Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Ozenoxacin

October 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Ozenoxacin

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one in vivo bioequivalence study with clinical endpoint

I. Option 1: Two in vitro bioequivalence studies and other characterization tests

To demonstrate bioequivalence for ozenoxacin topical cream, 1% using in vitro studies, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*[a], and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

2. The test product and reference standard should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization tests with a minimum of three batches of the test product and three batches (as available) of the reference standard. The test product and reference standard batches should ideally represent the product at different ages throughout its shelf life. Refer to the most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*[a] for additional information regarding comparative Q3 characterization tests. The comparison of the test product and reference standard should include characterizations of the following Q3 attributes:

a. Characterization of visual appearance and texture
b. Characterization of phase states and structural organization of matter
    - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
    - Analysis of particle size distribution, crystal habit, and polymorphic form of ozenoxacin in the drug product
    - Analysis of globule size distribution
c. Characterization of 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 vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
    - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
    - 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. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured and reported.
d. Characterization of pH
e. Characterization of specific gravity
f. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard should have an equivalent rate of ozenoxacin release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVRT method.

    Type of study: Bioequivalence study with IVRT endpoint
    Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro
    Strength: 1%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Ozenoxacin in receptor solution
    Equivalence based on: Ozenoxacin (IVRT endpoint: drug release rate))
    Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test product and reference standard evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

4. The test product and reference standard should have an equivalent rate and extent of ozenoxacin permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVPT method.

   Type of study: Bioequivalence study with IVPT endpoints
   Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an unoccluded finite dose, in vitro
   Strength: 1%
   Test system: Barrier-competent human skin from male and/or female donors of at least 18 years of age in a diffusion cell system
   Analyte to measure: Ozenoxacin in receptor solution
   Equivalence based on: Ozenoxacin (IVPT endpoints: total cumulative amount (AMT) and maximum flux (J_{max}))
   Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies. The batches of test product and reference standard evaluated in the IVPT bioequivalence study should be the same as those evaluated in the IVRT bioequivalence study.

II. Option 2: One in vivo bioequivalence study with clinical endpoint

1. Type of study: Bioequivalence study with clinical endpoint
   Design: Randomized, double blind, parallel, placebo controlled, in vivo
   Strength: 1%
   Subjects: Males and non-pregnant, non-lactating females with impetigo
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a bioequivalence study with clinical endpoint in the treatment of impetigo. Subjects are to be randomized to receive the test ozenoxacin topical cream, 1%, the reference standard 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 males or non-pregnant females aged ≥ 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 SIRS

Sign/symptom	Score	Definition
Blistering	0=Absent 1=Mild 2=Moderate 3=Severe	No evidence of blisters Few raised vesicles present on close evaluation Fluid filled vesicles are obvious and are bothersome to the patient Extensive area covered with many vesicles which may include large bullous vesicles
Exudate/pus	0=Absent 1=Mild 2=Moderate 3=Severe	No evidence of exudate or pus Small amounts of fluid/pus coming from the lesions Exudate/pus infected area is moderate Extensive areas infected and there is draining exudate
Crusting	0=Absent 1=Mild 2=Moderate 3=Severe	No evidence of crusting A few areas have some evidence of crusting lesions Crusting is present throughout the infected area Thick crusting appears over the entire impetiginous area
Erythema/ inflammation	0=Absent 1=Mild 2=Moderate 3=Severe	Skin tone and color are normal; no signs of erythema or inflammation Skin is pink with minimal signs of inflammation Skin is red with definite signs of inflammation Skin is red and severe inflammation is present
Itching/pain	0=Absent 1=Mild 2=Moderate 3=Severe	No signs of itching or indication of pain Some evidence of scratching or rubbing the area is evident and patient reports minor discomfort Evidence of scratching and patient reports bothersome, painful lesions 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 SIRS score of 0 each for blistering, exudate/pus and crusting, and a SIRS score of ≤ 1 each for erythema/inflammation and itching/pain on a 4-point scale provided in Comment #2 above) at Day 6-7 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. 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
v. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
w. Total SIRS score at baseline for the target lesion
x. Clinical outcome (cure/failure)
y. Compliance rate (%)
z. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
aa. Adverse event reported (yes/no)
bb. Concomitant medication (yes/no)

9. 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. mITT population flag (yes/no)
    i. 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)

10. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoint.

11. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

Revision History: Recommended February 2019; Revised October 2022

Unique Agency Identifier: PSG_208945

[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[b] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.