

Draft Guidance on Linagliptin; Metformin Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Linagliptin; Metformin Hydrochloride

Form/Route: Tablet/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 2.5 mg/1000 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: To avoid hypoglycemic episodes in healthy volunteers, the drug products should be administered with 240 mL of a 20% glucose solution in water, followed by 60 mL of the glucose solution administered every 15 min for up to 4 hours after dosing during fasting and fed studies.

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 2.5 mg/1000 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: Please see comments above. Please refer to the Amantadine Hydrochloride Tablet Guidance for additional information regarding fed studies.

Analytes to measure (in appropriate biological fluid): Linagliptin and metformin in plasma

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

Waiver request of in vivo testing: 2.5 mg/500 mg and 2.5 mg/850 mg based on (i) acceptable bioequivalence studies on the 2.5 mg/1000 mg 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:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Information Regarding Long Half-Life Drugs

Linagliptin has a long terminal elimination half-life. Please ensure adequate washout periods between treatments in the crossover studies. Please also consider using a parallel study design due to linagliptin's long half-life. For a long half-life drug product, an AUC truncated to 72 hours may be used in place of AUC_{0-t} or AUC_{0-inf} if the drug demonstrates low intrasubject variability in distribution and clearance.