

Draft Guidance on Empagliflozin; Linagliptin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Empagliflozin; Linagliptin

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting

Design: Single-dose, two-way crossover *in vivo*

Strength: 25 mg/5 mg

Subjects: Healthy males and non-pregnant females, general population

Additional comments:

- Females should not be pregnant or lactating, and, if applicable, should practice abstinence or contraception during the study.
- To avoid hypoglycemic episodes, 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 minutes for up to 4 hours after dosing.
- Linagliptin has a long terminal elimination half-life (>24 hours); therefore adequate washout periods should be ensured between treatments in the crossover studies. A parallel study design may also be considered due to its long half-life. For either a crossover or parallel study, sample collection time should be adequate to ensure completion of gastrointestinal transit of the drug product and absorption of the drug substance. For long half-life drug products that demonstrate low intrasubject variability in distribution and clearance, an AUC truncated to 72 hours may be used in place of AUC_{0-t} or AUC_{0-∞}.

2. Type of study: Fed

Design: Single-dose, two-way crossover *in vivo*

Strength: 25 mg/5 mg

Subjects: Healthy males and non-pregnant females, general population

Additional comments: See comments above.

Analytes to measure (in appropriate biological fluid): Empagliflozin and linagliptin in plasma

Bioequivalence based on (90% CI): Empagliflozin and linagliptin

Waiver request of in vivo testing: 10 mg/5 mg strength based on (i) acceptable bioequivalence studies on the 25 mg/5 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods Web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. 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 abbreviated new drug application (ANDA).