

Drug Class Update with New Drug Evaluation: Topical Antibiotics

Date of Review: May 2018

Generic Name: ozenoxacin

End Date of Literature Search: 01/09/2018

Brand Name (Manufacturer): Xepi™ (Medimetriks)

Dossier Received: Yes

Current Status of PDL Class: See **Appendix 1.**

Purpose for Class Update:

To define place in therapy for a new topical quinolone antibiotic (ozenoxacin) recently approved by the United States (U.S.) Food and Drug Administration (FDA) for the treatment of impetigo. In addition, new comparative evidence for existing topical antibiotics for management of skin and soft tissues infections will be reviewed.

Research Questions:

1. Is there new comparative evidence that topical antibiotics differ in efficacy or effectiveness?
2. Is there any new comparative evidence the topical antibiotics differ in harms?
3. Are there specific subpopulations for which one agent is better tolerated or more effective than other available agents?

Conclusions:

- There is no new comparative evidence that demonstrates differences in efficacy or safety between topical antibiotics.
- Infectious Disease Society of America (IDSA) recommendations support treatment of impetigo with topical mupirocin or retapamulin for five days.¹
- The efficacy of ozenoxacin compared to placebo in treating impetigo was demonstrated in one published, moderate quality trial.² The clinical success after 5 days of therapy was 34.8% in the ozenoxacin group and 19.2% in the placebo group (treatment difference = 15.6%; 95% Confidence Interval [CI] 5.8 to 25.3; $p = 0.002$, number needed to treat [NNT] =6).²
- Adverse effects with topical ozenoxacin are relatively rare. Of the 362 patients who were treated with ozenoxacin in clinical trials, only one adult reported adverse effects of rosacea and seborrheic dermatitis.³ To date, no serious adverse events have been reported with ozenoxacin use.³
- There is insufficient evidence to evaluate comparative efficacy of ozenoxacin with mupirocin or retapamulin.

Recommendations:

- No preferred drug list (PDL) recommendations for ozenoxacin based on efficacy/safety data.
- No PDL changes recommended after evaluation of costs in executive session.

Previous Conclusions:

- There is no new clinical evidence that can further inform PDL decisions for topical antibiotics.

Previous Recommendations:

- No further review or research needed. After evaluation of comparative drugs costs in the executive session, no changes to the Preferred Drug List (PDL) recommended.

Background:

Impetigo is a contagious skin infection that occurs commonly in children aged 2 to 5 years, although older children and adults may also be affected.⁴ It is estimated that at any one time, 162 million children in the world have impetigo.⁵ There are two principal types of impetigo: non-bullous (70% of cases) and bullous (30% of cases).⁴ Nonbullous impetigo is caused by *Staphylococcus aureus* (*S. aureus*) or *Streptococcus pyogenes* (*S. pyogenes*), and is characterized by erosions covered with golden-colored crusts on the face and extremities.⁴ Bullous impetigo, which is caused exclusively by *S. aureus*, results in large, flaccid blister-like sores filled with pus and is more likely to affect the trunk, extremities and intertriginous areas.⁴ Both forms of impetigo are highly contagious through skin-to-skin contact or contact with articles that have touched the lesions.⁶ Impetigo usually occurs in warm, humid conditions.⁶ Risk factors for contracting impetigo include poverty, crowding, poor hygiene, or underlying scabies.⁷ Impetigo itself is not usually serious and often improves within a week of treatment or within a few weeks without treatment.⁶ Complications of impetigo include cellulitis, septicemia, osteomyelitis, and post-streptococcal glomerulonephritis.⁶ Although glomerulonephritis following a streptococcal infection is relatively rare, it is a severe adverse event associated with impetigo.⁶

A gram stain and culture of pus or exudate is recommended to identify whether *S. aureus* or *S. pyogenes* is the cause of impetigo.¹ However, treatment may be initiated without obtaining cultures in patients with typical impetigo clinical presentation.¹ According to 2014 Infectious Diseases Society of America (IDSA) recommendations, treatment of impetigo includes topical antibiotics such as mupirocin or retapamulin twice daily for 5 days.¹ A 7-day regimen of oral antibiotic therapy can be used for impetigo with large bullae or when topical therapy is impractical.¹ Amoxicillin/clavulanate, dicloxacillin, cephalexin, clindamycin, and erythromycin are oral options for impetigo treatment.¹ However, there is increasing evidence of bacterial strains resistant to penicillin, erythromycin, cloxacillin, clindamycin, cephalexin, and more recently, mupirocin.⁶ Patients with suspected or confirmed methicillin-resistant *S. aureus* (MRSA) infections can be treated with doxycycline, clindamycin, or trimethoprim-sulfamethoxazole, provided the isolate is susceptible to the selected antibiotic.⁸

During the fourth quarter of 2017 (10/1/17 to 12/3/17) there were over 500 claims for mupirocin (a preferred topical antibiotic) in the Medicaid Fee-for-Service (FFS) population. The current manufacturer of retapamulin has not signed a rebate agreement with the Centers for Medicare/Medicaid Services (CMS), so it is currently not included on the Oregon Health Plan (OHP) Preferred Drug List (PDL).

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched

for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

A 2017 Canadian Agency for Drugs and Technologies in Health (CADTH) Rapid Response report reviewed the evidence and guidelines supporting the clinical effectiveness of topical antibiotics for patients with impetigo.⁹ Evidence was evaluated for the following topical antibiotics: polymixin B-bacitracin, polymixin B-gramicidin, polymixin B-bacitracin-gramicidin, bacitracin, mupirocin, silver sulfadiazine, and fusidic acid compared to each other, placebo or oral antibiotics. The search was limited to English language documents published between January 1, 2007 and January 23, 2017. The literature included in the report consists of one systematic review, one Cochrane meta-analysis, one health technology assessment from Provider Synergies, and two guidelines. The evidence evaluated for the CADTH publication supports the clinical efficacy of topical mupirocin and fusidic acid for the treatment of impetigo.⁹ Fusidic acid has not been reviewed by the FDA and is not available in the U.S. Insufficient evidence was identified to support the clinical efficacy of bacitracin and a lack of evidence was identified on other topical antibiotics of interest.⁹ The evidence identified for the systemic treatment of impetigo supports the superiority of topical mupirocin over oral erythromycin (10 RCTs; pooled Relative Risk (RR) 1.07; 95% Confidence Interval (CI) 1.01 to 1.13; $p = 0.032$).⁹ However, the evidence also suggests existing local antimicrobial resistance patterns may strongly influence this comparative efficacy assessment.⁹ Guidelines from Australia (Joanna Briggs Institute) and the United States (National Athletic Trainers' Association) contain impetigo treatment recommendations for the use of topical mupirocin and topical fusidic acid consistent with the clinical evidence identified in the rapid response report.⁹ Both of the guidelines referenced in the CADTH report were described as having significant quality limitations including very little methodological information on the literature search, broad focus and research question, no information on stakeholder involvement, and no conflict of interest statement.⁹

Guidelines:

A 2014 publication updated the 2005 IDSA practice guidelines for the diagnosis and management of skin and soft tissue infections (SSTIs).¹ The recommendations discuss a wide range of SSTIs from minor superficial infections to life-threatening infections. The guidelines were developed to be concordant with 2014 IDSA recommendations for treatment of MRSA infections. Evaluation and treatment of impetigo are discussed as part of the SSTI recommendations. Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection.¹ Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for 5 days.¹ Oral therapy for impetigo should be a 7-day regimen with an agent active against *S.aureus* unless cultures yield streptococci alone (in which case oral penicillin is the recommended agent).¹ Because *S.aureus* isolates from impetigo are usually methicillin susceptible, dicloxacillin or cephalexin is recommended.¹ When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended.¹

New Formulations or Indications:

None identified.

New FDA Safety Alerts:

None identified.

Randomized Controlled Trials:

A total of 57 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

NEW DRUG EVALUATION: Ozenoxacin

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Ozenoxacin is a non-fluorinated quinolone FDA-approved for the topical treatment of impetigo due to *S.aureus* or *S.pyogenes* in adult and pediatric patients 2 months of age and older.³ Two phase 3 trials have been conducted to assess the efficacy of ozenoxacin 1% cream in treating impetigo compared to placebo or retapamulin. One trial has been published,² while the study details for the second trial are only available at the clinicaltrials.gov website.¹⁰ Both trials were submitted to the FDA by the manufacturer for approval of ozenoxacin.¹¹

The first trial was a multicenter, randomized, placebo-controlled, parallel, blinded, three-arm trial comparing ozenoxacin cream to placebo; the third arm with retapamulin ointment was included to test internal validity. The trial was conducted in patients with a clinical diagnosis of nonbullous or bullous impetigo.² The trial was double-blinded for the ozenoxacin cream versus placebo comparison and investigator-blinded for retapamulin ointment versus placebo because of the different formulation appearances. Treatments in each of the 3 arms were administered twice daily for 5 days. The study was performed in 27 centers in 5 countries including Germany, Romania, South Africa, Ukraine, and the U.S.² Most patients (67%) were from South Africa and 6% were from the U.S.¹¹ Evaluation of efficacy was based upon a clinical assessment by the investigator using a 7-point skin infection rating scale (SIRS). The signs or symptoms evaluated via the SIRS included: 1) exudate/pus, 2) crusting, 3) erythema/inflammation, 4) tissue warmth, 5) edema, 6) itching and 7) pain. Each component was rated on a scale of 0 to 6: a score of 0 = absent, 1-2 = mild, 3 or 4 = moderate, 5 or 6 = severe symptoms; with a maximum score of 42.² Clinical improvement was defined as a decrease in total SIRS score of greater than 10% compared with baseline.² The primary efficacy end point was clinical response measured by the SIRS by the third follow-up visit on day 6 or 7.² Clinical cure at visit 3 was defined as SIRS score 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.² The clinical cure rate at end of therapy was 34.8% in the ozenoxacin group and 19.2% in the placebo group (treatment difference=15.6%; 95% CI 5.8 to 25.3; p = 0.002; NNT=6).² Clinical success was observed in 37% of the patients who received retapamulin, which supported the internal validity of the trial.² The trial was not powered to compare the efficacy of ozenoxacin with retapamulin.

One limitation of this trial is funding by the manufacturer, possibly increasing the risk of bias in the results. Two of the study authors are employees of the manufacturer. Another limitation is that ozenoxacin was not analyzed for comparative efficacy to retapamulin due to insufficient power. Finally, a small proportion (6%) of patients were enrolled from the U.S. Most of the patients were from South Africa (67%), which may limit the applicability to the Oregon Medicaid population as well as the U.S. population as a whole.

The second manufacturer-sponsored trial compared ozenoxacin cream with placebo; in each arm the treatments were administered twice daily for 5 days.¹⁰ Four hundred and twelve patients were randomized 1:1 with similar inclusion and exclusion criteria as the published trial. However, a different version of the SIRS scale was used in this trial both in evaluation and scoring. Response to treatment was based on five-point SIRS scale: 1) blistering, 2) exudate/pus, 3)

crusting, 4) erythema/inflammation, and 5) itching/pain. The rating scale ranged from 0 to 3: a score of 0 = absent, 1 = mild, 2= moderate, and 3 = severe; the maximum score was 15.¹¹ Clinical cure, the primary endpoint, was defined differently than the previous trial. In the unpublished trial, clinical cure was defined as having a SIRS score of 0 for blistering, exudate/pus, crusting, itching/pain, and 0 or 1 for erythema/inflammation and no additional antimicrobial therapy of the baseline lesion required.¹¹ The reported clinical cure rate was 54.4% for ozenoxacin and 37.9% for placebo (treatment difference = 16.5%, 95% CI 6.9 to 25.8; p <0.001, NNT = 6).¹¹ Limitations of this trial include manufacturer funding and sponsorship. The trial results have not been published in a peer reviewed journal. Utilization of a different version of the SIRS tool to assess impetigo improvement limits comparison to other trials.

Clinical Safety:

The safety profile reported by the manufacturer is supported by administration of ozenoxacin cream in 362 adults and pediatric patients 2 months of age and older. Adverse reactions (rosacea and seborrheic dermatitis) were reported in 1 adult patient.³

Look-alike / Sound-alike Error Risk Potential: None identified

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Clinical cure
- 2) Clinical response
- 3) Treatment failure
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Clinical cure (SIRS score 0-1)

Table 1. Pharmacology and Pharmacokinetic Properties.³

Parameter	
Mechanism of Action	Non-fluorinated quinolone antibiotic
Absorption	Minimally absorbed after topical administration, therefore minimal pharmacokinetic data studies were completed by the manufacturer
Protein Binding	80-85% independent of concentration
Metabolism	Minimally metabolized by hepatocytes

Table 2. Comparative Evidence Table.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Gropper et al. ² Phase 3, DB, PC, RCT N=465	1. Ozenoxacin 1% cream BID x 5 days 2. Placebo BID x 5 days 3. Retapamulin 1% ointment BID x 5 days Duration: 6-7 days	<u>Demographics:</u> -Mean age: 16 years (68% of patients were 2-12 yo) -Male: 62% -Black: 50% -White: 12% -Nonbullous: 79% -Mean SIRS score: 15 <u>Key Inclusion Criteria:</u> -Aged 2 years or older -Clinical diagnosis of impetigo that covers 1-100 cm ² of total BSA - SIRS of at least 8 with a pus/exudate score at least 1 <u>Key Exclusion Criteria:</u> -Bacterial infection not suitable for topical therapy -No systemic signs of infection	<u>ITT:</u> 1.155 2.156 3.154 <u>PP:</u> 1.153 2.150 3.152 <u>Attrition:</u> 1.2 (1%) 2.6 (4%) 3.2 (1%)	<u>Primary Endpoint:</u> Response to treatment (cure) by day 6 – 7: SIRS score of 0-1 1.34.8% (n=54) 2.19.2% (n=30) 3.37.7% (n=58) 1 vs. 2: Difference in cure rates: 15.6%, 95% CI (5.8 to 25.3); p = 0.002 <u>Secondary Endpoints:</u> Microbiologic response at visit 2 (Day 3-4) and visit 3 (Day 6-7) Visit 2: 1.70.8% 2. 38.2% Difference 32.6%; 95% CI NR; p<0.0001 Visit 3: 1.79.2% 2.56.6% Difference 22.6%; 95% CI NR; p<0.0001	15.6%/6 18.4%/6 32.6/4 22.6/4	<u>TEAE</u> (nasopharyngitis and rhinitis) 1. 4 2. 0 3. 7 <u>Application Site Reaction</u> 1.0 2.0 3.2 <u>Serious AE</u> 1.0 2.0 3.0	NA NA NA	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> LOW. Randomized 1:1:1 via IVRS, stratified into age subsets. <u>Performance Bias:</u> LOW. Ozenoxacin and placebo creams did not differ in appearance. Since retapamulin is an ointment, it could not be included in the double-blind design, but was administered in investigator-blinded fashion. <u>Detection Bias:</u> UNCLEAR. Investigators were blinded to treatment arms. Ozenoxacin and placebo were creams, retapamulin in ointment form, which may have resulted in unblinding during assessment to therapy. <u>Attrition Bias:</u> LOW. Attrition rates were very low (1-4%). <u>Reporting Bias:</u> HIGH. Funded by manufacturer. Two of the authors is are employees of the manufacturer. Applicability: <u>Patient:</u> 68% of patients were pediatric patients. Baseline SIRS scores were also on average 15/42 likely indicating less severe disease. <u>Intervention:</u> Placebo controlled trial, would have been more meaningful to use mupirocin as an active comparator. <u>Comparator:</u> Retapamulin response rates were used as internal control, but assessment in efficacy differences between ozenoxacin and retapamulin would have provided more meaningful data. <u>Outcomes:</u> SIRS scale is a subjective assessment. <u>Setting:</u> 27 centers in 5 countries: Germany (4) , Romania (2), South Africa (13) Ukraine (5), U.S. (3). 67% of the patients were from South Africa, 6% were from the U.S. May limit applicability to Oregon Medicaid and U.S. population.
<u>Abbreviations</u> [alphabetical order]: AE = adverse events; ARR = absolute risk reduction; BID = twice daily; BSA = body surface area; CI = confidence interval; DB = double blind; ITT = intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SIRS = skin infection rating scale; TEAE = treatment-emergent adverse effect; YO = years old								

References:

1. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis*. 2014;59(2):147-159.
2. Gropper S, Albareda N, Chelius K, et al. Ozenoxacin 1% cream in the treatment of impetigo: a multicenter, randomized, placebo- and retapamulin-controlled clinical trial. *Future microbiology*. 2014;9(9):1013-1023.
3. Xepi (ozenoxacin) Cream Prescribing Information. Fairfield, NJ; Medimetriks Pharmaceuticals, Inc. December 2017.
4. Hartman-Adams H, Banvard C, Juckett G. Impetigo: diagnosis and treatment. *Am Fam Physician*. 2014;90(4):229-235.
5. Bowen AC, Mahe A, Hay RJ, et al. The Global Epidemiology of Impetigo: A Systematic Review of the Population Prevalence of Impetigo and Pyoderma. *PLoS ONE*. 2015;10(8):e0136789.
6. Bangert S, Levy M, Hebert AA. Bacterial resistance and impetigo treatment trends: a review. *Pediatr Dermatol*. 2012;29(3):243-248.
7. Romani L, Steer AC, Whitfield MJ, Kaldor JM. Prevalence of scabies and impetigo worldwide: a systematic review. *The Lancet Infectious diseases*. 2015;15(8):960-967.
8. Baddour, LM. Impetigo. Sexton DJ. ed. UpToDate. Waltham, MA: UpToDate Inc. <http://www.uptodate.com> Accessed January 22, 2018.
9. Topical antibiotics for impetigo: a review of the clinical effectiveness and guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2017 Feb. (CADTH rapid response report:summary with critical appraisal). Accessed January 23, 2018.
10. Efficacy and Safety of Ozenoxacin 1% Cream Versus Placebo in the Treatment of Patients With Impetigo. <https://clinicaltrials.gov/ct2/show?term=ozenoxacin&rank=1>. Accessed January 24, 2018.
11. Summary Review of Ozenoxacin 1% cream. Center for Drug Evaluation and Research. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208945orig1s000sumr.pdf. Accessed 3/13/18.

Appendix 1: Current Preferred Drug List

Route	Form	Generic	Brand	PDL
TOPICAL	OINT. (G)	BACITRACIN/POLYMYXIN B SULFATE	DOUBLE ANTIBIOTIC	Y
TOPICAL	OINT. (G)	MUPIROCIN	CENTANY	Y
TOPICAL	OINT. (G)	MUPIROCIN	MUPIROCIN	Y
TOPICAL	CREAM (G)	GENTAMICIN SULFATE	GENTAMICIN SULFATE	Y
TOPICAL	OINT. (G)	BACITRACIN	BACITRACIN	Y
TOPICAL	OINT. (G)	BACITRACIN ZINC	ANTIBIOTIC	Y
TOPICAL	OINT. (G)	BACITRACIN ZINC	BACITRACIN ZINC	Y
TOPICAL	OINT. (G)	BACITRACIN ZINC/POLYMYXIN B	DOUBLE ANTIBIOTIC	Y
TOPICAL	OINT. (G)	BACITRACIN ZINC/POLYMYXIN B	POLY BACITRACIN	Y
TOPICAL	OINT. (G)	NEOMYCIN/BACITRACIN/POLYMYXIN B	TRIPLE ANTIBIOTIC	Y
TOPICAL	GEL (GRAM)	ERYTHROMYCIN/BENZOYL PEROXIDE	BENZAMYCIN	N
TOPICAL	GEL (GRAM)	ERYTHROMYCIN/BENZOYL PEROXIDE	ERYTHROMYCIN-BENZOYL PEROXIDE	N
TOPICAL	KIT	MUPIROCIN	CENTANY AT	N
TOPICAL	OIN/PF APP	MUPIROCIN	MUPIROCIN	N
TOPICAL	OINT. (G)	GENTAMICIN SULFATE	GENTAMICIN SULFATE	N
TOPICAL	GEL (GRAM)	CLINDAMYCIN PHOSPHATE	CLEOCIN T	N
TOPICAL	GEL (GRAM)	CLINDAMYCIN PHOSPHATE	CLINDAMYCIN PHOSPHATE	N
TOPICAL	SOLUTION	CLINDAMYCIN PHOSPHATE	CLINDAMYCIN PHOSPHATE	N
TOPICAL	LOTION	CLINDAMYCIN PHOSPHATE	CLEOCIN T	N
TOPICAL	LOTION	CLINDAMYCIN PHOSPHATE	CLINDAMYCIN PHOSPHATE	N
TOPICAL	MED. SWAB	CLINDAMYCIN PHOSPHATE	CLEOCIN T	N
TOPICAL	MED. SWAB	CLINDAMYCIN PHOSPHATE	CLINDACIN ETZ	N
TOPICAL	MED. SWAB	CLINDAMYCIN PHOSPHATE	CLINDACIN P	N
TOPICAL	MED. SWAB	CLINDAMYCIN PHOSPHATE	CLINDAMYCIN PHOSPHATE	N
TOPICAL	FOAM	CLINDAMYCIN PHOSPHATE	CLINDAMYCIN PHOSPHATE	N
TOPICAL	FOAM	CLINDAMYCIN PHOSPHATE	EVOCLIN	N
TOPICAL	PACKET	BACITRACIN	BACITRACIN	N
TOPICAL	PACKET	BACITRACIN ZINC	BACITRACIN ZINC	N
TOPICAL	CREAM (G)	MUPIROCIN CALCIUM	MUPIROCIN	N
TOPICAL	MED. SWAB	ERYTHROMYCIN BASE/ETHANOL	ERY	N
TOPICAL	MED. SWAB	ERYTHROMYCIN BASE/ETHANOL	ERYTHROMYCIN	N
TOPICAL	GEL (GRAM)	ERYTHROMYCIN BASE/ETHANOL	ERYGEL	N
TOPICAL	GEL (GRAM)	ERYTHROMYCIN BASE/ETHANOL	ERYTHROMYCIN	N
TOPICAL	SOLUTION	ERYTHROMYCIN BASE/ETHANOL	ERYTHROMYCIN	N
TOPICAL	CREAM (G)	NEOMYCIN/POLYMYXIN B/PRAMOXINE	ANTIBIOTIC PLUS	N

TOPICAL	OINT PACK	NEOMYCIN/BACITRACIN/POLYMYXINB	TRIPLE ANTIBIOTIC	N
TOPICAL	OINT. (G)	NEOMYCN/BACITRC/POLYMYX/PRAMOX	TRIPLE ANTIBIOTIC EXTRA	N
TOPICAL	OINT. (G)	NEOMYCN/BACITRC/POLYMYX/PRAMOX	TRIPLE ANTIBIOTIC PLUS	N
TOPICAL	KIT	CLINDAMYCIN PHOS/SKIN CLNSR 19	CLINDACIN ETZ	N
TOPICAL	KIT	CLINDAMYCIN PHOS/SKIN CLNSR 19	CLINDACIN PAC	N

Appendix 2: Medline Search Strategy

1	bacitracin.mp.	1
2	Neomycin	7947
3	Erythromycin/	14440
4	Clindamycin/	5772
5	Gentamicin/	18916
6	retapamulin.mp.	98
7	Mupirocin/	1180
8	Polymixin b.mp.	260
9	Chlorhexidine/	8037
10	Metronidazole/	12874
11	Sulfacetamide/	365
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	65780
13	limit 12 to yr="2016 -Current"	2199
14	Administration, Topical/	38858
15	13 and 14	66
16	limit 15 to (english language and humans)	57

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XEPI™ safely and effectively. See full prescribing information for XEPI™.

XEPI™ (ozenoxacin) cream, for topical use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

XEPI is a quinolone antimicrobial indicated for the topical treatment of impetigo due to *Staphylococcus aureus* or *Streptococcus pyogenes* in adult and pediatric patients 2 months of age and older (1).

DOSAGE AND ADMINISTRATION

- Apply a thin layer of XEPI topically to the affected area twice daily for 5 days (2).
- Affected area may be up to 100 cm² in adult and pediatric patients 12 years of age and older or 2% of the total body surface area and not exceeding 100 cm² in pediatric patients less than 12 years of age (2).
- For topical use only (2).
- Not for oral, ophthalmic, intranasal, or intravaginal use (2).

DOSAGE FORMS AND STRENGTHS

Cream: Each gram contains 10 mg of ozenoxacin (1%) (3).

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

Potential for Microbial Overgrowth: Prolonged use of XEPI may result in overgrowth of nonsusceptible bacteria and fungi. If such infections occur, discontinue use and institute alternative therapy (5).

ADVERSE REACTIONS

Adverse reactions (rosacea and seborrheic dermatitis) were reported in 1 adult patient treated with XEPI (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Medimetriks at 866-262-0222 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2017