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Draft Guidance on Ixazomib Citrate

December 2025

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Active Ingredient:	Ixazomib citrate
Dosage Form:	Capsule
Route:	Oral
Strengths:	EQ 2.3 mg Base, EQ 3 mg Base, EQ 4 mg Base
Recommended Studies:	Two options: (1) Biopharmaceutics Classification System (BCS)-based biowaiver, or (2) one in vivo bioequivalence study with pharmacokinetic endpoints

I. Option 1: BCS Class III-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, very rapid dissolution of the test product and reference listed drug (RLD), and the test product formulation is qualitatively the same and quantitatively similar as detailed in the most recent version of the FDA guidance for industry *M9 Biopharmaceutics Classification System-Based Biowaivers*[a] is submitted in the application. Applicants may use the information contained in the approved labeling of the 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: Multiple-dose, two-treatment, two-period crossover in vivo
Strength: EQ 4 mg Base
Subjects: Male and female patients who are receiving ixazomib capsules based on the approved indications
Additional comments:
    - Exclude patients who may require dosage modification or dosing schedule or with expected changes in concomitant medications that may potentially affect the pharmacokinetics of ixazomib during the study. Females of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and 3 months after the last dose of ixazomib citrate. Implement safety precautions and monitoring during treatment as recommended in the labeling. Submission of an investigational new drug application is required prior to the conduct of a bioequivalence study for a cytotoxic drug such as ixazomib citrate pursuant to the 21CFR § 320.31.
    - A treatment cycle of ixazomib citrate consists of one dose taken orally on Days 1, 8, and 15 of a 28-day cycle (three doses total per cycle). The study can be conducted in a four-cycle crossover design where patients receive two consecutive cycles of one treatment followed by two consecutive cycles of the alternate treatment (e.g., RLD-RLD-Test-Test or Test-Test-RLD-RLD sequence design). Collect blood samples on the third dose (Day 15) of the second treatment cycle for statistical analysis. Alternatively, a single-dose, parallel study design may be considered in patients not previously treated with ixazomib citrate. In this approach, blood samples from the first dose (Day 1) of the first dosing cycle should be used for statistical analysis. $AUC_{(0\text{-}72h)}$ may be used in place of $AUC_{(0\text{-}t)}$ for both multiple-dose crossover study and single-dose parallel study, due to the long half-life of ixazomib.

Analyte to measure: Ixazomib in plasma

Bioequivalence based on (90% CI): Ixazomib

Waiver request of in vivo testing: EQ 2.3 mg Base and EQ 3 mg Base strengths based on (i) an acceptable bioequivalence study on the EQ 4 mg base strength, (ii) acceptable in vitro dissolution testing of all the 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.[1] Specifications will be determined upon review of the abbreviated new drug application.

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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

[1] If the RLD is not available, refer to the most recent version of the guidance for industry *Referencing Approved Drug Products in ANDA Submissions.*