Contains Nonbinding Recommendations

Draft Guidance on Hydralazine Hydrochloride; Isosorbide Dinitrate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Hydralazine Hydrochloride; Isosorbide Dinitrate

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Randomized, single-dose, two-way crossover or parallel, *in-vivo*
   Strength: 37.5 mg/20 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Individuals taking monoamine-oxidase inhibitors, potent parenteral antihypertensive agents, sildenafil, vardenafil, or tadalafil should be excluded from the study. Given the potential of a large drop-out rate due to headaches, sponsors may pursue a parallel study design.

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2. Type of study: Fed
   Design: Randomized, single-dose, two-way crossover or parallel, *in-vivo*
   Strength: 37.5 mg/20 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Please see comments above.

Analytes to measure (in appropriate biological fluid): Isosorbide Dinitrate, Isosorbide-5-Mononitrate, Isosorbide-2-Mononitrate, and Hydralazine in plasma.

Bioequivalence based on (90% CI): Isosorbide Dinitrate and Hydralazine

Please submit isosorbide dinitrate's active metabolites data (isosorbide-5-mononitrate and isosorbide-2-mononitrate) 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.If isosorbide dinitrate can be reliably measured, a confidence interval approach for bioequivalence determination should be used for isosorbide dinitrate. If isosorbide dinitrate cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for isosorbide-5-mononitrate and isosorbide-2-mononitrate.

Waiver request of in-vivo testing: Not Applicable.

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 the test and reference products. Specifications will be determined upon review of the application.