

Draft Guidance on Empagliflozin; Linagliptin; Metformin Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 Ingredients: Empagliflozin; Linagliptin; Metformin hydrochloride

Dosage Form; Route: Extended release tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 25 mg; 5 mg; 1 g
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: To avoid hypoglycemic episodes, administer the drug products 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. 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.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 25 mg; 5 mg; 1 g
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above

Analytes to measure: Empagliflozin, linagliptin, and metformin in plasma

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

Additional strengths: Bioequivalence of the 5 mg; 2.5 mg; 1 g, 10 mg; 5 mg; 1 g, and 12.5 mg; 2.5 mg; 1 g strengths to the corresponding reference product strengths may be demonstrated based on principles laid out in the FDA guidance on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.

Dissolution test method and sampling times:

For modified release drug products, applicants should develop specific discriminating dissolution methods. Alternatively, applicants may use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database (available at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>), provided that applicants

submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed, submit the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

In addition to the method above, submit dissolution profiles on 12 dosage units for each of all strengths of the test and reference products generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer). Agitation speeds may be increased if appropriate. It is acceptable to add a small amount of surfactant if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released to provide assurance against premature release of drug (dose dumping) from the formulation.

Due to concerns of dose dumping of metformin hydrochloride from this drug product when taken with alcohol, conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium as follows:

Testing Conditions: 900 mL, 0.1N HCl, USP Apparatus 1 (basket) at 100 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl) with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Conduct testing on both test and reference products accordingly, and provide data on individual unit, means, range and %CV.