Contains Nonbinding Recommendations

Draft Guidance on Hydrocortisone Acetate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Metered aerosol; rectal

Recommended Studies: In vivo and in vitro studies

FDA recommends the following in vivo and in vitro studies to establish bioequivalence (BE) of the test (T) and reference (R) hydrocortisone acetate rectal aerosol foam, provided that the T drug product is qualitatively (Q1) [1] and quantitatively (Q2) [2] the same as the R drug product.

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1. Type of Study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-way crossover study under fasted conditions
   Strength: 10%
   Subjects: Health males and nonpregnant females, general population
   Additional comments:
   a. A 4 mg dose of dexamethasone should be administered 10 hours prior to drug administration as a pre-treatment to lower endogenous hydrocortisone levels.
   b. ANDA applicants are obligated to consider the data evaluation process (e.g., baseline correction) and ensure its appropriateness.

Analytes to measure (in appropriate biological fluid): Hydrocortisone in plasma

Bioequivalence based on (90% CI): Baseline-corrected C_{max} and AUC for hydrocortisone. The 90% confidence interval for the geometric mean T/R ratios of baseline-corrected C_{max} and AUC should fall within the limits of 80.00 – 125.00%.

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2. Type of Study: In vitro comparative physicochemical characterization of the T and R formulations
   Design: The following in vitro tests should be performed on 3 separate lots of R drug product and 3 separate lots of T drug product (with each lot manufactured separately):

   a. Test: pH
      Design: pH should be evaluated on the dispensed and collapsed foam.

[1] Q1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.
[2] Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T product are within ±5% of those used in the R product.

b. Test: Weight per Volume and Delivery Amount per Dose
Design: Weight per volume should be conducted on the uncollapsed foam. Delivery amount per dose should be conducted over the entire contents of the canister using the proposed canister and applicator following the approved labeling.

c. Test: Comparative Pressure Test
Design: Canister pressure should be compared between the T and R drug product.

d. Test: Microscopic Birefringence Analysis
Design: Microscopic birefringence analysis should be conducted on the dispensed foam after complete collapse to determine whether any crystals of undissolved drug form during dispensing.

e. Test: Time to Break Analysis
Design: Time to break analysis should be conducted at 30 °C, 33 °C, 35 °C, and 40 °C. Time to break is the time from dispensing to complete foam collapse (i.e., break).

Additional comments: If microscopic birefringence analysis demonstrates the presence of suspended API particles in the dispensed foam, both particle size analysis and in vitro release testing (IVRT) should be conducted on the dispensed foam.

Additional Information

Device:

FDA recommends sponsors consider the following characteristics of the R drug product in designing the T drug product:

- A multi-dose device capable of delivering the same number of doses as the R drug product
- Similar external design (size, shape, and components) as the R drug product
- Similar external operating principles as the R drug product

Sponsors should refer to FDA's guidance entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies* (January 2017), which provides the Agency's current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug-device combination product when compared to its RLD.[3]

Early in product development and/or prior to the submission of an ANDA, FDA recommends applicants submit to OGD via controlled correspondence and/or pre-ANDA meeting request, the results of the comparative analyses (e.g., comparative labeling analysis, comparative task analyses, comparison in the design of the delivery device constituent), including overall

[3] https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.

assessment, of any identified differences between the user interface of the T product when compared to the R product, as described in the guidance referenced above.