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Draft Guidance on Disulfiram

October 2024

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Active Ingredient: Disulfiram

Dosage Form: Tablet

Route: Oral

Strengths: 250 mg, 500 mg

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 500 mg
   Subjects: Healthy males and non-pregnant non-lactating females
   Additional comments: None

Analytes to measure: Disulfiram and its active metabolites N,N-diethyldithiocarbamate (DDC) and S-methyl N,N-diethyldithiocarbamate (MeDDC) in plasma

Submit the metabolite data as supporting 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 $C_{max.}$

Bioequivalence based on (90% CI): Disulfiram

If disulfiram can be reliably measured, analyze the data for the parent compound using the confidence interval approach. The data for the active metabolites can be used as supportive evidence. However, if applicants can demonstrate that it is not possible to measure disulfiram in plasma accurately and reliably, analyze the primary metabolite DDC using the confidence interval approach. If applicants demonstrate the DDC in plasma cannot be reliably and accurately measured, analyze the secondary metabolite MeDDC using the confidence interval approach.

Waiver request of in vivo testing: 250 mg based on (i) acceptable bioequivalence study on the 500 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths

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 both strengths 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*.