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Draft Guidance on Clindamycin Phosphate

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Active Ingredient: Clindamycin phosphate

Dosage Form; Route: Gel; vaginal

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

I. Option 1: One in vitro bioequivalence study and other characterization tests

To demonstrate bioequivalence for clindamycin phosphate vaginal gel, EQ 2% Base 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
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. Rheological behavior of the test product and reference standard should be assessed at both 25°C and 37°C. 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.
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 clindamycin phosphate 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: EQ 2% Base
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Clindamycin phosphate in receptor solution
    Equivalence based on: Clindamycin phosphate (IVRT endpoint: drug release rate)
    Additional comments: The IVRT study should be conducted at 37°C based on the route of administration of this drug product. 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.

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, three-arm, placebo controlled, in vivo
   Strength: EQ 2% Base
   Subjects: Non-pregnant, non-lactating females with bacterial vaginosis
   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 non-pregnant, non-lactating female subjects with a confirmed clinical diagnosis of Bacterial Vaginosis (BV). Subjects are to be randomized to receive the test product versus the reference standard (5 g of gel containing 100 mg of clindamycin) or vehicle (placebo) as one applicator full administered once intravaginally at any time of the day.

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Non-pregnant, non-lactating female age ≥18 years.
   b. Diagnosis of BV, defined as the presence of all of the following:
      - Off-white or gray, thin, homogenous vaginal discharge associated with minimal or absent pruritus inflammation of the vulva and vagina
      - Saline wet mount of vaginal discharge demonstrating the proportion of clue cell to be ≥ 20% of the total epithelial cells
      - Vaginal pH > 4.5, using pH paper that measures from pH 4.0-6.0
      - Positive "whiff test" (a fishy odor of the vaginal discharge) after addition of a drop of 10% potassium hydroxide (KOH) to vaginal discharge
      - Gram stain Nugent score ≥ 7 on first day of dosing (study Day 1)
   c. Any subject with childbearing potential has a negative urine pregnancy test on the first day of dosing (study Day 1) using a pregnancy test with a sensitivity down to at least 50 mIU/mL hCG and are willing to use adequate birth control.
   d. Willing to refrain from using any intra-vaginal product or device other than the study treatment (e.g., other vaginal drugs, spermicide, tampon, douche, diaphragm, condom, or other objects) throughout the first 7 days following treatment.
   e. Agrees to abstain from sexual intercourse throughout the first 7 days following the treatment.

3. Exclusion Criteria (the sponsor may add additional criteria):
   a. Pregnant, lactating, or planning to become pregnant during the study period.
   b. Menstruating at the baseline visit (when evaluation for BV is performed) or anticipate onset of menses during study drug administration.
   c. Evidence of any active vulvovaginitis other than BV (e.g., candidiasis, *Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoeae, Herpes simplex*, or human papilloma virus).
   d. Subject with another vaginal or vulvar condition, which would confound the

interpretation of clinical response.

e. Subject will be under treatment during the study period for cervical intraepithelial neoplasia or cervical carcinoma.
f. History of hypersensitivity or allergy to clindamycin, other lincosamides or other ingredients of the formulation.
g. History of regional enteritis, ulcerative colitis, or *Clostridium difficile*-associated diarrhea.
h. Use of any of the following medications within 2 weeks of the baseline: systemic steroids (oral or injectable), topical or systemic antibiotics, or topical or systemic antifungal.

4. At the baseline visit, documentation of the participant's medical history should include menopausal status. For postmenopausal women, document the month and year of the last menses. For premenopausal women, documented information should include: the first day of the last menstrual period, regularity of menses, use of contraception, past episodes of BV, and sexual history (e.g., sex of intimate partners and history of sexually transmitted infections).

5. The protocol should include a list of the prescription and nonprescription/over-the-counter drug products that are prohibited during the study, such as: systemic steroids (oral or injectable), antifungal or antibacterial therapy (systemic or intravaginal).

6. The primary endpoint of the study is the therapeutic cure rate, defined as both a clinical cure (resolution of clinical signs and symptoms, e.g., normal physiological vaginal discharge, whiff test is negative for any amine "fishy" odor, saline wet mount is negative for clue cells, and vaginal pH is < 4.7, using pH paper that measures pH from 4.0-6.0) and a bacteriological cure (Nugent score <4), evaluated at the Test of Cure visit (study Day 22-30). Subjects who used any BV therapy, other than study product, during the study or had a Nugent score >3 at the Test of Cure visit should be considered therapeutic failures.

7. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Study site identifier
    d. Age
    e. Age units (years)
    f. Sex
    g. Race
    h. Name of planned treatment: test product, reference standard, placebo
    i. Name of actual treatment: test product, references standard, placebo
    j. Date of enrollment
    k. Date of randomization
    l. Date/time of exposure to treatment
    m. End of study date

n. Completed the study (yes/no)
o. Reason for premature discontinuation of subject
p. Per-protocol (PP) population inclusion (yes/no)
q. Reason for exclusion from PP population
r. Modified Intent to Treat (mITT) population inclusion (yes/no)
s. Reason for exclusion from mITT population
t. Safety population inclusion (yes/no)
u. Reason for exclusion from safety population
v. Subject required additional treatment due to unsatisfactory treatment response (yes/no).
w. Baseline vaginal discharge consistent with clinical diagnosis bacterial vaginosis (yes/no)
x. Baseline clue cells on wet mount (≥20%, <20%, or none)
y. Baseline vaginal pH
z. Baseline KOH "whiff test" (positive/negative)
aa. Baseline Nugent score
bb. Baseline Nugent score ≥ 7 (yes/no)
cc. Chlamydia trachomatis (positive/negative)
dd. Neisseria gonorrhoeae test (positive/negative)
ee. Urine pregnancy test (positive/negative)
ff. Normal physiological vaginal discharge (Day 22-30) (yes/no)
gg. KOH "whiff test" (Day 22-30) (positive/negative)
hh. Clue cells on wet mount (Day 22-30) (2'20%, <20%, or none)
ii. Clinical cure (Day 22-30) (yes/no)
jj. Nugent score (Day 22-30) (0, 1, 2, 3, or 4)
kk. Bacteriological cure (Day 22-30) (yes/no)
ll. Therapeutic cure (Day 22-30) (responder; treatment success) (yes/no)
mm. Adverse event reported (yes/no)
nn. Concomitant medication (yes/no)

8. Provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Study site identifier
    d. Name of planned treatment
    e. Name of actual treatment (exposure): test product, reference standard, placebo
    f. Visit number
    g. Visit date
    h. Number of days since baseline visit
    i. Study visit within the designated window (yes/no)
    j. Evaluator: identity of evaluator
    k. Abnormal vaginal discharge (yes/no)
    l. Normal physiological vaginal discharge (yes/no)
    m. KOH "whiff test" (positive/negative)
    n. Clue cells on wet mount (≥20%, <20%, or none)

o. Clinical cure (yes/no)
p. Nugent score (0, 1, 2, 3, or 4)
q. Bacteriological cure (yes/no)
r. Therapeutic cure (responder) (yes/no)
s. Additional treatment required during the visit (yes/no)
t. Adverse event reported during the visit (yes/no)
u. Use of any vaginal products other than study product (yes/no)
v. Concomitant medication during the visit (yes/no)

9. 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.

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

Additional information:

Device:
The Reference Listed Drug (RLD) is presented in an aluminum tube co-packaged with one single-dose, user-filled, disposable vaginal applicator, which is the device constituent.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD device when designing the test device including:

- End of vaginal applicator can attach to opening of drug container to fill the applicator with the correct dose

User interface assessment:
An Abbreviated New Drug Application (ANDA) for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

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[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.