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Draft Guidance on Loteprednol Etabonate

February 2024

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Active Ingredient:	Loteprednol etabonate
Dosage Form:	Ointment
Route:	Ophthalmic
Strength:	0.5%
Recommended Studies:	Two options: (1) one in vitro bioequivalence study with supportive comparative characterization studies, or (2) one in vivo bioequivalence study

I. Option 1: One in vitro bioequivalence study with supportive comparative characterization studies

To demonstrate bioequivalence by this option, the test product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).[3]

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD product.
[3] For ophthalmic drug products, FDA has determined that, as a scientific matter, any qualitative or quantitative deviations from the RLD, even in inactive ingredients listed in 21 CFR 314.94(a)(9)(iv), should be accompanied by an appropriate in vivo BE study or studies. *ANDA Submissions – Refuse-to-Receive Standards: Guidance for Industry.*

One in vitro bioequivalence study:

1. Type of study: In vitro drug release testing (IVRT) of loteprednol etabonate
   Design: Should be performed on three batches of both test and reference standard (RS) products using at least 12 units from each batch
   Strength: 0.5%
   Additional comments: The IVRT method study should include information on the method development and validation to detect potential formulation differences and capture the complete release profile of loteprednol etabonate from the test and RS formulations. A prospective applicant may use the same method or different methods for IVRT of loteprednol etabonate.

   Bioequivalence based on: Comparative analysis of release profiles should be established using an appropriate statistical method.

Comparative characterization studies:

Comparative physicochemical characterization of the test and RS products. The comparative study should be performed on at least three batches of both the test[4] and RS products and should include:

a. Appearance
b. Acidity and alkalinity of the extracted ointment base
c. Rheological properties including yield stress and viscosity. The applicant should characterize viscosity over a range of shear rates
d. Drug particle size and size distribution

II. Option 2: One in vivo bioequivalence study

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, crossover or parallel design in vivo in aqueous humor
   Strength: 0.5%
   Subjects: Patients undergoing indicated cataract surgery

Additional comments: Refer to the most recent version of the FDA product-specific guidance on *Loteprednol Etabonate Ophthalmic Suspension/drops* (NDA 020583)[a] for additional comments regarding the in vivo pharmacokinetic study design in aqueous humor.

Analyte to measure: Loteprednol etabonate in aqueous humor

Bioequivalence based on (90% CI): Loteprednol etabonate

[4] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

Additional information:

Quality assessment:
For quality-related recommendations for supporting drug product development, refer to the most recent version of the FDA guidance for industry on *Quality Considerations for Topical Ophthalmic Drug Products*.[b]

Document History: Recommended July 2018; Revised February 2024

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[a] For the most recent version of the product-specific guidance, check the FDA product-specific guidance website at: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.