

Draft Guidance on Darunavir Ethanolate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Darunavir Ethanolate

Form/Route: Tablet/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in-vivo
Strength: 800 mg
Subjects: Healthy males and females, general population.
Additional Comments:
 - Single doses of both the test and reference drug product (RLD) should be administered with ritonavir 100 mg twice daily. The ritonavir dosing should be started at least two days before administration of darunavir ethanolate tablet and maintained until the end of pharmacokinetic sampling of each treatment.
 - Applicants may consider using a reference-scaled average bioequivalence approach for this drug product. If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters AUC and/or C_{max} (i.e., within-subject variability $\geq 30\%$). For general information on this approach, please refer to Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008). For the method of statistical analysis using the reference-scaled average bioequivalence approach, please refer to the Progesterone Capsule Draft Guidance.

-
2. Type of study: Fed
Design: Single-dose, two-way crossover in-vivo
Strength: 800 mg
Subjects: Healthy males and females, general population.
Additional Comments: Please see comments above regarding ritonavir and reference-scaled bioequivalence. Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.
-

Analytes to measure (in appropriate biological fluid): Darunavir in plasma

Bioequivalence based on (90% CI): Darunavir

Waiver request of in-vivo testing: Darunavir Ethanolate Tablet, 75 mg, 150 mg, 300 mg, 400 mg, and 600 mg (base), based on (i) acceptable bioequivalence studies on the 800 mg (base) strength, (ii) acceptable in vitro dissolution testing across all strengths, and (iii) proportional similarity of the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in-vivo testing.

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