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*Draft – Not for Implementation*

## **Draft Guidance on Milnacipran Hydrochloride**

**October 2024**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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<b>Active Ingredient:</b>	Milnacipran hydrochloride
<b>Dosage Form:</b>	Tablet
<b>Route:</b>	Oral
<b>Strengths:</b>	12.5 mg, 25 mg, 50 mg, 100 mg
<b>Recommended Studies:</b>	Two options: (1) Biopharmaceutics Classification System (BCS)-based biowaiver or (2) one in vivo bioequivalence study 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 may be considered 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<sup>a</sup>* is submitted in the application. Applicants may use the information contained in the approved labeling of the reference listed drug (RLD). 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: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 50 mg  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments: Due to safety concerns, the in vivo studies should be conducted on the 50 mg strengths. Females of reproductive potential should use effective contraception during the study.

**Analyte to measure:** Milnacipran in plasma

**Bioequivalence based on (90% CI):** Milnacipran

**Waiver request of in vivo testing:** 12.5 mg, 25 mg, and 100 mg strengths based on (i) acceptable bioequivalence study on the 50 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all 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 product and RLD.<sup>1</sup> Specifications will be determined upon review of the abbreviated new drug application.

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**Document History:** Recommended June 2011; Revised September 2011, October 2024

**Unique Agency Identifier:** PSG\_022256

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

<sup>1</sup> If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions*.