

Draft Guidance on Metformin Hydrochloride; Saxagliptin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Metformin Hydrochloride; Saxagliptin

Form/Route: Extended Release Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting

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

Strength: 1000 mg Metformin Hydrochloride; 5 mg Saxagliptin

Subjects: Healthy males and nonpregnant females, general population.

Additional Comments: 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.

2. Type of study: Fed

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

Strength: 1000 mg Metformin Hydrochloride; 5 mg Saxagliptin

Subjects: Healthy males and nonpregnant females, general population.

Additional Comments: Please see comment above.

Analytes to measure (in appropriate biological fluid): Saxagliptin, its metabolite, M2, and Metformin in plasma. For M2 ((S)-3, 5-dihydroxy adamantlyl glycine-L-*cis*-4,5-methanoprolinenitrile), 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 C_{max}.

Bioequivalence based on (90% CI): Saxagliptin and Metformin

Waiver request of in-vivo testing: 1000 mg Metformin Hydrochloride; 2.5 mg Saxagliptin and 500 mg Metformin; 5 mg Saxagliptin based on acceptable (i) bioequivalence studies on the 1000 mg /5 mg strength (ii) proportional similarity of the formulations and (iii) acceptable in vitro dissolution testing cross strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please 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 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. 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. Specifications will be determined upon review of the data submitted in the application.

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted 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 on both strengths.