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Draft Guidance on Macitentan; Tadalafil

November 2024

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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. Macitentan; tadalafil tablet is under a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU), which restricts its use. All pertinent elements of the REMS/ETASU must be incorporated into the protocol and informed consent.

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.

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[1] 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*.