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Draft Guidance on Dapagliflozin; Metformin Hydrochloride

August 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredients: Dapagliflozin; Metformin hydrochloride

Dosage Form: Tablet, extended release

Route: Oral

Strengths: 2.5 mg; 1 gm, 5 mg; 500 mg, 5 mg; 1 gm, 10 mg; 500 mg, 10 mg; 1 gm

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strengths: 10 mg; 1 gm
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comment: Monitor blood glucose concentrations and symptoms of hypoglycemia during the study.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strengths: 10 mg; 1 gm
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comment: See comment above.

Analytes to measure: Dapagliflozin and metformin in plasma

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

Additional strengths: Bioequivalence of the 2.5 mg; 1 gm, 5 mg; 500 mg, 5 mg; 1 gm, and 10 mg; 500 mg strengths to the corresponding reference product strengths may be demonstrated based on principles laid out in the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[a]

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, 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 strength 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 strength 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 (e.g., 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.

Alcohol dose dumping studies: Due to concerns of dose dumping of drug from this 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: 1000 mL, 0.1 N HCl, Apparatus 1 (basket, 20 mesh) 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.

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.