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Draft – Not for Implementation

Draft Guidance on Acyclovir; Hydrocortisone

October 2022

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Active Ingredient: Acyclovir; Hydrocortisone

Dosage Form; Route: Cream; topical

Recommended Studies: Three options: (1) two in vitro bioequivalence studies and other characterization tests (2) two in vitro bioequivalence studies, one in vivo (vasoconstrictor) bioequivalence study with pharmacodynamic endpoint, and other characterization tests or (3) one in vivo (vasoconstrictor) bioequivalence study with pharmacodynamic endpoint and 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 and hydrocortisone topical cream, 5%; 1% 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 and hydrocortisone in the drug product
    - Analysis of globule size distribution
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 and hydrocortisone 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%; 1%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Acyclovir and hydrocortisone in receptor solution
    Equivalence based on: Acyclovir and hydrocortisone (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 equivalent rate and extent of acyclovir and hydrocortisone 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%; 1%
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 and hydrocortisone in receptor solution
Equivalence based on: Acyclovir and hydrocortisone (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: Two in vitro bioequivalence studies, one in vivo (vasoconstrictor) bioequivalence study with pharmacodynamic endpoint, and other characterization tests

To demonstrate bioequivalence for acyclovir and hydrocortisone topical cream, 5%; 1% using a combination of in vitro studies and in vivo vasoconstrictor studies, the following criteria should be met:

1. The test product should meet the criteria outlined in the Option 1: 1-2.

2. 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%; 1%
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.

3. The test product and reference standard should have 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%; 1%
   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.

4. The test product and reference standard should demonstrate bioequivalence of hydrocortisone based upon an acceptable in vivo vasoconstrictor study with one batch each of the test product and reference standard. The batches of test product and reference standard evaluated in the vasoconstrictor study should be the same as those evaluated in the IVRT and IVPT studies.

   A. Type of study: Pilot vasoconstrictor study
      Design: A pilot dose duration-response study using the reference standard
      Strength: 5%; 1%
      Subjects: Males and non-pregnant, non-lactating females, general population
      Additional comments: Refer to the most recent version of the FDA guidance for

industry on *Topical Dermatological Corticosteroids: In Vivo Bioequivalence.*[a]

B. Type of study: Pivotal vasoconstrictor bioequivalence study
Design: A pivotal bioequivalence study
Strength: 5%; 1%
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.

III. Option 3: One in vivo (vasoconstrictor) bioequivalence study with pharmacodynamic endpoint and one in vivo bioequivalence study with clinical endpoint

1. A. Type of study: Pilot vasoconstrictor study
Design: A pilot dose duration-response study using the reference standard
Strength: 5%; 1%
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: Refer to the most recent version of the FDA guidance for industry on *Topical Dermatological Corticosteroids: In Vivo Bioequivalence.*[a]

B. Type of study: Pivotal vasoconstrictor bioequivalence study
Design: A pivotal bioequivalence study
Strength: 5%; 1%
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.

2. Type of study: Bioequivalence study with clinical endpoint
Design: Randomized, double-blind, parallel, three-arm, placebo-controlled, in vivo
Strength: 5%; 1%
Subjects: Males and non-pregnant, non-lactating female adults with recurrent herpes labialis (cold sores)
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 adult males and non-pregnant, non-lactating females with recurrent herpes labialis (RHL) comparing the test product versus the reference standard and placebo control with treatment initiated as early as possible following the onset of signs or symptoms of herpes labialis, i.e., during the prodrome or when lesions (e.g., erythema or papule) appear, and applied five times per day for 5 days (25 applications).

2. Inclusion Criteria (the sponsor may add additional criteria):
    a. Males or non-pregnant, non-lactating females, between 18 and 80 years of age.
    b. History of RHL with at least 3 recurrences for 12 months prior to the study.
    c. History of herpes labialis recurrences that were typically associated with prodromal symptoms (>50% of episodes).

d. History of at least 75% of herpes recurrences producing ulcerative lesions (development of a lesion that undergoes vesicle, ulcer and/or crust 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 (HSV-1) isolates resistant to acyclovir, valaciclovir, famciclovir or ganciclovir.
    d. Significant skin conditions 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. Systemic and/or topical treatment with antiviral agents within 2 weeks prior to the study.
    f. Systemic and/or topical treatment with immunosuppressive agents including corticosteroids, cyclosporin, mycophenolate mofetil, tacrolimus, pimecrolimus and azathioprine within 2 weeks prior to the study.
    g. Continuous daily treatment with analgesics, pain medication or non-steroidal anti-inflammatory drugs (intermittent use of acetaminophen is allowed).
    h. History of immediate hypersensitivity to any nucleoside analogue antiviral agent, or to any topical steroid, or to the placebo control.
    i. Females of child-bearing potential not using a medically accepted form of birth control during the study.

4. The protocol should include a list of the prescription and nonprescription/over-the-counter 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, over-the-counter or cosmetic products applied to the cold sore and analgesic drugs other than intermittent acetaminophen.

5. The primary efficacy endpoint is the proportion of subjects with non-ulcerative recurrences that is measured as the proportion of subjects in whom the study recurrence does not progress beyond the papule stage (e.g., vesicle, ulcer or crust).

6. All non-ulcerative lesions or ulcerative recurrences should be evaluated by assessor until the lesion progresses to the stage when the hard crust finally falls off or the time of no signs or symptoms (normal skin) have been reached. Type of herpes recurrences, ulcerative and non-ulcerative recurrences, should be clearly defined in the protocol.

7. Subjects should visit study site as soon as possible after initiating treatment, but no later than midnight of the following day and return to study site for assessments of non-ulcerative lesions or ulcerative recurrences.

8. 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).

9. 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 actual treatment (exposure): test product, reference standard, placebo
    i. Date of enrollment
    j. Date of randomization
    k. Date/time of first exposure to treatment
    l. Date/time of last exposure to treatment
    m. Duration of treatment (total exposure in days)
    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. Type of baseline lesion
    w. Baseline absolute lesion count
    x. Ulcerative recurrence (yes/no)
    y. Description of ulcerative recurrence lesion
    z. Time to complete healing of lesions
    aa. Subject required additional treatment for herpes labialis due to unsatisfactory treatment response (yes/no)
    bb. Treatment compliance: number of missed doses per subject
    cc. Concomitant medication (yes/no)
    dd. Adverse event(s) reported (yes/no)

10. 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 actual treatment (exposure): test product, reference standard, placebo
    e. Visit number

f. Visit date
g. Number of days since baseline visit
h. Evaluator: identity of evaluator
i. Type of herpes labialis
j. Signs/symptoms of herpes labialis infection
k. Time from baseline lesion (days)
l. Treatment compliance: number of missed doses per subject
m. Concomitant medication (yes/no)
n. Adverse event(s) reported (yes/no)

11. 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.

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

Unique Agency Identifier: PSG_022436

[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.