Contains Nonbinding Recommendations

Draft Guidance on Doxepin Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Cream; topical

Recommended Studies: A combination of in vitro and in vivo studies with pharmacokinetic endpoints

To demonstrate bioequivalence for this drug product using studies with pharmacokinetic endpoints, including one in vitro study evaluating local (cutaneous) pharmacokinetics and one in vivo study evaluating systemic (plasma) pharmacokinetics, all of the following criteria should be met:

A. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference product that may significantly affect the local or systemic availability of the active ingredient. For example, if the test and reference products are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the guidance for industry ANDA Submissions – Refuse-to-Receive Standards and the criteria below are also satisfied, the bioequivalence of the test product with respect to the reference product may be established using a characterization based bioequivalence approach.

B. The test and reference products should be physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three batches of the test and three batches (as available) of the reference product. The characterization of the test and reference products should include the following comparisons of physical and structural attributes between the test and reference products:

   i. Assessment of appearance with representative microscopic images at multiple magnifications.

   ii. Characterization of the globule size distribution.

   iii. Analysis of the 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:

1 Guidance for industry ANDA Submissions – Refuse-to-Receive Standards

Recommended Nov 2018; Revised Nov 2019
• A complete flow curve of shear stress (or viscosity) vs. shear rate should consist of multiple data points across the range of attainable shear rates, until low or high shear plateaus are identified. The comparative viscosity data at low, medium and high shear rates should be provided.

• 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.

iv. Analysis of pH, specific gravity and any other potentially relevant physical and structural similarity characterizations.

C. The test and reference products should have an equivalent rate of doxepin release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one batch each of the test and reference products using an appropriately validated IVRT method. Refer to the Guidance on Acyclovir (for acyclovir topical cream, 5%) for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test and reference products evaluated in the IVRT study should be included among those for which the physical and structural similarity is characterized and compared.

D. The test and reference products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of doxepin permeation through excised human skin from a minimum of one batch each of the test and reference products using an appropriately validated IVPT method.

Type of study: IVPT study
Design: Parallel, single-dose, multiple-replicate per treatment group study design
Strength: 5%
Skin: Barrier-competent skin from male and/or female donors of at least 18 years of age, general population
Additional comments: The batches of test and reference products evaluated in the IVPT study should be the same as those evaluated in the IVRT study, and that these batches should be included among those for which the physical and structural similarity is characterized and compared. Refer to the Guidance on Acyclovir (for acyclovir topical cream, 5%) for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies.

E. The test and reference products should demonstrate bioequivalence based upon an acceptable in vivo pharmacokinetic study with one batch each of the test and reference products.

Type of study: In vivo pharmacokinetic study

Guidance on Acyclovir for acyclovir topical cream, 5%
Design: Single-application, two-way crossover study design  
Strength: 5%  
Subjects: Males and nonpregnant, nonlactating females, general population  
Additional comments: The batches of test and reference products evaluated in the in vivo pharmacokinetic study should be the same as those evaluated in the IVRT and IVPT studies.

Analytes to measure (in appropriate biological fluid): Doxepin and its active metabolite nordoxepin in plasma (in vivo pharmacokinetic study) or doxepin in IVPT receptor solution (in vitro).

Bioequivalence based on (90% CI): Doxepin. Refer to the Guidance on Acyclovir (for acyclovir topical cream, 5%)\(^2\) for additional information regarding the analysis of in vitro studies.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the guidance for industry Controlled Correspondence Related to Generic Drug Development and the guidance for industry Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.