

## Draft Guidance on Ozenoxacin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

**Active Ingredient:** Ozenoxacin

**Dosage Form; Route:** Cream; topical

**Recommended Studies:** Two options: in vitro or in vivo study

### 1. In vitro option:

To qualify for the in vitro option to demonstrate bioequivalence for ozenoxacin cream, 1% the following criteria should be met:

- A. The test and reference products should be qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*<sup>1</sup>.
- B. The test and reference products should be physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three batches of the test and three batches (as available) of the reference product. Physicochemical characterizations should include:
  - i. Assessment of appearance and microscopic examination with representative microscopic images at multiple magnifications
  - ii. Analysis of the ozenoxacin polymorphic form in the drug product
  - ii. Analysis of globule size, particle size distribution and crystal habit with representative high resolution microscopic images at multiple magnifications.
  - iii. Analysis of the rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:
    - A characterization of shear stress and viscosity vs. shear rate. At minimum this should consist of numerical viscosity data at three shear rates (low, medium and high), and may include a complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.

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<sup>1</sup> The current version of the referenced guidance at the time of publication of this product specific guidance is Guidance for Industry: ANDA Submissions – Refuse-to-Receive Standards, Revision 2 (December 2016). However, we update guidances periodically, and current information related to guidances is maintained at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

- Yield stress values should be reported if the material tested exhibits plastic flow behavior.
  - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported.
- iv. Analysis of pH, specific gravity, as well as any other potentially relevant physical and structural attributes.
- C. The test and reference products should have an equivalent rate of ozenoxacin release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one batch each of the test and reference products using an appropriately validated IVRT method. Refer to the *Draft Guidance on Acyclovir* (for acyclovir topical cream, 5%)<sup>2</sup> for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test and reference products evaluated in the IVRT study should be included among those for which physical and structural similarity is characterized and compared.
- D. The test and reference products should have an equivalent rate and extent of ozenoxacin permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) comparing a minimum of one batch each of the test and reference products using an appropriately validated IVPT method. Refer to the *Draft Guidance on Acyclovir* (for acyclovir topical cream, 5%)<sup>2</sup> for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies. The batches of test and reference products evaluated in the IVPT study should be the same as those evaluated in the IVRT study.

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## 2. In vivo option:

Type of study: Clinical Endpoint Bioequivalence Study

Design: Randomized, double blind, parallel, placebo controlled, in vivo

Strength: 1%

Subjects: Males and nonpregnant, nonlactating females with impetigo.

Additional comments: Specific recommendations are provided below.

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**Analytes to measure (in appropriate biological fluid):** Not applicable

**Bioequivalence based on (90% CI):** See additional comments below for the bioequivalence study with clinical endpoint

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<sup>2</sup> The current version of the referenced guidance at the time of publication of this product specific guidance is Draft Guidance on Acyclovir for acyclovir topical cream, 5% (recommended Dec 2014; revised Dec 2016). However, we update guidances periodically, and current information related to product specific guidances is maintained at <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm>.

**Waiver request of in vivo testing:** Not applicable

**Dissolution test method and sampling times:** Not applicable

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**Additional comments regarding the bioequivalence study with clinical endpoint:**

1. The Office of Generic Drugs (OGD) recommends conducting a clinical endpoint bioequivalence study in the treatment of impetigo. Subjects are to be randomized to receive the generic ozenoxacin topical cream, 1%, the reference product or the placebo vehicle applied to the affected area twice daily for 5 days. The primary endpoint is the proportion of subjects with clinical cure at the end of treatment (EOT) (study Day 6-7). Study visits should occur at Day 1 (baseline, Visit 1), Day 2 (24 to 36 hours after and baseline, Visit 2), and Day 6-7 (end of treatment, Visit 3). A follow up visit can occur at 7 days from the EOT (Visit 4).
2. Inclusion Criteria (the sponsor may add additional criteria)
  - a. Healthy male or nonpregnant female aged  $\geq 2$  months with a clinical diagnosis of impetigo.
  - b. Positive baseline culture for *Staphylococcus aureus* and/or *Streptococcus pyogenes* from a sample taken from the target site.
  - c. Skin Infection Rating Scale (SIRS) total score for the target lesion of at least 4 with at least 3 of the five signs/symptom categories present at baseline (per Table 1).

**Table 1. Sample Skin Infection Rating Scale**

| <b>Sign/symptom</b>       | <b>Score</b> | <b>Definition</b>  |
|---------------------------|--------------|--|
| 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 exudate 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 exudate                             |
| Crusting                  | 0=Absent     | No evidence of crusting  |
|                           | 1=Mild       | A few areas have some evidence of crusting lesions                                 |
|                           | 2=Moderate   | Crusting is present throughout the infected area                                   |
|                           | 3=Severe     | Thick crusting appears over the entire impetiginous area                           |
| Erythema/<br>inflammation | 0=Absent     | Skin tone and color 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                                    |

| Sign/symptom | Score      | Definition  |
|--------------|------------|---|
|              | 3=Severe   | Skin is red and severe inflammation is present  |
| Itching/pain | 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. |

3. Exclusion Criteria (the sponsor may add additional criteria)
  - a. Pregnant, breast feeding, or planning a pregnancy.
  - b. Any dermatological disorder that may interfere with the evaluation of the subject's impetigo, including presence of *staphylococcal* and/or *streptococcal* ecthyma, cellulitis, furunculosis, abscess, acute dermatitis, contact dermatitis, impetiginized eczema, or impetigo secondary to any human or animal bite.
  - c. Use of systemic antibiotic or systemic corticosteroid within 1 week prior to baseline.
  - d. Use of topical corticosteroid, topical antibiotic, or topical antifungal within 48 hours prior to baseline.
  - e. Subject whose disease is so widespread or severe that, in the opinion of the investigator, systemic treatment is needed.
  - f. Signs and symptoms of a concurrent infection requiring additional antibiotic therapy.
  - g. Primary or secondary immunodeficiency.
  - h. Diabetes.
  - i. Presence of any other medical condition that might adversely impact the safety of the study participants or confound the study results.
  - j. History of hypersensitivity or allergy to ozenoxacin and/or any of the study medication ingredients.
4. The study protocol should include early observation of the patients (as early as day 2 or 3 of therapy) and provision for switching to an approved treatment if the patient is not improving. These patients should be discontinued and analyzed as treatment failures.
5. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
  - a. Any other topical products (including antibacterial soaps) applied on or near the affected area of impetigo
  - b. Systemic (e.g., oral or injectable) antibiotics.
  - c. Systemic corticosteroids, systemic anti-inflammatory agents or immunosuppressive drugs.
6. The recommended primary endpoint is the proportion of subjects in each treatment group with clinical cure (defined as no additional antibiotic therapy required to treat impetigo and a Skin Infection Rating Scale (SIRS) score of 0 each for blistering, exudate/pus and

crusting, and a SIRS score of  $\leq 1$  each for erythema/inflammation and itching/pain on a 4-point scale provided in Comment #3 above) at Day 6-7 end of therapy (EOT) visit.

7. The proportion of subjects with clinical cure at the end of treatment visit and bacteriological cure (defined as elimination of *Staphylococcus aureus* and *Streptococcus pyogenes* or response was such that no culture material was available and therefore evidence of pathogen eradication) at the end of treatment visit, and bacteriological cure at the follow-up visit should be treated as secondary endpoints for supportive evidence.
8. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
  - a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who:
    - i. Meet all inclusion/exclusion criteria
    - ii. Had positive baseline bacteriological culture
    - iii. Are dosed a pre-specified proportion of the scheduled doses (Generally At least 75% and no more than 125%) of the assigned product for the specified duration of the study. The protocol should specify how compliance will be verified, (e.g., using subject diaries).
    - iv. Do not miss a pre-specified number of scheduled doses for more than pre-specified number of consecutive days.
    - v. Complete the evaluation within the designated visit window with no protocol violations that would affect the treatment evaluation.
  - b. The mITT and safety populations include all randomized subjects who use at least one dose of product.
9. Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population using Last Observation Carried Forward (LOCF). Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of their condition during the treatment phase of the study should be discontinued, included in the mITT and PP population analyses using LOCF, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF. Applicants should provide a pre-specified definition of lack of treatment effect.
10. The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g. Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly note whether the medication was used prior to baseline visit, during the study, or both.
11. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test and reference products.

12. All pregnancies should be reported, including outcome information.
13. If the inactive ingredients are different than those contained in the reference product or in significantly different amounts, then the Applicant is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy, or systemic or local availability of the drug. Inactive ingredients used should provide adequate margins of safety for the proposed clinical exposure in the target population (e.g., 2 months and older).
14. The method of randomization should be described in the protocol and the randomization schedule should be provided. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The Applicant may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.
15. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.
16. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, “Good Clinical Practice: Consolidated Guideline”, for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received for each shipment prior to dispensing to subjects. Retention samples should not be returned to the Applicant at any time.
17. It is the Applicant's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
18. A placebo control arm is recommended to demonstrate that the test and reference products are active and as a parameter that the study is sufficiently sensitive to detect differences between products
19. To establish bioequivalence for a dichotomous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

$$H_0: \pi_T - \pi_R < \Delta_1 \text{ or } \pi_T - \pi_R > \Delta_2 \text{ versus } H_A: \Delta_1 \leq \pi_T - \pi_R \leq \Delta_2$$

where  $\pi_T$  = the success rate of the primary endpoint for the treatment group, and  
 $\pi_R$  = the success rate of the primary endpoint for the reference group.

The null hypothesis,  $H_0$ , is rejected with a type I error ( $\alpha$ ) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the difference of the success rates between test and reference products ( $\pi_T - \pi_R$ ) is contained within the interval  $[\Delta_1, \Delta_2]$ , where  $\Delta_1 = -0.20$  and  $\Delta_2 = 0.20$ . Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

20. To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the test and reference products should both be statistically superior to the placebo. Conduct an appropriate two-sided inferential test with a type I error ( $\alpha$ ) of 0.05, using the mITT population.
21. The study data should be submitted in standardized format. Please refer to study data standards published at [www.FDA.gov](http://www.fda.gov)<sup>3</sup>.
22. The protocol should include a section with fully detailed statistical analysis plan.
23. Please provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
  - a. Study identifier
  - b. Unique subject identifier
  - c. Subject identifier for the study
  - d. Study site identifier (if applicable)
  - e. Age
  - f. Age units (years)
  - g. Sex
  - h. Race
  - i. Name of planned treatment
  - j. Name of actual treatment
  - k. Safety population flag (yes/no)
  - l. Reason for exclusion from safety population
  - m. Modified Intent-to-Treat (mITT) population flag (yes/no)
  - n. Reason for exclusion from mITT population
  - o. Per-Protocol (PP) population flag (yes/no)
  - p. Reason for exclusion from PP population
  - q. Randomized population flag (yes/no)
  - r. Date/time of first exposure to treatment
  - s. Date/time of last exposure to treatment
  - t. End of study date
  - u. End of study status

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<sup>3</sup> Study Data Standards for Submission to CDER available at:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

- v. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
  - w. Clinical outcome (cure/failure)
  - x. Compliance rate (%)
  - y. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
  - z. Adverse event reported (yes/no)
  - aa. Concomitant medication (yes/no)
24. Please provide a dataset containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
- a. Study identifier
  - b. Unique subject identifier
  - c. Subject identifier for the study
  - d. Study site identifier (if applicable)
  - e. Name of planned treatment
  - f. Name of actual treatment
  - g. Safety population flag (yes/no)
  - h. Modified ITT population flag (yes/no)
  - i. Per-Protocol (PP) population flag (yes/no)
  - j. Analysis date
  - k. Analysis visit
  - l. Study visit within the designated window (yes/no)
  - m. Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
  - n. Lesion count
  - o. Individual blistering SIRS score
  - p. Individual exudate/pus SIRS score
  - q. Individual crusting SIRS score
  - r. Individual erythema/inflammation SIRS score
  - s. Individual itching/pain SIRS score
  - t. Total SIRS score
  - u. Culture results (if applicable)
  - v. Bacterial cure (yes/no; if applicable)
  - w. Clinical cure (yes/no; if applicable)
  - x. Additional treatment required during the visit (yes/no)
  - y. Concomitant medication reported during this visit (yes/no)
  - z. Adverse event reported during this visit (yes/no)
  - aa. Laboratory testing during this visit (yes/no)