Contains Nonbinding Recommendations

Draft Guidance on Empagliflozin; Metformin Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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; 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 (empagliflozin)/1000 mg (metformin hydrochloride)
   Subjects: Males and non-pregnant, non-lactating 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.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 25 mg (empagliflozin) /1000 mg (metformin hydrochloride)
   Subjects: Males and non-pregnant, non-lactating females, general population.
   Additional Comments: See comments above.

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

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

Waiver request of in vivo testing: 5 mg/1000 mg, 10 mg/1000 mg, 12.5 mg/1000 mg based on (i) acceptable bioequivalence studies on the 25 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: 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).

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please 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 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, 0.1 N HCl, USP apparatus 1 (basket) @100 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N 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.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV.