Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Atorvastatin Calcium; Ezetimibe

October 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredients:	Atorvastatin calcium; Ezetimibe
Dosage Form:	Tablet
Route:	Oral
Strengths:	EQ 10 mg Base; 10 mg, EQ 20 mg Base; 10 mg, EQ 40 mg Base; 10 mg, EQ 80 mg Base; 10 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: EQ 80 mg Base; 10 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Female subjects of reproductive potential should practice abstention or contraception during the study. 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 detailed information on this approach, refer to the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.*[a]

Analytes to measure: Atorvastatin and its metabolites, ortho- and para-hydroxylated atorvastatin, and ezetimibe (unconjugated) and total ezetimibe (ezetimibe + ezetimibe glucuronide) in plasma

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 C_{max}.

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

Waiver request of in vivo testing: Atorvastatin; ezetimibe, EQ 10 mg Base; 10 mg, EQ 20 mg Base; 10 mg, and EQ 40 mg Base; 10 mg strengths based on (i) acceptable bioequivalence study on the EQ 80 mg Base; 10 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all 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 all 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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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

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