

Draft Guidance on Atorvastatin Calcium and Ezetimibe

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Tablet/Oral

Recommended studies: 2 studies

1. Type of study: Fasting

Design: Single dose, two way crossover, in vivo

Strength: 80 mg (base); 10 mg

Subjects: Healthy males and non-pregnant females, general population.

Additional Comments: 1. Females should practice abstinence or contraception during the study. 2. Considering the high variability of Atorvastatin, applicants may consider using a reference-scaled average bioequivalence approach for this drug product. If this approach is used, please provide evidence of high variability in the bioequivalence parameters of AUC and/or C_{max} (i.e., within-subject variability $\geq 30\%$). For general information on this approach, please refer to the Individual Product Bioequivalence Recommendations Guidance on Progesterone Capsules. 3. Study subjects should swallow tablets whole. Do not crush, dissolve or chew tablets. 4. Statins may cause fetal harm when administered to a pregnant woman. Because the product contains atorvastatin, it should not be administered to women of childbearing potential. Also these female subjects should be informed of the potential hazards. If the woman becomes pregnant while taking this product, discontinue it immediately. Because of the potential for adverse reactions in nursing infants, women taking these products should not breast-feed.

2. Type of study: Fed

Design: Single dose, two way crossover, in vivo

Strength: 80 mg (base); 10 mg

Subjects: Healthy males and non-pregnant females, general population.

Additional Comments: Please see above.

Analytes to measure (in appropriate biological fluid): Atorvastatin and the metabolites, ortho- and para-hydroxylated atorvastatin, as well as Ezetimibe (unconjugated) and total ezetimibe (ezetimibe + ezetimibe glucuronide) in plasma

Bioequivalence based on (90% CI): Atorvastatin and Ezetimibe (unconjugated) and total ezetimibe (ezetimibe + ezetimibe glucuronide).

Please submit the atorvastatin metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, submit the following data: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

Waiver request of in vivo testing: Atorvastatin; Ezetimibe, i) 40 mg (base); 10 mg, ii) 20 mg (base); 10 mg and iii) 10 mg (base). 10 mg strengths based on (1) acceptable bioequivalence study on the 80 mg (base); 10 mg strength, (2) acceptable in vitro dissolution testing of all strengths, and (3) proportional similarity of the formulations across 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.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.