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Draft Guidance on Doxepin Hydrochloride

February 2024

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Active Ingredient:	Doxepin hydrochloride
Dosage Form:	Tablet
Route:	Oral
Strengths:	EQ 3 mg Base, EQ 6 mg Base
Recommended Studies:	Two options: (1) Biopharmaceutics Classification System (BCS) Class I-based biowaiver or (2) two 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: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: EQ 6 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Due to the potential for serious adverse events, monoamine oxidase inhibitors should be discontinued at least two weeks prior to study initiation.

2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: EQ 6 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: See comments above.

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 3 mg Base strength based on (i) acceptable bioequivalence studies on the EQ 6 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.

Document History: Recommended September 2010; Revised February 2024

Unique Agency Identifier: PSG_022036

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