

Draft Guidance on Macitentan; Tadalafil

November 2025

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredients: Macitentan; Tadalafil

Dosage Form: Tablet

Route: Oral

Strengths: 10 mg; 20 mg, 10 mg; 40 mg

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 10 mg; 40 mg
Subjects: Healthy males and healthy females not of reproductive potential
Additional comments: Exclude subjects with cardiovascular risk factors (e.g., hypotension). Exclude geriatric subjects.

Analytes to measure: Macitentan and tadalafil in plasma

Bioequivalence based on (90% CI): Macitentan and tadalafil

Waiver request of in vivo testing: 10 mg; 20 mg strength based on (i) an acceptable bioequivalence study on the 10 mg; 40 mg 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 both strengths of the test product and reference listed drug (RLD).¹ Specifications will be determined upon review of the abbreviated new drug application.

Document History: Recommended November 2024; Revised November 2025

Unique Agency Identifier: PSG_218490

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*.