

## Draft Guidance on Tetrabenazine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active ingredient:** Tetrabenazine

**Form/Route:** Tablet; Oral

**Recommended studies:** 2 studies

1. Type of study: Fasting  
Design: Single-dose, two-way crossover in vivo  
Strength: 25mg  
Subjects: Healthy males and nonpregnant females aged 18-45 years, general population  
Additional comments: Xenazine® (tetrabenazine) Tablets was approved with a Risk Evaluation and Mitigation Strategy (REMS) to reduce the risk of drug-associated depression and suicidality in patients receiving the drug product, to promote informed prescribing and proper titration and dosing of tetrabenazine, and to minimize the risk of drug-drug interactions with strong CYP2D6 inhibitors. All pertinent elements of the REMS must be incorporated into the protocol and informed consent.

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2. Type of study: Fed  
Design: Single-dose, two-way crossover in vivo  
Strength: 25mg  
Subjects: Healthy males and nonpregnant females aged 18-45 years, general population  
Additional comments: Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies. See Study 1 “Additional comments” re: REMS.

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**Analytes to measure (in appropriate biological fluid):** Tetrabenazine and its active metabolite, HTBZ, in plasma using achiral assay.

**Bioequivalence based on (90% CI):** Tetrabenazine. If tetrabenazine plasma concentrations can be reliably measured and its pharmacokinetics accurately determined, please analyze the data for the parent compound using the confidence interval approach. The data for the active metabolite can be used as supportive evidence. However, if you demonstrate, using state of the art assay methods, that it is not possible to measure tetrabenazine in plasma accurately and reliably, please analyze the metabolite using the confidence interval approach.

**Waiver request of in-vivo testing:** 12.5mg based on (i) acceptable bioequivalence studies on the 25mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across both strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing.

**Dissolution test method and sampling times:**

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

**Risk Evaluation and Mitigation Strategy (REMS):** This drug product has an innovator developed REMS. Any ANDA citing the innovator drug product will also be required to have a REMS. Please refer to 73 FR 16313: March 27, 2008 and Section 505-1 of the Food, Drug and Cosmetic Act.