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Draft – Not for Implementation

Draft Guidance on Hydrocortisone; Neomycin Sulfate; Polymyxin B Sulfate

February 2024

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Active Ingredients:	Hydrocortisone; Neomycin sulfate; Polymyxin B sulfate
Dosage Form:	Suspension/drops
Route:	Otic
Strength:	1%; EQ 3.5mg Base/mL; 10,000 units/mL
Recommended Studies:	Two options: (1) two in vitro bioequivalence studies with supportive comparative characterization studies, or (2) one comparative clinical endpoint bioequivalence study

I. Option 1: Two in vitro bioequivalence studies with supportive comparative characterization studies

To demonstrate bioequivalence by this option, the test product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

Two in vitro bioequivalence studies

1. Type of study: Drug particle size and particle size distribution of hydrocortisone
   Design: In vitro bioequivalence study on three batches of both test and reference standard (RS) products
   Strength: 1%; EQ 3.5mg Base/mL; 10,000 units/mL

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD 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 RLD product.

Additional comments: The sample preparation method and selected particle sizing methodology should be adequately optimized and validated to demonstrate the adequacy of the selected method in accurately and reliably identifying and measuring the size of the drug particles. Prospective applicant should perform size characterization at different dilution conditions as part of method development to demonstrate the impact of dilution. Full particle size distribution profiles representative of all test product and RS product batches tested should be submitted as supporting information.

Parameters to measure: D_{50} and SPAN $[(D_{90}-D_{10})/D_{50}]$

Bioequivalence based on (95% upper confidence bound): Population bioequivalence (PBE) analysis of the D_{50} and SPAN. Prospective applicants should provide no less than 10 datasets from three batches each of the test and RS products to be used in the PBE analysis. For additional information on PBE statistical analysis, refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929).[a]

2. Type of study: Comparative in vitro release testing (IVRT) of hydrocortisone
Design: Should be performed on three batches of both test and RS products using at least 12 units from each batch
Strength: 1%; EQ 3.5mg Base/mL; 10,000 units/mL
Additional comments: The IVRT method study should include information on the method development and validation to detect potential formulation differences and capture the complete release profile of hydrocortisone.

Bioequivalence based on: Comparative analysis of release profiles should be established using an appropriate statistical method (e.g., model independent approach using similarity factor (f_2)). For more information on calculation of f_2 factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[b]

Comparative characterization studies:

Comparative physicochemical characterization of the test and RS products. The comparative study should be performed on at least three batches of both the test[3] and RS products and should include:

a. Crystalline habit of hydrocortisone
b. Appearance
c. pH
d. Specific gravity
e. Osmolality
f. Surface tension
g. Viscosity
h. Soluble fraction of hydrocortisone in the final drug product

[3] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

II. Option 2: One comparative clinical endpoint bioequivalence study

1. Type of study: Comparative clinical endpoint bioequivalence study
   Design: Randomized, double-blind, parallel, placebo-controlled, in vivo
   Strength: 1%; EQ 3.5mg Base/mL; 10,000 Units/mL
   Subjects: Males and females (non-pregnant) with superficial bacterial infections of the external auditory canal

Additional comments:

1. A comparative clinical endpoint bioequivalence study is requested for any generic hydrocortisone; neomycin sulfate; polymyxin B sulfate otic suspension/drops product that has differences in inactive ingredient compared to the RLD, or unacceptable data from in vitro comparative studies.

2. FDA recommends conducting a comparative clinical endpoint bioequivalence study in the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of neomycin and polymyxin B sulfates, comparing the test product versus the RS and vehicle (placebo) control, each administered as four drops instilled into the affected ear thrice daily for seven days (1 week). Prior to administration, the suspension should be warmed by holding the bottle in the hand for one to two minutes and shaken well immediately before using. The subject should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the drops into the ear canal. In the event of bilateral otitis externa, both ears should be treated. However, the ear with the more severe signs and symptoms at baseline, designated as the "study ear", will be used for the evaluations throughout the course of the study. The two co-primary endpoints are clinical cure (defined as complete resolution of signs and symptoms with no further requirement for antimicrobial therapy) and time to end of pain. Both determined at the test of cure visit on study day 14-21 (i.e., 7-14 days after the end of treatment).

3. A placebo (vehicle) control arm is recommended to demonstrate that the test and RS products are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.

4. Inclusion criteria (the sponsor may add additional criteria):
   a. Male or non-pregnant female aged 18 to 65 years.
   b. Clinical diagnosis of bacterial otitis externa with signs and symptoms of otalgia, edema, and tenderness.
   c. Culture-based diagnosis of acute bacterial otitis externa (i.e., positive baseline bacterial culture for the presence of *Staphylococcus aureus, Escherichia coli, Haemophilus influenzae, Klebsiella- Enterobacter species, Neisseria species, and Pseudomonas aeruginosa*). As the results of the baseline bacterial culture may not be known until after the subject has completed treatment, subjects who meet all the other inclusion/exclusion criteria may be enrolled in the study pending the results of the bacterial culture. A baseline bacterial culture negative for

Staphylococcus aureus, Escherichia coli, Haemophilus influenzae, Klebsiella-Enterobacter species, Neisseria species, and Pseudomonas aeruginosa will exclude the subject from the Per Protocol (PP) and modified intent-to-treat (mITT) analyses.

5. Exclusion criteria (the sponsor may add additional criteria):
    a. Females who are pregnant, breast feeding, or who wish to become pregnant during the study period.
    b. Current diagnosis or history of tympanic membrane perforation or damage or tympanostomy tubes.
    c. Current diagnosis or history of diabetes mellitus, psoriasis, otitis media, malignant otitis externa, mastoid cavities, stenosis, exostosis, or tumors of either ear.
    d. Current diagnosis of fungal or viral infection of either ear.
    e. Current diagnosis of dermatitis of the affected ear or surrounding area.
    f. Current presence of any other infection of the ears or other medical condition that might adversely impact the safety of the study participants or confound the study results.
    g. Known hypersensitivity to neomycin, kanamycin, paromomycin, streptomycin, gentamicin, polymyxin B sulfates, hydrocortisone, or any component of the test or RLD.
    h. Use of any systemic antibacterial within four weeks prior to baseline.
    i. Use of any topical medication in the affected ear within two weeks prior to baseline.

6. 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:
    a. Otic product administered to either ear, other than the assigned study product.
    b. Topical or systemic antibiotics, other than the assigned study product.
    c. Topical or systemic corticosteroids, other than the assigned study product.
    d. Systemic or topical immunosuppressive drugs or immunomodulators (e.g., azathioprine, infliximab, calcineurin inhibitors).
    e. Assigned study product should not be used if the tympanic membrane is perforated or in the presence of viral infections of the external canal, including herpes simplex, vaccinia, and varicella infections.
    f. Subjects should be instructed to not use the assigned study product in the eyes, to avoid contaminating the bottle tip with material from the ear, fingers, or other source, and to discontinue study product at the first appearance of a skin rash or any other sign of hypersensitivity or an allergic reaction.

7. Subjects who do not respond to therapy after 48 hours will receive standard therapy (i.e., early escape clause). Patients need close clinical observation for the risk of neomycin-associated sensorineural hearing loss.

8. The two co-primary endpoints are the proportion of subjects in the PP population with clinical cure (defined as complete resolution of signs and symptoms with no further

requirement for antimicrobial therapy) of the study ear and time to end of pain for the study ear. The two co-primary endpoints are to be evaluated at the test of cure visit on study day 14 to 21 (7 to 14 days after the end of treatment). If both ears of the subject are infected, the ear with the more severe signs and symptoms at baseline should be designated as the study ear and evaluated at each study visit (i.e., Baseline visit, end of treatment visit, and test of cure visit).

9. During each study visit, score each of the following signs and symptoms using the following scale:
    a. Signs: Edema, erythema, and otorrhea
    b. Symptoms: Otalgia and tenderness
    c. Scoring Scale:
        0 = none (complete absence of any signs or symptoms)
        1 = mild (slight)
        2 = moderate (definitely present)
        3 = severe (marked, intense)

10. Time to end of pain for the affected ear should be evaluated at each post-baseline evaluation visit [(i.e., at the end of treatment visit (study day 8-10) and the test of cure visit (study day 14-21)]. Throughout the study, subjects should record pain severity at least twice daily (prior to dosing) on a visual analog scale of 0 to 15, where 0 = no pain and 15 = severe pain. Each subject should record the time and date at which the study ear pain ended. The time to end of pain is the interval (in hours) between the first dose of study drug and the time when the study ear pain ended. If study ear pain continued to the end of the study, the value of the time to end of pain variable is set to the length of time between the time of the first dose of study drug and the last time point when a pain measurement was recorded. If the "time to end of ear pain" field is blank, then it should be considered that the pain did not end for the subject while the subject was under observation and the value of the time to end of pain variable is set to the length of time between the time of the first dose of study drug and the last time point when a pain measurement was recorded.

11. Post-therapy cultures are necessary only if the subject's clinical response is unsatisfactory. Routine post-therapy cultures frequently yield positive results due to the presence of normal flora or other colonization after treatment. If the use of an ear wick or debridement of the ear is permitted during the study, the use of these procedures should be comparable among treatment groups.

12. Subjects with a negative culture at baseline should be discontinued from the study and excluded from the mITT and PP populations, but included in the safety population.

13. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Site identifier: study center

d. Age
e. Age units (years)
f. Sex
g. Race
h. Name of actual treatment (exposure): test product, RS, placebo
i. Duration of treatment (total exposure in days)
j. Completed the study (yes/no)
k. Reason for premature discontinuation of subject
l. Subject required additional treatment for acute otitis externa due to unsatisfactory treatment response (yes/no)
m. PP population inclusion (yes/no)
n. Reason for exclusion from PP population
o. Modified Intent to Treat (mITT) population inclusion (yes/no)
p. Reason for exclusion from mITT population
q. Safety population inclusion (yes/no)
r. Reason for exclusion from safety population
s. Baseline edema score
t. Baseline otalgia score
u. Baseline tenderness score
v. Final designation as clinical cure (yes/no)
w. Pain relief achieved while on study (yes/no)
x. If pain relief achieved, time to relief of pain (hours)
y. Treatment compliance: number of missed doses per subject
z. Concomitant medication (yes/no)
aa. Adverse event(s) reported (yes/no)

14. 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. Name of actual treatment (exposure): test product, RS, placebo control
    d. Visit number
    e. Visit date
    f. Number of days since baseline visit
    g. Evaluator: identity of evaluator
    h. Edema score
    i. Erythema score
    j. Otorrhea score
    k. Otalgia score
    l. Tenderness score
    m. Composite (total) signs and symptoms score
    n. Culture result
    o. Concomitant medication reported during this visit (yes/no)
    p. Adverse event reported during this visit (yes/no)
    q. Laboratory testing during this visit (yes/no)

15. 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.

16. Refer to the Study Data Standards Resources website https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources.

Additional information:

Device:
The RLD is presented in a bottle fitted with a dropper tip. The bottle with dropper tip is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test device.

User interface assessment:
An abbreviated new drug application (ANDA) for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[b]

Delivery and dispensing characteristics:
For quality purposes, an ANDA for this product should include a one-time drop volume/drop weight study to determine the drop size during delivery or dispensing. The drop size of the generic product should be within ± 10% of the drop size of the RS product. For any deviations from the RS, the ANDA applicant should demonstrate that the product can dispense a similar number of doses as the RS. Dose uniformity should also be demonstrated by a one-time dose-uniformity study (from top, middle, and bottom of the container) from at least three pilot or exhibit batches to demonstrate that the drug substance is uniformly dispersed, and the labeled dose can be consistently delivered throughout the shelf life.

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[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.