include cephalexin, clindamycin, cloxacillin, and macrolides.[7] In methicillin-resistant *S. aureus* (MRSA) infections, doxycycline and sulfamethoxazole-trimethoprim represent additional options.[8] Information on oral antibiotic therapies for the treatment of impetigo in Canada is provided in Appendix 7.

The patient input submission identified a few limitations with current therapy, as well as expectations for new therapies. Concerns with current therapy include difficulty in applying topical formulations that are messy and sticky, as well as lack of efficacy in some cases. Therapies that can limit the spread of affected areas and promote faster resolution of the infection would limit painful symptoms and reduce the number of days missed at school and work.

While antimicrobial resistance is reduced with topical therapy compared with systemic therapy, mupirocin and fusidic acid resistance have been reported in Canada. In 4,980 MRSA isolates from 32 hospitals associated with the Canadian Nosocomial Infection Surveillance Program tested from 1995 to 2004, high-level mupirocin resistance (minimum inhibitory concentration [MIC] of at least 512 mcg/mL) was present in 4% and low-level mupirocin resistance (MIC of 8 mcg/mL to 256 mcg/mL) was present in 8% of isolates.[11] Both high-level and low-level mupirocin resistance were more prevalent in MRSA isolates during the last five years of study compared with the first five years (an increase from 1.6% to 7.0% for high-level resistance and 6.4% to 10.0% for low-level resistance). In a study of 150 staphylococcal isolates collected from 2007 to 2008 in two Canadian hospitals, 100 were *S. aureus* isolates and seven of these demonstrated fusidic acid resistance (MIC of at least 2 mcg/mL).[10] A sampling program from 1997 to 2006 tested 217 *S. aureus* isolates, 46.5% of them MRSA, from five Canadian hospitals.[9] Of these, seven methicillin-resistant and seven methicillin-susceptible *S. aureus* isolates (6.5% of all *S. aureus* isolates) demonstrated resistance to fusidic acid (MIC of at least 2 mcg/mL). The percentage of isolates resistant to fusidic acid in each of the five two-year periods increased over the previous period from 3.7% in 1997 to 1998 to 12.2% in 2005 to 2006. However, resistance rates in nosocomial infections may not be generalizable to community-acquired infections.

Drug

Ozenoxacin 1% cream is indicated for the topical treatment of impetigo in patients aged two months and older. It is applied in a thin layer to the affected area twice daily for five days. Ozenoxacin is a non-fluorinated quinolone and inhibits the bacterial DNA replication enzymes DNA gyrase A and topoisomerase IV.

Table 2: Key Characteristics of Ozenoxacin, Fusidic Acid, and Mupirocin

	Ozenoxacin 1% Cream	Fusidic Acid 2% Cream; Sodium Fusidate 2% Ointment	Mupirocin 2% Cream; Mupirocin 2% Ointment
Mechanism of Action	Inhibition of the DNA replication enzymes DNA gyrase A and topoisomerase IV.	Inhibition of bacterial protein synthesis through interference with amino acid transfer from aminoacyl-sRNA to protein on the ribosomes.	Arrest of bacterial protein synthesis through inhibition of isoleucyl transfer-RNA synthetase.
Indication[a]	Topical treatment of impetigo in patients aged 2 months and older.	Treatment of primary and secondary skin infections caused by sensitive strains of *Streptococcus aureus*, *Streptococcus* species, and *Corynebacterium minutissimum*.	Topical treatment of secondarily infected traumatic lesions such as small lacerations, sutured wounds, or abrasions.
Route of Administration	Topical		
Recommended Dose	Thin layer applied to the affected area 2 times daily for 5 days.	Small amount applied to the lesion 2 to 3 times daily for 7 to 14 days. Whenever the lesion is to be covered with a gauze dressing, less frequent applications (1 or 2 daily) may be used.	Small amount applied to the affected area 3 times daily for up to 10 days.
Warnings and Precautions; In Vivo Activity	• Contains benzoic acid, which may increase jaundice in jaundiced neonates due to absorption through the skin. • Shows in vivo activity against *Streptococcus aureus* (including methicillin-resistant strains) and *Streptococcus pyogenes*.	• Virtually inactive against Gram-negative bacteria.	• Shows in vivo activity against *S. aureus* (including methicillin-resistant strains), *Staphylococcus epidermidis,* and beta-hemolytic Streptococcus species.
	• Prolonged use may result in overgrowth of non-susceptible microorganisms. • Prescribing in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patients and risks the development of resistant organisms. • May cause local skin irritation or reaction.		

RNA = ribonucleic acid; sRNA = soluble ribonucleic acid.

[a] Health Canada indication.

Sources: Product monographs for Ozanex,[22] Bactroban,[21] and Fucidin.[20]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of ozenoxacin 1% cream (Ozanex) for the topical treatment of impetigo in patients aged two months and older.

Methods

Studies selected for inclusion in the systematic review include all manufacturer-provided trials considered pivotal by Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Patients two months of age or older with impetigo. **Subgroups:** • Bullous versus non-bullous impetigo • Primary versus secondary impetigo • Previous treatment failure or reinfection • Causative bacterial species (including antibiotic resistance pattern) • Age • Extent of involvement (e.g., severity, location, size, and number of lesions)
Intervention	Ozenoxacin 1% cream (Ozanex), applied as a thin layer to the affected area twice daily for five days.
Comparators	**Topical antibiotics:** • Mupirocin • Fusidic acid • Gramicidin / polymyxin B / bacitracin **Oral antibiotics:** • Amoxicillan / clavulanic acid • Cephalexin • Clindamycin • Cloxacillin • Doxycycline • Trimethoprim / sulfamethoxazole • Macrolides (e.g., erythromycin, clarithromycin, azithromycin)
Outcomes	**Key efficacy outcomes:** • Clinical cure (e.g., per cent achieving, time to clinical cure) • Symptoms of impetigo[a] (e.g., exudates, crusting, tissue warmth, pain, blistering, itching, erythema/inflammation, fever) • Microbiological cure • Health-related quality of life[a] **Other efficacy outcomes:** • Complications of impetigo (e.g., glomerulonephritis, rheumatic fever, cellulitis) • Need for additional therapy for impetigo • Adherence to medication • Tolerability of medication[a] • Caregiver burden[a] • Time away from school or work for patient or caregiver due to impetigo

Outcomes	**Harms outcomes:** • AEs, SAEs, WDAEs, mortality Notable harms (development of antibiotic resistance)
Study Design	Published and unpublished RCTs; phase III and higher

AE = adverse event; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Using a validated scale.

The literature search was performed by an information specialist using a peer-reviewed search strategy, which is presented in Appendix 2.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Ozanex (ozenoxacin).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on February 27, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on June 20, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

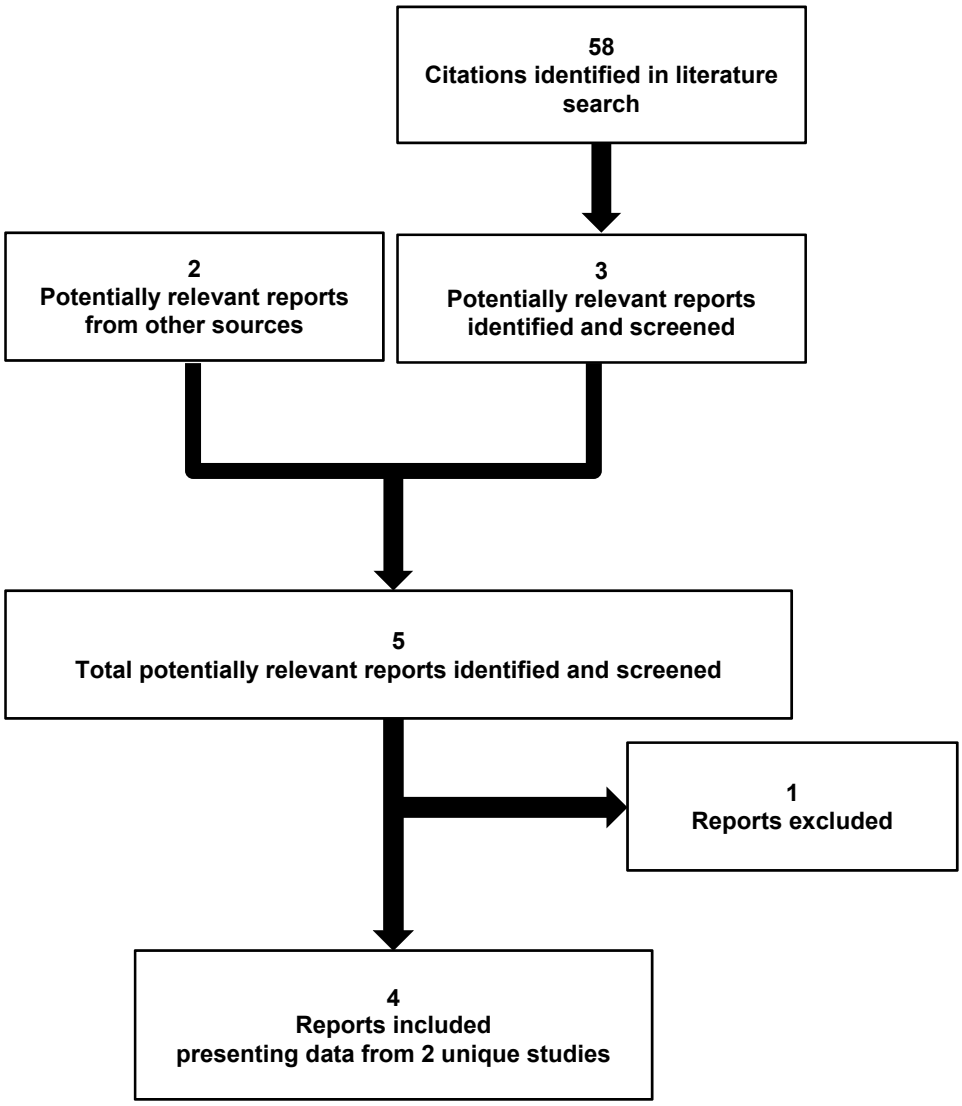

Table 4: Details of Included Studies

		P-110880-01	P-110881-01
Designs & Populations	**Study Design**	Phase III, double-blind, parallel-groups RCT	Phase III, double-blind, parallel-groups RCT
	Locations	27 centres in the US, 11 centres in Europe, and 13 centres in South Africa	34 sites in the US, Europe, South Africa, and Russia
	Randomized (N)	465	411
	Inclusion Criteria	• At least 2 years of age • Clinical diagnosis of bullous or non-bullous impetigo • Total affected area of 1 cm^2 to 100 cm^2 (not exceeding 2% of body surface area for patients < 12 years old) with surrounding erythema not extending more than 2 cm from the edge of any affected area • Total SIRS score ≥ 8 and pus/exudate score of ≥ 1	• At least 2 months of age • Clinical diagnosis of bullous or non-bullous impetigo • Total affected area of 2 cm^2 to 100 cm^2 (not exceeding 2% of body surface area for patients < 12 years old) with surrounding erythema not extending more than 2 cm from the edge of any affected area • Total SIRS score ≥ 3 and pus/exudate score of ≥ 1
	Exclusion Criteria	• Underlying skin disease with clinical evidence of secondary infection • Bacterial infection which, in the opinion of the investigator, could not be appropriately treated by a topical antibiotic • Systemic signs and symptoms of infection (e.g., fever) • Documented or suspected bacteremia • Treatment (of lesions where topical) with: o oral antibiotic within 7 days o topical antibiotic within 7 days o long-acting injectable antibiotic within 30 days o any topical therapeutic drug within 24 hours o any topical antiseptics within 8 hours o any systemic or topical analgesic, anti-inflammatory, or anti-histaminic drugs within 8 hours o systemic prednisone (> 15 mg daily or equivalent) for > 10 days within 14 days o any other investigational drug within 30 days • Known HIV infection or evidence of clinically significant immunosuppression • Current medical history of uncontrolled diabetes • Previous enrolment in the study	
Drugs	**Intervention**	Ozenoxacin 1% cream applied topically as a thin layer to affected areas twice a day (morning and evening) for 5 days.	
	Comparator(s)	Placebo cream applied topically as a thin layer to affected areas twice a day (morning and evening) for 5 days. Study P-110880-01 also included: Retapamulin 1% ointment applied topically as a thin layer to affected areas twice a day (morning and evening) for 5 days.	
Duration	**Phase**		
	Run-in	NA	
	Double-blind	10 to 13 days	
	Follow-up	Visit 1: baseline Visit 2: during study treatment (day 3 or 4) Visit 3: at end of study treatment (day 6 or 7) Visit 4: follow-up after study treatment (day 10 to 13)	

		P-110880-01	P-110881-01
Outcomes	**Primary End Point**	Clinical response (cure or failure) at visit 3	
	Secondary End Points	• Clinical response (improvement or no improvement) at visit 2 • Clinical response (cumulative cure or no cumulative cure) at visit 4 • Difference from baseline in SIRS total score at visits 2, 3, and 4 • Size of affected area as a proportion of baseline area at visits 2, 3, and 4 • Microbiological response (success or failure) at visits 2 and 3 • Microbiological status (documented or presumed eradication, persistence, recurrence, reinfection, presumed reinfection and/or recurrence) at visit 4 • Therapeutic (combined clinical and microbiological) response at visits 2, 3, and 4 • First visit at which sustained clinical response was achieved • First visit at which sustained microbiological eradication was achieved	• Clinical response (success or failure) at visit 3 with additional criteria based on number and size of lesions • Clinical response (early cure, improvement, no improvement) at visit 2 • Clinical response (cumulative cure or no cumulative cure) at visit 4 • Difference from baseline in SIRS total score at visits 2, 3, and 4 • Size of affected area as a proportion of baseline area at visits 2, 3, and 4 • Microbiological response (success or failure) at visits 2 and 3 • Microbiological status (presumed eradication, recurrence, reinfection, presumed reinfection and/or recurrence) at visit 4 • Therapeutic (combined clinical and microbiological) response at visits 2, 3, and 4 • First visit at which sustained clinical response was achieved • First visit at which sustained microbiological eradication was achieved • Use of additional antimicrobial therapy at visits 2 and 3 • Patients with new lesions at visits 2 and 3 • Patients with baseline lesions absent at visits 2, 3, and 4 • Questionnaire on effects of condition on attendance at school or work
Notes	**Publications**	Gropper et al. (2014)[12]	Rosen et al. (2018)[23]

NA = not applicable; RCT = randomized controlled trial; SIRS = Skin Infection Rating Scale.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report,[18] Gropper et al.,[12] Rosen et al.[23]

Included Studies

Description of Studies

This systematic review identified two published phase III, placebo-controlled, double-blind, parallel-groups Randomized Controlled Trails (RCTs). Study P-110880-01 (N = 465, referred to in this report as “Study P-880”) was conducted from 2012 to 2013 and included three treatment groups (ozenoxacin, placebo, and retapamulin) while Study P-110881-01 (N = 412, referred to in this report as “Study P-881”) was conducted from 2014 to 2015 and included two treatment groups (ozenoxacin and placebo). Both studies were conducted at centres spanning multiple continents, including North America, Europe, and Africa.

Populations

Inclusion and Exclusion Criteria

Patients in Study P-880 were aged two years and older with bullous or non-bullous impetigo with a total affected area of 1 cm^2 to 100 cm^2. The lesion (or most severe lesion in the case of multiple lesions) had to be of a minimum severity (seven-symptom Skin Infection Rating Scale [SIRS] total score of at least 8) with some pus or exudate present (SIRS score of ≥ 1). The inclusion criteria were identical in Study P-881, except that the minimum age was two months, the minimum total affected area was 2 cm^2, and a five-symptom SIRS was used to determine lesion severity (with a minimum total score of 3).

Patients in both trials were excluded if the infection was secondary to an underlying skin disease, if the infection could not be appropriately treated by a topical antibiotic (in the investigator's opinion), or if there was a systemic infection present. Patients were also excluded if they had taken oral antibiotics or had applied topical antibiotics to the lesions within a week of screening. Those with uncontrolled diabetes and those who had previously enrolled in the study were also excluded. Additional information on patient selection criteria is provided in Table 4.

Minimum numbers of patients in specified age categories had to be enrolled in each study; at least 58 patients aged less than 12 years, and at least 24 patients aged 12 to less than 18 years in Study P-880; and at least 226 patients aged less than 12 years, and at least 20 patients aged 12 years to less than 18 years in Study P-881.

Baseline Characteristics

Detailed information on baseline characteristics in both treatment groups in both trials is provided in Table 5. The majorities of patients in both trials were under 12 years of age and had non-bullous impetigo. Baseline characteristics were well-balanced between the ozenoxacin and placebo groups in both trials, aside from differences in total affected area. Total affected area was smaller in the ozenoxacin group compared with the placebo group in Study P-880, and larger in the ozenoxacin group compared with the placebo group in Study P-881.

There were some differences in baseline characteristics between studies. While the gender ratio was approximately 1:1 in Study P-881, Study P-880 included a higher proportion of males. At least 85% of patients in both treatment group in both trials were black or white, with higher proportions of patients who are black in Study P-880. Higher proportions of patients were Hispanic or Latino in Study P-881 compared with study P-880. Most patients had non-bullous impetigo, which was more prevalent in Study P-881. Total score on SIRS was higher relative to the maximum total score in Study P-881 (about 7.6 points out of 15 points in Study P-881 compared with 15 points out of 42 points in Study P-880), indicating that lesions in Study P-881 may have been more severe. Multiple areas of involvement were more common in Study P-881.

While almost all patients in Study P-880 had either *S. aureus*, *S. pyogenes*, or both pathogens isolated from their lesions, less than 65% of patients in Study P-881 had those pathogens isolated from their lesions (see intention-to-treat bacteriological [ITTB] population in Table 9).

Table 5: Summary of Baseline Characteristics

	P-110880-01		P-110881-01	
	Ozenoxacin N = 156 Safety Set	**Placebo N = 156 Safety Set**	**Ozenoxacin N = 206 Safety Set**	**Placebo N = 205 Safety Set**
Mean age, years (SD)	16.1 (17.7)	17.3 (17.2)	18.7 (18.1)	18.5 (18.6)
Age, n (%)				
≥ 2 years and < 12 years	95 (61)	94 (60)	NA	NA
≥ 2 months and < 12 years	NA	NA	114 (55)	112 (55)
≥ 12 years and < 18 years	19 (12)	18 (12)	23 (11)	23 (11)
≥ 18 years	NR	NR	69 (34)	70 (34)
≥ 18 years and < 65 years	36 (23)	40 (26)	NR	NR
≥ 65 years	6 (4)	4 (3)	NR	NR
Gender, n (%)				
Male	100 (64)	96 (62)	112 (54)	98 (48)
Female	56 (36)	60 (39)	94 (46)	107 (52)
Race, n (%)				
White	58 (37)	62 (40)	122 (59)	139 (68)
Black	78 (50)	77 (49)	53 (26)	38 (19)
Mixed race	19 (12)	15 (10)	15 (7)	13 (6)
Asian	1 (0.6)	0	16 (8)	15 (7)
Native American	0	2 (1)	0	0
Ethnicity, n (%)				
Hispanic or Latino	7 (5)	14 (9)	57 (28)	62 (30)
Mean weight, kg (SD)	38.9 (26.4)	41.5 (25.9)	47.3 (28.9)	45.6 (28.1)
Mean body surface area, m^2 (SD)	1.17 (0.53)	1.24 (0.50)	1.32 (0.56)	1.29 (0.53)
Type of impetigo, n (%)				
Bullous	34 (22)	34 (22)	25 (12)	33 (16)
Non-bullous	122 (78)	122 (78)	181 (88)	172 (84)
Mean number of affected areas (SD)	3.0 (3.7)	2.8 (3.4)	2.6 (2.2)	2.5 (2.2)
Number of affected areas, n (%)				
1	72 (46)	78 (50)	78 (38)	89 (43)
2 to 4	59 (38)	54 (35)	104 (51)	85 (42)
5 to 10	18 (12)	18 (12)	21 (10)	27 (13)
> 10	7 (5)	6 (4)	2 (1)	3 (2)
Missing	0	0	1 (0.5)	1 (0.5)
Lesion location, n (%)				
Face	80 (51)	68 (44)	113 (55)	104 (51)
Upper trunk	5 (3)	3 (2)	27 (13)	20 (10)
Lower trunk	12 (8)	10 (6)	19 (9)	26 (13)
Right arm	24 (15)	22 (14)	33 (16)	39 (19)
Left arm	26 (17)	21 (14)	23 (11)	21 (10)
Right leg	30 (19)	37 (24)	28 (14)	32 (16)
Left leg	47 (30)	47 (30)	27 (13)	31 (15)
Mean total affected area, cm^2 (SD)	9.3 (16.7)	12.8 (21.4)	10.3 (13.0)	8.8 (8.1)
Total affected area, n (%)				
< 2 cm^2	46 (30)	34 (22)	0	0
≥ 2 cm^2 and < 10 cm^2	74 (47)	80 (51)	141 (68)	144 (70)

	P-110880-01		P-110881-01	
≥ 10 cm^2 and < 50 cm^2	28 (18)	30 (19)	58 (28)	60 (29)
≥ 50 cm^2 and < 100 cm^2	8 (5)	12 (8)	6 (3)	0
Missing	0	0	1 (0.5)	1 (0.5)
Mean total affected area, % of body surface area (SD)	0.08 (0.13)	0.10 (0.14)	0.10 (0.15)	0.07 (0.06)
Mean SIRS total score [a] (SD)	15.1 (4.5)	15.0 (4.0)	7.6 (2.2)	7.6 (2.3)
SIRS total score[a], n (%)				
< 15	80 (51)	78 (50)	NR	NR
15 to 28	75 (48)	78 (50)	NR	NR
29 to 42	1 (0.6)	0	NR	NR
Pathogens isolated, n (%)				
Staphylococcus aureus	93 (60)	98 (63)	115 (56)	108 (53)
Streptococcus pyogenes	73 (47)	67 (43)	19 (9)	20 (10)
Staphylococcus aureus and *Streptococcus pyogenes*	NR	NR	9 (4)	9 (4)
Missing	13 (8)	10 (6)	NR	NR
Pathogens other than *Staphylococcus aureus* or *Streptococcus pyogenes*	NR	NR	79 (38)	68 (33)
Prior use of disallowed medication, n (%)	5 (3)	2 (1)	8 (4)	4 (2)

NA = not applicable; NR = not reported; SD = standard deviation; SIRS = Skin Infection Rating Scale.

[a] Out of a maximum of 42 in Study P-110880-01 and 15 in Study P-110881-01.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Interventions

In both trials, each patient was assigned a unique patient number upon enrolment (in chronological order of screening). Patients were randomized with stratification according to age subset and allocated using an interactive Web response system. In Study P-880, patients were randomized (1:1:1) to one of ozenoxacin, placebo, or retapamulin. In Study P-881, patients were randomized (1:1) to either ozenoxacin or placebo.

In both trials, study medication (ozenoxacin 1% cream, placebo cream, or retapamulin 1% ointment) was applied topically twice a day, in the morning and evening, as a thin layer to the affected areas identified at baseline. Patients or caregivers were instructed to wash their hands before and after application of the study medication and they applied a thin, uniform film about the thickness of a sheet of paper to the affected area and rubbed it in gently. The duration of study treatment was five days. Any new lesions were treated as they appeared, but were not included in assessments of clinical and microbiological response. Patients or caregivers recorded information on medication applications in a patient diary and the number of tubes of study medication dispensed and returned was recorded by study personnel. The ingredients of the ozenoxacin and placebo creams were identical, with the exception of the active ingredient in the ozenoxacin cream and the use of quinoline yellow in the placebo cream to match the appearance of the ozenoxacin cream. The creams were also identical in smell and consistency and were packaged in matching tubes.

Blinding to treatment assignment was maintained in patients and investigators by storing study medication in identical opaque boxes, dispensing study medication in the absence of the investigator, and instructing patients not to inform the investigator about the medication

dispensed. Because of the different appearance of the retapamulin ointment, any comparisons involving the retapamulin group in Study P-880 were considered to be investigator-blinded and not patient-blinded.

Retapamulin is a topical antibiotic not currently available in Canada. The primary efficacy end point in Study P-880 was compared between the retapamulin and placebo groups to establish interval validity, with the rationale that the efficacy of retapamulin for impetigo had already been established. However, given that retapamulin in not available in Canada, the data for this treatment group are not included in this report.

Patients were excluded from the studies if they had taken antibiotics or used topical drugs in the period before screening. In addition, the following medications were not allowed during the studies: systemic antibiotics, topical therapeutic drugs applied to the treated area (including antibacterial soaps, lotions, or wipes, as well as antiseptics), more than 15 mg of systemic prednisone or equivalent, and other treatments that in the investigator's opinion could confound the evaluation of treatment effect. However, patients could discontinue study medication and, at the discretion of the investigator, continue with another antimicrobial therapy (topical or systemic) for the affected area. At the end of the five days of study treatment, the patient could receive another antimicrobial therapy, also at the discretion of the investigator. Antibacterial therapies taken on or after the same date as the first dose of study medication were reported under concomitant medications in both trials.

Efficacy Outcomes

Study Visits

Both trials had the same schedule of assessments. Screening, baseline assessments, and treatment initiation took place at visit 1 on day 1. Patients were contacted by phone 24 to 36 hours after visit 1 and were asked to return for clinical evaluation if the infection had worsened. If the investigator determined that the infection had worsened, the patient discontinued the study medication, was withdrawn from the study, and attended an early termination visit during which efficacy and safety outcomes were assessed. Patients whose infection had not worsened attended visit 2 on day 3 or 4 during the five-day course of study treatment. Assessments were also performed at visit 3 on day 6 or 7 (one to two days after the end of study treatment) and at visit 4 on day 10 to 13 (five to eight days after the end of study treatment).

Clinical Response

In both trials, the primary efficacy end point was clinical response, categorized as cure or failure, at the end of study treatment at visit 3. All end points other than the primary end point were classified as secondary end points and should be considered exploratory as there was no control for type I error. Clinical response was a dichotomous outcome at each of visits 2, 3, and 4 and was determined by the clinical status assigned (see Table 8). Categorization of clinical status at each visit was determined through sets of criteria based on SIRS scores and the need for additional antimicrobial therapy. The criteria for each clinical status are provided in Table 6. The first visit at which there was a clinical status of "early cure," "improvement," "cure," or "post-therapy cure" that was then sustained or improved was also reported.

The SIRS was based on seven signs or symptoms (exudate/pus, crusting, erythema/inflammation, pain, itching, tissue warmth, and tissue edema) in the affected area in Study P-880 and five signs or symptoms (exudate/pus, crusting, erythema/inflammation,

itching/pain, and blistering) in Study P-881. Details on SIRS scoring for each individual sign or symptom are provided in Appendix 5. Individual sign or symptoms were scored on an ordinal scale of 0 to 6 in Study P-880 and 0 to 3 in Study P-881, with 0 indicating absence of the sign or symptom and higher numbers indicating higher severity. 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 baseline lesions.

An alternative clinical efficacy end point at visit 3, clinical success, was evaluated as a secondary end point in Study P-881. Clinical success was defined as the total absence of treated lesions, treated lesions becoming dry without crusts (a SIRS score of 0 for exudate and crusting), or enough improvement (a decline in size of affected area, number of lesions, or both) that further antimicrobial therapy was not needed.

In Study P-881, the presence and absence of baseline lesions were reported for visits 2, 3, and 4 and the appearance of new lesions was reported for visits 2 and 3.

Table 6: Clinical Status Definitions

Clinical Status	Criteria
Visit 2 (On Therapy)	
Early cure, applicable to Study P-110881-01 only	• Total SIRS score decreased > 10% compared with baseline (visit 1) • According to the investigator criteria no additional antimicrobial therapy was necessary • The patient continued treatment with study medication
Improvement	• Total SIRS score decreased > 10% compared with baseline (visit 1) • The patient continued treatment with study medication
No improvement	• One of the following: o No change in total SIRS score o Total SIRS score increased compared with baseline (visit 1) o Total SIRS score decreased ≤ 10% compared with baseline (visit 1) • The patient could continue treatment with study medication or other antimicrobial therapy at the discretion of the investigator
Visit 3 (End of Therapy)	
Cure	• For Study P-110880-01: SIRS score 0 for exudates/pus, crusting, tissue warmth, and pain; and no more than 1 each for erythema/inflammation, tissue edema, and itching • For Study P-110881-01: SIRS score 0 for blistering, exudates/pus, crusting, and itching/pain; and no more than 1 for erythema/inflammation • No additional antimicrobial therapy in the baseline affected area was necessary
Improvement	• Total SIRS score decreased > 10% compared with baseline and not fulfilling the criteria of individual SIRS scores for cure • The patient could continue treatment with another antimicrobial therapy at the discretion of the investigator
Failure	• One of the following: o No change in total SIRS score o Total SIRS score increased compared with baseline o Total SIRS score decreased ≤ 10% compared with baseline • Additional antimicrobial therapy of the baseline affected area was necessary
Visit 4 (Follow-Up)	
For patients classified as cure at visit 3:	
Cure	• Total SIRS score of 0 • No further antimicrobial therapy in the baseline affected area is necessary
No change	• Total SIRS score > 0 • For Study P-110880-01: SIRS score 0 for exudates/pus, crusting, tissue warmth, and pain; and no more than 1 each for erythema/inflammation, tissue edema, and itching

Clinical Status	Criteria
	• For Study P-110881-01: SIRS score 0 for blistering, exudates/pus, crusting, and itching/pain; and no more than 1 for erythema/inflammation • No additional antimicrobial therapy in the baseline affected area is necessary
Relapse	• Total SIRS score > 0 not fulfilling the criteria of individual SIRS scores for no change • Additional antimicrobial therapy of the baseline affected area was necessary
For patients classified as improvement or failure at visit 3:	
Post-therapy cure	• Patients classified as improvement at visit 3 who, at the discretion of the investigator, did not receive any further antimicrobial therapy • Total SIRS score of 0 at visit 4
Failure	• For Study P-110880-01, one of the following: o Patients classified as improvement at visit 3 who did not receive any further antimicrobial therapy, and with a total SIRS score > 0 at visit 4 o Patients classified as improvement at visit 3 who received another antimicrobial therapy o Patients classified as failure at visit 3 • For Study P-110881-01, one of the following: o Patients who received another antimicrobial therapy o Patients with total SIRS score > 0
For all patients:	
Unable to determine	Patients who did not meet any of the classifications previously listed

SIRS = Skin Infection Rating Scale.

Note: A patient had to meet all of the criteria corresponding to a clinical status to be categorized under that status.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Microbiological Response

Determination of microbiological status at visits 2, 3, and 4 was based on the presence of the pathogen(s) identified from the baseline microbiological specimen, the presence of other microorganisms, and the clinical response at the same visit (Table 7). In turn, microbiological response at each visit was determined from microbiological status (Table 8). Microbiological response (success or failure) was compared between treatment groups at visits 2 and 3, and microbiological statuses were summarized at visit 4. The first visit at which there was a microbiological response of confirmed or presumed eradication that was then sustained was also reported.

The baseline microbiological sample was taken from the most severe area (as determined by the investigator) and the same area was preferably sampled at subsequent visits. In bullous lesions, samples were collected either by aseptic needle aspiration or swabbing of exudate. In non-bullous lesions, samples were collected by swabbing. Crusted lesions were cleaned and then raised to access fresh exudate for swabbing. Since both Gram stain and culture were performed on samples, separate swabs were obtained for these tests. Microbiological specimens were sent to a central laboratory for culture, Gram stain, and characterization of resistance to methicillin, ciprofloxacin, mupirocin, fusidic acid, and retapamulin. Resistance to ozenoxacin was also assessed in Study P-881.

Patients with infections resistant to antimicrobial drugs were also analyzed separately for clinical and microbiological response at visits 2, 3, and 4 for each type of resistance. The subgroup of patients with S. aureus and S. pyogenes coinfection was also evaluated separately for clinical and microbiological response in Study P-881.

Table 7: Microbiological Status Definitions

Microbiological Status	Criteria
Visit 2 (On Therapy)	
If material collected and cultured; patients with clinical status "improvement" at visit 2:	
Eradication	The absence of the original pathogen(s) from the visit 2 specimen, with or without the presence of any new microorganisms.
Persistence	The presence of the original pathogen(s) in the visit 2 specimen, with or without the presence of any new microorganisms.
If material collected and cultured; patients with clinical status "no improvement" at visit 2:	
Superinfection	The absence of the original pathogen(s) from the visit 2 specimen, with the presence of a new microorganism (documented or presumed).
Persistence	The presence of the original pathogen(s) in the visit 2 specimen, with or without the presence of any new microorganisms.
If material not collected:	
Presumed eradication	A clinical status of "improvement" or "early cure" (Study P-110881-01) at visit 2.
Presumed persistence	A clinical status of "no improvement" at visit 2.
All other cases:	
Unable to determine	Patients who did not meet any of the classifications previously listed.
Visit 3 (End of Therapy)	
If material collected and cultured; patients with clinical status "early cure" or "improvement" at visit 3:	
Eradication	The absence of the original pathogen(s) from the visit 3 specimen, with or without the presence of any new microorganisms.
Persistence	The presence of the original pathogen(s) in the visit 3 specimen, with or without the presence of any new microorganisms.
If material collected and cultured; patients with clinical status "failure" at visit 3:	
Reinfection	• The absence of the original pathogen(s) from the visit 3 specimen, with the presence of a new microorganism (documented or presumed), or • The presence of the original pathogen(s) in the visit 3 specimen (with or without the presence of any new microorganisms) and a microbiological status of "eradication" (documented or presumed) at visit 2.
Persistence	The presence of the original pathogen(s) in the visit 3 specimen (with or without the presence of any new microorganisms) and a microbiological status of "persistence" (documented or presumed) at visit 2.
If material not collected:	
Presumed eradication	A clinical status of "cure" or "improvement" at visit 3.
Presumed persistence	A clinical status of "failure" at visit 3 and a microbiological status of "persistence," "presumed persistence," or "presumed eradication" at visit 2.
Presumed reinfection	A clinical status of "failure" at visit 3 and a microbiological status of "eradication," "superinfection," or "presumed superinfection" at visit 2.
All other cases:	
Unable to determine	Patients who did not meet any of the classifications previously listed.
Visit 4 (Follow-Up)	
If material collected and cultured; patients with clinical status "cure" at visit 3 and "relapse" at visit 4:	
Recurrence	The presence of the original pathogen(s) in the visit 4 specimen, with or without the presence of any new microorganisms.
Reinfection	The absence of the original pathogen(s) from the visit 4 specimen, with the presence of a new microorganism (detected or presumed).
If material collected and cultured; patients with clinical status "failure" at visit 4:	
Samples at visit 4 were used only for microbiological characterization.	

Microbiological Status	Criteria
If material not collected:	
Presumed eradication	A clinical status of "cure," "no change," or "post-therapy cure" at visit 4.
Presumed reinfection/recurrence	A clinical status of "relapse" at visit 4.
For all patients:	
Unable to determine	Patients who did not meet any of the classifications previously listed.

Note: A patient had to meet all of the criteria corresponding to a microbiological status to be categorized under that status.
"Original pathogen(s)" refers to the pathogen(s) identified in the baseline microbiological sample.
Specimens at each visit refer to the microbiological specimen sample from the baseline affected area at that visit.
Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Table 8: Definitions of Clinical and Microbiological Response

	Response	Corresponding Statuses
Clinical		
Visit 2, Study P-880	Improvement	Improvement
	No improvement	No improvement
Visit 2, Study P-881	Early cure	Early cure
	No early cure	Improvement, no improvement
Visit 3	Cure	Cure
	Failure	Improvement, failure
Visit 4	Cumulative cure	Cure, post-therapy cure, no change[a]
	No cumulative cure	Relapse, failure, no change[a]
Microbiological		
Visit 2	Success	Documented or presumed eradication
	Failure	Documented or presumed persistence, superinfection
Visit 3	Success	Documented or presumed eradication
	Failure	Documented or presumed persistence, documented or presumed reinfection
Visit 4	Success	Presumed eradication
	Reinfection/recurrence	Presumed reinfection/recurrence
	Recurrence	Documented recurrence
	Reinfection	Documented reinfection

[a] "No change" was defined as "cumulative cure" in Study P-110881-01 and "no cumulative cure" in Study P-110880-01.
Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Symptoms of Impetigo

The total SIRS score was calculated by summing the individual sign and symptom scores, and the mean total SIRS score and its change from baseline were reported for visits 2, 3, and 4 in both studies.

Length (in the head-to-toe orientation) and width (perpendicular to length) of each lesion were recorded using the vesicle or crusting edge as the boundary, and the affected area was obtained by multiplying the two measurements. The total affected area was reported as a proportion of the baseline affected area for visits 2, 3, and 4.

Other Efficacy Outcomes

Therapeutic response at visit 3 was determined by combining the clinical and the microbiological response in both studies. Therapeutic success was only attained if there was clinical cure and microbiological success (documented or presumed "eradication") at visit 3.

Any patients with clinical failure ("improvement" or "failure") or microbiological failure ("persistence," "reinfection," "presumed persistence," or "presumed reinfection") were categorized under therapeutic failure and all other patients were categorized under "unable to determine."

In Study P-881, patients with additional antimicrobial therapies were reported at visits 2 and 3, and patients (parents or legal guardians if self-report was not possible) answered questions on whether or not attendance at work or school was affected by the patient's condition.

Statistical Analysis

In both trials, the primary end point was the proportion of patients with clinical cure at visit 3 in the intention-to-treat clinical (ITTC) set (see the next section for descriptions of the analysis populations) with missing responses excluded from analysis. The difference in proportions between the ozenoxacin and placebo groups was evaluated using the Mantel–Haenszel chi-square test without continuity correction and the 95% asymptotic (Wald) confidence interval (CI) was created for the difference. Sensitivity analyses were performed for primary end point in the other analysis sets per-protocol clinical (PPC), ITTB, and per-protocol bacteriological [PPB]). In Study P-881, results from the early termination visit for patients who discontinued the study before visit 2 due to worsened infection were included in the primary end point analysis and were not considered to be missing.

In Study P-880, sample size was determined based on the assumption of 70% of patients in the ozenoxacin group achieving clinical cure at visit 3 and a difference of 20% with the placebo group. A sample size of 124 in each group was required to provide 90% power to detect the difference at a 5% two-sided significance level using the Mantel–Haenszel chi-square test without continuity correction. Assuming a 20% dropout rate, it was determined that 155 patients were needed for each treatment group. In Study P-881, sample size was calculated assuming 35% of patients in the ozenoxacin group would achieve clinical cure at visit 3 with a difference of 15% with the placebo group. A sample size of 185 patients per group was required to provide 90% power at a 5% two-sided significance level using the Mantel–Haenszel chi-square test without continuity correction. A dropout rate of 10% was assumed, yielding the requirement for 206 patients in each group. A rationale was not provided for the different assumptions in Study P-881, though the estimates for the primary end point match those observed in Study P-880 (which preceded Study P-881).

Sensitivity analyses in both studies were conducted in which missing responses (patients with status "unable to determine") were imputed as failure. In Study P-880, missing responses were also imputed using the Markov chain Monte Carlo method and values were rounded to 0 or 1. In Study P-881, missing responses were imputed using the monotone logistic regression method with the total SIRS score at baseline and clinical response at visit 2 as covariates. A further sensitivity analyses (worst-case approach) was conducted in Study P-881 in which missing responses in the ozenoxacin and placebo groups were imputed as clinical failure and cure, respectively.

The primary efficacy end point was evaluated for pre-specified subgroups based on the following baseline characteristics: type of impetigo (bullous and non-bullous), number of baseline affected areas (one, two to four, five to 10, and more than 10), total affected area (cutoffs of 2 cm^2, 10 cm^2, 50 cm^2, and 100 cm^2), and the SIRS total score (ranges of up to 15, 28, and 42 points for Study P-880, and ranges of up to 9 and 15 for Study P-881).

All other end points should be considered exploratory due to the lack of control for type I error. The proportions of patients at visit 2 with improvement in Study P-880 and early cure in Study P-881, as well as the proportion of patients at visit 4 with cumulative cure, were analyzed in the same manner as the primary clinical end point, but without the sensitivity analyses for missing data. Microbiological success at visits 2 and 3 and therapeutic response at visit 3 were analyzed using the same method in the ITTB and PPB sets. Patients assigned the clinical or microbiological status "unable to determine" were not included in the analyses, with the exception of those with the clinical status "unable to determine" at visit 4 in Study P-880 who were assigned a clinical response of no cumulative cure. The same statistical testing approach was used for all other comparisons of proportions of patients (clinical success using combined SIRS and size and/or extent criteria, patients with baseline lesions absent, patients with new lesions, patients using additional antimicrobial therapy, and subgroup analyses of clinical response at visit 3).

The distributions of clinical status at visit 2 in Study P-881 ("early cure," "improvement," and "no improvement") were compared between the ozenoxacin and placebo groups using the Mantel–Haenszel chi-square test for all four analysis sets.

Change in the total SIRS score from baseline at each of visits 2, 3, and 4 was compared between the ozenoxacin and placebo groups in Study P-881 using analysis of covariance adjusted for the baseline total SIRS score. In Study P-880, an additional approach for the subgroup analyses for the primary efficacy end point was used. Two different logistic regression models were used. The first model included the main effect for the subgroup covariate and the second model included both the main effect and interaction with treatment group for the subgroup covariate.

Although not explicitly stated in Study P-881, the low numbers of missing responses at visit 3 compared with visits 2 and 4 for therapeutic response, clinical success, total SIRS score, total affected area, patients with baseline lesions absent, and patients with new lesions strongly suggest that results from the early termination visit were included for these outcomes.

Analysis Populations

Details on the analysis populations are presented in Table 9. The safety population consisted of all patients who received at least one dose of study drug, and patients were analyzed according to actual treatment received for the safety outcomes. The ITTC population was defined as all randomized patients and patients were analyzed according to allocated treatment. The PPC population included patients in the ITTC population without any protocol violations, which were defined during a blinded data review meeting.

The ITTB population was defined as all randomized patients with a pathogen identified from the baseline microbiological specimen (which had to be *S. aureus*, *S. pyogenes*, or both in Study P-881), and patients were analyzed according to allocated treatment. The PPB population included patients in the ITTB populations without any protocol violations.

Patient Disposition

Details on patient disposition are provided in Table 9. In Study P-880, more patients in the placebo group discontinued the study prematurely than in the ozenoxacin group (4% versus 1%) and in Study P-881, more patients in the placebo group discontinued the study than in the ozenoxacin group (10% versus 3%). The most notable discrepancies between treatment groups were in patients discontinuing because of worsening patient condition as at least half

of the discontinuations in the placebo groups were because of this, compared with none of the discontinuations in the ozenoxacin groups. The sensitivity analyses in which missing data were imputed for the primary end point explored the potential effects of these imbalances in discontinuations. Although the numbers were not reported, at least some patients in Study P-881 who discontinued study treatment would have attended an early termination visit and been assigned a clinical response of failure at visit 3.

Protocol deviations were balanced between the treatment groups in both trials (Table 10) and a greater proportion of patients in Study P-880 had deviations (14% and 15% compared with 5% in Study P-881). Most of the deviations in Study P-880 were due the inclusion and exclusion criteria not being met (with the most common reason being the baseline affected area not meeting the 1 cm^2 minimum) or visits not being scheduled according to the study protocol. The most common deviations in Study P-881 were disallowed medications and visits not being scheduled according to protocol.

Table 9: Patient Disposition and Analysis Sets

	P-110880-01		P-110881-01	
	Ozenoxacin	**Placebo**	**Ozenoxacin**	**Placebo**
Screened, N	NR		420	
Randomized, N	155	156	206	206
Discontinued, N (%)	2 (1)	6 (4)	6 (3)	20 (10)
Adverse event	0	0	1	3
Withdrawal of consent	2	1	2	1
Lost to follow-up	0	2	2	2
Worsening patient condition	0	3	0	13
Other	0	0	1	1
Prematurely discontinued study treatment, N	NR	NR	4	20
ITTC, N	155	156	206	206
PPC[a], N	134	132	195	195
ITTB[b], N	154	152	125	119
PPB[c], N	133	128	119	112
Safety, N	156[d]	156	206	205

ITTB = intention-to-treat bacteriological; ITTC = intention-to-treat clinical; NR = not reported; PPB = per-protocol bacteriological; PPC = per-protocol clinical.

[a] All ITTC patients who did not deviate from the protocol.

[b] All randomized patients who had a pathogen (which had to be *S. aureus*, *S. pyogenes*, or both in Study P-110881-01) identified at study entry.

[c] All ITTB patients who did not deviate from the protocol.

[d] One patient randomized to the retapamulin group received ozenoxacin instead.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Table 10: Major Protocol Deviations

	P-110880-01		P-110881-01	
	Ozenoxacin ITTC Set N = 155	Placebo ITTC Set N = 156	Ozenoxacin ITTC Set N = 206	Placebo ITTC Set N = 206
Patients with any major protocol deviation, n (%)	21 (14)	24 (15)	11 (5)	11 (5)
Inclusion and/or exclusion criteria	13	12	2	0
Visit schedule not according to protocol	10	11	6	4
Disallowed medications	0	0	5	4
Incorrect study treatment dose (< 80% compliance)	1	1	0	0
Study blind broken	0	1 (4)	NR	NR
A significant assessment or procedure not performed	NR	NR	1	1
Early termination visit performed after starting of additional antimicrobial therapy	NR	NR	0	2
Non-compliance that could have impact on safety of patient	NR	NR	0	1
Randomized but not treated	NR	NR	0	1

ITTC = intention-to-treat clinical; NR = not reported.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Exposure to Study Treatments

More than 90% of patients in both treatment groups in both trials received between 80% and 120% of doses in the treatment regimen (Table 11). In both trials, a greater proportion of patients in the placebo group (versus the ozenoxacin group) had less than 80% treatment compliance. The difference was larger in Study P-881 (9% and 2% in the placebo and ozenoxacin groups, respectively). In Study P-881, compliance was calculated as a percentage of the 10 planned doses regardless of treatment discontinuation, and trends in patients with less than 80% compliance and those discontinuing study treatment were similar. In Study P-880, compliance in patients who discontinued study treatment was calculated as a percentage of the planned doses from baseline to treatment discontinuation.

Table 11: Treatment Exposure

	P-110880-01		P-110881-01	
	Ozenoxacin N = 156 Safety Set	Placebo N = 156 Safety Set	Ozenoxacin N = 206 Safety Set	Placebo N = 205 Safety Set
Treatment compliance, % of study medication doses administered				
Mean (SD)	99.6 (7.2)	97.9 (14.3)	99.9 (11.9)	95.9 (17.4)
Median (range)	100 (33, 120)	100 (10, 120)	100 (10, 120)	100 (10, 120)
< 80%, n (%)	2 (1)	6 (4)	4 (2)	18 (9)
≥ 80% and ≤ 120%, n (%)	154 (99)	150 (96)	202 (98)	187 (91)

SD = standard deviation.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Critical Appraisal

Internal Validity

Randomization, Allocation, and Blinding

In both studies, the randomization list was prepared by a statistician using specific software. Patient baseline characteristics were mostly balanced between the ozenoxacin and placebo groups in each study and differences between groups in affected area were not expected by the clinical expert consulted for this review to alter the effect-size estimate. Patients were allocated by an interactive Web response system based on chronological order of screening; thus, risk of bias from inadequate allocation concealment would have been low. Patients and investigators (who were the outcome assessors) were blinded to treatment within the ozenoxacin and the placebo group as the two medications were identical in appearance, smell, consistency, and packaging. There was the possibility that patients on the placebo whose condition worsened could have surmised their treatment allocation. Given the identical composition of the study medications, with the exception of the active ingredient, the likelihood of unblinding was otherwise low.

Study Design and Interventions

The superiority design, outcome assessments, and study populations in both trials were appropriate for the purpose of establishing the clinical efficacy of ozenoxacin in the topical treatment of impetigo. Treatment compliance was excellent and the 9% of patients in the placebo group in P-881 with a compliance of less than 80% may have represented some of the patients who discontinued the study early.

The use of concomitant antibiotic therapy was differential across the ozenoxacin and placebo groups in both studies, which may bias treatment outcome.

Study Population and Attrition

There were differences in the pathogens identified at baseline between the two trials. In Study P-880, all identified pathogens, including *S. aureus* and *S. pyogenes*, were recorded and any patients with an identified pathogen were included in the ITTB analysis set, which included almost all of the ITTC set. Although information on *S. aureus* and *S. pyogenes* coinfections was not reported in study P-880, there were higher proportions of patients with *S. aureus* and higher proportions of patients with *S. pyogenes* than in Study P-881. In Study P-881, only patients with *S. aureus* or *S. pyogenes* were included in the ITTB set and this amounted to only 56% of the ITTC set. While analyzing the ITTB set of Study P-881 ensures that only impetigo infections are included, this requires the assumption that randomization was preserved in this population.

Baseline characteristics were well-balanced between treatment groups within each trial aside from total affected area. The clinical expert consulted for this review indicated that the differences between groups were not expected to affect the observed treatment effect of ozenoxacin versus placebo.

In Study P-880, less than 5% of randomized patients discontinued the study in each group and discontinuation of study treatment was not reported. In Study P-881, a notably greater proportion of patients in the placebo group discontinued the study than in the ozenoxacin group (10% versus 3%), and almost all of the discontinuations involved premature

discontinuation of study treatment. In the placebo group, 6.3% of patients discontinued due to worsening patient condition. The clinical expert consulted for this reviewed agreed that it was possible investigators were more sensitized to worsening infection in the younger children (aged two months to two years) in Study P-881 and therefore more likely to discontinue study medication.

Assessment of Outcomes

The primary efficacy end point was assessed at the end of the treatment regimen, which was considered by the clinical expert to be appropriate for assessing treatment success. The earlier and later visits were also considered to be appropriate by the clinical expert for evaluating early response and completeness of healing. Clinical response was determined mostly by SIRS, which is not a validated scale. When asked to provide input on validity and reliability of the two SIRS versions used in the studies, the clinical expert noted that changes in all of the signs and symptoms would be expected to move in the same direction and that there should be reasonable concordance between raters. The determination of whether signs or symptoms were absent and therefore warranted a score of 0 was expected to be relatively objective, while the determination of a score of 1 or less for erythema/inflammation, tissue edema, and itching was expected to be more subjective. The inclusion of both exudate/pus and crusting put extra weight on very similar signs and/or symptoms, though this may not be problematic given that these are the cardinal features of impetigo. While the FDA draft guidance on mupirocin[24] recommends the use for assessment of clinical efficacy of a SIRS similar to the version used in Study P-881, it recommends that the target lesions be assessed seven days after the end of treatment and does not provide direction on applying SIRS to multiple affected areas.

The 10% minimum decrease in total SIRS score from baseline required for the definition of clinical improvement at visit 2 may not represent a clinically significant change in signs and symptoms. However, a decrease in score would at least ensure that the patient's condition was not worsening during the study treatment period. No information was provided on when and how patients were asked questions regarding time away from work and school, and the questions were not part of a validated instrument.

Statistical Methods

There was no control for type I error and all tests beyond those for the primary end point should be considered exploratory. Subgroup analysis of the primary end point, despite being pre-specified, were not controlled for type I error and randomization was stratified by age only. Tests for interaction between treatment groups and baseline covariates were only performed in Study P-881. The results of the subgroup analyses should be interpreted with caution.

Appropriate statistical methods were used and pre-specified before database lock and the numbers of randomized patients in each treatment group were sufficient according to the sample size calculations.

Missing data were ignored in the main analyses but was imputed for sensitivity analyses of the primary end point using several methods. In the sensitivity analyses for missing data, the imputation of missing data as "failure" in both trials would have biased the effect-size estimate toward the null, and the worst-case approach used in Study P-881 was a conservative approach. The amount of missing data at visit 3 was minimal and unlikely to change the results of the sensitivity analyses; however, the greater proportion of patients in the placebo group of Study P-881 than in the ozenoxacin group who discontinued study

treatment could have biased therapeutic response, clinical success, total SIRS score, total affected area, patients with baseline lesions absent, and patients with new lesions at visit 3 if results from the early termination visit were imputed. If these patients would have improved from the early termination visit to visit 3 while remaining on study treatment, the results at visit 3 would have been biased in favour of ozenoxacin. If the patients would have worsened instead, the results would have been biased against ozenoxacin.

More than 5% of patients in the placebo group in Study P-881 at visits 2 and 4 were missing from assessment of clinical response and there was no imputation of missing data for these time points. If these patients withdrew due to lack of response and were less likely to experience clinical success at these visits, the exclusion of these patients should bias the results against ozenoxacin.

In the Study P-880 ITTB set, 10% of patients in the ozenoxacin group and 7% in the placebo group had a microbiological status of "unable to determine" at visit 3. In Study P-881, 9% of patients in the ITTB set had a microbiological status of "unable to determine" in the placebo group at visit 2, while 2% in the ozenoxacin group and 10% in the placebo group had this status at visit 3. There were no explanations available for the missing microbiological data at these visits, though it is possible that some patients fell into categories that were not accounted for in the definitions of microbiological status. For example, a patient experiencing clinical failure with the original baseline pathogen present at visit 3 and a microbiological status of "superinfection" at visit 2 would be categorized as "unable to determine" at visit 3. There is not enough information to predict the likelihood or direction of bias from this missing data.

External Validity

Study Population

Microbiological resistance and causative species patterns can vary between regions and because there were no Canadian centres included in Study P-880 or Study P-881, there is uncertainty in their generalizability to the Canadian setting. There is also a possibility that some of the patients in the ITTC set in study P-881 had a skin infection or condition other than impetigo as *S. aureus* or *S. pyogenes* were not identified in a large proportion of the patients. According to the clinical expert consulted for this review, possible factors contributing to the significant proportion of patients without one of the pathogens associated with impetigo include regional differences in causative species, the inclusion of patients with skin infections other than impetigo, and variation in hygiene practices.

The inclusion criteria of 1 cm^2 and 2 cm^2 as the minimum affected area were reasonable as the clinical expert indicated that the infection would likely reach those minimum sizes by the time patients with impetigo present to clinicians. There were limited numbers of patients with affected areas of 50 cm^2 and above, with SIRS total scores in the upper third of the range (particularly in Study P-880), and with bullous impetigo. However, this reflects the patients likely to receive topical therapy for impetigo (those with less severe and less extensive lesions), as well as the relative prevalence of the bullous and non-bullous forms of impetigo in Canada (with the latter confirmed by the clinical expert consulted for this review).

Interventions

The relevant topical comparators in Canada, fusidic acid and mupirocin, were not included in the studies. According to the clinical expert, oral antibiotic therapies would also have been

relevant as a patient with impetigo could receive either topical or oral treatment, depending on their clinician. The treatment regimen for ozenoxacin followed the product monograph.

Outcomes

According to the clinical expert consulted for this review, the outcomes of clinical cure and clinical success at visit 3 were appropriate for assessing response to treatment. The clinical expert indicated that diagnosis and treatment decisions are typically based on clinical assessment and culturing lesion specimens would be reserved for atypical or extensive lesions or cases of recurrence or reinfection. Therefore, outcomes related to lesion assessment are more relevant to clinical practice than microbiological response. The clinical expert agreed that the alternative visit 3 clinical outcome, clinical success, was more in line with clinical practice than the primary end point due to its greater emphasis on the decision of whether to provide additional treatment. The clinical expert also agreed that the timing of visit 2 was appropriate for assessing early response to treatment and the timing of visit 4 would have allowed for assessment of complete healing.

The need for further antimicrobial therapy after the end of study treatment, reported in Study P-881, reflects the need to prescribe a different topical or systemic antibiotic when there is insufficient response to the first treatment. The appearance of new lesions (reported in Study P-881), may also be relevant as patient input indicated the need for limiting spread of the infection.

Total size of affected area may not reflect response to treatment as well as lesion severity does given that successful treatment in a large affected area entails a longer healing period than in smaller areas. Health-related quality of life and tolerability outcomes were not included in the studies.

Efficacy

Only those efficacy outcomes identified in the CDR review protocol (Table 3) are subsequently reported. See Appendix 4 for detailed efficacy data. Comparisons aside from the primary efficacy end point were not controlled for type I error and should be considered exploratory.

Key Efficacy Outcomes

Clinical Response

Primary Efficacy Outcome

The efficacy of ozenoxacin was demonstrated in both trials for the primary efficacy end point, clinical cure at visit 3 or end of therapy (Table 12). In the ITTC population of Study P-880, 35% of patients in the ozenoxacin group had clinical cure at visit 3, compared with 19% of patients in the placebo group. In the main analysis that excluded missing responses, the difference in the proportion of patients with clinical cure was 15.5% in favour of ozenoxacin (95% CI, 5.6% to 25.5%; $P = 0.003$). In Study P-881, 54% of patients in the ozenoxacin group had clinical cure at visit 3, compared with 38% of patients in the placebo group. The difference in the proportion of patients with clinical cure was 16% in favour in ozenoxacin (95% CI, 6.3% to 25.6%; $P = 0.001$). None of the sensitivity analyses conducted in the trials with regards to missing responses or analysis sets affected the conclusion of the primary analysis.

The subgroup analyses by baseline characteristics for the primary efficacy end point are provided in Appendix 4, Table 17. There were trends of greater effect size in non-bullous infections (differences of 22.2% [95% CI, 10.9% to 33.4%] in Study P-880 and 17.0% [95% CI, 6.7% to 27.4%] in Study P-881 for ozenoxacin versus placebo) than in bullous infections (differences of –9.4% [95% CI, –29.0% to 10.2%] in Study P-880 and 8.6% [95% CI, –18.2% to 35.5%] in Study P-881 for ozenoxacin versus placebo). There were also trends of lower efficacy of both treatments for affected areas of more than 50 cm^2 and smaller effect size for ozenoxacin compared with the placebo for affected areas with a SIRS total score above 9 (out of a maximum total score of 15) in Study P-881. There were no subgroup analyses available for the other subgroups specified in the systematic review protocol, namely age, primary versus secondary impetigo, and prior treatment.

For results from the ITTB analysis of clinical response, see Appendix 4, Table 16.

In the nine patients in each of the treatment groups with coinfections of *S. aureus* and *S. pyogenes* in Study P-881, more patients in the ozenoxacin group compared with the placebo group had clinical cure at visit 3 (78% versus 22%) and clinical cumulative cure at visit 4 (89% versus 56%). Detailed information on patients with coinfection is provided in Appendix 4, Table 18.

In Study P-880, only four patients in the ozenoxacin group and three patients in the placebo group had resistant *S. aureus* infections, and only one patient in the ozenoxacin group and two patients in the placebo group had resistant *S. pyogenes* infections (Appendix 4, Table 19). Although this subset of patients was limited in number, similar trends were observed in the full population with more patients achieving clinical cumulative cure at visit 4 than clinical cure at visit 3, and greater proportions of patients achieving clinical cure and cumulative cure with ozenoxacin treatment.

In Study P-881, 32 patients in the ozenoxacin group and 26 patients in the placebo group had resistant *S. aureus* infections and one patient in the ozenoxacin group had a resistant *S. pyogenes* infection. In both treatment groups, most patients with resistant infections had clinical failure at visit 3 and clinical cumulative cure at visit 4. Clinical response overall was similar between the treatment groups (Appendix 4, Table 20).

Clinical Success

Under the alternative definition of clinical response, using combined SIRS score and lesion size and extent criteria at visit 3 in Study P-881, 89% of patients had clinical success in the ozenoxacin group compared with 78% of patients in the placebo group (Table 12). The difference in proportions when excluding missing responses was 10.4% in favour of ozenoxacin (95% CI, 3.5% to 17.3%).

Early Clinical Response

Almost all patients achieved clinical status of “early cure” or “improvement” in both trials at visit 2 and the proportions of patients with “improvement” in Study P-880 (95% and 94% for the ozenoxacin and placebo groups, respectively) and “early cure” in Study P-881 (13% and 10% for the ozenoxacin and placebo groups, respectively) were similar in the ozenoxacin and placebo groups (Table 12). The distribution of patients with “early cure,” “improvement,” and “no improvement” at visit 2 was also similar between treatment groups in Study P-881. The results at visit 2 were similar for the PPC, ITTB, and PPB analysis sets.

Post-Therapy Clinical Response

Greater proportions of patients achieved clinical cumulative cure at visit 4 than clinical cure at visit 3 in both trials (Table 12). In Study P-880, 53% of patients in the ozenoxacin group compared with 40% of patients in the placebo group had cumulative cure, with a difference in proportions of 12.5% in favour of ozenoxacin (95% CI, 1.5% to 23.5%). In Study P-881, 77% of patients in the ozenoxacin group compared with 61% of patients in the placebo group had cumulative cure, with a difference in proportions of 10.6% (95% CI, 1.9% to19.4%). The results at visit 4 were similar for the PPC, ITTB, and PPB analysis sets.

Time to Clinical Response

Results for this outcome are provided in Appendix 4, Table 21. Time to clinical response was analyzed in patients who achieved a clinical status of “early cure” or “improvement” at visit 2, or a clinical status of “cure” or “improvement” at visit 3 and maintained or improved upon (e.g., “improvement” followed by “cure” or “post-therapy cure”) that clinical status at subsequent visits. In Study P-880, a greater proportion of patients in the ozenoxacin group compared with the placebo group achieved this response first at visit 2 (57% compared with 41%). This corresponded to 35 and 37 patients in the ozenoxacin and placebo groups who did not achieve clinical “improvement” at visit 2 and achieved clinical “cure” or “improvement” at visit 3. However, this contradicted the results for visit 2 clinical response (Table 12) in which there were only 8 and 10 patients in the ozenoxacin and placebo groups who did not achieve clinical “improvement.”

In Study P-881, almost all patients included in this analysis first achieved sustained or improved clinical response at visit 2 in both groups (99% and 97% in the ozenoxacin and placebo groups, respectively).

Absence of Baseline Lesions

In Study P-881, the proportion of patients in whom baseline lesions were absent increased from 4% in the ozenoxacin group and 3% in the placebo group at visit 2 to 81% in the ozenoxacin group and 74% in the placebo group at visit 4 (Table 12). The proportion of patients with lesions absent was greater in the ozenoxacin group compared with the placebo group at all visits, with the most pronounced difference at visit 3 (mean difference of 11.2% [95% CI, 1.9% to 20.5%]).

Appearance of New Lesions

New lesions appeared in only 6% or less of patients in each group at visits 2 and 3 in Study P-881 (Table 12). A lower proportion of patients in the ozenoxacin group at visit 3 had new lesions, with a mean difference of –5.0% (95% CI, –8.5% to –1.4%) for ozenoxacin versus placebo.

Symptoms of Impetigo

SIRS Total Score

The mean SIRS total score in both treatment groups in both trials decreased with each visit, with the largest decreases in SIRS total score from baseline to visit 2 (Table 14). The largest differences between treatment groups in change from baseline were observed at visit 3. In Study P-880, the mean SIRS total score had decreased by 12.4 points (standard deviation [SD] of 4.9 points) in the ozenoxacin group compared with a decrease of 10.7 points (SD of 4.8 points) in the placebo group by visit 3. The mean decrease in total score in the ozenoxacin group was consistently numerically greater than in the placebo group, though the difference between groups in mean change was less than 2 points for each visit. At visit 3 in Study P-881, the between-treatment difference in change in the SIRS total score from baseline was –0.72 points (95% CI, –1.22 to –0.23) for ozenoxacin versus placebo according to analysis of covariance adjusted for baseline score. The same trend was observed at visits 2 and 4, though differences in SIRS total score change between treatment groups were less than half a point.

Total Affected Area as a Proportion of Baseline Affected Area

The mean total affected area at visits 2, 3, and 4 as a proportion of baseline affected area was numerically smaller in the ozenoxacin group compared with the placebo group in both trials (Table 14). At visit 3, the proportions for the ozenoxacin and placebo groups were 0.304 (SD of 0.344) and 0.464 (SD of 0.424) for Study P-880, and 0.196 (SD of 0.315) and 0.406 (SD of 0.782) for Study P-881. In each group, the mean affected area as a proportion of baseline affected area numerically decreased at each visit (from the previous visit).

Microbiological Response

Microbiological Success at End of Therapy

A greater proportion of patients in the ozenoxacin group compared with the placebo group in both trials had microbiological success at visit 3 (Table 13). The differences between the ozenoxacin and placebo groups in proportion of patients with microbiological success at visit 3 when missing values were excluded was 27% (95% CI, 18% to 37%) for Study P-880, and 12.2% (95% CI, 3.6% to 20.8%) for study P-881. Results in the PPB analysis sets were similar for both trials. Microbiological success was achieved at both visits 3 and 4 for most patients.

Proportions of patients with microbiological success were higher overall in Study P-881 than in Study P-880. Almost all patients with microbiological success at visit 3 in Study P-880 had confirmation by specimen testing, whereas almost all patients with microbiological success in Study P-881 had “presumed eradication.” Patients with “presumed eradication” could have had a clinical status of “improvement,” which would have been considered clinical failure.

Early Microbiological Response

A greater proportion of patients in the ozenoxacin group compared with the placebo group in both trials had microbiological success at visit 2 (Table 13). At visit 2, the differences between the ozenoxacin and placebo groups were 35% (95% CI, 25% to 46%) for Study P-880 and 16.8% (95% CI, 6.4% to 27.2%) for Study P-881. Results in the PPB analysis sets were similar for both trials.

Post-Therapy Microbiological Response

There were large proportions of missing data for microbiological response at visit 4 and it was not possible to interpret the numbers of patients with microbiological success or failure (Table 13). This may be partly due to the exclusion of patients with a visit 4 clinical status of "failure" from the microbiological categories. A planned analysis of microbiological status of patients with a clinical status of "relapse" at visit 4 was not performed due to the limited numbers of patients in this category.

Time to Microbiological Response

Results for this outcome are provided in Table 21 of Appendix 4. Time to microbiological response only included patients with confirmed or presumed microbiological eradication that was then sustained at subsequent visits. In Study P-880, a greater proportion of patients in the ozenoxacin group compared with the placebo group achieved sustained eradication by visit 2 (75% compared with 40%). By contrast, the proportions of patients in both treatment groups with sustained eradication by visit 2 in Study P-881 were similar in both groups (90% and 85% in the ozenoxacin and placebo groups, respectively).

Therapeutic Response

Therapeutic success at visit 3 was also achieved in a greater proportion of patients in the ozenoxacin group compared with the placebo group in both trials, with differences of 13.8% (95% CI, 4.1% to 23.4%) in Study P-880, and 22.6% (95% CI, 10.2% to 35.0%) in Study P-881 (Table 13).

Health-Related Quality of Life

Outcomes on health-related quality of life assessed using validated scales were not available.

Other Efficacy Outcomes

There were no outcomes available regarding complications of impetigo, tolerability of medication, or caregiver burden assessed on a validated scale.

Need for Additional Therapy for Impetigo

Use of Additional Antimicrobial Therapy

Investigators could prescribe additional antimicrobial therapy (topical or oral) at visits 2 and 3 at their discretion. The manufacturer confirmed that no patients in either trial received additional antibiotic therapy before the end of the study treatment. At visit 3 in Study P-881, a greater proportion of patients in the placebo group needed additional antimicrobial therapy according to the investigator's discretion, with a difference of –9.9% (95% CI, –16.7% to –3.1%) for ozenoxacin versus placebo (Table 22, Appendix 4).

Concomitant Antibacterial Therapies

In both trials, use of concomitant antibacterial therapy at any time during the study was reported. Concomitant antibacterial therapy use was more prevalent in the placebo groups than in the ozenoxacin groups and in both trials, more patients used topical antibiotics than systemic antibiotics. The most commonly prescribed concomitant dermatologic antibiotic was mupirocin. More details on concomitant antibacterial medications are provided in Appendix 4, Table 23.

Adherence to Medication

As reported in Table 11, the proportion of patients adhering to the study medication was high, with more than 90% of patients in both treatment groups in both trials being administered at least 80% of planned doses.

Time Away From School or Work

In terms of impetigo preventing patients, or parents or guardians of patients, from attending work or school, a larger proportion of pediatric patients were prevented from attending school in the placebo group compared with the ozenoxacin group in Study P-881 (Appendix 4, Table 24), where the proportions of pediatric patients missing school were 18% in the ozenoxacin group and 22% in the placebo group. These outcomes were not reported in Study P-880.

Table 12: Clinical Response

	P-110880-01		P-110881-01	
	Ozenoxacin N = 155 ITTC Set	**Placebo N = 156 ITTC Set**	**Ozenoxacin N = 206 ITTC Set**	**Placebo N = 206 ITTC Set**
Clinical response at visit 3, n (%)				
Cure	54 (35)[a]	30 (19)[a]	112 (54)[b]	78 (38)[b]
Failure	98 (63)	120 (77)	91 (44)	121 (59)
Improvement	97 (63)	119 (76)	84 (41)	105 (51)
Failure	1 (0.6)	1 (0.6)	7 (3)	16 (8)
Unable to determine	3 (2)	6 (4)	3 (2)	7 (3)
Mean difference in % of patients with cure, ozenoxacin vs. placebo (95% CI)	15.5 (5.6, 25.5) *P* = 0.003		16.0 (6.3, 25.6) *P* = 0.001	
Clinical response at visit 2, n (%)				
Early cure	NA	NA	26 (13)	21 (10)
Improvement	147 (95)	146 (94)	166 (81)	152 (74)
No improvement	5 (3)	7 (5)	9 (4)	17 (8)
Unable to determine	3 (2)	3 (2)	5 (2)	16 (8)
Difference in % of patients with improvement, ozenoxacin vs. placebo, mean (95% CI)	1.3 (–3.1, 5.6) *P* = 0.564[c]		NA	
Mean difference in % of patients with early cure, ozenoxacin vs. placebo (95% CI)	NA		1.9 (–4.6, 8.3) *P* = 0.567[c]	
Difference in distribution of patients with early cure, improvement, and no improvement, *P* value for Mantel–Haenszel chi-square test	NA		*P* = 0.152[c]	
Clinical response at visit 4, n (%)				
Cumulative cure	82 (53)	63 (40)	159 (77)	126 (61)
Cure	48 (31)	26 (17)	104 (51)	72 (35)
Post-therapy cure	34 (22)	37 (24)	51 (25)	51(25)
No change	NA	NA	4 (2)	3 (2)
No cumulative cure	73 (47)	93 (60)	41 (20)	57 (28)
No change	3 (2)	2 (1)	NA	NA
Relapse	1 (0.6)	2 (1)	3 (2)	3 (2)
Failure	64 (41)	82 (53)	38 (18)	54 (26)
Unable to determine	5 (3)[d]	7 (5)[d]	NA	NA
Unable to determine	NA	NA	6 (3)	23 (11)

	P-110880-01		P-110881-01	
Mean difference in % of patients with cumulative cure, ozenoxacin vs. placebo (95% CI)	12.5 (1.5, 23.5) *P* = 0.027[c]		10.6 (1.9, 19.4) *P* = 0.017[c]	
Clinical response at visit 3 using combined SIRS and size/extent criteria, n (%)				
Success	NA	NA	183 (89)	161 (78)
Failure	NA	NA	20 (10)	41 (20)
Unable to determine	NA	NA	3 (1)	4 (2)
Mean difference in % of patients with success, ozenoxacin vs. placebo (95% CI)	NA		10.4 (3.5, 17.3) *P* = 0.003[c]	
Patients with baseline lesions absent at subsequent visit, n (%)				
Visit 2	NR	NR	N = 200	N = 190
Baseline lesions absent	NR	NR	8 (4)	5 (3)
Baseline lesions present	NR	NR	192 (96)	185 (97)
Mean difference in % of patients with baseline lesions absent (95% CI)	NR		1.4 (–2.2, 4.9) *P* = 0.452[c]	
Visit 3	NR	NR	N = 203	N = 202
Baseline lesions absent	NR	NR	84 (41)	61 (30)
Baseline lesions present	NR	NR	119 (59)	141 (70)
Mean difference in % of patients with baseline lesions absent (95% CI)	NR		11.2 (1.9, 20.5) *P* = 0.019[c]	
Visit 4	NR	NR	N = 199	N = 185
Baseline lesions absent	NR	NR	161 (81)	137 (74)
Baseline lesions present	NR	NR	38 (19)	48 (26)
Mean difference in % of patients with baseline lesions absent (95% CI)	NR		6.9 (–1.5, 15.2) *P* = 0.108[c]	
Patients with new lesions, n (%)				
Visit 2				
Yes	NR	NR	3 (2)	8 (4)
No	NR	NR	197 (96)	182 (88)
Unknown	NR	NR	6 (3)	16 (8)
Mean difference in % of patients with new lesions, ozenoxacin vs. placebo (95% CI)	NR		–2.7 (–6.0, 0.6)	
Visit 3				
Yes	NR	NR	2 (1)	12 (6)
No	NR	NR	200 (97)	190 (92)
Unknown	NR	NR	4 (2)	4 (2)
Mean difference in % of patients with new lesions, ozenoxacin vs. placebo (95% CI)	NR		–5.0 (–8.5, –1.4)	

CI = confidence interval; ITTC = intention-to-treat clinical; NA = not applicable; NR = not reported; SIRS = Skin Infection Rating Scale; vs. = versus.

Note: Asymptotic (Wald) CI was used for all 95% CIs. *P* values are for the Mantel–Haenszel chi-square test without continuity correction.

Except where noted, patients with missing or "unable to determine" status were not included in calculations of mean differences between groups.

[a] Criteria for clinical cure at visit 3: SIRS score of 0 for exudates/pus, crusting, tissue warmth, and pain; no more than 1 each for erythema/inflammation, tissue edema, and itching; no additional antimicrobial therapy of the baseline affected area(s) necessary.

[b] Criteria for clinical cure at visit 3: SIRS score of 0 for blistering, exudates/pus, crusting, and itching pain; no more than 1 each for erythema/inflammation; no additional antimicrobial therapy of the baseline affected area(s) necessary.

[c] *P* value is descriptive as there was no adjustment for multiplicity.

[d] These patients were included in the calculation of difference in percentage of patients with cumulative cure.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Table 13: Microbiological and Therapeutic Response

	P-110880-01		P-110881-01	
	Ozenoxacin N = 154 ITTB Set	**Placebo N = 152 ITTB Set**	**Ozenoxacin N = 125 ITTB Set**	**Placebo N = 119 ITTB Set**
Microbiological response at visit 3, n (%)				
Success	122 (79)	86 (57)	115 (92)	87 (73)
Eradication	112 (73)	74 (49)	3 (2)	0
Presumed eradication	10 (7)	12 (8)	112 (90)	87 (73)
Failure	16 (10)	55 (36)	8 (6)	20 (17)
Persistence	16 (10)	55 (36)	5 (4)	18 (15)
Presumed persistence	0	0	1 (0.8)	0
Reinfection	0	0	2 (2)	2 (2)
Presumed reinfection	0	0	0	0
Unable to determine	16 (10)	11 (7)	2 (2)	12 (10)
Mean difference in % of patients with success, ozenoxacin vs. placebo (95% CI)	27 (18, 37) *P* < 0.0001		12.2 (3.6, 20.8) *P* = 0.005	
Microbiological response at visit 2, n (%)				
Success	109 (71)	58 (38)	109 (87)	76 (64)
Eradication	102 (66)	51 (34)	22 (18)	4 (3)
Presumed eradication	7 (5)	7 (5)	87 (70)	72 (61)
Failure	37 (24)	90 (59)	16 (13)	32 (27)
Persistence	34 (22)	90 (59)	13 (10)	30 (25)
Presumed persistence	0	0	1 (0.8)	1 (0.8)
Superinfection	3 (2)	0	2 (2)	1 (0.8)
Unable to determine	8 (5)	4 (3)	0	11 (9)
Mean difference in % of patients with success, ozenoxacin vs. placebo (95% CI)	35 (25, 46) *P* < 0.001		16.8 (6.4, 27.2) *P* = 0.002	
Microbiological response at visit 4, n (%)			N = 103[a]	N = 69[a]
Eradication	103 (67)	84 (55)	NA	NA
Presumed eradication	11 (7)	10 (7)	100 (97)	66 (95)
Persistence	2 (1)	20 (13)	NA	NA
Recurrence	0	1 (0.7)	0	2 (3)
Reinfection	1 (0.6)	0	1 (1)	0
Presumed reinfection/recurrence	0	0	1 (1)	0
Unable to determine	37 (24)	37 (24)	1 (1)	1 (1)
Therapeutic response (combined clinical and microbiological) at visit 3, n (%)				
Success	43 (28)	23 (15)	72 (59)	41 (36)
Failure	100 (65)	118 (78)	51 (42)	73 (64)
Unable to determine	11 (7)	11 (7)	2 (2)	5 (4)
Mean difference in % of patients with success, ozenoxacin vs. placebo (95% CI)	13.8 (4.1, 23.4) *P* = 0.006		22.6 (10.2, 35.0) *P* < 0.001	

CI = confidence interval; ITTB = intention-to-treat bacteriological; NA = not applicable; vs. = versus.

Note: *P* values are descriptive as there was no adjustment for multiplicity.

Patients with "unable to determine" status were not included in calculations of mean difference in per cent of patients with success.

Asymptotic (Wald) CI was used for all 95% CIs. *P* values are for the Mantel–Haenszel chi-square test without continuity correction.

[a] Microbiological response at visit 4 for patients with clinical response of "failure" at visit 4 were not reported in Study P-110881-01.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Table 14: Symptoms of Impetigo

	P-110880-01		P-110881-01	
	Ozenoxacin N = 155 ITTC Set	**Placebo N = 156 ITTC Set**	**Ozenoxacin N = 206 ITTC Set**	**Placebo N = 206 ITTC Set**
Total SIRS score				
Baseline, N	155	156	206	206
Mean (SD)	15.1 (4.5)	15.0 (4.0)	7.6 (2.2)	7.6 (2.3)
Visit 2, N	153	154	201	190
Mean (SD)	6.1 (4.1)	7.9 (4.5)	3.8 (2.2)	4.1 (2.3)
Mean change from baseline (SD)	–8.9 (4.6)	–7.0 (4.4)	–3.8 (2.1)	–3.4 (2.6)
LSM difference in change,[a] ozenoxacin vs. placebo (95% CI)	NR		–0.36 (–0.76, 0.03) *P* = 0.071	
Mean % change from baseline (SD)	–59.2 (24.1)	–46.9 (23.8)	NR	NR
Visit 3, N	153	151	204	203
Mean (SD)	2.7 (2.9)	4.3 (3.9)	1.6 (2.3)	2.4 (2.9)
Mean change from baseline (SD)	–12.4 (4.9)	–10.7 (4.8)	–6.0 (2.7)	–5.2 (3.3)
LSM difference in change,[a] ozenoxacin vs. placebo (95% CI)	NR		–0.72 (–1.22, –0.23) *P* = 0.004	
Mean % change from baseline (SD)	–81.7 (20.1)	–71.6 (23.8)	NR	NR
Visit 4, N	152	150	200	186
Mean (SD)	1.2 (2.1)	2.0 (3.2)	0.6 (1.5)	0.6 (1.2)
Mean change from baseline (SD)	–13.9 (4.6)	–12.9 (4.4)	–7.1 (2.5)	–6.9 (2.6)
LSM difference in change,[a] ozenoxacin vs. placebo (95% CI)	NR		–0.03 (–0.30, 0.24) *P* = 0.835	
Mean % change from baseline (SD)	–92.5 (12.9)	–86.9 (19.7)	NR	NR
Mean size of affected as a proportion of baseline affected area				
Visit 2, N	153	154	200	190
Mean (SD)	0.544 (0.318)	0.694 (0.351)	0.529 (0.311)	0.601 (0.419)
Visit 3, N	153	151	203	202
Mean (SD)	0.304 (0.344)	0.464 (0.424)	0.196 (0.315)	0.406 (0.782)
Visit 4, N	152	150	199	185
Mean (SD)	0.163 (0.289)	0.310 (0.620)	0.063 (0.182)	0.088 (0.271)

CI = confidence interval; ITTC = intention-to-treat clinical; LSM = least squares mean; NR = not reported; SD = standard deviation; SIRS = Skin Infection Rating Scale; vs. = versus.

Note: *P* values are descriptive as there was no adjustment for multiplicity.

Maximum total SIRS score was 42 in P-110880-01 and 15 in P-110881-01.

[a] Analysis of covariance adjusted for baseline total SIRS score.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Harms

Only those harms identified in the review protocol (Table 3) are subsequently reported.

Adverse Events

In Study P-880, 5.1% of patients in the ozenoxacin group and 6.4% of patients in the placebo group had an adverse event (AE). In Study P-881, 3.9% of patients in the ozenoxacin group and 3.4% of patients in the placebo group had an AE. The only AEs occurring in at least 1% of patients in at least one treatment group were nasopharyngitis (four patients in the ozenoxacin group) and rash (two patients in the placebo group), both of which occurred in Study P-880.

Serious Adverse Events

There were no serious AEs in either of the studies.

Withdrawals Due to Adverse Events

There were no withdrawals due to AEs in Study P-880. In Study P-881, one patient in the ozenoxacin group withdrew due to rosacea and seborrheic dermatitis, and three patients in the placebo group withdrew due to AEs, one due to eczema, one due to skin tightness, and one due to herpes zoster.

Mortality

There were no mortalities in either of the studies.

Notable Harms

There were no AEs involving antibiotic resistance.

Table 15: Harms

	P-110880-01		P-110881-01	
	Ozenoxacin N = 156 Safety Set	**Placebo N = 156 Safety Set**	**Ozenoxacin N = 206 Safety Set**	**Placebo N = 205 Safety Set**
Patients with ≥ 1 AE, n (%)	8 (5.1)	10 (6.4)	8 (3.9)	7 (3.4)
Patients with ≥ 1 SAE, n (%)	0	0	0	0
Death, n (%)	0	0	0	0
WDAEs, n (%)	0	0	1 (0.5)	3 (1.5)
Most common AEs (> 1% in at least 1 group), n (%)				
Nasopharyngitis	4 (2.6)	0	0	0
Rash	0	2 (1.3)	0	0

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Discussion

Summary of Available Evidence

Two phase III, double-blind, parallel-groups RCTs comparing ozenoxacin with a placebo for efficacy and safety (Study P-880 and Study P-881) were included in the CDR systematic review. Both were considered pivotal trials by Health Canada. A systematic review and an ITC used to inform the pharmacoeconomic model on the comparative efficacy of ozenoxacin versus fusidic acid and mupirocin were provided by the manufacturer and are summarized in Appendix 6.

Interpretation of Results

Efficacy

Results from the two pivotal trials demonstrated the efficacy of ozenoxacin treatment in the primary efficacy end point of clinical cure assessed at the end of therapy. Clinical cure at visit 3, or the end of therapy, meant that signs and symptoms were minimal and that no additional antimicrobial therapy was necessary following the study treatment. Differences in the proportion of patients with clinical cure were statistically significant at 15.5% and 16.0% in favour of ozenoxacin in Study P-880 and Study P-881, respectively. Using a definition of clinical success at visit 3 in Study P-881 more reflective of clinical practice, the proportions of patients with clinical success were higher and the mean difference between groups was 10.4%. Subgroup analysis in Study P-880 suggested that the efficacy of ozenoxacin was greater in patients with non-bullous impetigo (the most common form of impetigo) compared with patients with bullous impetigo. All end points aside from the primary efficacy end point should be considered exploratory as there was no control for type I error.

Post-therapy follow-up showed a between-treatment difference in clinical cumulative cure five to eight days after the end of therapy at visit 4. The numbers of patients with clinical cure or cumulative cure increased from visit 3 to visit 4 in both treatment groups in both trials. The differences between treatment groups at visit 4 were smaller than at visit 3, and it was possible that missing responses from patients who discontinued Study P-881 biased the effect size against ozenoxacin at visit 4.

Early clinical response at visit 2 was favourable (early cure or improvement) for most patients in both treatment groups in both trials, and was similar between the ozenoxacin and placebo groups. The requirement of a 10% decrease in the SIRS total score was not considered by the clinical expert consulted this review to be a clinically meaningful improvement in disease status, which likely explains the high numbers of patients with early clinical improvement.

The analysis of microbiological response at the end of therapy supported the results for the primary end point. The proportions of patients with microbiological success were higher than the proportions of patients with clinical cure at visit 3; this discrepancy may be due to the stringent requirements for clinical cure. In contrast, the proportions of patients with microbiological success were lower than the proportions of patients with clinical early cure or improvement at visit 2. Unlike the similarity in clinical response between treatment groups at visit 2, the proportions of patients with microbiological success at visit 2 were higher in the ozenoxacin groups than in the placebo groups in both studies. However, the results for microbiological response should be interpreted with caution in Study P-881, as a large

proportion of these responses were determined by clinical response as opposed to specimen testing.

The ITTB population in Study P-881 consisted of patients with *S. aureus* or *S. pyogenes* identified at baseline and made up only 56% of the ITTC population. The comparative efficacy of ozenoxacin versus placebo in terms of clinical response was greater in the ITTB population than in the ITTC population, and this may reflect the expected efficacy of ozenoxacin against *S. aureus* and *S. pyogenes*.

Coinfections of *S. aureus* and *S. pyogenes* and drug-resistant infections did not show any notable differences from the full study population in clinical or microbiological response. There were coinfections of *S. aureus* and *S. pyogenes* in 18 patients in Study P-881 (these data were not provided in Study P-880), and, over both trials, there were 65 patients with drug-resistant *S. aureus* infections and four patients with drug-resistant *S. pyogenes* infections. In patients with drug-resistant infections, most had clinical failure at visit 3, cumulative cure at visit 4, and microbiological success at all visits. Small sample sizes precluded an analysis of differences between treatment groups.

A measure of the time from baseline to the resolution of impetigo would have allowed for the assessment of the clinical benefit provided by shortening the time spent with symptoms of impetigo. While the first visit at which sustained or improved clinical response was achieved was recorded in both studies, the interpretation of the results in Study P-880 was unclear and almost all patients in Study P-881 had a favourable clinical response by visit 2. The corresponding microbiological results suggested that eradication of the baseline pathogen was more likely to be achieved at an earlier visit with ozenoxacin treatment.

Measures of the symptoms of impetigo supported the results for clinical response. The SIRS total score was numerically lower in the ozenoxacin group at all post-baseline visits, though the between-group differences in change from baseline were of unclear clinical importance given the lack of evidence of validity or an established minimal clinically meaningful difference found for SIRS. Total affected area relative to baseline followed the same trends as the SIRS total score. According to the clinical expert, measures of lesion size may not accurately reflect clinical response as successful treatment in a large affected area entails a longer healing period than in smaller areas. Total affected area relative to baseline tended to be larger in Study P-880 than in Study P-881. In Study P-880, there were more patients with baseline affected areas of 50 cm^2 or more and their results may account for some of the between-study differences. Results from Study P-881 suggested trends toward more patients with an absence of the baseline affected area and less frequent development of new lesions at visit 3 with ozenoxacin treatment. Possible bias against ozenoxacin from missing responses at visits 2 and 4 in Study P-881 may have affected symptom-related outcomes, including the absence of baseline affected area and appearance of new lesions.

In terms of antimicrobial therapy use (topical or systemic antibiotics) other than the study medication, higher proportions of patients in the placebo group required additional therapy following the study treatment course in Study P-881, while concomitant antibacterial medications were used by more patients in the placebo group throughout both studies. Concomitant topical therapies were prescribed more commonly than systemic therapies. The greater use of concomitant antibacterial medications in the placebo groups could have biased the results for the alternative definition of clinical success, SIRS total score, total size of affected area, absence of baseline lesions, and patients with new lesions against ozenoxacin.

In terms of the impact of impetigo on work or school attendance in Study P-881, only a minority of pediatric patients (or their family members) were prevented from attending work or school due to the child's condition, and the between-treatment differences were small.

It is unclear what factors contributed to the lower proportion of patients with clinical cure in Study P-880 compared with Study P-881. The SIRS was defined differently in each study and the criteria for the clinical cure at visit 3 were more stringent in Study P-880 as there were more signs and symptoms that had to be minimized, and a score of 1 or less was a stricter requirement in Study P-880 than in Study P-881. The clinical expert consulted for this review noted that the erythema, one of the scores that had to be 1 or less, is one of the last symptoms of impetigo to disappear. In a post hoc analysis reported in the Study P-880 publication,[12] clinical success was defined in a manner similar to the alternative definition used in Study P-881. Under the alternative definition of clinical success, proportions with clinical success at visit 3 were similar between studies (85.2% versus 73.7% for ozenoxacin versus placebo in Study P-880, and 89% versus 78% for ozenoxacin versus placebo in Study P-881). The alternative definition of clinical success may reflect clinical practice more accurately as it incorporates both lesion severity and extent as opposed to severity alone.

The study entry criteria in the phase III RCTs generally reflected the population of patients that would be expected to receive topical therapy for impetigo in Canada. There were limited numbers of patients with large baseline affected areas (50 cm^2 or more), more than 10 baseline affected areas, and severe lesions (defined as a total SIRS scores in the upper third of the range). However, patients with extensive or severe lesions are more likely to receive systemic rather than topical antibiotic therapy. Although it was possible that some of the study patients had a skin infection or condition other than impetigo, the use of clinical diagnosis of impetigo to identify study patients may be more akin to clinical practice than requiring microbiological confirmation. According to the clinical expert consulted for this review, impetigo is typically diagnosed by visual inspection with culture being requested only in cases of atypical or extensive involvement, or recurrent disease.

Microbiological resistance and causative species patterns vary between regions and there were no Canadian centres included in the studies. However, clinical efficacy of ozenoxacin was consistent in the ITTC and ITTB populations, as well as in the subset of patients with drug-resistant infections, demonstrating that ozenoxacin was efficacious against the pathogens that cause impetigo. The clinical expert confirmed that the relative prevalence of the bullous and non-bullous forms of impetigo in the studies were similar to that in Canada.

The relevant topical comparators in Canada, fusidic acid and mupirocin, were not included in the pivotal studies. According to the clinical expert, oral antibiotic therapies would also have been relevant as different clinicians will have different thresholds for prescribing systemic therapies based on extent and severity of impetigo.

Given the absence of direct comparisons of ozenoxacin with relevant comparators, the manufacturer's submission considered ITCs of ozenoxacin versus sodium fusidate and mupirocin. Two trials, one of them being Study P-880, were used to conduct an ITC of ozenoxacin with sodium fusidate using retapamulin as a common comparator. Although the studies were generally similar, limitations of the ITC included the use of a post hoc end point in Study P-880 (from the publication by Gropper et al.[12]) and the lack of information on the use of concomitant antimicrobial therapies in the sodium fusidate study. The ITC suggested no statistically significant differences in clinical success between ozenoxacin and sodium fusidate in patients with impetigo (with a risk ratio for sodium fusidate versus ozenoxacin of 0.93 [95% CI, 0.83 to 1.04]).

In the second ITC, two trials were included to compare clinical cure between ozenoxacin and mupirocin with placebo as a common comparator. There were differences between the trials in terms of the proportion of patients with lesions positive for *S. 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 analysis. There was 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 was used to estimate the comparative efficacy of ozenoxacin versus mupirocin 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.

In addition to the limitations identified above, both ITCs are limited by the availability of only one study per direct comparison. Comparisons of ozenoxacin with systemic antibiotics were not available. Given the identified limitations, the comparative efficacy of ozenoxacin with other therapies for impetigo remains uncertain.

Harms

There were no serious AEs and only four withdrawals due to AEs. The most common AEs were nasopharyngitis in four patients and rash in two patients, and skin disorders were present in only four patients or less in each treatment group. According to the clinical expert, the safety profile was similar to that in other topical therapies for impetigo. The Health Canada Reviewer's Report[25,26] indicated that Ozanex was evaluated for safety in a total of 31 patients aged two months to two years, 20 in a phase I study, and the remainder in Study P-881.

Potential Place in Therapy[2]

Impetigo, a superficial, contagious bacterial infection, manifests with lesions that can be popular, pustular, and erosive with crusting. It is a common skin infection in children, and can require repeated medical visits and treatment courses. Children are generally excluded from group care or school until 24 hours after therapy has started, thus affecting parental quality of life, as well as that of the child. Less commonly, poststreptococcal infection complications, such as glomerulonephritis, can be observed. Although more common in warm and humid conditions, impetigo is still a common primary care issue in Canada, with increased risk in lower socioeconomic status settings.

Treatment of impetigo hastens healing and might reduce infection spread. Topical mupirocin or fusidic acid are commonly used therapeutic options, while extensive disease is usually treated with oral cloxacillin or cephalexin. Over-the-counter topical options, such as bacitracin, might also be expected to be useful; however, they may not be as effective as prescription topical drugs[13] and may induce contact dermatitis or other allergic reactions. The benefits of topical therapy for impetigo include fewer side effects and possibly less contribution to bacterial resistance. Other drugs active against the causative pathogens (the most common of which are group A streptococci and *S. aureus)* may be used.

There is a potential benefit in adding ozenoxacin 1% cream to current treatments for impetigo, as bacterial resistance may be a concern. In places where topical fusidic acid is

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

commonly used, emergence of *S. aureus* resistance has been observed.[14] There is no Canadian data on MRSA involvement in impetigo, although MRSA has been seen in a proportion of impetigo cases in some studies elsewhere.[15,16] Also, clinical microbiology labs do not ordinarily test or report resistance to topical drugs.

Ozenoxacin 1% cream appears to be safe and reasonably effective, though the trials did not compare it to other therapies. However, the greater cost of this drug may be a barrier to some of the population at risk of having impetigo. Although the prescribed amount of ozenoxacin is likely sufficient to complete a single course of therapy, the amounts of fusidic acid and mupirocin dispensed are likely to suffice for more than one course should there be a recurrence. In cases where repeat treatment is necessary, the overall cost per treatment course may be reduced for fusidic acid or mupirocin, but not for ozenoxacin. Adding this to currently available options in the absence of a head-to-head trial of ozenoxacin 1% cream versus mupirocin or fusidic acid expands the options available, but as resistance to these drugs is not commonly tested or reported, choice would be guided by clinical relapse or by financial means to pay for therapy.

Conclusions

Results from the two included phase III studies showed the efficacy of ozenoxacin twice daily for five days in the treatment of impetigo. A greater proportion of patients achieved clinical cure one to two days after the end of study treatment with ozenoxacin than with the placebo in both trials. The results were supported by analyses of microbiological success, outcomes related to severity and extent of affected areas, and additional antimicrobial therapy use. Cumulative cure five to eight days after the end of study treatment was also achieved in a greater proportion of patients with ozenoxacin treatment compared with the placebo in both trials. Clinical efficacy was not notably different in patients with drug-resistant infections. The AEs reported did not give rise to any safety concerns and the safety profile of ozenoxacin was similar to that of other topical treatments for impetigo.

Adjusted ITCs of ozenoxacin versus sodium fusidate and of ozenoxacin versus mupirocin suggested similar clinical efficacy between ozenoxacin and the topical comparators; however, the ITCs were based on only one study per direct comparison. The ITC of ozenoxacin and sodium fusidate was also limited by the use of a post hoc end point in Study P-880 and the lack of information on the use of concomitant antimicrobial therapies in the sodium fusidate study. The ITC of ozenoxacin and mupirocin was limited by a high risk of attrition bias, small sample size in one study, and differences between the studies in patient characteristics and study design. Another approach was used to compare ozenoxacin with mupirocin, in which the assumption of similar efficacy between ozenoxacin and mupirocin was based on a naive comparison between results of the ITC of ozenoxacin versus sodium fusidate and the results of a meta-analysis of four RCTs comparing mupirocin with fusidic acid — this approach is not methodologically sound. These limitations contribute uncertainty to the estimates of relative efficacy of ozenoxacin versus topical comparators and the comparative efficacy of ozenoxacin with systemic therapies for impetigo remains unknown.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group, the Canadian Skin Patient Alliance (CSPA), responded to the call for patient input for this CADTH Common Drug Review. The CSPA is a non-profit organization that serves patients with dermatological conditions, diseases, and traumas in Canada. It focuses on education and advocacy for these patients, as well as for more than 20 additional affiliated disease-specific organizations in Canada.

The CSPA declared that the following companies have provided its group with financial payment in the last two years and may have an interest in the drug under review: Cipher Pharmaceuticals, GlaxoSmithKline, Pfizer, and the Institute of Musculoskeletal Health and Arthritis of the Canadian Institutes of Health Research. The patient groups declared no conflict of interests in the preparation of this submission.

2. Condition-Related Information

Condition-related information was collected through an online patient survey, which was advertised on social media and shared with "mom bloggers," affiliate member groups, and personal contacts of the CSPA. Five respondents completed the survey. Online disease discussion boards where patients share their experiences with impetigo and associated treatments were also researched and used by the patient group to inform this submission.

As described by the patient group, impetigo is a bacterial skin infection that causes red sores that can form anywhere on the body. These sores can break open, ooze fluid, and develop a yellowish crust. All of those surveyed reported having experienced red sores that crusted over, with some increasing in size and number, and/or turning into large blisters. Soreness, pain, and itching are also commonly reported issues for patients.

Most of the survey respondents experienced impetigo on their hands and feet or nose and mouth, although some also reported it on their buttocks or entire body. One patient indicated that they experienced such *"…extreme pain and couldn't sit for weeks…*" due to the impetigo on their buttocks.

In adults, impetigo may occur along with other skin problems, including eczema, or after an upper respiratory tract infection. Patients described fever as a symptom that caused the most difficulty, as it impacted their normal functioning and everyday activities. Several mentioned the stigma of having such a horrible condition that made them feel self-conscious about their outward appearance. Furthermore, patients reported that knowing that impetigo is very contagious and can spread through contact can lead to feelings of isolation.

According to the patient group, impetigo is a very common infection and, while it can occur in both adults and children, it is seen far more often in children. It was noted that given how contagious impetigo is, children with impetigo may not be able to attend school or daycare for days to weeks, depending on the severity of their infection. Furthermore, they felt that this has the biggest impact on families, as sick children need a caregiver for these situations and parents often need to stay home from work to provide care. The other consequence of impetigo being so contagious is that the patients can easily pass it onto their caregivers, allowing it to spread quickly throughout families. Like many childhood illnesses, there can also be outbreaks in schools and daycares that complicate the situation for all who have

been in contact. Another impact on the family or caregiver is the time to clean sheets, towels, and toys, which is an important but time-consuming task that is imperative to limit the spread of the disease.

3. Current Therapy-Related Information

The patient group identified topical and oral antibiotics as current treatments for impetigo, with varying degrees of efficacy from one patient to another. Reoccurrence of infection with use of current therapy was another concern described by patients. Ease of use for current treatments was also addressed, as current topical treatments were reported as messy and sticky, making it difficult to apply and use on young children, and infants in particular. Side effects including yeast infections, bad breath, diarrhea, and nausea were noted, as were issues with current therapy such as medication that stopped working altogether, and the expensive costs of treatment (oral and topical antibiotics).

4. Expectations About the Drug Being Reviewed

The patient group was not able to gather information from patients who had experience with ozenoxacin; however, those without experience indicated that limiting the potential to spread the infection, as well as preventing *"…the pain that spreads like wildfire…"* would be something they consider important in a new treatment. New therapies are expected to be effective and to limit the potential spread of the infection to others, as well as to quickly ease the pain symptoms that have been reported. A treatment that is quick and effective would also mean less missed days at school and/or work, which was also highlighted by the patient group.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE ALL (1946 -) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 27, 2018
Alerts:	Bi-weekly search updates until June 20, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
medall	Ovid database code; MEDLINE ALL 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

#	Searches
1	(ozenoxacin or Ozanex* or Zebiax* or Xepi* or Ozaenex* or Ozadub* or dubine* or t-3912 or t3912 or V0LH498RFO or 245765-41-7).ti,ab,ot,kf,hw,rn,nm.
2	1 use medall
3	ozenoxacin/
4	(ozenoxacin or Ozanex* or Zebiax* or Xepi* or Ozaenex* or Ozadub* or dubine* or t-3912 or t3912).ti,ab,ot,kw,hw,rn,nm.
5	3 or 4
6	5 use oemezd
7	6 not conference abstract.pt.
8	2 or 7
9	remove duplicates from 8

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	February 2018
Keywords:	ozenoxacin, Zebiax, Xepi, Ozaenex, Ozadub, Dubine, quinolone, bacterial skin infection, impetigo, pyoderma, ecthyma, staphylococcus aureus, staphylococcus pyogenes
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey matters: a practical tool for evidence-based searching* (http://www.cadth.ca/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Gupta AK, Versteeg SG, Abramovits W. Ozenoxacin Cream, 1% — Topical Treatment of Impetigo. Skinmed. 2017;15(1):57-9.	Not an RCT

RCT = randomized controlled trial.

Appendix 4: Detailed Outcome Data

Table 16: Clinical Response in the Intention-to-Treat Bacteriological Population

	P-110880-01		P-110881-01	
	Ozenoxacin N = 154 ITTB Set	**Placebo N = 152 ITTB Set**	**Ozenoxacin N = 125 ITTB Set**	**Placebo N = 119 ITTB Set**
Clinical response at visit 3, n (%)				
Cure	54 (35)[a]	30 (20)[a]	74 (59)[b]	42 (35)[b]
Failure	97 (63)	116 (76)	51 (41)	73 (61)
Improvement	96 (62)	115 (76)	48 (38)	61 (51)
Failure	1 (0.6)	1 (0.7)	3 (2)	12 (10)
Unable to determine	3 (2)	6 (4)	0	4 (3)
Mean difference in % of patients with cure, ozenoxacin vs. placebo (95% CI)	15.2 (5.1, 25.3) *P* = 0.004		22.7 (10.4, 35.0) *P* < 0.001	
Clinical response at visit 2, n (%)				
Early cure	NA	NA	23 (18)	13 (11)
Improvement	146 (95)	142 (93)	97 (78)	84 (71)
No improvement	5 (3)	7 (5)	5 (4)	12 (10)
Unable to determine	3 (2)	3 (2)	0	10 (8)
Mean difference in % of patients with improvement (95% CI)	1.4 (–3.1, 5.8) *P* = 0.540		NA	
Mean difference in % of patients with early cure, ozenoxacin vs. placebo (95% CI)	NA		6.5 (–2.6, 15.6) *P* = 0.171	
Difference in distribution of patients with early cure, improvement, and no improvement, *P* value for Mantel–Haenszel chi-square test	NA		*P* = 0.031	
Clinical response at visit 4, (n (%)				
Cumulative cure	82 (53)	62 (41)	101 (81)	67 (56)
Cure	48 (31)	26 (17)	69 (55)	38 (32)
Post-therapy cure	34 (22)	36 (24)	30 (24)	27 (23)
No change	NA	NA	2 (2)	2 (2)
No cumulative cure	72 (47)	90 (59)	22 (18)	35 (29)
No change	3 (2)	2 (1)	NA	NA
Relapse	1 (0.6)	2 (1)	2 (2)	2 (2)
Failure	63 (41)	79 (52)	20 (16)	33 (28)
Unable to determine	5 (3)	7 (5)	NA	NA
Unable to determine	NA	NA	2 (2)[c]	17 (14)[c]
Mean difference in % of patients with cumulative cure, ozenoxacin vs. placebo (95% CI)	12.5 (1.4, 23.6) *P* = 0.029		16.4 (5.0, 27.9) *P* = 0.005	
Clinical response at visit 3 using combined SIRS and size/extent criteria, n (%)				
Success	NA	NA	116 (93)	83 (70)
Failure	NA	NA	9 (7)	34 (29)
Unable to determine	NA	NA	0	2 (2)

	P-110880-01		P-110881-01	
	Ozenoxacin N = 154 ITTB Set	Placebo N = 152 ITTB Set	Ozenoxacin N = 125 ITTB Set	Placebo N = 119 ITTB Set
Mean difference in % of patients with success, ozenoxacin vs. placebo (95% CI)	NA		21.9 (12.5, 31.3) $P < 0.001$	

CI = confidence interval; ITTB = intention-to-treat bacteriological; NA = not applicable; SIRS = Skin Infection Rating Scale; vs. = versus.

Note: Asymptotic (Wald) CI was used for all 95% CIs. *P* values are for the Mantel–Haenszel chi-square test without continuity correction.

P values are descriptive as there was no adjustment for multiplicity.

Except where noted, patients with missing or "unable to determine" status were not included in calculations of mean differences between groups.

[a] Criteria for clinical cure at visit 3: SIRS score of 0 for exudates/pus, crusting, tissue warmth, and pain; no more than 1 each for erythema/inflammation, tissue edema, and itching; no additional antimicrobial therapy of the baseline affected area(s) necessary.

[b] Criteria for clinical cure at visit 3: SIRS score of 0 for blistering, exudates/pus, crusting, and itching pain; no more than 1 each for erythema/inflammation; no additional antimicrobial therapy of the baseline affected area(s) necessary.

[c] These patients were included in the calculation of difference in percentage of patients with cumulative cure.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Table 17: Clinical Response at Visit 3 by Baseline Characteristics

	P-110880-01		P-110881-01	
	Ozenoxacin N = 155 ITTC Set	Placebo N = 156 ITTC Set	Ozenoxacin N = 206 ITTC Set	Placebo N = 206 ITTC Set
Clinical response at visit 3 by				
Type of impetigo, n (%)				
Bullous	N = 33	N = 34	N = 24	N = 29
Cure	5 (15)	8 (24)	12 (50)	12 (41)
Failure	27 (82)	24 (71)	12 (50)	17 (59)
Unable to determine	1 (3)	2 (6)	NR	NR
Mean difference in % of patients with cure (95% CI)	–9.4 (–29.0, 10.2) $P = 0.351$		8.6 (–18.2, 35.5)	
Non-bullous	N = 122	N = 122	N = 179	N = 170
Cure	49 (40)	22 (18)	100 (56)	66 (39)
Failure	71 (58)	96 (79)	79 (44)	104 (61)
Unable to determine	2 (2)	4 (3)	NR	NR
Mean difference in % of patients with cure (95% CI)	22.2 (10.9, 33.4) $P < 0.001$		17.0 (6.7, 27.4)	
Interaction of treatment and type of impetigo[a]	$P = 0.016$		NR	
Number of baseline affected areas, n (%)				
1	N = 72	N = 78	N = 76	N = 88
Cure	20 (28)	17 (22)	43 (57)	35 (40)
Failure	49 (68)	61 (78)	33 (43)	53 (60)
Unable to determine	3 (4)	0	NR	NR
Mean difference in % of patients with cure (95% CI)	7.2 (–6.9, 21.3) $P = 0.316$		16.8 (1.7, 31.9)	
2 to 4	N = 59	N = 54	N = 103	N = 81
Cure	27 (46)	10 (19)	56 (54)	31 (38)
Failure	32 (54)	39 (72)	47 (46)	50 (62)
Unable to determine	0	5 (9)	NR	NR

	P-110880-01		P-110881-01	
Mean difference in % of patients with cure (95% CI)	25.4 (8.4, 42.4) *P* = 0.006		16.1 (1.8, 30.4)	
5 to 10	N = 18	N = 18	N = 21	N = 26
Cure	5 (28)	2 (11)	11 (52)	11 (42)
Failure	13 (72)	15 (83)	10 (48)	15 (58)
Unable to determine	0	1 (6)	NR	NR
Mean difference in % of patients with cure (95% CI)	16.0 (–9.7, 41.8) *P* = 0.237		10.1 (–18.5, 38.7)	
> 10	N = 6	N = 6	N = 2	N = 3
Cure	2 (33)	1 (17)	1 (50)	1 (33)
Failure	4 (67)	5 (83)	1 (50)	2 (67)
Unable to determine	0	0	NR	NR
Mean difference in % of patients with cure (95% CI)	16.7 (–31.4, 64.7) *P* = 0.505		16.7 (–70.8, 100.0)	
Interaction of treatment and number of baseline affected areas[a]	*P* = 0.560		NR	
Size of total affected area, n (%)				
< 2 cm^2	N = 46	N = 34	NA	NA
Cure	19 (41)	9 (26)	NA	NA
Failure	26 (57)	24 (71)	NA	NA
Unable to determine	1 (2)	1 (3)	NA	NA
Mean difference in % of patients with cure (95% CI)	14.9 (–6.0, 35.9) *P* = 0.174		NA	
≥ 2 cm^2 and < 10 cm^2	N = 74	N = 80	N = 138	N = 141
Cure	24 (32)	15 (19)	83 (60)	61 (43)
Failure	48 (65)	62 (78)	55 (40)	80 (57)
Unable to determine	2 (3)	3 (4)	NR	NR
Mean difference in % of patients with cure (95% CI)	13.9 (–0.2, 27.9) *P* = 0.055		16.9 (5.3, 28.4)	
≥ 10 cm^2 and < 50 cm^2	N = 27	N = 30	N = 58	N = 57
Cure	10 (37)	4 (13)	26 (45)	17 (30)
Failure	17 (63)	24 (80)	32 (55)	40 (70)
Unable to determine	0	2 (6.7)	NR	NR
Mean difference in % of patients with cure (95% CI)	22.8 (0.4, 45.1) *P* = 0.053		15.0 (–2.5, 32.5)	
≥ 50 cm^2 and < 100 cm^2	N = 8	N = 12	N = 6	N = 0
Cure	1 (13)	2 (17)	2 (33)	0
Failure	7 (88)	10 (83)	4 (67)	0
Unable to determine	0	0	NR	NR
Mean difference in % of patients with cure (95% CI)	–4.2 (–35.3, 27.0) *P* = 0.798		NA	
Interaction of treatment group and size of total affected area[a]	*P* = 0.732		NR	
SIRS total score				
< 15	N = 80	N = 78	NA	NA
Cure	35 (44)	22 (28)	NA	NA
Failure	44 (55)	54 (69)	NA	NA
Unable to determine	1 (1)	2 (3)	NA	NA

	P-110880-01		P-110881-01	
Mean difference in % of patients with cure (95% CI)	15.4 (0.4, 30.3) *P* = 0.047		NA	
15 to 28	N = 74	N = 78	NA	NA
Cure	18 (24)	8 (10)	NA	NA
Failure	54 (73)	66 (85)	NA	NA
Unable to determine	2 (3)	4 (5)	NA	NA
Mean difference in % of patients with cure (95% CI)	14.2 (1.9, 26.4) *P* = 0.025		NA	
29 to 42	N = 1	N = 0	NA	NA
Cure	1 (100)	NA	NA	NA
3 to 9	NA	NA	N = 166	N = 161
Cure	NA	NA	93 (56)	57 (35)
Failure	NA	NA	73 (44)	104 (65)
Mean difference in % of patients with cure (95% CI)	NA		20.6 (10.1, 31.2)	
10 to 15	NA	NA	N = 37	N = 38
Cure	NA	NA	19 (51)	21 (55)
Failure	NA	NA	18 (49)	17 (45)
Mean difference in % of patients with cure (95% CI)	NA		–3.9 (–26.5, 18.7)	
Interaction of treatment group and SIRS total score[a]	*P* = 0.551		NR	

CI = confidence interval; ITTC = intention-to-treat clinical; NA = not applicable; NR = not reported; SIRS = Skin Infection Rating Scale.

Note: Criteria in Study P-110880-01 for clinical success at visit 3: SIRS score of 0 for exudates/pus, crusting, tissue warmth, and pain; no more than 1 each for erythema/inflammation, tissue edema, and itching; no additional antimicrobial therapy of the baseline affected area(s) necessary.

Criteria in Study P-110881-01 for clinical success at visit 3: SIRS score of 0 for blistering, exudates/pus, crusting, and itching pain; no more than 1 each for erythema/inflammation; no additional antimicrobial therapy of the baseline affected area(s) necessary.

P values are descriptive as there was no adjustment for multiplicity.

Asymptotic (Wald) CI was used for all 95% CIs. *P* values for comparisons within each subgroup are for the Mantel–Haenszel chi-square test without continuity correction.

Patients with missing or "unable to determine" status were not included in calculations of mean difference in % of patients with cure.

[a] Analysis of covariance with the following three terms: treatment group, baseline covariate, and interaction between treatment group and baseline covariate.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Table 18: Clinical and Microbiological Response in Patients with *Staphylococcus Aureus* and *Streptococcus Pyogenes* Coinfection at Baseline

	P-110881-01	
	Ozenoxacin N = 9	**Placebo N = 9**
Clinical response of patients with *Staphylococcus aureus* and *Streptococcus pyogenes* coinfection at baseline, n (%)		
Visit 2, n (%)		
Early cure	1 (11)	1 (11)
Improvement	8 (89)	8 (89)
No improvement	0	0
Unable to determine	0	0
Visit 3, n (%)		
Cure	7 (78)	2 (22)
Improvement	2 (22)	6 (67)

	P-110881-01	
Failure	0	0
Unable to determine	0	1 (11)
Visit 4, n (%)		
Cure	7 (78)	2 (22)
Post-therapy cure	1 (11)	3 (33)
No change	0	0
Relapse	0	0
Failure	1 (11)	3 (33)
Unable to determine	0	1 (11)
Microbiological response of patients with *Staphylococcus aureus* and *Streptococcus pyogenes* coinfection at baseline, n (%)		
Visit 2, n (%)		
Eradication	1 (11)	0
Presumed eradication	8 (89)	7 (78)
Persistence	0	2 (22)
Presume persistence	0	0
Superinfection	0	0
Unable to determine	0	0
Visit 3, n (%)		
Eradication	0	0
Presumed eradication	8 (89)	6 (67)
Persistence	1 (11)	2 (22)
Presumed persistence	0	0
Reinfection	0	0
Presumed reinfection	0	0
Unable to determine	0	1 (11)
Visit 4, n (%)		
Presumed eradication	8 (89)	5 (56)
Reinfection	0	0
Recurrence	0	0
Presumed reinfection/recurrence	0	0
Unable to determine	1 (11)	4 (44)

Source: P-110881-01 clinical study report.[18]

Table 19: Clinical Response of Patients With Resistant Infections

	P-110880-01		P-110881-01	
	Ozenoxacin N = 154 ITTB Set	**Placebo N = 152 ITTB Set**	**Ozenoxacin N = 125 ITTB Set**	**Placebo N = 119 ITTB Set**
Resistant *Staphylococcus aureus* infections, n	4	3	32	26
Methicillin resistant, n	N = 1	N = 0	N = 9	N = 9
Visit 2, early cure or improvement / no improvement / unable to determine	1 / 0 / 0	NA	9 / 0 / 0	9 / 0 / 0
Visit 3, cure / no cure / unable to determine	1 / 0 / 0		2 / 7 / 0	3 / 6 / 0
Visit 4, cumulative cure / no cumulative cure / unable to determine	1 / 0 / 0		6 / 3 / 0	8 / 1 / 0
Ciprofloxacin resistant, n	N = 2	N = 0	N = 21	N = 15

	P-110880-01		P-110881-01	
Visit 2, early cure or improvement / no improvement / unable to determine	2 / 0 / 0	NA	20 / 1 / 0	15 / 0 / 0
Visit 3, cure / no cure / unable to determine	1 / 1 / 0		5 / 16 / 0	4 / 11 / 0
Visit 4, cumulative cure / no cumulative cure / unable to determine	2 / 0 / 0		18 / 3 / 0	14 / 1 / 0
Mupirocin resistant, n	N = 1	N = 2	N = 10	N = 10
Visit 2, early cure or improvement / no improvement / unable to determine	1 / 0 / 0	1 / 1 / 0	9 / 1 / 0	8 / 2 / 0
Visit 3, cure / no cure / unable to determine	0 / 1 / 0	0 / 2 / 0	4 / 6 / 0	3 / 6 / 1
Visit 4, cumulative cure / no cumulative cure / unable to determine	1 / 0 / 0	1 / 1 / 0	6 / 4 / 0	3 / 4 / 3
Fusidic acid resistant, n	N = 1	N = 1	N = 0	N = 0
Visit 2, early cure or improvement / no improvement / unable to determine	1 / 0 / 0	1 / 0 / 0	NA	NA
Visit 3, cure / no cure / unable to determine	0 / 1 / 0	0 / 1 / 0		
Visit 4, cumulative cure / no cumulative cure / unable to determine	0 / 1 / 0	0 / 1 / 0		
Retapamulin resistant, n	N = 0	N = 0	N = 1	N = 1
Visit 2, early cure or improvement / no improvement / unable to determine	NA	NA	1 / 0 / 0	1 / 0 / 0
Visit 3, cure / no cure / unable to determine			0 / 1 / 0	1 / 0 / 0
Visit 4, cumulative cure / no cumulative cure / unable to determine			1 / 0 / 0	1 / 0 / 0
Ozenoxacin resistant, n	Not tested		N = 15	N = 14
Visit 2, early cure or improvement / no improvement / unable to determine			15 / 0 / 0	14 / 0 / 0
Visit 3, cure / no cure / unable to determine			3 / 12 / 0	3 / 11 / 0
Visit 4, cumulative cure / no cumulative cure / unable to determine			12 / 3 / 0	13 / 1 / 0
Resistant *Streptococcus pyogenes* infections	1	2	1	0
Ciprofloxacin resistant, n	N = 1	N = 1	N = 1	N = 0
Visit 2, early cure or improvement / no improvement / unable to determine	1 / 0 / 0	1 / 0 / 0	1 / 0 / 0	NA
Visit 3, cure / no cure / unable to determine	1 / 0 / 0	0 / 1 / 0	0 / 1 / 0	
Visit 4, cumulative cure / no cumulative cure / unable to determine	1 / 0 / 0	0 / 1 / 0	1 / 0 / 0	
Retapamulin resistant, n	N = 0	N = 1	N = 0	N = 0
Visit 2, early cure or improvement / no improvement / unable to determine	NA	1 / 0 / 0	NA	NA
Visit 3, cure / no cure / unable to determine		0 / 1 / 0		
Visit 4, cumulative cure / no cumulative cure / unable to determine		1 / 0 / 0		

ITTB = intention-to-treat bacteriological; NA = not applicable.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Table 20: Microbiological Response of Patients With Resistant Infections

	P-110880-01		P-110881-01	
	Ozenoxacin N = 154 ITTB Set	**Placebo N = 152 ITTB Set**	**Ozenoxacin N = 125 ITTB Set**	**Placebo N = 119 ITTB Set**
Resistant *Staphylococcus aureus* infections, n	4	3	32	26
Methicillin resistant, n	N = 1	N = 0	N = 9	N = 9
Visit 2, success / failure / unable to determine	1 / 0 / 0	NA	6 / 3 / 0	7 / 2 / 0
Visit 3, success / failure / unable to determine	1 / 0 / 0		8 / 1 / 0	8 / 1 / 0
Visit 4, success / reinfection or recurrence / unable to determine	0 / 0 / 1		6 / 0 / 3	8 / 0 / 1
Ciprofloxacin resistant, n	N = 2	N = 0	N = 21	N = 15
Visit 2, success / failure / unable to determine	2 / 0 / 0	NA	17 / 4 / 0	13 / 2 / 0
Visit 3, success / failure / unable to determine	2 / 0 / 0		19 / 2 / 0	14 / 1 / 0
Visit 4, success / reinfection or recurrence / unable to determine	1 / 0 / 1		18 / 0 / 3	14 / 0 / 1
Mupirocin resistant, n	N = 1	N = 2	N = 10	N = 10
Visit 2, success / failure / unable to determine	1 / 0 / 0	0 / 2 / 0	8 / 2 / 0	6 / 3 / 1
Visit 3, success / failure / unable to determine	1 / 0 / 0	0 / 0 / 2	10 / 0 / 0	7 / 2 / 1
Visit 4, success / reinfection or recurrence / unable to determine	1 / 0 / 0	1 / 1 / 0	6 / 0 / 4	3 / 0 / 7
Fusidic acid resistant, n	N = 1	N = 1	N = 0	N = 0
Visit 2, success / failure / unable to determine	1 / 0 / 0	0 / 1 / 0	NA	NA
Visit 3, success / failure / unable to determine	1 / 0 / 0	0 / 1 / 0		
Visit 4, success / reinfection or recurrence / unable to determine	1 / 0 / 0	0 / 1 / 0		
Retapamulin resistant, n	N = 0	N = 0	N = 1	N = 2
Visit 2, success / failure / unable to determine	NA	NA	0 / 1 / 0	2 / 0 / 0
Visit 3, success / failure / unable to determine			1 / 0 / 0	2 / 0 / 0
Visit 4, success / reinfection or recurrence / unable to determine			1 / 0 / 0	1 / 0 / 1
Ozenoxacin resistant, n	Not tested		N = 15	N = 14
Visit 2, success / failure / unable to determine			12 / 3 / 0	12 / 2 / 0
Visit 3, success / failure / unable to determine			13 / 2 / 0	13 / 1 / 0
Visit 4, success / reinfection or recurrence / unable to determine			12 / 0 / 3	13 / 0 / 1
Resistant *Streptococcus pyogenes* infections	1	2	1	0
Ciprofloxacin resistant, n	N = 1	N = 1	N = 1	N = 0
Visit 2, success / failure / unable to determine	1 / 0 / 0	1 / 0 / 0	1 / 0 / 0	NA
Visit 3, success / failure / unable to determine	1 / 0 / 0	1 / 0 / 0	1 / 0 / 0	
Visit 4, success / reinfection or recurrence / unable to determine	1 / 0 / 0	1 / 0 / 0	1 / 0 / 0	
Retapamulin resistant, n	N = 0	N = 1	N = 0	N = 0
Visit 2, success / failure / unable to determine	NA	1 / 0 / 0	NA	NA
Visit 3, success / failure / unable to determine		1 / 0 / 0		
Visit 4, success / reinfection or recurrence / unable to determine		1 / 0 / 0		

ITTB = intention-to-treat bacteriological; NA = not applicable.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Table 21: Time to Clinical and Microbiological Response

	P-110880-01		P-110881-01	
	Ozenoxacin ITTC Set	**Placebo ITTC Set**	**Ozenoxacin ITTC Set**	**Placebo ITTC Set**
First visit at which sustained or improved clinical response (early cure, improvement, cure, or post-therapy cure) was achieved	N = 82	N = 63	N = 158	N = 126
Visit 2, n (%)	47 (57)	26 (41)	156 (99)	122 (97)
Visit 3, n (%)	35 (43)	37 (59)	2 (1)	4 (3)
First visit at which microbiological eradication (confirmed or presumed) was achieved	N = 114	N = 94	N = 99	N = 65
Visit 2, n (%)	86 (75)	38 (40)	89 (90)	55 (85)
Visit 3, n (%)	18 (16)	28 (30)	10 (10)	10 (15)
Visit 4, n (%)	10 (9)	28 (30)	0	0

ITTC = intention-to-treat clinical.

Note: Values are expressed as percentages of patients out of patients achieving sustained or improved clinical response or microbiological eradication.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Table 22: Use of Additional Antimicrobial Therapy

	P-110881-01	
	Ozenoxacin N = 206 ITTC Set	**Placebo N = 206 ITTC Set**
Patients using additional antimicrobial therapy, n (%)		
Visit 2[a]		
Using	1 (0.5)	2 (1)
Not using	200 (97)	188 (91)
Unknown	5 (2)	16 (8)
Mean difference in % of patients using additional antimicrobial therapy, ozenoxacin vs. placebo (95% CI)	–0.6 (–2.3, 1.2)	
Visit 3[b]		
Using	20 (10)	40 (19)
Not using	184 (89)	163 (79)
Unknown	2 (1)	3 (2)
Mean difference in % of patients using additional antimicrobial therapy, ozenoxacin vs. placebo (95% CI)	–9.9 (–16.7, –3,1)	

CI = confidence interval; ITTC = intention-to-treat clinical; vs. = versus.

Note: *P* values are descriptive as there was no adjustment for multiplicity.

Asymptotic (Wald) CI was used for all 95% CIs. *P* values are for the Mantel–Haenszel chi-square test without continuity correction.

Patients with "unknown" status were not included in calculations of mean difference in per cent of patients using additional antimicrobial therapy or with new lesions.

[a] Based on concomitant medications recorded at visit 2.

[b] Based on whether additional antimicrobial therapy was needed at visit 3.

Source: P-110881-01 clinical study report.[18]

Table 23: Concomitant Antibacterial Medications

	P-110880-01		P-110881-01	
	Ozenoxacin N = 156 Safety Set	**Placebo N = 156 Safety Set**	**Ozenoxacin N = 206 Safety Set**	**Placebo N = 205 Safety Set**
Number of patients using antibacterials for systemic use, n (%)	5 (3)	8 (5)	10 (5)	22 (11)
Amoxicillin	3 (2)	3 (2)	1 (0.5)	2 (1)
Amoxicillin / clavulanic acid	1 (0.6)	0	0	0
Azithromycin	0	0	1 (0.5)	2 (1)
Sulfamethoxazole / trimethoprim	1 (0.6)	1 (0.6)	1 (0.5)	0
Cefadroxil	0	0	0	1 (0.5)
Cefalexin	0	0	2 (1)	8 (4)
Cefprozil	0	0	1 (0.5)	0
Cefuroxime	0	0	1 (0.5)	3 (2)
Cefuroxime axetil	0	1 (0.6)	0	1 (0.5)
Ciprofloxacin	0	0	1 (0.5)	0
Cozole	0	1 (0.6)	0	0
Co-trimoxazole	0	0	1 (0.5)	3 (2)
Doxycycline	0	0	1 (0.5)	0
Doxycycline hydrochloride	0	0	0	1 (0.5)
Flucloxacillin	0	1 (0.6)	0	0
Fusidin	0	1 (0.6)	0	0
Metronidazole	1 (0.6)	1 (0.6)	0	0
Roxithromycin	0	1 (0.6)	0	0
Number of patients using antibiotics for topical use, n (%)	14 (9)	25 (16)	17 (8)	35 (17)
Bacitracin / neomycin sulfate	0	0	2 (1)	2 (1)
Chloramphenicol	0	0	2 (1)	3 (2)
Fusidic acid	0	1 (0.6)	4 (2)	12 (6)
Kanamycin	0	0	0	1 (0.5)
Mupirocin	14 (9)	24 (15)	9 (4)	17 (8)

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report.[18]

Table 24: Time Away From Work and School

	P-110881-01	
	Ozenoxacin N = 206 ITTC Set	**Placebo N = 206 ITTC Set**
Patients self-reporting, n (%)	N = 100	N = 95
Response to "Did the Condition Prevent you to Attend Work, School, or University?"		
Yes	14 (14)	11 (12)
No	70 (70)	70 (74)
Not applicable	16 (16)	14 (15)
Parents or guardians of pediatric patients reporting, n (%)	N = 105	N = 108
Response to "Did your Child's Condition Prevent you or Anyone in your Family to Attend Work?"		
Yes	12 (11)	11 (10)
No	83 (79)	81 (75)
Not applicable	10 (10)	16 (15)
Response to "Did your Child's Condition Prevent him/her to Attend School?"		
Yes	19 (18)	24 (22)
No	61 (58)	45 (42)
Not applicable	25 (24)	39 (36)

ITTC = intention-to-treat clinical.

Source: P-110881-01 clinical study report.[18]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the Skin Infection Rating Scale (SIRS).

Findings

SIRS is used to assess the severity of skin infections. The earliest study identified by the CADTH Common Drug Review that used SIRS was in patients with secondarily infected dermatitis.[27] Two different versions of SIRS were used in the P-110880-01 (referred to here as P-880) and P-110881-01 (referred to here as P-881) studies.

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. Each sign or symptom was rated by the investigator on an ordinal scale from 0 to 6. Scores of 0, 2, 4, and 6 corresponded to the following symptom ratings, respectively: "absent," "mild," "moderate," and "severe." Definitions for the severity ratings were not provided. The total SIRS score was obtained from the sum of the individual sign or symptom scores, with a possible maximum total score of 42. 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 baseline lesions.

The version of SIRS used in Study P-881 was based on five signs or symptoms: blistering, exudate/pus, crusting, erythema/inflammation, and itching/pain. Unlike in the first study, each sign or symptom was rated on an ordinal scale from 0 to 3 and each score was associated with a severity rating and definition (Table 25). The individual scores were summed for a total SIRS score, allowing for a possible maximum total score of 15. Scoring of multiple affected areas was handled the same way as in Study P-880.

While previous studies have used some version of SIRS as part of their inclusion criteria for patients with impetigo[28,29] or to assess response to therapy for skin infections,[27] the scale does not appear to have been validated, and a minimal clinically important difference has not been identified. The SIRS used in Study P-881 is identical to the one defined in the FDA's draft guidance on the conduct of mupirocin bioequivalence studies.[24] However, the draft guidance recommends using the scale in a target lesion and does not provide direction on applying SIRS to multiple affected areas.

Table 25: Skin Infection Rating Scale in Study P-110881-01

Sign/Symptom	Score	Rating	Definition
Blistering	0	Absent	No evidence of blisters
	1	Mild	Few raised vesicles present on close evaluation
	2	Moderate	Fluid filled vesicles are obvious and are bothersome to the patient
	3	Severe	Extensive area covered with many vesicles which may include large bullous vesicles
Exudate/pus	0	Absent	No evidence of exudates or pus
	1	Mild	Small amounts of fluid/pus coming from the lesions
	2	Moderate	Exudate/pus infected area is moderate
	3	Severe	Extensive areas infected and there is draining exudates
Crusting	0	Absent	No evidence of crusting
	1	Mild	A few areas have some evidence of crusting lesions

Sign/Symptom	Score	Rating	Definition
	2	Moderate	Crusting is present throughout the infected area
	3	Severe	Thick crusting appears over the entire impetiginious area
Erythema/ inflammation	0	Absent	Skin tone and colour are normal; no signs of erythema or inflammation
	1	Mild	Skin is pink with minimal signs of inflammation
	2	Moderate	Skin is red with definite signs of inflammation
	3	Severe	Skin is red and severe inflammation is present
Itching/pain (adult patients and pediatric patients able to self-report)	0	Absent	No signs of itching or indication of pain
	1	Mild	Some evidence of scratching or rubbing the area is evident and patient reports minor discomfort
	2	Moderate	Evidence of scratching and patient reports bothersome painful lesions
	3	Severe	Evidence of extensive scratching and patient reports pain that interferes with daily activities or sleep
Itching/pain (pediatric patients not able to self-report)	0	Absent	No signs of itching or indication of pain Normal behaviour
	1	Mild	Some evidence of scratching and the patients is crying more than usual with no effect on normal activities/behaviour
	2	Moderate	Evidence of scratching and the patient is crying more than usual and interference with normal activity/behaviour
	3	Severe	Evidence of extensive scratching and the patient crying cannot be comforted and prevents normal activity/behaviour and/or sleep

Source: P-110881-01 clinical study report.[18]

Conclusion

SIRS is a non-validated scale for which a minimal clinically important difference has not been identified. Furthermore, the parameters of the SIRS used in the two included studies differ slightly in terms of the signs and symptoms included and their scoring. The FDA draft guidance on mupirocin recommends use of SIRS to assess clinical cure seven days after the end of treatment and does not provide direction on applying SIRS to multiple affected areas.

Appendix 6: Summary of Indirect Comparisons

Background

Given the absence of head-to-head studies comparing ozenoxacin against other treatments for impetigo, indirect treatment comparisons (ITCs) that include ozenoxacin may provide information on the comparative efficacy and safety of this drug to existing therapies. This section of the report seeks to provide a summary and critical appraisal of the methods and results of any identified ITCs comparing ozenoxacin 1% cream to relevant comparators (topical or oral antibiotics) identified in the review protocol (Table 3) in the target population.

Methods

The manufacturer-submitted systematic review (SR) and ITC between ozenoxacin and sodium fusidate that were used to inform the clinical inputs of the manufacturer's pharmacoeconomic model[30,31] were summarized and critically appraised. A second ITC between ozenoxacin and mupirocin based on the studies identified in the SR was provided by the manufacturer to further justify the clinical inputs. A comprehensive literature search was also undertaken by the CADTH Common Drug Review (CDR) to identify any additional relevant published ITCs.

Description of Indirect Treatment Comparisons Identified

There were no published ITCs identified in the literature search conducted by CDR.

The manufacturer-submitted SR of interventions for impetigo did not identify randomized controlled trials (RCTs) comparing ozenoxacin with any of the relevant comparators in the CDR systematic review protocol. The results of the SR informed the manufacturer-submitted ITCs.

Summary of Manufacturer-Submitted Systematic Review and Indirect Treatment Comparison

Objectives and Rationale

According to the manufacturer-submitted SR, the management options for impetigo include topical antibiotics, systemic antibiotics, topical disinfectants, and non-pharmacological treatments. An SR of interventions for impetigo was performed by Koning et al. in 2012, and the manufacturer-submitted SR aimed to update the 2012 review with the most recent studies.[2,31] ITCs were conducted, based on the findings of the updated SR, to provide comparative efficacy estimates.

Methods

Study Eligibility and Selection Process

RCTs that enrolled patients with impetigo, or impetigo contagiosa, diagnosed by a medically-trained person, as well as patients with secondary impetigo, were included in the SR. Studies using a broader diagnostic category, such as "bacterial skin infections" or "pyoderma," were only eligible for inclusion if the analyses were conducted separately in a subgroup of patients with impetigo. Only RCTs with topical or systemic (oral, intramuscular, or intravenous) treatments including antibiotics, disinfectants, antifungals, and steroids were

included, and studies only comparing multiple dosages of the same drug were excluded. Studies with interventions for prophylaxis were also excluded. Multiple databases such as The Cochrane Skin Group Specialized Register, The Cochrane Central Register of Controlled Trials, MEDLINE, Embase, PUBMED, and the Latin American and Caribbean Health Sciences Information database were searched without any limits on date or language (with searches conducted on January 4, 2017). Additional searches were conducted on the reference lists of the included trials to identify any further articles for inclusion. Search terms and strategies were provided for each database.

Title and abstract screening, as well as full-text screening, were performed in duplicate by two independent reviewers. All reasons for exclusion were recorded and any disagreements were settled based on the opinion of a third reviewer.

Data Extraction

The SR identified a total of 68 studies meeting the necessary inclusion criteria. Two reviewers independently extracted predefined data items from the included trials. Any disagreements were settled based on the opinion of a third reviewer.

Comparators

The comparators of interest in the SR included all topical and systemic treatments for impetigo. However, to inform the pharmacoeconomic model, only the relative efficacy of ozenoxacin compared with fusidic acid and mupirocin were of interest as these were considered by the manufacturer to be the most relevant comparators in Canada.

Outcomes

RCTs evaluating clinical success or improvement via investigator assessment and/or microbiological success as the primary outcome, as well as those evaluating relief of symptoms, recurrence rate, adverse effects, and development of bacterial resistance as secondary outcomes were considered for inclusion in the SR.

Risk of Bias Assessment of Included Studies

The risk of bias of the RCTs selected for inclusion in the SR were assessed by two independent reviewers based on the following considerations: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias, randomization, and specification of the inclusion and exclusion criteria. Risk of bias was listed as low, high, or unclear.

Direct and Indirect Treatment Comparison Methods

Meta-analyses of direct comparisons in the SR were conducted using fixed-effects models unless the I^2 statistic was above 50%. Random-effects models were used when there was statistical heterogeneity. Differences between treatments for dichotomous outcomes were pooled as risk ratios and corresponding 95% confidence intervals (CI) were reported.

Given that Study P-110880-01 (referred to here as “Study P-880”) was designed to compare ozenoxacin with a placebo, an ITC of ozenoxacin and sodium fusidate using a placebo as the intermediate was initially considered; however, the manufacturer reported methodological differences between the trials included in the SR (such as in lesion care and assessment of efficacy). Issues with the placebo group of Study P-880 were also noted, such as concomitant antibiotics and the potential antibacterial effects of one of the placebo

ingredients (benzoic acid).[12,30,32] Since Study P-880 (published in Gropper et al.) included a retapamulin group to establish internal validity, retapamulin was used as the common comparator.

Although the method used to conduct the ITC was not explicitly reported, it can be inferred from the submitted materials that the ITC compared ozenoxacin versus sodium fusidate using the Bucher method with retapamulin as the common comparator.

Two approaches were used to assess the comparative efficacy of ozenoxacin and mupirocin. In the first approach, the efficacy of fusidic acid and mupirocin was found to be equivalent based on the pooled meta-analysis (included in the SR) of four head-to-head studies comparing fusidic acid and mupirocin. Therefore, the assumption estimates that the comparative efficacy for ozenoxacin and mupirocin is the same as that of ozenoxacin and sodium fusidate; however, not all of the four RCTs appeared to be restricted to impetigo, rather the condition of interest in each trial was described: primary and secondary skin infections, superficial skin sepsis, facial impetigo, and superficial skin infections. In addition, it is unclear if the definition of clinical success in the four RCTs comparing mupirocin with fusidic acid employed the same definition of clinical success as was used in the ITC. A second approach indirectly compared ozenoxacin with mupirocin using placebo as the common comparator, using the same methodology as for the ozenoxacin versus sodium fusidate ITC.

Results

A total of 68 studies were identified in the SR. Of these, two relevant trials included retapamulin as a comparator and were included in the ITC of ozenoxacin and sodium fusidate: the Gropper et al. (Study P-880) and Oranje et al. trials. Two trials were also available to indirectly compare ozenoxacin with mupirocin, using placebo as a common comparator: Study P-880 and the Eells et al. trial. The Eells et al. trial compared mupirocin with placebo. Study P-110881-01 (referred to in this report as “Study P-881”) was not included in the SR as it was not published at the time.

Study and Patient Characteristics

The baseline patient characteristics reported in the SR were limited to age range, proportion of male and female patients, and bacterial species in lesions. Given the lack of reporting, CDR also reviewed the individual study publications (Gropper et al.,[12] Oranje et al.,[28] and Eells et al.[33]) for additional details on the studies’ characteristics and the patient baseline characteristics.

A review of the individual publications showed similarities between the methodology and design of the Gropper et al. and Oranje et al. trials (Table 26). Both trials restricted the total affected area to 100 cm^2 or less. Gropper et al. restricted the total affected area to no more than 2% of body surface area in patients under 12 years of age, while Oranje et al. used the same restriction in patients younger than 18 years of age. Across both trials, enrolled patients were required to have a total score of at least 8 on the 42-point Skin Infection Rating Scale (SIRS). Patients were excluded in both studies if they had underlying skin diseases with evidence of infection, they had systemic infection, their lesions could not be treated appropriately with topical antibiotics, or they had received antibacterial treatment prior to screening; however, the trials employed different exclusion criteria regarding time since prior antibiotic treatments.

Baseline patient characteristics were generally similar between the Gropper et al. and Oranje et al. trials and across treatment groups. The trials were both multi-centre and multi-national, including patients between nine months and older than 65 years of age (approximately 60% under 12 years of age and under 13 years of age, respectively). Overall, more patients under the age of 13 were included in the sodium fusidate treatment group compared with the retapamulin treatment group in Oranje et al. (65% compared with 59%, respectively). Most patients in the Gropper et al. and Oranje et al. studies were male (62% and 54%, respectively) and had lesions positive for *Staphylococcus aureus* (64% and 65%, respectively). However, generally there were fewer males in the retapamulin groups versus the comparators in both trials (59% compared with 64% and 52% compared with 58% in Gropper et al. and Oranje et al., respectively). Lesions positive for *Streptococcus pyogenes* were present in 50% of patients in Gropper et al. and in 26% of patients in Oranje et al. Approximately 80% of patients across all treatment groups in both included trials had non-bullous impetigo. The proportion of patients with bullous impetigo was approximately 20% in both studies (20.7% and 21.3% in Gropper et al. and Oranje et al., respectively). The total affected area was larger across all treatment groups in Gropper et al. compared with Oranje et al. (9.3 cm^2 and 12.1 cm^2 in the ozenoxacin and retapamulin groups, respectively, versus 6.4 cm^2 and 6.9 cm^2 in the sodium fusidate and retapamulin groups, respectively).

Patients in Eells et al. had primary impetigo infections and ranged in age from one and a half months to 13 years, with the oldest patient in the placebo group being nine years old. One patient in each treatment group had ecthyma, and these patients were excluded from analysis. *S, aureus* was isolated from lesions in 94% and 85% of patients in the mupirocin and placebo groups, respectively, and there was no mention of testing for *S. pyogenes*. Female patients represented 67% and 65% of patients in the mupirocin and placebo groups. Out of the 52 patients randomized, 14 patients (eight in the mupirocin group and six in the placebo group) were excluded from analysis due to various reasons.

Table 26: Characteristics of the Studies Included in the Indirect Treatment Comparison

	P-110880-01	Oranje et al.	Eells et al.
Study design	DB (SB for ozenoxacin vs. retapamulin), Phase III RCT, multi-centre, multi-national	SB, Phase III RCT, multi-centre, multi-national	DB RCT
Geographical region	Europe, South Africa, and USA	Canada, South America, Europe, India, and South Africa	US
Number of patients randomized, N	465 (309 for ozenoxacin vs. retapamulin and 311 for ozenoxacin vs. placebo)	519	52 (38 analyzed)
Follow-up	10 to 13 days	14 days	8 days
Inclusion criteria	• Clinical diagnosis of bullous or non-bullous impetigo • Total SIRS score ≥ 8		• Primary impetigo infection • Patients aged 13 years or younger
	• Patients at least 2 years of age • Total affected area of 1 cm^2 to 100 cm^2 (not exceeding 2% of body surface area for patients < 12 years old) with surrounding erythema not extending more than 2 cm from the edge of any affected area	• Patients at least 9 months of age • Total affected area of 1 cm^2 to 100 cm^2 (not exceeding 2% of body surface area for patients < 18 years old) with surrounding erythema not extending more than 2 cm from the edge of any affected area	

	P-110880-01	Oranje et al.	Eells et al.
Exclusion criteria	• Underlying skin disease with clinical evidence of secondary infection • Bacterial infection that, in the opinion of the investigator, could not be appropriately treated by a topical antibiotic • Systemic signs and symptoms of infection (e.g., fever)		• Use of topical or systemic antibacterial agents within the 24 hours prior to study entry • Concurrent use of topical or systemic therapy
	• Documented or suspected bacteremia • Treatment (of lesions where topical) with: o oral antibiotic within 7 days o topical antibiotic within 7 days o long-acting injectable antibiotic within 30 days o any topical therapeutic drug within 24 hours o any topical antiseptics within 8 hours o any systemic or topical analgesic, anti-inflammatory, or anti-histaminic drugs within 8 hours o systemic prednisone (> 15 mg daily or equivalent) for > 10 days within 14 days o any other investigational drug within 30 days	• Treatment of lesion(s) within the 24 hours prior to study entry with: o a systemic antibacterial o steroid o any topical therapeutic drug (including glucocorticoid steroids, antibacterials, and antifungals)	
Intervention	Ozenoxacin 1% cream, twice a day for 5 days	Retapamulin 1% ointment, twice a day for 5 days	Mupirocin 2% ointment, 3 times a day for 7 to 9 days
Comparator(s)	Placebo cream (vehicle only), twice a day for 5 days Retapamulin 1% ointment, twice a day for 5 days	Sodium fusidate 2% ointment, three times a day for 7 days	Placebo ointment (vehicle only), three times a day for 7 to 9 days
Primary outcome	Clinical response at 6 to 7 days. Clinical cure was defined as SIRS score of zero for exudates/pus, crusting, tissue warmth and pain; and no more than one each for erythema/ inflammation, tissue edema and itching; and no additional antimicrobial therapy of the baseline lesion required. Outcome extracted for ITC: Clinical success as assessed by the absence of the treated lesions, improvement in lesions or a reduction in the affected area such that no further antimicrobial therapy was required.	Clinical success at 7 days for the retapamulin group and 9 days for the sodium fusidate group. Clinical success was defined as total absence of treated lesions; or if the treated lesions had become dry without crusts, with or without erythema, compared with appearance at baseline; or if the lesions showed improvement (defined as a decrease in the size of the affected area, number of lesions or both) so that no further antimicrobial therapy was necessary.	Clinical response at 8 days (up to 12 days). Clinical cure was defined as all lesions having resolved with no evidence of infection
Risk of bias (unclear, low or high)[a]			
Random sequence generation (selection bias)	Low	Unclear	NR

	P-110880-01	Oranje et al.	Eells et al.
Allocation concealment (selection bias)	Low	Low	NR
Blinding of participants and personnel (performance bias)	Unclear	High	NR
Blinding of outcome assessment (detection bias)	Low	Low	NR
Incomplete outcome data (attrition bias)	Low	Unclear	NR
Selective reporting (reporting bias)	Unclear	Unclear	NR
Other bias	Low	Low	NR
Randomization	Low	Low	NR
Were both inclusion and exclusion criteria specified	Low	Low	NR

DB = double blind; ITC = indirect treatment comparison; NR = not reported; SB = single blind; RCT = randomized controlled trial; SIRS = Skin Infection Rating Scale; vs. = versus.

Source: P-110880-01 clinical study report,[17] P-110881-01 clinical study report,[18] Gropper et al.,[12] Oranje et al.,[28] Eells et al.,[33] manufacturer-submitted ITC.[30,31]

[a] As assessed in the manufacturer-submitted systematic review.

Intervention and Comparators

Retapamulin 1% ointment was applied twice a day for five days in both the Gropper et al. and Oranje et al. studies, while ozenoxacin 1% and vehicle cream was applied twice a day for five days in the Gropper et al. study, and sodium fusidate 2% ointment was applied three times a day for seven days in the Oranje et al. study. In the Eells et al. study, mupirocin 2% ointment and placebo ointment were applied three times a day for seven to nine days. In the Gropper et al. study, concomitant topical antibiotics were used by 10.5% of retapamulin patients and 9% of ozenoxacin patients, while concomitant systemic antibiotics were used by 2.6% and 3.2% of patients in the retapamulin and ozenoxacin groups, respectively. Information on concomitant antibiotic therapies was not reported in Oranje et al. In the Eells et al., patients were excluded from analysis if they used concomitant systemic antibacterial therapy.

Outcomes

The only outcome reported in the ITC of ozenoxacin and sodium fusidate was clinical success. The primary efficacy outcome in the Oranje et al. study was the absolute difference between the treatment groups in the percentage of patients with clinical success, defined as the following: treated lesions were completely absent; treated lesions had become dry without crusts compared with baseline appearance; there was a decrease in the size of the affected area, number of lesions, or both, such that no further antimicrobial treatment was necessary. Patients had clinical failure if they required additional therapy due to deterioration or insufficient improvement. Clinical failure included lesions with crusts and/or exudate and increase in affected area from baseline. The primary efficacy outcome was analyzed in the intention-to-treat population, defined as all randomized patients who received at least one dose of the study treatment. The study was designed to demonstrate the non-inferiority of retapamulin to sodium fusidate using a non-inferiority margin of 10%.

The primary efficacy outcome in the Gropper et al. study was the absolute difference between the treatment groups in the percentage of patients with clinical cure, defined as the following: a SIRS score of 0 for exudates/pus, crusting, tissue warmth, and pain; a SIRS score of no more than 1 for erythema/inflammation, tissue edema, and itching, and no additional antimicrobial therapy of the baseline lesion required. Given that the definitions for clinical efficacy between the two trials were not consistent, a post hoc analysis based on a similar definition for clinical success, as defined in the Oranje et al. study (absence of treated lesions, improvement in lesions, or a reduction in the affected area such that no further antimicrobial treatment was required), was used for the ITC instead. Both outcomes were analyzed in the intention-to-treat population. The study conducted by Gropper et al. was designed to demonstrate the superiority of ozenoxacin treatment over a placebo, with the retapamulin comparison serving as a test of internal validity.[17]

Clinical success was assessed at six or seven days post-baseline in all groups in the Gropper et al. study, whereas clinical success was assessed at seven days post-baseline in the retapamulin group and nine days post-baseline in the sodium fusidate group in the Oranje et al. study. Therefore, clinical response was assessed at approximately the same time point relative to the end of treatment for both treatment groups in both studies.

In the Eells et al. study, a patient was considered to have clinical cure if all of the lesions had resolved and there was no evidence of infection. Unlike in the other studies, patients continued treatment until assessment of clinical cure 7 to 12 days post-baseline. If bacteriological assessments were incomplete for a patient, that patient was excluded from analysis. Intention-to-treat analysis was not performed as 27% of randomized patients were excluded from analysis for various reasons. In the ITC for ozenoxacin and mupirocin, clinical cure was the outcome used and the proportion of patients with clinical cure in each treatment group was calculated for the ITC based on patients with impetigo and not ecthyma.

Risk of Bias

The results for each of the evaluated biases were presented and it was noted that there was insufficient information to determine risk of bias for some of the quality assessment criteria. Risk of bias was not used to exclude any studies from the SR.

The full risk of bias assessments were reported for the Gropper et al. and Oranje et al. trials in the manufacturer's pharmacoeconomic report with quotations from the publications to support the assessments. For the Oranje et al. publication, the risk of bias was judged to be low for most potential sources, with unclear risk for random sequence generation, incomplete outcome data (attrition bias), and selective reporting. However, this study was single blind (only investigators were blinded to treatment allocation); therefore, the risk of bias associated with blinding was considered high. More patients in the retapamulin group discontinued the study prematurely (26 versus 15 patients) with the largest difference in patients lost to follow-up (8 patients versus 1 patient). However, this represented less than 8% of patients in the retapamulin group.

For the Gropper et al. publication, the risk of bias was judged to be low for all potential sources, with the exception of unclear risk for blinding of participants, and personnel and selective reporting. Although double blind in design, patients and caregivers received open-label retapamulin, and only investigators were blinded to treatment allocation in the retapamulin group; however, they may have surmised which treatment was administered due to apparent differences between the ozenoxacin cream and retapamulin ointment. Thus,

the risk of bias resulting from lack of adequate blinding in Gropper et al. may also be considered high.

A risk of bias assessment was not provided for the Eells et al. publication.

Efficacy

Using the Bucher method for adjusted ITCs, the reported risk ratio for clinical success between sodium fusidate and ozenoxacin was not statistically significant different at 0.93 (95% CI, 0.83 to 1.04; *P* = 0.2082). Using the Bucher method to compare clinical cure between mupirocin and ozenoxacin, the risk ratio was 1.08 (95% CI, 0.54 to 2.16; *P* = 0.82152) with no statistically significant difference between the two treatments.

In the alternate approach for comparing ozenoxacin with mupirocin, the adjusted pooled meta-analysis of four head-to-head studies comparing fusidic acid and mupirocin using a fixed-effects model found no statistically significant difference between the two treatments (N = 440, pooled risk ratio 1.03 [95% CI, 0.95 to 1.11]). The risk ratio and its associated uncertainty for efficacy of mupirocin compared with ozenoxacin were assumed to be identical to that of sodium fusidate compared with ozenoxacin.

Critical Appraisal of Manufacturer-Submitted Systematic Review and Indirect Treatment Comparison

The methodological rigour of the ITC was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research Task Force on Indirect Treatment Comparisons, as well as guidance provided in CADTH's *Guidance Document on Reporting Indirect Treatment Comparisons* (October 2015).[34,35] The methodological quality of the SR was appraised according to the A MeaSurement Tool to Assess systematic Reviews criteria.[36]

Systematic Review

The research question and inclusion criteria for the SR were clearly reported. The literature search was comprehensive, involving multiple databases (e.g., The Cochrane Skin Group Specialised Register, The Cochrane Central Register of Controlled Trials, MEDLINE, Embase, PUBMED, and the Latin American and Caribbean Health Sciences Information database). The literature search was well-reported with a complete copy of the search strategy included in the report.

Title and abstract screening, as well as full-text screening, were performed in duplicate independently by two reviewers. All reasons for exclusion were recorded and any disagreements were settled based on the opinion of a third reviewer. Two reviewers independently extracted predefined data items from all included trials. Any disagreements were settled based on the opinion of a third reviewer. Both study screening and data extractions performed in the SR were consistent with SR methodology.

Two independent reviewers performed a risk of bias evaluation for the included studies based on a tool that considered random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias, randomization, and specification of the inclusion and exclusion criteria. However, overall assessment of risk of bias was not reported for each study; instead, the risk of bias was reported for each of the criteria for quality assessment. Overall, the risk of bias in was only reported for the two studies included in the ITC of ozenoxacin and sodium fusidate, in which most criteria were ranked as being low, with some

exceptions where the risk of bias was unclear or high. No risk of bias assessments were provided for the remainder of the trials included in the SR, including the Eells et al. study used in the ITC of ozenoxacin versus mupirocin. Quality assessments were not used to exclude any studies from the ITCs.

Indirect Treatment Comparison

Reporting

The rationale for the ITCs was clearly stated (i.e., absence of head-to-head RCTs evaluating the relative efficacy and safety of ozenoxacin against other treatments). Baseline patient characteristics were reported in the ITCs for age range, proportion of male and female patients, and bacterial species in lesions only.

CDR reviewed the individual study publications for additional details on the study methodology and design, as well as patient baseline characteristics required to further assess heterogeneity. Description of trial design, allocation concealment, region in which the studies were conducted, eligibility (inclusion and exclusion) criteria, and methodology for assessing clinical success were reported in the individual trials only. All three trials (Gropper et al., Oranje et al., and Eells et al.) reported appropriate dose regimens of pharmacological treatments.

The analytical methods used for the ITC were not well-reported; however, it can be inferred from the submitted materials that the manufacturer conducted the ITCs using the Bucher method. The ITC did report rationale for use of fixed- and random-effects models for the direct comparison meta-analyses.

No sensitivity analyses to address the heterogeneity between studies or analyses of secondary outcomes were conducted in the ITC.

Analytical Methods

Adjusted ITCs were performed for sodium fusidate versus ozenoxacin and mupirocin versus ozenoxacin using the Bucher method based on the proportion of patients who experienced clinical success and clinical cure, respectively. The evidence networks consisted of single-study connections with no closed loop, precluding examination of consistency between direct and indirect evidence.

Alternatively, the approach for quantifying the comparative efficacy of mupirocin and ozenoxacin relied on the assumption of similar efficacy between ozenoxacin and mupirocin based on a naive comparison between results of the ITC of ozenoxacin versus sodium fusidate, and the results of a meta-analysis of four RCTs comparing mupirocin with fusidic acid, as described by Koning et al.[2] It was unclear if the definition of clinical success in the four RCTs included in the meta-analysis comparing mupirocin with fusidic acid was the same as that used in the ITC.

Risk of Bias

Risk of bias evaluations were performed as part of the SR for Gropper et al. and Oranje et al., the majority of which yielded low risk of bias. However, some quality assessment criteria were ranked as unclear or high risk for bias. Although appropriate measures were taken to conceal treatment allocation, only investigators were blinded in both Gropper et al. and Oranje et al. Given the apparent differences between the ozenoxacin cream and the retapamulin ointment, investigators may have surmised which treatment was administered. Considering that the outcomes of clinical cure can be considered subjective outcomes

(based on investigator judgment), treatment unblinding can potentially introduce biases in the results, although the direction remains unclear. The risk of bias was ranked as unclear for both trials. The primary end point was used from Oranje et al. and risk of bias from selective reporting of this trial was likely low. In Gropper et al., using a post hoc end point different from the original primary end point could have introduced bias, given that the trial was not designed to test the post hoc end point and the end point was selected after unblinding of data.

CDR performed a risk of bias assessment for the Eells et al. publication. Risk of bias from random sequence generation was low as a computer-generated list in blocks of five was used for randomization. Methods for concealing treatment allocation were not reported and the risk of bias from this source is unclear. Although the study was a double-blind study, methods for blinding of patients, personnel, and investigators were not reported and risk of bias from blinding of these individuals is unclear. The risk of bias from selective reporting or other sources of bias is unclear. There is a high risk of bias from attrition due to 27% of randomized patients being excluded from analysis. The most common reason for exclusion was loss to follow-up (five patients in the mupirocin group and two patients in the placebo group) and it was not possible to determine the likely direction of potential bias.

Patient Characteristics

Patient baseline characteristics were mostly similar between Gropper et al. and Oranje et al. and between treatment groups within the studies, and were representative of those who would be prescribed topical treatment for bullous or non-bullous impetigo. Baseline affected area was larger in the Gropper et al. study compared with the Oranje et al. study and differed across treatment groups (12.1 cm^2 versus 9.3 cm^2 in the retapamulin group and the ozenoxacin group, respectively). The clinical expert consulted for this CDR review suggested these differences are unlikely to have an impact on treatment effect.

Overall, the patient population in the Eells et al. study was younger, had a greater proportion of infections positive for *S. aureus*, and had a greater proportion of females than in the Gropper et al. study. The reported baseline characteristics were similar between treatment groups.

Study Characteristics

In general, the studies included in the ITC of ozenoxacin and sodium fusidate were conducted in the relevant population and were multi-centre and multi-national (the study by Oranje et al. enrolled patients from Canada). Many study characteristics (e.g., duration of trial, trial design and methodology, inclusion) were similar across the two studies. Contrary, different exclusion criteria regarding time since prior antibiotic treatments were identified and may have resulted in important differences in the patient populations; however, the extent to which these differences would affect the results remains unclear. Furthermore, the primary end point differed between trials and it was unclear whether the use of additional antimicrobial therapies was permitted during the treatment period in the Oranje et al. study.

Since the primary outcomes were defined differently in the two studies, the ITC used a post hoc analysis in the Gropper et al. study based on an end point more closely aligned with primary end point in the Oranje et al. study. The end point used to indirectly compare impetigo therapies was based on clinical success, as defined in Oranje et al. as the absence of treated lesions, an improvement in lesions, or a reduction in the affected area such that no further antimicrobial treatment was required. The post hoc end point was not defined in further detail in the Gropper et al. study and it was not clear if clinical success was evaluated

over the same treatment period as the original primary end point. The concomitant antimicrobial therapy use in the Gropper et al. study, and the lack of information on the same in the Oranje et al. study, add another source of uncertainty in the interpretation of the results.

The studies employed in the ITC of ozenoxacin versus mupirocin (Gropper et al. and Eells et al.) had differences in study design. The selection criteria in Eells et al. did not have restrictions on the severity or extent of impetigo and did not exclude patients based on previous glucocorticoid steroid use, unlike in the Gropper et al. study. While the primary outcome in Gropper et al. was assessed one to two days following the end of therapy, in Eells et al. patients were treated up to the visit at which clinical response was assessed. The time from baseline to clinical assessment was similar in the studies (seven to nine days in Eells et al. and six to seven days in Gropper et al.), though patients in the Eells et al. study could be assessed up to 12 days post-baseline. Clinical cure was the outcome used in the ITC of ozenoxacin versus mupirocin. The definition of clinical cure was more stringent in the Eells et al. study (resolution of lesions with no evidence of infection) than in the Gropper et al. study. Patients using concomitant therapy in Eells et al. were excluded from the analysis, but not in Gropper et al.

Aside from clinical response, the CDR review protocol identified symptoms of impetigo, microbiological cure, and health-related quality of life as key efficacy outcomes of interest. The ITCs did not include these key efficacy outcomes and also did not report any outcomes related to safety, such as adverse events.

Comparators

In the studies included in the ITCs, both intervention and comparator dosages followed guidelines for topical treatment of impetigo.[7,8]

In the Gropper et al. study, more patients in the placebo group received concomitant topical antibiotics, compared with the ozenoxacin group. According to the Health Canada Reviewer's report, this likely contributed to the higher placebo response rate.[25,26] Furthermore, the same report also indicated that the greater placebo response may also be due to the presence of benzoic acid (a non-medicinal ingredient) included in the product formulation.[25,26] In contrast, the clinical expert consulted for this CDR review suggested that the quantity of benzoic acid included in the formulation is not likely to have a significant effect on resolution of impetigo.

Given the higher response rate in the placebo group in the Gropper et al. study compared with the placebo group of the one study identified comparing sodium fusidate and placebo, retapamulin was used as the common comparator instead of a placebo.

With the lack of other options for common comparators, placebo was used as the common comparator for the ozenoxacin versus mupirocin ITC. Because the second pivotal ozenoxacin study (Study P-110881-01) had not been published at the time of the SR, it was not included in the ITC. The SR did not identify any studies comparing an oral antibiotic relevant to the CDR protocol with placebo.

In response to a CDR request for additional information, the manufacturer noted that oral comparators were not relevant as the ozenoxacin trials excluded patients with lesions not suitable for topical treatment.[37] However, the clinical expert consulted for this review considered oral comparators to be relevant in clinical practice because different clinicians have different thresholds for lesion severity requiring oral antibiotic treatment.

Summary and Conclusion

The manufacturer-submitted SR and two ITCs are summarized and critically appraised in this section. In one ITC, two trials were included to examine the comparative benefits of ozenoxacin versus sodium fusidate (with retapamulin as a common comparator) for the treatment of impetigo based on clinical success. Although the studies were generally similar, limitations of the ITC included the use of a post hoc end point in one study and the lack of reporting of concomitant antimicrobial therapies in the other study. The ITC suggested no statistically significant differences in clinical success between ozenoxacin and sodium fusidate in patients with impetigo.

In the second ITC, two trials were included to compare clinical cure between ozenoxacin and mupirocin with placebo as a common comparator. There were differences between the trials in terms of the proportion of patients with lesions positive for *S. 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 analysis. There was no statistically significant difference in clinical cure between ozenoxacin and mupirocin in patients with impetigo. However, there was a greater degree of uncertainty in this indirect estimate (as indicated by the wider confidence interval), likely due to the small sample size (38 patients) in the mupirocin trial. The alternative approach 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.

In addition to the limitations identified above, both ITCs are limited by the availability of only one study per direct comparison. Comparisons of ozenoxacin with systemic antibiotics were not available. Given the identified limitations, the comparative efficacy of ozenoxacin with other therapies for impetigo remains uncertain.

Appendix 7: Summary of Systemic Therapies for Impetigo

Table 27: Key Characteristics of Oral Antibiotics Recommended for the Treatment of Impetigo

	Mechanism of Action	Indication[a]	Recommended Dose	Contraindications
Amoxicillin / clavulanic acid	Amoxicillin is a beta-lactam antibiotic that inhibits the biosynthesis of bacterial cell-wall mucopeptides during the stage of active multiplication. Clavulanic acid inhibits specific beta-lactamases of some microorganisms.	Treatment of the following skin and soft tissue infection when caused by beta-lactamase producing strains of *Staphylococcus aureus*.	**Adults** One 500 mg tablet every 12 hours. **Children 3 months and older** Mild-to-moderate skin and soft tissue infections: 25 mg/kg per day in divided doses every 12 hours, or 20 mg/kg per day in divided doses every 8 hours. Severe skin and soft tissue infections: 45 mg/kg per day in divided doses every 12 hours, or 40 mg/kg per day in divided doses every 8 hours. **Duration** 7 to 10 days and at least 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained.	• History of hypersensitivity to penicillin or cephalosporin group of beta-lactams • Confirmed or suspected infectious mononucleosis
Cephalexin	Inhibition of cell-wall synthesis. Cephalexin is bactericidal against many Gram-positive and Gram-negative organisms.	Treatment of bacterial infections of skin and soft tissue when the infection is caused by susceptible organisms.	**Adults** 1 g per day in divided doses every 6 hours. **Children** 25 mg/kg to 50 mg/kg per day in divided doses every 6 hours. Adult and children: In severe infection or infections caused by less susceptible organisms, larger doses may be needed.	• Known allergy to the cephalosporin group of antibiotics • Cephalexin should be given only with caution to penicillin-sensitive patients
Clindamycin	Cessation of protein synthesis and reduction in the rate of synthesis of nucleic acids.	Treatment of serious infections due to sensitive anaerobic bacteria (including anaerobic streptococci and microaerophilic streptococci) or sensitive Gram-positive aerobic	**Adults** 150 mg every 6 hours. Moderately severe infections: 300 mg every 6 hours. Severe infections: 450 mg every 6 hours.	• Known hypersensitivity to clindamycin or lincomycin

	Mechanism of Action	Indication[a]	Recommended Dose	Contraindications
		organisms (staphylococci) when the patient is intolerant of, or the organism is resistant to, other appropriate antibiotics.	**Children weighing ≥ 40 pounds** 8 mg/kg to 16 mg/kg per day, or 16 mg/kg to 20 mg/kg per day, depending on severity of the infection.	
Cloxacillin	Inhibition of biosynthesis of cell-wall mucopeptides during the active multiplication stage.	Treatment of infections caused by streptococci when associated with sensitive penicillinase-producing staphylococci and treatment of all staphylococcal infections, whether penicillin G-sensitive or resistant.	**Adults** Mild-to-moderate infections: 250 to 500 mg every 6 hours. **Children** Up to 5 kg body weight: 250 mg per day. More than 5 kg body weight: 50 mg/kg per day divided into 4 doses. **Duration** Minimum of 5 days and minimum of 10 days in infections associated with *Streptococcus pyogenes*.	• History of allergic reactions to penicillin or cephalosporins
Doxycycline	Inhibition of protein synthesis.	Treatment of impetigo and other skin and soft tissue infections caused by susceptible strains of *Staphylococcus aureus* and *epidermidis*, *Streptococcus* species, *E. coli, Klebsiella* species, and *Enterobacter aerogenes*.	**Adults** Single loading dose of 200 mg followed by 100 mg per day thereafter. More severe infections: 200 mg per day throughout the treatment period. **Duration** Therapy should be continued for at least 24 to 46 hours after symptoms and fever have subsided. In streptococcal infections, therapy should be continued for 10 days.	• History of hypersensitivity to doxycycline hyclate or any other tetracycline • Myasthenia gravis • Patients taking isotretinoin
Trimethoprim / sulfamethoxazole	Inhibition of folate coenzyme synthesis.	Treatment of infections associated with many different Gram-positive and Gram-negative organisms, including *Streptococcus pyogenes* and *Staphylococcus aureus*.	**Adults** 800 mg SMZ and 160 mg TMP twice a day. Severe bacterial infections: 1,200 mg SMZ and 240 mg TMP twice a day. **Children 2 months and older** 15 mg/kg of SMZ and 3 mg/kg of TMP twice a day.	• Known hypersensitivity to trimethoprim or sulfonamides, co-trimoxazole • History of megaloblastic anemia due to folate deficiency • Marked liver parenchymal damage • Blood dyscrasias • Marked renal impairment • Pregnant patients and nursing mothers

	Mechanism of Action	Indication[a]	Recommended Dose	Contraindications
			Severe systemic infections: 5 mg/kg to 10 mg/kg per day TMP and 25 mg/kg to 50 mg/kg per day SMZ. **Duration** At least 5 days or until asymptomatic for 48 hours.	
Macrolides (e.g., erythromycin, clarithromycin, azithromycin)	Inhibition of protein synthesis through binding with the 50S ribosomal subunit.	Treatment of uncomplicated skin and skin structure infections caused by *Streptococcus pyogenes* and *Staphylococcus aureus*.	Daily dosage and duration vary depending on the drug.	• Known hypersensitivity to a macrolide antibacterial drug • Known hypersensitivity to a ketolide antibacterial drug (for azithromycin) • For azithromycin and clarithromycin: history of cholestatic jaundice / hepatic dysfunction associated with prior use of the drug • For clarithromycin: • Severe hepatic failure in combination with renal impairment; history of QT prolongation or ventricular cardiac arrhythmia; concomitant therapy with saquinavir, oral midazolam, colchicine, statins extensively metabolized by CYP3A4 • For erythromycin and clarithromycin: concomitant therapy with terfenadine, astemizole, pimozide, ergotamine, dihydroergotamine, or cisapride

SMZ = sulfamethoxazole; TMP = trimethoprim.

[a] Health Canada indication.

Sources: Product monographs for AMOXI-CLAV,[38] Teva-Cephalexin,[39] Apo-Clindamycin,[40] Teva-Cloxacillin,[41] Teva-Doxycycline,[42] ACT Azithromyicn,[43] ERYC,[44] Apo-Clarithymycin.[45]

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