Contains Nonbinding Recommendations

Draft Guidance on Dapagliflozin; Metformin Hydrochloride; Saxagliptin Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 Ingredient: Dapagliflozin; Metformin hydrochloride; Saxagliptin 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: 10 mg; 1 g; EQ 5 mg Base
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: 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.

---

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 10 mg; 1 g; EQ 5 mg Base
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above.

Analytes to measure: Dapagliflozin, metformin, and saxagliptin and its active metabolite, 5-hydroxy saxagliptin in plasma

Submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.
Bioequivalence based on (90% CI): Dapagliflozin, metformin and saxagliptin

Additional strengths: Bioequivalence of 2.5 mg; 1 g; EQ 2.5 mg Base, 5 mg; 1 g; EQ 2.5 mg Base and 5 mg; 1 g; EQ 5 mg Base 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, FDA recommends that applicants develop specific discriminating dissolution methods. Applicants may also 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 for the modified release drug product, FDA recommends that the submission includes the dissolution method development and validation report with the complete information/data supporting the proposed method. 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.

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. 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) at 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 reference products should be tested accordingly, and data should be provided on individual unit, means, range and %CV.