Contains Nonbinding Recommendations

Draft Guidance on Loteprednol Etabonate; Tobramycin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or the Agency) on this topic.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

Dosage Form; Route: Suspension/Drops; ophthalmic

Recommended Studies: Two studies

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% / 0.3%
   Subjects: Patients undergoing indicated cataract surgery
   Additional comments: Specific recommendations are provided below.

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2. Type of study: In vitro bioequivalence study
   Design: In vitro microbial kill rate study
   Strength: 0.5% / 0.3%
   Subjects: Not applicable
   Additional comments: Specific recommendations are provided below.

In vivo pharmacokinetic study in aqueous humor: This study should be conducted in order to evaluate the steroid component (loteprednol etabonate) of the combination product.

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

Bioequivalence based on (90% CI): Loteprednol

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 of 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 a 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 (Cmax) and extent (AUC) of loteprednol 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 Cmax and Tmax and assess bioequivalence for Cmax.

3. A protocol may be submitted to the Division of Bioequivalence for review and comment prior to conducting the study. 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.

4. Generally, a drug product intended for ophthalmic use contains the same inactive ingredients and in the same concentration as the Reference Listed Drug (RLD). For an ophthalmic drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent [as permitted by the chemistry, manufacturing, and controls (CMC) regulation for abbreviated new drug applications (ANDAs), 21 CFR 314.94(a)(9)(iv)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

5. Changes in any of the inactive ingredients can change the safety and efficacy of an ophthalmic drug product. Therefore, an applicant may need to also conduct an in vivo BE

study with clinical endpoint for any Loteprednol Etabonate and Tobramycin Ophthalmic Suspension that has a different inactive ingredient or a difference of more than 5% in the amount of any inactive ingredient compared to that of the RLD. The sponsor is advised to submit a protocol to the Division of Clinical Review Team in the Office of Generic Drugs for review and concurrence prior to conducting the in vivo BE study with clinical endpoint for such a product.

Additional comments regarding the in vitro microbial kill rate study:

1. An in vitro microbial kill rate study should be conducted in order to evaluate the antibiotic portion (tobramycin) of the combination product. The study should compare the antimicrobial activity of tobramycin in the test and reference product against the following:

   - All organisms listed in the USP Preservative Effectiveness Test
   - All organisms listed in the "Indications" section of the reference product labeling

   The antimicrobial activity of tobramycin in the test and reference products should be compared in the in vitro BE study, at a minimum, against the following 17 organisms: *Candida albicans, Aspergillus niger, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii, Proteus vulgaris, Haemophilus influenzae, Haemophilus aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus, Neisseria perflava* OR *Neisseria sicca*.

   The in vitro microbial kill rate study should be conducted by using at least 12 replicates for each kill rate study of each organism to demonstrate bioequivalence (BE) between the test and reference products.

2. The test and reference formulations, along with a negative control, should be compared in vitro for bacterial kill rates. The population for each test organism/product for designated time intervals should be determined by counting surviving colonies after incubation. Kill rates should be determined for each product and equivalence declared if both the test and reference products produce the same in vitro kill rates on all organisms tested. The following are additional recommendations regarding the study design:

   a. The solution in which the testing for activity of the antibacterial agent in the test product is done should mimic as closely as possible the lacrimal fluid of the eye in composition, molarity, pH, etc.
   b. The testing procedure should include some way for the antimicrobial agent to be inactivated at the time samples are withdrawn to perform colony counts for surviving organisms (e.g. filtration, dilution, chemical).
   c. The times at which samples are withdrawn to determine organism survival should be: 0, 7.5, 15, 30 and 60 minutes. The two one-sided test procedure is recommended to determine the 90% confidence interval for the test/reference ratios of average kill rate for each sampling time point.
   d. The organisms to be tested are those listed in USP <51> Antimicrobial Effectiveness

Testing and organisms to be listed in the package insert for the product.

e. The final inoculum concentration of bacteria, yeast or spores that are tested should be at least 5 x 10^5 CFU/mL.
f. Media used to determine organism survival should be appropriate to allow for recovery of surviving organisms.
g. The temperature at which organism recovery media are incubated should be the temperature of the eye.
h. All recovery media should be incubated for the appropriate amount of time to allow for the growth of the organism for which recovery is being attempted.
i. The method of determining colony counts of the organism on survival media should be described in the protocol (e.g. counted under magnification).
j. The test methodology will need to be validated prior to using it to determine activity of the product against the organisms. It is suggested that, at the time a test method is being written, a validation protocol be written.

3. Sponsors may submit the test protocol and validation protocol for review and comment prior to conducting the study.

In vitro dissolution test method and sampling times: Please develop an in vitro drug release testing method for this drug product for stability and quality controls. Specifications will be determined upon review of the data submitted in the abbreviated new drug application (ANDA).