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Draft Guidance on Acyclovir

October 2022

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Active Ingredient: Acyclovir

Dosage Form; Route: Ointment; topical

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 acyclovir topical ointment, 5% 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 and reference standard 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 acyclovir in the drug product
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.
d. Characterization of specific gravity
e. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard should have an equivalent rate of acyclovir 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: 5%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Acyclovir in receptor solution
    Equivalence based on: Acyclovir (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.

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: 5%
   Subjects: Immunocompromised males and non-pregnant, non-lactating females with recurrent herpes simplex labialis
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a bioequivalence study with a clinical endpoint in immunocompromised males and non-pregnant, non-lactating females with recurrent herpes simplex labialis comparing the test product versus the reference standard and placebo control with treatment initiated at the onset of signs or symptoms and applied every 3 hours 6 times daily for 7 days.

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Immunocompromised (defined according to underlying disease and/or the administration of immunosuppressant medication) males or non-pregnant, non-lactating females aged at least 18 years with limited, non-life-threatening, recurrent herpes simplex labialis.
   b. At least 3 recurrences of herpes simplex labialis per year for the past 2 years
      - At least half of recurrences preceded by recognizable prodromal symptoms.
      - At least half of prodromes followed by classical lesions.

3. Exclusion Criteria (the sponsor may add additional criteria):
   a. Females who are pregnant, breast feeding, or planning a pregnancy.
   b. Females of childbearing potential who do not agree to utilize an adequate form of contraception.
   c. Subject who is unable or is not expected to reliably comprehend or satisfactorily assess a herpetic lesion.
   d. Subject with any abnormal skin condition, e.g., acne, eczema, rosacea, psoriasis, albinism, or chronic vesiculo-bullous disorders, known to occur or currently present in the area ordinarily affected by recurrent herpes simplex labialis.
   e. Candidate for parental antiviral treatment or for prophylactic antiviral therapy of their recurrent herpes simplex labialis.
   f. Recent organ transplant.
   g. CD4 counts below 200 cells/µl (HIV subjects are generally considered to be immunocompromised without regard to an upper limit for CD4 counts).
   h. Recent major change in immune status that could seriously affect the clinical manifestations of herpes simplex labialis and need for treatment.
   i. Current episode of herpes simplex labialis that is not completely healed.
   j. History of herpes keratitis.

k. Contraindication to antiviral therapy or known hypersensitivity to any component of acyclovir therapy.
l. Use within four weeks prior to baseline of any over-the-counter or prescription antiviral treatment.

4. A positive viral culture is not required for enrollment.

5. Subjects should be instructed to use a finger cot or rubber glove when applying the study product to prevent autoinoculation of other body sites and transmission of infection to other persons.

6. 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. Antiviral therapies, other than study product.
    b. Corticosteroids.
    c. Topical lip-balms.
    d. Treatments for cold sores.
    e. Cosmetics applied to the treatment area.
    f. Prolonged sun exposure (i.e., sunbathing or sunburn).
    g. Subjects should be instructed to avoid contact of the study product with the eye.

7. The recommended primary endpoint is the duration of episode (DOE) assessed by the investigator, based on both clinical observation and review of the subject diary, and defined as:
    a. For subjects who experience a vesicular lesion, DOE is the time from the treatment initiation to the healing of primary lesions (loss of crust; residual erythema may be present after loss of hard crust).
    b. For subjects whose primary lesions were not vesicular in nature, DOE is the time from the treatment initiation to the return to normal skin or to the cessation of symptoms, whichever occurs last.

8. The primary endpoint is calculated by subtracting the recorded time of the first application of study medication in the case report from the recorded time of the investigator-assessed healing.

9. Cessation of viral shedding has not been shown to correlate well with clinical outcome. It may be included as a secondary endpoint.

10. Within 24 hours (Study Day 1) of initiating treatment with study drug, recommend that subjects return to study site for investigator assessments and return to study site for investigator assessments daily thereafter (or as often as possible) until either:
    a. Healing of the primary vesicular lesion, for those subjects who experience a vesicular lesion, OR
    b. Return to normal skin or the cessation of symptoms, whichever occurs last, for those subjects whose primary lesions are not vesicular in nature.

11. Provide subjects with a diary and instruct them to record their symptoms, such as pain, tenderness, tingling, itching, discomfort and the stage of their herpes lesions (normal lip, erythema, papule, vesicle, ulcer, crust), at a minimum of twice daily.

12. A rescue clause is recommended to allow subjects who significantly worsen (e.g., significant increase in size or number of lesions beyond the patient's usual pattern, progression of lesions after the first few days of therapy, development of severe pain, or evidence of tissue necrosis) during therapy to be discontinued from the study and provided with standard therapy.

13. An additional supportive time-to-event (survival) statistical analysis using the Kaplan/Meier methodology and the Cox proportional hazards model can be performed for the DOE primary endpoint. If a subject discontinued early, this subject is censored at the date of discontinuation, if a subject uses a rescue clause, this subject is censored at the date of rescue treatment, and if a subject is not completely healed at her/his last visit, this subject is censored at their last visit date.

14. Provide a 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
    d. Study site identifier
    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 of enrollment
    s. Date/time of first exposure to treatment
    t. Date/time of last exposure to treatment
    u. End of study date
    v. End of study status
    w. Subject completed the study (yes/no)
    x. Reason for premature discontinuation from the study
    y. Censoring status (1/0)
    z. Subject required additional treatment for herpes simplex labialis due to unsatisfactory treatment response (yes/no)
    aa. Date/time of additional treatment

bb. Time to complete healing of lesions (days)
cc. Time to healing for Kaplan-Meier analysis (End of study date-Date of first exposure treatment+1) (days) if a subject had rescue medications due to unsatisfactory treatment response, the time to healing should be (date of the rescue treatment –date of first exposure treatment+1)
dd. Type of primary lesion
ee. Baseline absolute lesion count
ff. Compliance rate (%)
gg. Subject missed pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
hh. Concomitant medication (yes/no)
ii. Adverse event(s) reported (yes/no)

15. 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. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier
    e. Name of planned treatment
    f. Name of actual treatment
    g. Safety population flag (yes/no)
    h. Modified ITT population flag (yes/no)
    i. PP population flag (yes/no)
    j. Completers population flag (yes/no)
    k. Analysis visit
    l. Analysis date
    m. Study visit within designated window (yes/no)
    n. Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
    o. Primary vesicular lesion OR return to normal skin or the cessation of symptoms
    p. Stage of recurrent herpes labialis infection
    q. Signs/symptoms of herpes labialis infection
    r. Additional treatment required during the visit (yes/no)
    s. Concomitant medication during the visit (yes/no)
    t. Adverse event reported during the visit (yes/no)
    u. Laboratory testing during the visit (yes/no)

16. 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.

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

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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.