

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208945Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	208945
PDUFA Goal Date	January 17, 2018
OSE RCM #	2016-1513
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Acting Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D. Division of Risk Management
Review Completion Date	December 1, 2017
Subject	Addendum to DRISK Review to determine if a REMS is necessary, dated February 23, 2017.
Established Name	Ozenoxacin
Trade Name	Xepi
Name of Applicant	Ferrer Internacional S.A.
Therapeutic Class	Quinolones
Formulation(s)	Cream 1%
Dosing Regimen	Apply a thin layer of cream to the affected area twice daily for 5 days.

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1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) ozenoxacin is necessary to ensure the benefits outweigh its risks. Ferrer resubmitted a New Drug Application (NDA) 208945 for ozenoxacin with the proposed indication for the topical treatment of impetigo in adults and pediatric patients 2 months of age and older after receiving a Complete Response (CR) letter on July 22, 2017, due to chemistry, manufacturing, and control (CMC) deficiencies.¹ DRISK completed a full REMS Review in the first cycle and concluded that based on the risk-benefit profile, a REMS was not needed.² This application is under review in the Division of Anti-Infective Products (DAIP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Ozenoxacin (1-cyclopropyl-8-methyl-7-[5-methyl-6-methylamino-pyridin-3-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid), a new molecular entity, a novel antibacterial agent that belongs to the chemically related family of quinolones. Ozenoxacin is pharmacologically classified as a non-fluorinated quinolone antibiotic and is a member of the pharmacotherapeutic group of J01M-quinolone antibacterials. Ozenoxacin acts as a selective inhibitor of DNA replication with a dual target of action, blocking the bacterial DNA gyrase and the topoisomerase IV enzymes.³

Ozenoxacin is an antibacterial agent that has been developed into a cream with the proposed indication of short term topical use in the treatment of impetigo in adults and children aged 2 months and older, to be applied as a thin layer of cream to the affected area twice daily for 5 days.^a Ozenoxacin is a NME NDA type 505(b)(1) pathway application.^b Ozenoxacin is not currently marketed or available in any formulation in the U.S. or internationally.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for ozenoxacin (NDA 208945) relevant to this review:

- 02/24/2010: Investigation New Drug (IND) 105567 submission was received
- 01/13/2016: pre-NDA meeting was held. The agency and sponsor agreed on formats, components, and analyses to be included in the NDA submission. A pooled Integrated Summary of Efficacy and Safety combining results from the two Phase 3 studies (P-110880-01 and P-110881-01) was requested by the FDA along with individualized study data from individual Phase 1 and 2 studies. The agency agreed on a waiver for patients <2 months of age.

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

- 06/23/2016: NDA 208945 submission for ozenoxacin cream 1% with proposed indication for short term topical use in the treatment of impetigo in adults and children aged 2 months and older, received.
- 12/09/2016: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for ozenoxacin cream 1%. The agency also informed the sponsor that there are substantive review issues related to manufacturing facility deficiencies.⁴
- 06/22/2017: The Sponsor was issued a Complete Response letter on June 22, 2017 for CMC deficiencies.
- 07/17/2017: Application resubmitted to the Agency.

3 Therapeutic Context and Treatment Options

The descriptions of medical condition and treatment options were contained in the February 2017 DRISK review for this product.**Error! Bookmark not defined.**

4 Benefit and Risk Assessment

The benefit and risk assessment were contained in the February 2017 DRISK review for this product.**Error! Bookmark not defined.** The Clinical Reviewer commented that there is no new safety/efficacy data presented in the Class 2 resubmission so there are no additions to the safety/efficacy review that the reviewer submitted in March 27, 2017.^{5,c}

5 Expected Postmarket Use

For the treatment of impetigo in adults and children 2 months of age and older, ozenoxacin 1% cream will be used mostly at out-patient settings unless patients are admitted to the hospitals.

6 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for ozenoxacin beyond routine pharmacovigilance and labeling that did not include a boxed warning.

7 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of ozenoxacin topical 1% cream on the basis of the efficacy and safety information currently available. The common adverse events most often reported included pruritus and erythema at application sites. DRISK evaluated these risks in a review dated February 23, 2017, and determined that a REMS was not needed to ensure the benefits of Ozenoxacin

^c Rister N. to Olickal T. (E-mail communication from DAIP Clinical Reviewer to DRISK RMA), dated November 29, 2017.

1% cream outweigh the risks.² At the time of this addendum review, the safety profile of Ozenoxacin 1% cream has not changed, as no new clinical data has been submitted to the application.^c

8 Conclusion & Recommendations

Based on the analysis detailed in the original REMS review², and the absence of new safety data in the resubmissions following the Complete Response letter^c, DRISK maintains its determination that a REMS is not needed to ensure the benefits of ozenoxacin topical 1% cream outweigh its risks. At the time of this writing, labeling negotiations were still ongoing with the Applicant. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

9 References

¹ Division of Anti-Infective Products (DAIP). Complete Response Letter for NDA 208945 Ozenoxacin cream 1%, June 22, 2017.

² Olickal T. Review of Risk Evaluation and Mitigation Strategy for NDA 208945 Ozenoxacin cream 1%, dated February 23, 2017.

³ Ferrer Internacional S.A. Clinical Overview for Ozenoxacin cream 1%, dated June 23, 2016.

⁴ Mid Cycle Communication, dated January 4, 2017.

⁵ Rister N. DAIP Clinical Review for NDA 208945 Ozenoxacin cream 1%, dated March 27, 2017.

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Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	208945
PDUFA Goal Date	June 22, 2017
OSE RCM #	2016-1513; 2016-1543
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Acting Team Leader	Doris Auth, Pharm.D., Associate Director (Acting)
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	February 22, 2017
Subject	Review to determine if a REMS is necessary
Established Name	Ozenoxacin
Trade Name	Pending
Name of Applicant	Ferrer Internacional S.A.
Therapeutic Class	Quinolones
Formulation(s)	Cream 1%
Dosing Regimen	Apply a thin layer of cream to the affected area twice daily for 5 days.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity ozenoxacin is necessary to ensure the benefits outweigh its risks. Ferrer submitted a New Drug Application (NDA) 208945 for ozenoxacin with the proposed indication for the topical treatment of impetigo in adults and pediatric patients 2 months of age and older.¹ The common adverse events most often reported included pruritus and erythema at application sites. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Anti-Infective Products (DAIP) agree that a REMS is not needed to ensure the benefits of ozenoxacin cream 1% outweigh its risks. Given the lack of systemic absorption demonstrated in preclinical and Phase 1 trials, there is no evidence for concern regarding systemic toxicity.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) ozenoxacin is necessary to ensure the benefits outweigh its risks. Ferrer submitted a New Drug Application (NDA) 208945 for ozenoxacin with the proposed indication for the topical treatment of impetigo in adults and pediatric patients 2 months of age and older. This application is under review in the Division of Anti-Infective Products (DAIP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION²

Ozenoxacin (1-cyclopropyl-8-methyl-7-[5-methyl-6-methylamino-pyridin-3-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid), a new molecular entity, a novel antibacterial agent that belongs to the chemically related family of quinolones. Ozenoxacin is pharmacologically classified as a non-fluorinated quinolone antibiotic and is a member of the pharmacotherapeutic group of J01M-quinolone antibacterials. Ozenoxacin acts as a selective inhibitor of DNA replication with a dual target of action, blocking the bacterial DNA gyrase and the topoisomerase IV enzymes.

Ozenoxacin is an antibacterial agent that has been developed into a cream with proposed indication for short term topical use in the treatment of impetigo in adults and children aged 2 months and older, to be applied as a thin layer of cream to the affected area twice daily for 5 days.^a Ozenoxacin is a new molecular entity (NME) NDA type 505(b)(1) pathway application.^b Ozenoxacin is not currently marketed or available in any formulation in the U.S. or internationally.

2.2 REGULATORY HISTORY

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

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- 02/24/2010: Investigation New Drug (IND) 105567 submission was received
- 01/13/2016: pre-NDA meeting was held. The agency and sponsor agreed on formats, components, and analyses to be included in the NDA submission. A pooled Integrated Summary of Efficacy and Safety combining results from the two Phase 3 studies (P-110880-01 and P-110881-01) was requested by the FDA along with individualized study data from individual Phase 1 and 2 studies. The agency agreed on a waiver for patients <2 months of age.
- 06/23/2016: NDA 208945 submission for ozenoxacin cream 1% with proposed indication for short term topical use in the treatment of impetigo in adults and children aged 2 months and older, received.
- 12/09/2016: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for ozenoxacin cream 1%. The agency also informed the sponsor that there are substantive review issues related to manufacturing facility deficiencies.³

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Impetigo or impetigo contagiosum is a common, superficial bacterial skin infection that is most prevalent in the pediatric population. Impetigo accounts for approximately 10% of skin problems observed in pediatric clinics in the United States.^{4,c} It is the most common bacterial skin infection and the third most common skin disease among children, behind dermatitis and viral warts.^{5,6,7,d} Because it occurs more frequently in a warm, humid environment, impetigo is more common in the southeastern United States than in the cooler northern states. The prevalence of impetigo varies seasonally, with peak incidence during summer and fall; however, in regions that remain warm and humid throughout the year, seasonality may not occur.⁸

The disease can be categorized as primary (direct bacterial invasion of previously healthy skin) or secondary (bacterial superinfection of disrupted skin barrier due to previous dermatologic condition such as eczema or scabies). Additionally, impetigo can be designated as bullous or non-bullous based on the presence or absence of bullae (blisters) on physical exam. The usual natural history of non-bullous

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

impetigo begins with the development of thin-walled vesicles that rapidly rupture leaving behind superficial erosions with yellowish-brown or honey-colored crusts. Crusted skin lesions then dry and separate leaving behind red marks which subsequently heal without scarring. Non-bullous lesions are most commonly found on the limbs and face. Bullous impetigo has a similar course except that larger bullae develop initially and remain for a few days before rupturing and are more commonly found on the trunk. Some patients report pain at the site of infection and swollen lymph nodes at sites of lymphatic drainage are common. Systemic symptoms such as fever, malaise, and anorexia are atypical and suggestive of a more severe infection. *Staphylococcus aureus* and *Streptococcus pyogenes* are considered to be the main bacterial causes of impetigo. *S. aureus* is more common in moderate climates while *S. pyogenes* appears to be more prevalent in warmer, humid regions. There has also been variation in time, with *S. aureus* impetigo becoming more prevalent in the United States during the past two decades.⁹ *S. aureus* is always the etiology of bullous impetigo and more common in secondary cases.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Management of impetigo includes a variety of approaches with the aim to reduce the soreness caused by the lesions and diseases' unsightly appearance, and to decrease recurrence and spread of disease. The approaches have included no pharmacological treatment with natural resolution, hygiene measures, topical disinfectants (such as saline, hexachlorophene, povidone iodine, and chlorhexidine), topical antibiotics (such as neomycin, bacitracin, polymyxin B, gentamycin, fusidic acid, mupirocin, retapamulin, or topical steroid/antibiotic combination), and systemic antibiotics (such as penicillin, cloxacillin, amoxicillin/clavulanic acid, erythromycin, and cephalexin).¹⁰ Two topical antibiotics have been approved for the indication of impetigo (see Table 1). These are mupirocin and retapamulin (Altabax ointment). The Infectious Diseases Society of America (IDSA) 2014 practice guidelines¹¹ for the diagnosis and management of skin and soft-tissue infections recommends that 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 with the following details:

- Treatment of bullous and nonbullous impetigo should be with topical mupirocin or retapamulin twice daily (bid) for 5 days.
- Oral therapy for impetigo should be a 7-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent. Because *S. aureus* isolates from impetigo are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim (SMX-TMP) is recommended
- Systemic antimicrobials should be used for infections during outbreaks of post streptococcal glomerulonephritis to help eliminate nephritogenic strains of *S. pyogenes* from the community.

Newer generations of topical antibiotics including retapamulin, and potentially ozenoxacin, have the benefit of decreased resistance compared to many systemic and older topical agents such as mupirocin thus opening the door as treatment options for patients with MRSA and other treatment resistant organisms.¹²

Table 1: Summary of Treatment Options Relevant to Proposed Indication

Trade Name (Generic)	Approved year	Indication	Dosing/ Administration	Warnings and Precautions	REMS
Bactroban ¹³ (mupirocin 2% cream)	1997	Indicated for the treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm ² in area) due to susceptible isolates of <i>Staphylococcus aureus</i> and <i>Streptococcus pyogenes</i> .	Apply 3x daily for 10 days; re-evaluate after 3-5 days if no clinical response ^{(b) (4)}	Anaphylaxis, urticarial, angioedema, and generalized rash, <i>Clostridium difficile</i> -Associated Diarrhea (CDAD), potential for microbial overgrowth	No REMS
Altabax ¹⁴ (retapamulin 1% ointment)	2007	Indicated for the topical treatment of impetigo due to <i>Staphylococcus aureus</i> (methicillin-susceptible isolates only) or <i>Streptococcus pyogenes</i> in patients aged 9 months or older.	Apply 2x daily for 5 days; total treatment area should not exceed 100 cm ² or 2% BSA in ages >9 months	Discontinue in the event of sensitization or severe local irritation.	No REMS

4 Benefit Assessment

The efficacy and safety of ozenoxacin cream 1% for the topical treatment of impetigo was demonstrated in two pivotal phase 3 studies (P-110880-01 and P-110881-0). Both studies were similar in design: multicenter, randomized, double-blinded, and placebo-controlled. Both studies utilized the clinical response (success or failure) at end of therapy (Visit 3, day 6-7) as the primary endpoint. While both studies compared ozenoxacin 1% cream with placebo cream, the key difference in study design was that Study P-110880-01 also included an active comparator (retapamulin 1% ointment), which was included for internal validity.

The integrated review of efficacy was based off of the pooled results from the 2 pivotal phase 3 studies, P-110880-01 and P-110881-0. Overall, in the pooled Phase 3 studies (P-110880-01 and P-110881-01) 877 subjects were enrolled and 875 of the 877 enrolled subjects received treatment. This included 361 subjects in the ozenoxacin 1% cream group, 361 subjects in the placebo cream group, and 153 subjects in the retapamulin 1% ointment group. In study P-110880-01, the difference in clinical success between the ozenoxacin arm and placebo arm was 0.156 (34.8% for ozenoxacin and 19.2% for placebo). In study P-110881-01, the difference in clinical success between the ozenoxacin arm and placebo arm was 0.160 (55.2% for ozenoxacin and 39.2% for placebo). The natural trend of impetigo to improve in many cases without treatment is reflected in the 31% of placebo cases which were classified in the clinical success category. Despite the self-limiting nature of many cases of impetigo, a difference in success rates of 0.160 between the treatment arms is expected to be clinically significant for patients and representative of a trend towards earlier improvement in signs/symptoms (see Table 2).¹² While the difference is small, more patients treated with ozenoxacin had resolution of symptoms at end therapy than those treated with placebo. For patients, this translates to less discomfort and visual deformity for a common condition. This difference is felt to be sufficient to justify the proposed efficacy for ozenoxacin 1% cream

for the treatment of impetigo in patients ≥ 2 months of age.^{12,e}

While alternative topical therapies for impetigo already exist on the market, mupirocin and retapamulin, there are possible benefits to an additional medication. Although skin reactions have been rare in the these products, it is of benefit to have an alternative available for patients that cannot tolerate one agent in such preparations. Ozenoxacin also provides a novel topical antibiotic mechanisms relative to available treatments which may provide an alternative should antibiotic resistance be a concern. However, there was limited data due to small sample sizes and interpretability of the microbiological data to show efficacy for ozenoxacin in such cases.

Table 2: Pooled Phase 3 Studies: Clinical Response at Visit 3 (End of Therapy) - Primary Efficacy Endpoint (ITTC Population)

	Ozenoxacin 1% Cream (N = 361)	Placebo Cream (N = 362)
N	357	354
Clinical Success, N (%)	167 (46.8%)	109 (30.8%)
Clinical Failure, N (%)	190 (53.2%)	245 (69.2%)
Difference in success rates (ozenoxacin – placebo)	0.160	
95% CI	0.089 – 0.231	
p-value	<0.001	

5 Risk Assessment

The safety profile of ozenoxacin was developed over a combined 17 clinical trials. This included two Phase 3 multi-center (P-110880-01 and P-110881-01), randomized, controlled, pivotal trials developed for the integrated safety analysis of topical ozenoxacin 1% cream for the indication of impetigo.

Joint AEs (tendinopathy and/or arthropathy) are considered safety issues of special importance with quinolone antibiotics, but likely not relevant to a topical preparation with no relevant systemic absorption. The most common reported, study-related AEs in Phase 1 & 2 studies were application site irritation and pruritus.

Deaths:

No deaths occurred in any of the 17 studies included in the clinical development program for ozenoxacin.

Serious Adverse Events (SAE), Dropouts and/or Discontinuations Due to Adverse Effects:

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Across all 17 studies, there was 1 SAE, which occurred in Study P-100847-01. A subject experienced an upper limb fracture which required hospitalization and surgery. The SAE lead to discontinuation from the study but is not felt to be related to the study drug. The discontinuation of study drug in patients across the 17 clinical trials was found to be rare and when present, generally due to AEs unrelated to the study drug. In cases of skin reactions that may have a pathophysiological mechanism related to a topical cream (worsening eczema, rosacea, seborrheic dermatitis), the AEs were mild and again rarely lead to discontinuation.

Treatment-emergent adverse events (TEAEs):

The 2 Phase 3 studies pooled safety data to report 64 AEs which included no severe AEs, SAEs, or AEs of special interest. The pooled phase 3 safety population had only 2 TEAEs that occurred with a frequency of >1% in any treatment arm. These included nasopharyngitis (1.1% of ozenoxacin arm, 0% placebo arm, and 2.6% in retapamulin arm) and rhinitis (0% in ozenoxacin arm, 0% in placebo arm, and 2% in retapamulin arm) similar to findings in all other clinical trials and not felt to be related to treatment.

The overall safety database is felt to be adequate and relevant for the evaluation of topical ozenoxacin safety in the US population. The database included adequate evaluation of pediatric patients. The database included appropriate definitions and assignment of AEs, SAEs, and TAEAs compared to established norms. Based on a review of this database, there is no evidence of any significant safety concerns in regard to the use of topical 1% ozenoxacin cream. There were no deaths or significant adverse events identified throughout a review of the safety database.^f Few serious adverse events were noted, which were felt to be unrelated to the use of ozenoxacin. Given the lack of systemic absorption demonstrated in preclinical and Phase 1 trials, there is no evidence for concern regarding systemic toxicity. The common adverse event most often reported included pruritus and erythema at application sites and was similar between treatment and placebo groups across multiple studies and dermal tolerability studies consistently demonstrated a well-tolerated topical preparation.

No safety concerns were identified in this review of topical ozenoxacin 1% cream for the proposed indication in the treatment of impetigo.

The safety database included a range of ozenoxacin strengths (0.25 to 2%) and durations (single dose to multi-dose regimens for 21 days). There was negligible evidence of systemic absorption for topical ozenoxacin across various studies including a range of concentrations and regimens.¹² The clinical reviewer states that in post-market use, it can be expected that ozenoxacin 1% cream will be utilized for longer durations and increased frequency than studied in the pivotal trials (BID x 5 days). Studies from the safety database in higher concentrations and longer durations of ozenoxacin in damaged skin did not reveal any additional safety concerns.¹²

There are no clinical studies of ozenoxacin in pregnant women. No clinical studies assessed whether ozenoxacin was excreted in human milk. However, in view of the negligible systemic availability of ozenoxacin after topical administration, as evidenced in the human PK studies, a risk to these special populations is not expected.

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

6 Expected Postmarket Use

For the treatment of impetigo in adults and children 2 months of age and older, ozenoxacin 1% cream will be used mostly at out-patient settings unless patients are admitted to the hospitals.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for ozenoxacin beyond routine pharmacovigilance and labeling that did not include a boxed warning.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of ozenoxacin topical 1% cream on the basis of the efficacy and safety information currently available. Ozenoxacin 1% cream shows efficacy in the resolution of impetigo when compared to placebo cream for a 5 day treatment course while having no significant safety concerns. While the difference in efficacy is small for a condition that generally self-resolves, the effect is comparable to similarly available products and the paucity of safety concerns to date suggests a very low risk to patients.

In conclusion, the available evidence shows a small benefit for the approval of ozenoxacin for the topical treatment of impetigo while demonstrating no significant risks. No serious safety signals have emerged to date for ozenoxacin that would require a REMS to ensure that the benefit outweighs the risks.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile appears favorable therefore, a REMS is not necessary for ozenoxacin to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Materials Reviewed

The following is a list of materials informing this review:

1. Ferrer Internacional S.A. Proposed Prescribing Information for Ozenoxacin cream 1%, dated November 30, 2016.
2. Ferrer Internacional S.A. Clinical Overview for Ozenoxacin cream 1%, dated June 23, 2016.
3. Ferrer Internacional S.A. Summary of Clinical Safety for Ozenoxacin cream 1%, dated June 23, 2016.

11 Appendices

11.1 REFERENCES

- ¹ Proposed Prescribing Information for Ozenoxacin cream 1%, dated November 30, 2016.
- ² Ferrer Internacional S.A. Clinical Overview for Ozenoxacin cream 1%, dated June 23, 2016.
- ³ Mid Cycle Communication, dated January 4, 2017.
- ⁴ Lewis L. Impetigo (Online). <http://emedicine.medscape.com/article/965254> Updated: May 04, 2016 (accessed January 27, 2017).
- ⁵ Cole C, Gazewood J. Diagnosis and treatment of impetigo. *Am Fam Physician*. 2007;75(6):859-64.
- ⁶ Brown J, Shriner DL, Schwartz RA, Janniger CK. Impetigo: an update. *Int J Dermatol*. 2003;42(4):251-5.
- ⁷ Sladden MJ, Johnston GA. Common skin infections in children. *BMJ*. 2004;329(7457):95-9.
- ⁸ Loffeld A, Davies P, Lewis A, Moss C. Seasonal occurrence of impetigo: a retrospective 8-year review (1996-2003). *Clin Exp Dermatol*. 2005;30(5):512-4.
- ⁹ Dagan R, Barr-David Y. Double-blind study comparing erythromycin and mupirocin for treatment of impetigo in children: implications of high prevalence of erythromycin-resistant *Staphylococcus aureus* strains. *Antimicrobial Agents & Chemotherapy* 1992;33(2):287-90.
- ¹⁰ Koning S, van der Sande R, Verhagen AP, et al. Interventions for impetigo. *Cochrane Database of Systematic Reviews* 2012, Issue 1. Art. No.: CD003261. DOI:10.1002/14651858.CD003261.pub3.
- ¹¹ 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):147-59.
- ¹² Rister, N. DAIP Clinical Review (draft) for NDA 208945 Ozenoxacin cream 1%, dated January 23, 2017.
- ¹³ Bactroban. Prescribing Information (last updated 12/2015).
- ¹⁴ Altabax. Prescribing Information (last updated 05/2015).

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/s/

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