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Draft Guidance on Acyclovir

November 2022

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Active Ingredient: Acyclovir

Dosage Form; Route: Tablet; buccal

Recommended Studies: Two options: (1) in vitro bioequivalence studies (comparative dissolution) and in vitro comparative adhesion studies or (2) in vitro bioequivalence studies (comparative dissolution), in vitro comparative adhesion studies, and one bioequivalence study with clinical endpoints

I. Option 1: In vitro bioequivalence studies (comparative dissolution) and in vitro comparative adhesion studies

If the test formulation is qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the Reference Listed Drug (RLD) with respect to inactive ingredients and the test formulation should have inactive ingredients of comparable grade (compendial/technical grade) to that used in the RLD, bioequivalence may be established by conducting both in vitro comparative dissolution and adhesion studies.

In vitro bioequivalence studies (comparative dissolution):

In addition to performing the acyclovir dissolution testing for quality control, provide in vitro comparative dissolution data for the test and the reference products under the following conditions:

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

Strength:	50 mg
Apparatus:	U.S. Pharmacopeia Apparatus 2 (paddle)
Speed:	60 rpm
Media:	pH 6.0 (KH_2PO_4) phosphate buffer (0.2 M) pH 4.0 (0.1 % NaCl solution, pH adjusted to pH 4.0) pH 6.0 (0.05M phosphate buffer solution) pH 7.0 (0.1 % NaCl solution, pH adjusted to pH 7.0) pH 6.8 simulated salivary fluid – phosphate buffer saline solution
Volume:	1000 mL
Temperature:	37ºC
Sampling times:	1, 2, 4, 6, 8, and 12 hours, or as needed for profile comparison Use at least 12 dosage units per test and f2 metric to compare dissolution profiles.

In vitro comparative adhesion studies:

Optimize relevant in vitro adhesion test conditions including contact time, applied force for adhesion, and withdrawal speed of the probe. This is primarily because the testing instrument variables can have a profound effect on the adhesion force (peak detachment force) and energy of adhesion (work of adhesion). The testing condition for adhesion study may need to be optimized considering that both test and reference formulations may differ in their physical attributes, such as hardness.

A tensiometry study is recommended to compare the peak detachment force for test and reference products.[3] Water is recommended between the buccal tablets and the base plate of the tensiometer. The loading weight and length of time the loading weight is applied to press the buccal tablet into contact with the base plate should be specified. Following removal of the weight, the rate at which the buccal tablet is pulled away from the base plate should be specified. The peak detachment force should be measured as the force required to detach the buccal tablet from the base plate. The in vitro comparative adhesion test should be conducted using 12 individual units of the test and reference products. Prior to conducting studies, determine appropriate loading weight, length of time the loading weight is applied to press the buccal tablet into contact with the base plate of the tensiometer, and the rate at which the buccal tablet is pulled away from the base plate.[4] These studies should be conducted to ensure the appropriateness of the test conditions to the test and reference products.

[3] HE Junginger et al. Mucoadhesive Hydrogels in Drug Delivery. Encyclopedia Pharm Technol, 2002.
[4] SJ Jackson, AC Perkins. In Vitro Assessment of the Mucoadhesion of Cholestyramine to Porcine and Human Gastric Mucosa. Eur J Pharm Biopharm. 2001;52:121-127.

II. Option 2: In vitro bioequivalence studies (comparative dissolution), in vitro comparative adhesion studies, and in vivo bioequivalence study with clinical endpoints

If the test product formulations are not Q1/Q2 the same as the RLD with respect to inactive ingredients or if the inactive ingredients are not of comparable grade (compendial/technical grade) to that used in the RLD, bioequivalence should be established by conducting in vitro comparative dissolution studies, in vitro comparative adhesion studies, and in vivo bioequivalence study with clinical endpoints.

In vitro bioequivalence studies (comparative dissolution): The same studies as recommended under Option 1

In vitro comparative adhesion studies: The same studies as recommended under Option 1

In vivo bioequivalence study with clinical endpoints:

1. Type of study: Bioequivalence study with clinical endpoints
   Design: Three-arm, randomized, double blind, parallel, placebo controlled in vivo
   Strength: 50 mg
   Subjects: Immunocompetent male and non-pregnant, non-lactating female patients with recurrent herpes labialis
   Additional comments: See specific recommendations below.

Additional comments regarding the in vivo bioequivalence study with clinical endpoints:

1. Conduct a bioequivalence study with clinical endpoints in immunocompetent adult males and females with recurrent herpes labialis comparing the test product versus the RLD and placebo control with treatment within one hour after the onset of prodromal symptoms (e.g., itching, tingling, pain etc.) and before the appearance of any signs of herpes labialis.

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Good general health (e.g., Eastern Cooperative Oncology Group < 2)
   b. History of recurrent herpes labialis with at least 4 recurrences for 12 months prior to the study
   c. History of herpes labialis recurrences that are typically associated with prodromal symptoms (>50% of episodes)
   d. History of at least 50% of herpes labialis recurrences producing classic lesions (development of a lesion that undergoes vesicle, papule, ulcer, curst and healing formation)

3. Exclusion Criteria (the sponsor may add additional criteria):
   a. Any evidence of an immunosuppressed state of the subject due to underlying disease (e.g., human immunodeficiency virus infection) or concomitant treatment (e.g., cancer chemotherapy)

b. A history of previous herpes simplex vaccine
c. Previous infection with herpes simplex virus 1 isolates resistant to acyclovir, valaciclovir, famciclovir or ganciclovir
d. Significant skin conditions or oral diseases that occur in the area typically affected by herpes recurrences and would interfere with assessment of lesions (e.g., atopic dermatitis, acne, eczema, psoriasis, chronic vesiculobullous disorders or rosacea)
e. Primary herpes lesion outside the lip (e.g., nose, chin etc.)
f. Upper full or partial dentures with acrylic border in the canine fossa
g. Systemic and/or topical treatment with antiviral agents within 2 weeks prior to the study
h. Systemic and/or topical treatment with corticosteroids or immunosuppressive agents within 4 weeks prior to the study
i. Continuous daily treatment with analgesics, pain medication or non-steroidal anti-inflammatory drugs
j. History of hypersensitivity to any nucleoside analogue antiviral agent or any component of the study product
k. Females who are pregnant, breast feeding, or planning a pregnancy
l. Females of reproductive potential who do not agree to utilize an adequate form of contraception

4. The protocol should include a list of the prescription and nonprescription/over-the-counter (OTC) drug products, procedures, and activities that are prohibited during the study, such as: systemic or topical antiviral agents, systemic or topical corticosteroids, other topical medical, OTC, and analgesic drugs.

5. Subjects should use the study product within one hour after the onset of prodromal symptoms and before the appearance of any signs of herpes labialis lesions. Subjects should be provided proper instructions for the study product as recommended in the current labeling of the RLD by reading the instruction for use before using it. If the study product does not adhere or falls off within 6 hours after the application, the product should be repositioned immediately.

6. The primary efficacy endpoint is the duration of episode (DOE) assessed by the investigator, based on both clinical observation and review of the subject diary. For subjects who experience vesicular lesions, DOE is the time from the treatment initiation to the healing of the lesions (e.g., loss of crust). For subjects who have no vesicular lesions in nature, DOE is the time from treatment initiation to return to normal skin or to cessation of symptoms whichever comes last.

7. All lesions should be evaluated until the lesion progresses to the normal skin when the time of no signs or symptoms have been reached. Stages of herpes lesions should be clearly defined in the protocol. Vesicular lesion recurrence should be recorded.

8. Subjects should visit study site within 24 hours or soon after initiating treatment with study drug and return to study site for assessments of herpes lesions.

9. Provide subjects with a diary and instruct them to record all study drug application times. Subjects should also record their symptoms, such as pain, tenderness, tingling, itching, discomfort, and the stage of their herpes lesions (normal lip, erythema, papule, vesicle, ulcer, crust).

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 unusual 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. Provide the Subject-Level Analysis Dataset, 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 actual treatment (exposure): test product, RLD, placebo
    i. Date of enrollment
    j. Date of randomization
    k. Date/time of exposure to treatment
    l. Completed the study (yes/no)
    m. Reason for premature discontinuation of subject
    n. Per protocol (PP) population inclusion (yes/no)
    o. Reason for exclusion from PP population
    p. Modified Intent to Treat (mITT) population inclusion (yes/no)
    q. Reason for exclusion from mITT population
    r. Safety population inclusion (yes/no)
    s. Reason for exclusion from safety population
    t. Type of lesion(s) at baseline (prodromal symptom and area)
    u. Baseline absolute lesion count
    v. Vesicular lesion recurrence (yes/no)
    w. Description of vesicular lesions(s) if occur
    x. Time from treatment initiation to the healing of vesicular lesions or to normal skin or cessation of symptoms whichever comes last
    y. Subject required additional treatment for herpes labialis due to unsatisfactory treatment response (yes/no)
    z. Use of additional study product (yes/no)
    aa. Concomitant medication (yes/no)
    bb. Adverse event(s) reported (yes/no)

12. Provide the basic data structure 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 actual treatment (exposure): test product, RLD, vehicle control
    e. Visit number
    f. Visit date
    g. Number of days since baseline visit
    h. Evaluator: identity of evaluator
    i. Stage of herpes labialis
    j. Signs/symptoms of herpes labialis infection
    k. Time from baseline lesion (days)
    l. Concomitant medication (yes/no)
    m. Adverse event(s) reported (yes/no)

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

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

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of the test and reference products. Specifications will be determined upon review of the Abbreviated New Drug Application (ANDA).

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[a] 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.