Contains Nonbinding Recommendations

Draft Guidance on Loteprednol Etabonate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient:	Loteprednol etabonate
Dosage Form; Route:	Gel; ophthalmic
Strength:	0.5%
Recommended Studies:	Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product all of the following criteria should be met:

i. The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same (Q1/Q2).[3]

ii. Acceptable comparative physicochemical characterizations of the test and Reference Standard (RS) products. The comparative study should be performed on at least three exhibit batches of both the test and RS products and should include:[4]

- Comparative crystalline habit of loteprednol etabonate.
- Comparative appearance, pH, specific gravity, and osmolality.
- Comparative soluble fraction of loteprednol etabonate in the final drug product.
- Comparable rheological properties including yield stress and viscosity. The applicant should characterize viscosity over a range of shear rates.
- Comparative drug particle size distribution. The particle size distribution should be compared using PBE (95% upper confidence bound) based on D_{50} and SPAN [i.e. $(D_{90}-D_{10})/D_{50}$]. The applicant should provide no fewer than ten data sets from three different batches of both the test and reference products for PBE analysis. Full profiles of the particle size distributions should also be submitted for all

[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. Guidance for industry: *ANDA Submissions –Refuse-to-Receive Standards*.
[4] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.

samples tested. Please refer to the *Guidance on Budesonide* inhalation suspension for additional information regarding PBE.

iii. Acceptable comparative in vitro drug release of loteprednol etabonate from the test and RS formulations.

II. In vivo option:

1. Type of study: Bioequivalence study with pharmacokinetic (PK) endpoints
Design: Single-dose, crossover or parallel design, in vivo in aqueous humor
Strength: 0.5%
Subjects: Patients undergoing indicated cataract surgery and scheduled to receive ophthalmic corticosteroids just prior to their eye surgery
Additional Comments: Specific recommendations are provided below

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Analytes to measure (in appropriate biological fluid): Loteprednol etabonate in aqueous humor

Bioequivalence based on (90% CI): Loteprednol etabonate

Additional Comments Regarding the In Vivo Pharmacokinetic Study in Aqueous Humor:

1. The study is conducted in patients undergoing indicated cataract surgery and scheduled to receive ophthalmic corticosteroids just prior to their eye surgery. A single dose of the test or reference product is instilled into the inferior cul de sac of the eye prior to cataract extraction. Only one single sample of aqueous humor is collected from one eye from each patient, at one assigned sampling time point.

   Applicant may consider a parallel design for the bioequivalence study. If using a parallel study design, please note that each patient should receive only one treatment, test or reference, but not both. Alternatively, a crossover study design may be used in patients undergoing indicated cataract surgery for both eyes. When crossover study design is used, each patient should receive both test and reference treatments. The wash-out period for the crossover study should not exceed 35 days.

2. In order to demonstrate bioequivalence, an adequate estimation of the rate (C_{max}) and extent (AUC) of loteprednol etabonate absorption is needed.

   The following statistical model is recommended:

   The mean AUC_t for each product and time point *t* of measurement is calculated by using the mean concentrations ($\overline{C_t}$) at each time point t to derive the mean profile for each product. On the basis of the trapezoid rule, mean AUC_t is computed as the weighted linear combination of these mean concentrations at each time point through time *t*. The AUC_t is the area under the

concentration - time curve from zero to the time *t*. Generally, we have j concentration measurements at times $t_1 < t_2 < t_3 ..., < t_j$ ($t_1 > 0$).

AUC_{t_j} is calculated for time from 0 to t_j as:

$$AUC_{t_j} = t_1 \times \overline{C_{t_1}} / 2 + \sum_{i=1}^{j-1} \left(\overline{C_{t_i}} + \overline{C_{t_{i+1}}} \right) \times \left(t_{i+1} - t_i \right) / 2$$

The ratio (R_t) of AUC_t from the test product to AUC_t from the reference product is used to assess bioequivalence for each time t of interest. Estimation of the standard deviation(s) of R_t may be done via the bootstrapping technique or a parametric method.

Bioequivalence is supported if the 90% confidence interval for R_t ($R_t \pm 1.645\ s_t$) lies within (0.8, 1.25). The bootstrapping technique or a parametric method can be used to determine C_{max} and T_{max} and assess bioequivalence for C_{max}.

3. The study design and statistical analysis plan should be specified *a priori* in the protocol. All details of the computations, including computation code should be submitted.