Contains Nonbinding Recommendations

Draft Guidance on Permethrin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or Agency) on this topic.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

Dosage Form; Route: Cream; topical

Recommended Studies: One study

1. Type of study: Bioequivalence (BE) with Clinical Endpoint Study
   Design: Randomized, double blind, parallel, in vivo.
   Strength: 5%
   Subjects: male and females (nonpregnant) diagnosed with scabies (*Sarcoptes scabiei*) infestation
   Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Not Applicable

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times: Not Applicable

Additional comments regarding the BE with clinical endpoint study:

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with clinical endpoint in the treatment of active infestation with *Sarcoptes scabiei* (scabies) comparing the test product versus the reference-listed drug (RLD). The study drug is to be applied one time at home on study day 0 by the subject or their parent/caregiver from the head to the soles of the feet. Four site visits are recommended as follows: Day 0 (before home treatment), Day 1 (one day after home treatment), Day 14±2 (14 days after treatment), and Day 28±2 (28 days after treatment). Day 1 visit should include general skin evaluation for application site reaction and an active assessment for evidence of eye irritation. Day 0, 14, and 28 visits should include skin scrapings from characteristic lesions and examined microscopically for mites, ova, or mite feces.

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Male or female (nonpregnant and nonlactating)
   b. At least 2 months of age
   c. Clinical findings typical of scabies (burrows, erythematous papules, etc.) and microscopic confirmation of scabies mite, ova, or mite feces
   d. Subject and/or parent/guardian agree that the subject will not use any other form of scabies treatment during the duration of the study.

e. The youngest subject (with scabies infestation as defined above) from each household is considered to be the index or primary subject of the household for evaluation of the primary endpoint. Other members of the household and close contacts are enrolled in the study as secondary subjects (not included in primary endpoint analysis) and evaluated for all safety parameters. Secondary subjects should receive the same study treatment as the index subject.

3. 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. Skin conditions that could make it difficult to evaluate the extent of an infestation or would present a problem in the evaluation of response to therapy (e.g. atopic dermatitis, eczema, contact dermatitis, lichen planus, papular urticaria, seborrheic dermatitis).
   c. Use within 4 weeks of baseline visit (1) immunomodulators (2) systemic medications that suppress the immune system (3) topical or oral parasiticides.
   d. Use within 2 weeks of baseline visit (1) topical steroids (2) topical or systemic antibiotics
   e. Has crusted scabies
   f. Known history of irritation or sensitivity to parasiticides.
   g. Known allergy or hypersensitivity to permethrin, any synthetic pyrethroid or pyrethrin, plants in the Asteraceae/Compositae family (e.g. chrysanthemums, ragweed, marigolds, and daisies)
   h. Subjects whose household members and close contacts refuse treatment
   i. Subjects whose sexual contacts do not agree to restrict prolonged skin to skin contact with non-household members during the study period
   j. Subjects with a household member less than 2 months of age

4. The protocol should include a list of the prescription and over-the-counter drug products and treatments that are prohibited during the study, such as:
   a. Any therapy that might influence or mask the effects of treatment, such as topical or systemic corticosteroids
   b. any parasiticidies

5. The primary endpoint is the proportion of subject in the per protocol (PP) population with treatment cure on Day 28. Cure is defined as demonstration of clinical cure (all clinical findings have completely resolved, including inflammatory/non-inflammatory lesions) and microscopic cure (demonstration of the absence of mites, eggs, and/or mite feces) on Day 28. Negative microscopy can be declared if no mites, ova, or mite feces is found from a minimum of 3 skin scrapings from previously affected sites.

6. Subjects who do not respond to the initial treatment (i.e. subjects with new lesions or microscopic confirmation of mites, ova, or fecal matter on Day 14) will be treated as treatment failure in the final analysis (on Day 28) and should be provided with standard (approved) therapy for the second treatment (i.e. 14 days after the first treatment).

7. Provide oral and written instruction for administration of permethrin topical cream to the subject and/or parent/guardian as follows:
   - Thoroughly massage a thin layer of cream all over your skin from your neck down to your toes (including the soles of your feet). Be careful to apply cream in all skins folds, such as between your toes and fingers or around your waist or buttocks.
   - The cream should also be applied to the scalp or hairline, temples, and forehead
   - Avoid contact with your eye during application, and if the cream gets in the eyes, flush with water immediately

- Leave the permethrin cream on the skin for 8 to 14 hours.
- After 8 to 14 hours, wash off the cream by taking a shower or bath
- Put on clean clothes
- After treatment, itching may continue for up to 4 weeks

8. Provide details in the protocol regarding the procedures to be taken to decrease infestation, such as:
   Clothes and bed linens that were in contact with the subjects, their household members and close contacts during the previous 48 to 72 hours will be machine washed at 60°C and machine dried the day after the first treatment. For materials that cannot be laundered, insecticide powder or aerosolized insecticide may be used, or the items may be kept in a sealed bag for at least 48 to 72 hours.

9. The protocol should clearly define the per-protocol (PP) population, modified intent-to-treat (mITT), and safety populations.
   a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who met all inclusion/exclusion criteria, were compliant with the assigned study treatment, and completed the evaluation Day 28 within the designated visit window (i.e. ± 2 days) with no protocol violations that would affect the treatment evaluation. The protocol should provide a definition of compliant subjects and specify how compliance will be verified (e.g., subjects to return medication tubes and the use of subject diaries to document time the drug product was applied and washed off).
   b. The mITT and safety populations include all randomized subjects who applied at least one dose of the assigned product.

10. A standardized and thorough full-body examination at each assessment should be performed for each subject. Subject evaluation with dermoscopy is recommended. Detailed and systematic documentation of clinical findings, number of lesions, type of lesions, and lesion locations should be conducted and included in the case report form. To ensure that evaluators (experienced professionals) conduct a thorough and consistent evaluation for the presence of scabies, the time spent by the evaluator to assess for the presence of scabies should be recorded and included in the case report form.

11. Subjects whose condition worsens and require alternate or supplemental therapy or retreatment for scabies infestation during the study should be discontinued, included in the PP population analysis as treatment failure and provided with effective treatment. Subjects who are discontinued prematurely from the study due to lack of treatment effect should be included in the PP population as treatment failure (i.e., non-responders). Subjects who are discontinued prematurely for other reasons should be excluded from the PP population, but included in the mITT population.

12. The start and stop date of concomitant medications used during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.

13. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome, and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test

product and RLD. Any subject with an adverse event assessed as related to the study product should follow up within 7 days of the adverse event report.

14. Application site reactions such as erythema, edema, pruritus, rash, burning/stinging, pain, numbness, and tingling are to be recorded and scored at each visit using the scale: 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). A descriptive analysis comparing the application site reactions for each treatment group is recommended. It is important to ensure that the test product is no worse than the reference product with regard to the expected and unexpected application site reactions.

15. If the inactive ingredients are different from those contained in the RLD or in significantly different amounts, then the sponsor must clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy, and/or systemic or local availability of the drug. Inactive ingredients used should provide adequate margins of safety for the proposed clinical exposure in the target population (i.e. 2 months and older).

16. The method of randomization should be described in the protocol, and the randomization schedule provided. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity for each subject.

17. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test and reference products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

18. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, "Handling and Retention of BA and BE Testing Samples", regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, "Good Clinical Practice: Consolidated Guideline", for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

19. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

20. To establish bioequivalence for a dichotomous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

$$H_O: \pi_T - \pi_R < \Delta_1 \text{ or } \pi_T - \pi_R > \Delta_2 \text{ versus } H_A: \Delta_1 \leq \pi_T - \pi_R \leq \Delta_2$$

where π_T = the success rate of the primary endpoint for the treatment group, and
π_R = the success rate of the primary endpoint for the reference group.

The null hypothesis, H_O, is rejected with a type I error rate (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the difference of the success rates between test and reference products (π_T-π_R) is contained within the interval $[\Delta_1, \Delta_2]$, where Δ_1 = -0.20 and Δ_2 = 0.20. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

21. The study data should be submitted in standardized format. Please refer to the study data standards published at www.FDA.gov.[1]

22. Please 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 (if applicable)
    e. Age
    f. Age units (years)
    g. Sex
    h. Race
    i. Safety population flag (yes/no)
    j. Reason for exclusion from safety population
    k. Modified Intent-to-Treat (mITT) population flag (yes/no)
    l. Reason for exclusion from mITT population
    m. Per-Protocol (PP) population flag (yes/no)
    n. Reason for exclusion from PP population
    o. Completers population flag (yes/no)
    p. Randomized population flag (yes/no)
    q. Date of randomization
    r. Date of enrollment
    s. Description of planned arm
    t. Description of actual arm
    u. Planned treatment (character)
    v. Planned treatment (number)
    w. Actual treatment (character)
    x. Actual treatment (number)
    y. Date/time of first exposure to treatment
    z. Date/time treatment washed off
    aa. Length of time treatment was left on the subject (hours)
    bb. Number of skin lesions at baseline
    cc. New skin lesions on Day 14 (yes/no)
    dd. Number of skin lesions on Day 14
    ee. Microscopic evidence of mites, ova, or mite feces on Day 14 (yes/no)
    ff. New skin lesions on Day 28 (yes/no)
    gg. Number of skin lesions on Day 28
    hh. Microscopic evidence of mites, ova, or mite feces on Day 28 (yes/no)
    ii. Final designation as treatment success on Day 28 (yes/no)
    jj. End of study status

[1] Study Data Standards for Submission to CDER available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

kk. End of study date
ll. Subject required additional treatment or retreatment due to unsatisfactory treatment response (yes/no)
mm. Date/time of additional treatment
nn. Date/time additional treatment washed off
oo. Length of time additional treatment was left on the subject (hours)
pp. Compliance status (i.e., was the cream applied as instructed and removed within the time window (yes/no)
qq. Concomitant medication (yes/no)
rr. Adverse event reported (yes/no)
ss. Reason for discontinuation from study (character)
tt. Reason spec for discontinuation from study (character) – additional details regarding subject's discontinuation of study
uu. Reason for discontinuation of treatment (character)
vv. Reason spec for discontinuation of treatment (character) – additional details regarding subject's discontinuation of treatment
ww. Evaluator initial (character)

23. Please provide a basic data structure (BDS) dataset with records per subject, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Study site identifier (if applicable)
    d. Age
    e. Age units (years)
    f. Sex
    g. Race
    h. Safety population flag (yes/no)
    i. Modified Intent-to-Treat (mITT) population flag (yes/no)
    j. Per-Protocol (PP) population flag (yes/no)
    k. Description of planned arm
    l. Description of actual arm
    m. Planned treatment (character)
    n. Planned treatment (number)
    o. Actual treatment (character)
    p. Actual treatment (number)
    q. Completers population flag (yes/no)
    r. Visit date
    s. Visit number
    t. Number of days since baseline visit
    u. Study visit within the designated window (yes/no)
    v. Evaluator: identity of evaluator
    w. Number of skin lesions
    x. Description of skin lesions present (e.g., burrows, erythematous papules, etc.)
    y. New skin lesions present (yes/no)
    z. Description of new skin lesions present (e.g., burrows, erythematous papules, etc.)
    aa. Baseline lesions all healed (yes/no)
    bb. Number of skin scrapings performed
    cc. Mites, ova, or mite feces found on microscopic examination (yes/no)
    dd. Description of microscopic findings (mites, ova, mite feces)
    ee. Additional treatment required during the visit (yes/no)

ff. Date/time of additional treatment
gg. Date/time additional treatment washed off
hh. Length of time additional treatment was left on the subject (hours)
ii. Application site reaction score for each sign and symptom evaluated (e.g., erythema, edema, pruritus, rash, burning/stinging, pain, numbness, tingling)
jj. Final designation as treatment success on Day 28 (yes/no)
kk. Adverse event reported during the visit (yes/no)
ll. Concomitant medication during the visit (yes/no)

24. The protocol should include a complete and full detailed statistical analysis plan and describe how missing data will be prevented and handled if exist.