Contains Nonbinding Recommendations

Guidance on Metformin Hydrochloride; Pioglitazone Hydrochloride

This guidance represents 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; Pioglitazone Hydrochloride

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 850 mg metformin HCl; 15 mg pioglitazone HCl (as the base)
   Subjects: Normal healthy males and females, general population. Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study.
   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-way crossover *in-vivo*
   Strength: 850 mg metformin HCl; 15 mg pioglitazone HCl (as the base)
   Subjects: Normal healthy males and females, general population. Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study.
   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."

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

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

Waiver request of in-vivo testing: (500 mg; 15 mg) Metformin HCl, Pioglitazone HCl tablets, based on (i) acceptable bioequivalence study on the (850 mg; 15 mg) tablet, and (ii) 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.fda.gov/cder/ogd/index.htm. 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.