Active ingredient: Metformin Hydrochloride; Pioglitazone Hydrochloride

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/30 mg (base equiv)
   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 minutes for up to 4 hours after dosing during fasting and fed studies.

2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: 1000 mg/30 mg (base equiv)
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Please see comments above.

Analytes to measure (in appropriate biological fluid): Metformin, pioglitazone and hydroxypioglitazone (M-IV) in plasma.

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

Please submit the metabolite data including individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax, as supportive evidence of bioequivalence and comparable therapeutic outcome.

Waiver request of in vivo testing: 1000 mg metformin hydrochloride/15 mg pioglitazone (base equiv) based on (i) acceptable bioequivalence studies on the 1000 mg metformin hydrochloride/30 mg pioglitazone (base equiv), (ii) proportional similarity of all strengths, and (iii) acceptable in vitro dissolution testing of all 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

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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, water) 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.