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Draft Guidance on Leflunomide

October 2024

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Active Ingredient: Leflunomide

Dosage Form: Tablet

Route: Oral

Strengths: 10 mg, 20 mg, 100 mg

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 20 mg
   Subjects: Healthy males and healthy females not of reproductive potential
   Additional comments: Exclude males wishing to father a child during the study. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of the metabolite A77 1726. Alternatively, a parallel study design may be considered.

2. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 100 mg
   Subjects: Healthy males and healthy females not of reproductive potential
   Additional comments: None

Analyte to measure: Metabolite of leflunomide A77 1726 in plasma

Bioequivalence based on (90% CI): Metabolite of leflunomide A77 1726

Waiver request of in vivo testing: 10 mg strength based on (i) an acceptable bioequivalence study on the 20 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 August 2007; Revised October 2024

Unique Agency Identifier: PSG_020905

[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*.