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Draft – Not for Implementation

Draft Guidance on Acyclovir

October 2022

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Active Ingredient: Acyclovir

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 acyclovir topical cream, 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 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.
    - 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 water activity
e. Characterization of pH
f. Characterization of specific gravity
g. 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.

4. The test product and reference standard should have an equivalent rate and extent of acyclovir 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: 5%
   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: Acyclovir in receptor solution
   Equivalence based on: Acyclovir (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, three-arm, placebo controlled, in vivo
   Strength: 5%
   Subjects: Healthy, immunocompetent adult males and non-pregnant, non-lactating females with recurrent herpes labialis (cold sores)
   Additional comments: Specific recommendations are provided below. Due to the modest efficacy demonstrated by the reference standard, it is anticipated that a relatively large number of subjects would need to be enrolled.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a bioequivalence study with a clinical endpoint in immunocompetent adult males and non-pregnant, non-lactating females with recurrent herpes labialis (RHL) comparing the test product versus the reference standard and placebo (vehicle) control with treatment initiated as early as possible following the onset of signs or symptoms of herpes labialis (i.e., during prodrome or no later than when herpetic lesions first appear). Treatment should be applied five times per day for 4 days (20 applications).

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Healthy, immunocompetent males or non-pregnant, non-lactating females aged at least 18 years with RHL.

b. At least 3 recurrences of a typical herpes labialis lesion within the past year
    - At least half of recurrences preceded by recognizable prodromal symptoms (e.g., itching, redness, burning, tingling or a sense of irritation).
    - At least half of prodromes followed by classical lesions (e.g., ulcer, vesicle, and/or hard crust).

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 RHL).
    e. Current active immunodeficiency syndrome or disease.
    f. Current active malignancy.
    g. Current episode of herpes labialis that is not completely healed.
    h. Recent organ transplant.
    i. Chronic use of immunosuppressive drugs (e.g., systemic steroid) or topical steroids.
    j. Chronic use of antiviral medication with activity against herpes simplex virus (HSV).
    k. History of vaccination for HSV type 1 (typically oral herpes) or HSV type 2 (typically genital herpes).
    l. History of herpes keratitis.
    m. Candidate for parenteral antiviral treatment or for prophylactic antiviral therapy of their RHL.
    n. Contraindication to antiviral therapy or known hypersensitivity to acyclovir, valacyclovir or any component of acyclovir therapy.
    o. 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. 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. Treatments for cold sores, other than study product.
    d. Topical lip balms.
    e. Cosmetics or other skin products applied to the treatment area.
    f. Prolonged sun exposure (i.e., sunbathing or sunburn).
    g. Mechanical disruption (i.e., scrubbing, lancing, shaving) of the prodromal area or lesion.

h. Subjects should be instructed to wash their hands with soap and water before and after applying treatment, to avoid rubbing the cold sore and to avoid contact of the study product with the eye or the inside of mouth or nose.

6. 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.

    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.

7. 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 of the criteria are met:
    a. Healing of the primary vesicular lesion, for those subjects who experience a vesicular lesion.
    b. Return to normal skin or the cessation of symptoms, whichever occurs last, for those subjects whose primary lesions are not vesicular in nature.

8. 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.

9. 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.

10. 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.

11. 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
    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. Completers population flag (yes/no)
    r. Randomized population flag (yes/no)
    s. Date of randomization
    t. Date of enrollment
    u. Date/time of first exposure to treatment
    v. Date/time of last exposure to treatment
    w. Time to complete healing of lesions (days, not for Kaplan-Meier analysis)
    x. End of study date
    y. End of study status
    z. Subject completed the study (yes/no)
    aa. Subject required additional treatment for herpes labialis due to unsatisfactory treatment response (yes/no)
    bb. Date/time of additional treatment
    cc. Compliance rate (%)
    dd. Treatment compliance: number of missed doses per subject
    ee. Concomitant medication (yes/no)
    ff. Adverse event(s) reported (yes/no)
    gg. Censoring status (1/0)
    hh. Time to complete healing of lesions (days)
    ii. 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)
    jj. Type of primary lesion
    kk. Baseline absolute lesion count
    ll. Reason for discontinuation from study
    mm. Reason for discontinuation of treatment (character)

12. 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 (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. PP population flag (yes/no)
    j. Completers population flag (yes/no)
    k. Analysis date
    l. Analysis visit
    m. Study visit within the designated window (yes/no)
    n. Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
    o. Primary vesicular lesion healed OR return to normal skin or the cessation of symptoms (yes/no)
    p. Stage of recurrent herpes labialis infection
    q. Signs/symptoms of herpes labialis infection
    r. Additional treatment required during the visit (yes/no)
    s. Adverse event reported during the visit (yes/no)
    t. Concomitant medication during the visit (yes/no)

13. 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.

14. 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.