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Draft – Not for Implementation

Draft Guidance on Hydralazine Hydrochloride; Isosorbide Dinitrate

October 2024

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Active Ingredients: Hydralazine hydrochloride; Isosorbide dinitrate

Dosage Form: Tablet

Route: Oral

Strength: 37.5 mg; 20 mg

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

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 non-pregnant, non-lactating females
   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.

Analytes to measure: Isosorbide dinitrate, isosorbide-5- mononitrate, isosorbide-2-mononitrate, and hydralazine in plasma

Bioequivalence based on (90% CI): Isosorbide dinitrate and hydralazine

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 area under the curve (AUC) and maximum concentration (C_{max}). 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: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of the test product and reference listed drug (RLD).[1] Specifications will be determined upon review of the abbreviated new drug application.

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[1] If the RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions*.