Contains Nonbinding Recommendations

Draft Guidance on Acyclovir

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Ointment; topical

Recommended Studies: Two options: In Vitro or In Vivo Study

In Vitro option: to qualify for the in vitro option for this drug product the following criteria should be met:

A. The test and reference products are qualitatively (Q1) and quantitatively (Q2) the same as defined in FDA's guidance for industry *ANDA Submissions – Refuse-to-Receive Standards*.

B. The test and reference products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the reference product. The characterization of the test and reference products should include the following comparisons of physical and structural attributes:

   i. Assessment of appearance

   ii. Assessment of the acyclovir polymorphic form in the drug product

   iii. Analysis of particle size distribution and crystal habit with representative microscopic images at multiple magnifications

   iv. 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 complete flow curve of shear stress and viscosity vs. shear rate should consist of multiple data points across the range of attainable shear rates, until low or high shear plateaus are identified. The comparative viscosity data at low, medium and high shear rates should be provided.

      - Yield stress values should be reported if the material tested exhibits plastic flow behavior

C. The test and reference products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and reference products using an appropriately validated IVRT method. The batches of test and reference products evaluated in the IVRT study should be included among those for which the physical and structural similarity is characterized and compared. Refer to the *Guidance on Acyclovir* (topical cream) for additional information regarding the development, validation, conduct and analysis of acceptable IVRT studies.

In Vivo option:

Type of study: Bioequivalence Study with Clinical Endpoint
Design: Randomized, double-blind, parallel, placebo-controlled in vivo
Strength: 5%
Subjects: Immunocompromised males and nonpregnant females with recurrent herpes simplex labialis
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): Clinical endpoint (in vivo option)

Waiver request of in vivo testing: Not Applicable

Additional comments regarding the bioequivalence study with clinical endpoint:

1. The Office of Generic Drugs (OGD) recommends conducting a bioequivalence study with a clinical endpoint in immunocompromised males and nonpregnant females with recurrent herpes simplex labialis comparing the test product versus the reference product 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) male or nonpregnant 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. Candidate for parental antiviral treatment or for prophylactic antiviral therapy of their recurrent herpes simplex labialis.
d. Recent transplant.
e. CD4 counts below 200 cells/μl (HIV subjects are generally considered to be immunocompromised without regard to an upper limit for CD4 counts).
f. Recent major change in immune status that could seriously affect the clinical manifestations of herpes simplex labialis and need for treatment.
g. Current episode of herpes simplex labialis that is not completely healed.
h. History of herpes keratitis.
i. Contraindication to antiviral therapy or known hypersensitivity to any component of acyclovir therapy.
j. Use within 1 week prior to baseline of antiviral therapy

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

7. The recommended primary endpoint is time to complete healing of lesions (defined as loss of crust and re-epithelialization with or without erythema, as assessed by the investigator, based on both clinical observation and review of the subject diary), measured in days from the time of first dosing. Subjects who experience a prodrome and start treatment at that time, but who do not subsequently develop any lesion should be assigned a value of zero (0) for time to complete healing of lesions.

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

9. Within 24 hours (Study Day 1) of initiating treatment with study drug, recommend that subjects return to study site for investigator assessments. Site visits are recommended on Study Days 2, 3, and 4, and then every other day until the investigator deemed that lesion healing had occurred or up to Study Day 14. In any cases where healing did not occur by Study Day 14, another site visit is recommended at Study Day 21.

10. 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.

11. Please 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/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 for herpes simplex labialis due to unsatisfactory treatment response (yes/no)
    w. Time to complete healing of lesions (days)
    x. Compliance rate (%)
    y. Subject missed pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
    z. Concomitant medication (yes/no)
    aa. Adverse event(s) reported (yes/no)

12. Please 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 (exposure): test product, RLD, placebo
    g. Safety population flag (yes/no)
    h. Modified ITT population flag (yes/no)

i. Per-protocol (PP) population flag (yes/no)
j. Analysis visit
k. Analysis date
l. Study visit within designated window (yes/no)
m. Complete healing of lesions (yes/no)
n. Additional treatment required during the visit (yes/no)
o. Concomitant medication during the visit (yes/no)
p. Adverse event reported during the visit (yes/no)
q. Laboratory testing during the visit (yes/no)

13. Refer to the product-specific guidance on Adapalene; Benzoyl Peroxide Topical Gel 0.3%; 2.5% for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.[1]

14. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov[2]

[1] Product-Specific Guidances for Generic Drug Development available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
[2] Study Data Standards for Submission to CDER and CBER available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm