Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Doxepin Hydrochloride

May 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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Active Ingredient: Doxepin hydrochloride

Dosage Form; Route: Capsule; Oral

Recommended Studies: Two options: (1) Biopharmaceutics Classification System (BCS) I-based biowaiver or (2) five in vivo bioequivalence studies with pharmacokinetic endpoints

I. Option 1: BCS Class I-based biowaiver

A waiver request of in vivo testing for all the strengths of this product provided that the appropriate documentation regarding high solubility, high permeability and rapid dissolution as detailed in the most recent version of the FDA guidance for industry on *M9 Biopharmaceutics Classification System-Based Biowaivers*[a] is submitted in the application. Applicants may use the information contained in the approved labeling of the reference product. Peer reviewed articles may not contain the necessary details of the testing for the Agency to make a judgment regarding the quality of the studies. A decision regarding the acceptability of the waiver request can only be made upon assessment of the data submitted in the application.

II. Option 2: Five in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 150 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Exclude geriatric subjects due to risks of confusion and oversedation. Consider excluding CYP2D6 and/or CYP2C19 poor metabolizers. Monitor subjects for adverse events (e.g., drowsiness, dizziness, or dry mouth) for at least 24

hours after dosing or until resolution of adverse events. Refer to the corresponding reference standard product listed in the current publication of *Approved Drug Products with Therapeutic Equivalence Evaluations*.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 150 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: See comments above.

3. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 100 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Exclude geriatric subjects due to risks of confusion and oversedation. Consider excluding CYP2D6 and/or CYP2C19 poor metabolizers. Refer to the corresponding reference standard product listed in the current publication of *Approved Drug Products with Therapeutic Equivalence Evaluations*.

4. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 100 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: See comments above for the EQ 100 mg Base Fasting study.

5. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 25 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Exclude geriatric subjects due to risks of confusion and oversedation. Refer to the corresponding reference standard product listed in the current publication of *Approved Drug Products with Therapeutic Equivalence Evaluations*.

Analytes to measure: Doxepin and its active metabolite, nordoxepin, in plasma

Bioequivalence based on (90% CI): Doxepin

Submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for area under the curve and maximum concentration.

Waiver request of in vivo testing: EQ 50 mg Base and EQ 75 mg Base strengths based on (i) acceptable bioequivalence studies on the EQ 100 mg Base strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths

EQ 10 mg Base strength based on (i) acceptable bioequivalence study on the EQ 25 mg Base strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

Revision History: Recommended August 2010
Recommended March 2015 (100 mg strength)
Revised March 2015; Finalized August 2017 (150 mg strength)
Merged May 2023

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[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.