Contains Nonbinding Recommendations

Draft Guidance on Prednisolone Acetate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Suspension/Drops; ophthalmic

Recommended Studies: One study

1. Type of study: Bioequivalence study with pharmacokinetic (PK) endpoints
   Design: Single-dose, crossover or parallel design, in vivo in aqueous humor
   Strength: 1%
   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.

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

Bioequivalence based on (90% CI): Prednisolone acetate

In vitro dissolution test method: 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 abbreviated new drug application (ANDA).

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 prednisolone acetate 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 Prednisolone Acetate 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.