Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Linagliptin; Metformin Hydrochloride

October 2024

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Active Ingredients: Linagliptin; Metformin hydrochloride

Dosage Form: Tablet

Route: Oral

Strengths: 2.5 mg; 500mg, 2.5 mg; 850 mg, 2.5 mg; 1 gm

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 2.5 mg; 1 gm
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Monitor blood glucose concentrations and signs and symptoms of hypoglycemia during the study. Implement appropriate hypoglycemia management protocol. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of linagliptin. Alternatively, a parallel study design may be considered.

Analytes to measure: Linagliptin and metformin in plasma

Bioequivalence based on (90% CI): Linagliptin and metformin

Waiver request of in vivo testing: 2.5 mg; 500mg and 2.5 mg; 850 mg strengths based on (i) acceptable bioequivalence study on the 2.5 mg; 1 gm strength, (ii) acceptable in vitro dissolution testing of all 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 reference listed drug (RLD).[1] Specifications will be determined upon review of the abbreviated new drug application.

Document History: Recommended April 2014; Revised July 2014, October 2024

Unique Agency Identifier: PSG_201281

[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.*