Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Odevixibat

May 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 Ingredient: Odevixibat

Dosage Form; Route: Capsule, pellets; Oral

Recommended Studies: Two options: (1) two in vivo bioequivalence studies with pharmacokinetic endpoints and in vitro bioequivalence studies (comparative dissolution) or (2) one comparative clinical endpoint bioequivalence study

I. Option 1: Two in vivo bioequivalence studies with pharmacokinetic endpoints and in vitro bioequivalence studies (comparative dissolution)

If the test product formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD) with respect to inactive ingredients, bioequivalence may be established by conducting both in vivo bioequivalence studies and in vitro comparative dissolution studies.

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.6 mg (at a dose of 6 mg (10 capsule pellets of 0.6 mg))
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Mix the contents of the shell containing oral pellets into soft food or a liquid. Conduct a bioequivalence study according to the reference product labeling.

[1] Q1 refers to the test product uses the same inactive ingredient(s) as the RLD.
[2] Q2 refers to concentrations of the inactive ingredient(s) used in the test product are within +/-5% of those used in the RLD.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 0.6 mg (at a dose of 6 mg (10 capsule pellets of 0.6 mg))
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

Analyte to measure: Odevixibat in plasma

Bioequivalence based on (90% CI): Odevixibat

Waiver request of in vivo testing: 0.2 mg strength based on (i) acceptable bioequivalence studies on the 0.6 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths

In vitro bioequivalence studies (comparative dissolution): Comparative dissolution data should be provided for 12 dosage units each of test and reference products, in each of the multiple media covering physiologically relevant pH range. It is acceptable to add a small amount of surfactant if necessary. The selection of dissolution apparatus, agitation speed, sampling time, and surfactant level should be justified. An f2 test should be performed using mean profiles to assure comparable test and reference products drug release under a range of pH conditions. The f2 test comparing test and reference products in each medium should be 50 or greater.

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 each of both strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

II. Option 2: One comparative clinical endpoint bioequivalence study

If the test product formulations are not Q1/Q2 the same as the RLD with respect to inactive ingredients, bioequivalence should be established by conducting a comparative clinical endpoint bioequivalence study. Applicants intending to propose this alternative approach by which to demonstrate bioequivalence should refer to the most recent version of the FDA guidance for industry on *Controlled Correspondence Related to Generic Drug Development*[a] for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

Unique Agency Identifier: PSG_215498-Cap Pellets

[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.