Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Metformin Hydrochloride; Sitagliptin Phosphate

October 2024

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Active Ingredients: Metformin hydrochloride; Sitagliptin phosphate

Dosage Form: Tablet

Route: Oral

Strengths: 500 mg; EQ 50 mg Base, 1 gm; EQ 50 mg Base

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: 1 gm; EQ 50 mg Base
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Females of reproductive potential should use effective contraception during the study. The drug product should be administered with 240 mL of a 20% glucose solution in water, followed by 60 mL of the glucose solution administered every 15 minutes for up to 4 hours after dosing. Monitor blood glucose concentrations and signs and symptoms of hypoglycemia during the study. Implement appropriate hypoglycemia management protocol.

Analytes to measure: Metformin and sitagliptin in plasma

Bioequivalence based on (90% CI): Metformin and sitagliptin

Waiver request of in vivo testing: 500 mg; EQ 50 mg Base strength based on (i) acceptable bioequivalence study on the 1 gm; EQ 50 mg Base 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 each of both strengths of the test product and reference listed drug (RLD) products.[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.*