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Draft Guidance on Doxepin Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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

A. The test and Reference Listed Drug (RLD) products should be qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry: *ANDA Submissions – Refuse-to-Receive Standards*, Revision 2 (December 2016).[1]

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

      - 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.

[1] Guidance for Industry: ANDA Submissions – Refuse-to-Receive Standards, Revision 2 (December 2016)

- 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 RLD 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 RLD products using an appropriately validated IVRT method. Refer to the *Guidance on Acyclovir* (for acyclovir topical cream, 5%)[2] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test and RLD 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 RLD products should have an equivalent rate and extent of doxepin permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) comparing a minimum of one batch each of the test and RLD products using an appropriately validated IVPT method. Refer to the *Guidance on Acyclovir* (for acyclovir topical cream, 5%)[2] for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies. The batches of test and RLD products evaluated in the IVPT study should be the same as those evaluated in the IVRT study.

E. The test and RLD products should demonstrate BE based upon an acceptable in vivo PK study with one batch each of the test and RLD products.

Type of study: In vivo PK study

Design: Single-application, two-way crossover study design

Strength: 5%

Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments: The batches of test and RLD products evaluated in the in vivo PK 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 PK study).

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

[2] Guidance on Acyclovir for acyclovir topical cream, 5% (recommended Dec 2014; revised Dec 2016).