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Draft – Not for Implementation

Draft Guidance on Nepafenac

November 2024

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Active Ingredient:	Nepafenac
Dosage Form:	Suspension/drops
Route:	Ophthalmic
Strength:	0.1%
Recommended Studies:	Three options: (1) two in vitro studies with supportive comparative characterization studies, (2) one in vivo bioequivalence study with pharmacokinetic endpoints, or (3) one in vivo comparative clinical endpoint bioequivalence study

I. Option 1: Two in vitro studies with supportive comparative characterization studies

To demonstrate bioequivalence by this option, the test (T) 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 T 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 T 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. Refer to FDA guidance *ANDA Submissions – Refuse-to-Receive Standards: Guidance for Industry.*

Comparative characterization studies:

Comparative physicochemical characterization of the T product and reference standard (RS) products should be conducted. The comparative study should be performed on at least three batches of both the T product[4] and RS and should include:

- Appearance
- pH
- Specific gravity
- Osmolality
- Surface tension
- Viscosity
- Soluble fraction of nepafenac in the finished drug product

Two in vitro bioequivalence studies:

1. Type of study: Drug particle size and size distribution of nepafenac
   Design: In vitro bioequivalence study on three batches of both T and RS products
   Strength: 0.1%
   Additional comments: The sample preparation method and selected particle sizing methodology should be adequately optimized and validated to demonstrate the adequacy of the selected method in accurately and reliably identifying and measuring the size of the drug particles. Prospective applicant should perform size characterization at different dilution conditions as part of method development to demonstrate the impact of dilution. Full particle size distribution profiles representative of all T product and RS product batches tested should be submitted as supporting information.

   Parameters to measure: D_{50} and SPAN $[(D_{90}-D_{10})/D_{50}]$

   Bioequivalence based on (95% upper confidence bound): Population bioequivalence (PBE) analysis of the D_{50} and SPAN. Prospective applicants should provide no less than 10 datasets from 3 batches each of the T and RS products to be used in the PBE analysis. Refer to the section of "Recommendation Related to the PBE Statistical Analysis Procedure" in the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929)[a] for additional information regarding PBE computation.

2. Type of study: Comparative in vitro release testing (IVRT) of nepafenac
   Design: Should be performed on 3 batches of both T and RS products using at least 12 units from each batch
   Strength: 0.1%
   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 nepafenac.

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

Bioequivalence based on: Comparative analysis of release profiles should be established using an appropriate statistical method (e.g., model independent approach using similarity factor (f_2)). For more information on calculation of f_2 factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[b]

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, crossover or parallel design in vivo in aqueous humor
   Strength: 0.1%
   Subjects: Patients undergoing cataract surgery
   Additional comments: Specific recommendations are provided below.

Analytes to measure: Nepafenac and amfenac in aqueous humor

Bioequivalence based on (90% CI): Nepafenac

Additional comments regarding bioequivalence study with pharmacokinetic endpoints:

1. Generally, a drug product intended for ophthalmic use contains the same inactive ingredients and in the same concentrations as the 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 prospective 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.

2. The study is conducted in patients undergoing indicated cataract surgery and scheduled to receive ophthalmic NSAIDs just prior to their eye surgery. A single dose of the T product or RS is applied to the affected 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.

3. Applicants may consider a parallel design for the bioequivalence study. If using a parallel study design, note that each patient should receive only one treatment, T product or RS, 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 of T and RS treatments. The wash-out period for the crossover study should not exceed 35 days.

4. To demonstrate bioequivalence, an adequate estimation of the rate (C_{max}) and extent (AUC) of nepafenac 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 $t_1 < t_2 < t_3 \ldots, < t_j$ ($t_1 > 0$).

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

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

The ratio (R_t) of AUC_t from the T product to AUC_t from the RS 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 (0.80, 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}.

III. Option 3: One comparative clinical endpoint bioequivalence study

1. Type of study: Comparative clinical endpoint bioequivalence study
   Design: Randomized, double-masked, parallel, placebo controlled, in vivo
   Strength: 0.1%
   Subjects: Adult males and nonpregnant females who have a cataract and are planning to undergo cataract extraction.
   Additional comments: Specific recommendations are provided below.

Bioequivalence based on (90% CI): Clinical endpoint

Additional comments regarding the comparative clinical endpoint bioequivalence study:

1. The agency recommends conducting a comparative clinical endpoint BE study in the treatment of pain and inflammation associated with cataract surgery comparing the T product versus the RS and vehicle control, each administered as one drop to the operative eye three times daily beginning one day prior to cataract surgery (Day-1), continued on the day of surgery (Day 0) and through the first two weeks of the postoperative period (Post-Op Days 1-14). The recommended treatment duration is 16 days with office visits at Screening, Post-Op Day 1, Post-Op Day 7 and Post-Op Day 14. For safety, include visual acuity measurements at the Post- Op Day 7 and Post-Op Day 14 visits.

2. Inclusion criteria (the sponsor may add additional criteria):
    a. Males or nonpregnant females aged at least 18 years who have a cataract and are expected to undergo cataract extraction.
    b. No aqueous cells (i.e., Grade 0), no visible aqueous flare (i.e., Grade 0) and no significant ocular pain (i.e., Grade 0 or 1) in the operative eye noted during the Screening Visit slit-lamp examination (see Table 1).

Table 1. Aqueous Cells, Aqueous Flare and Ocular Pain Grading Scales

Grade	**Aqueous Cells:** Determined using a narrow slit beam (0.5 mm width and at least 8 mm length) at maximum luminance. Pigment and red blood cells are to be ignored.
0	None
1	1 to 5 cells
2	6 to 15 cells
3	16 to 30 cells
4	Greater than 30 cells
Grade	**Aqueous Flare:** Determined using a narrow slit beam (0.5 mm width at least 8 mm length) at maximum luminance.
0	No visible flare when compared with the normal eye
1	Mild – Flare visible against dark pupillary background but not visible against iris background.
2	Moderate – Flare is visible with the slit-lamp beam aimed onto the iris surface as well as the dark pupillary background.
3	Severe – Very dense flare. May also present as a "hazy" appearance of anterior segment structures when viewed with low power magnification of the slit-lamp. Presents as pronounced Tyndall effect.
Grade	**Ocular Pain:** A positive sensation of the eye, including foreign body sensation, stabbing, throbbing or aching
0	None – absence of positive sensation
1	Patient reports presence of mild sensation of discomfort typical of postoperative ocular surgery, e.g., diffuse or focal foreign body sensation, mild transient burning or stinging.
2	Mild – mild, tolerable aching of the eye
3	Moderate – moderate or more prolonged aching sufficient to require the use of over-the-counter analgesics (e.g., acetaminophen)

4	Moderately Severe – more prolonged aching requiring the use of any over-the-counter analgesics other than acetaminophen
5	Severe – Patient reports intense ocular, periocular or radiating pain (e.g., constant or nearly constant sharp stabbing pain, throbbing or aching, etc.) requiring prescription analgesics

3. Exclusion criteria (the sponsor may add additional criteria):
    a. Females who are pregnant, breast feeding or planning a pregnancy.
    b. Females of childbearing potential who do not agree to utilize an adequate form of contraception.
    c. Current or past history of severe hepatic or renal impairment, uncontrolled diabetes mellitus, rheumatoid arthritis or bleeding tendencies.
    d. Current or history within two months prior to baseline of significant ocular disease, e.g., corneal denervation, corneal epithelial defects, dry eye syndrome, ocular trauma to the operative eye, corneal edema, proliferative diabetic retinopathy in the operative eye or ocular infection.
    e. In the operative eye, history of chronic or recurrent inflammatory disease, e.g., iritis, scleritis, uveitis, iridocyclitis or rubeosis iritis, lens pseudo exfoliation syndrome with glaucoma or zonular compromise.
    f. Congenital ocular anomaly, e.g., aniridia or congenital cataract.
    g. Iris atrophy in the operative eye.
    h. Current corneal abnormalities that would prevent accurate IOP readings with the Goldmann applanation tonometer.
    i. Nonfunctional nonoperative eye.
    j. Known hypersensitivity to any component of nepafenac therapy or to other nonsteroidal anti- inflammatory drug (NSAID).
    k. Use within one week prior to baseline of: (1) contact lens, or (2) topical, ophthalmic or systemic NSAID.
    l. Use within two weeks prior to baseline of: (1) topical ophthalmic corticosteroid, (2) topical corticosteroid, or (3) medications which may prolong bleeding time.
    m. Use within one month prior to baseline of: (1) systemic corticosteroid, (2) high-dose salicylate therapy, or (3) topical ophthalmic prostaglandin analogs, e.g., bimatoprost, latanoprost or travoprost.
    n. Use within six months prior to baseline of intravitreal or subtenon injection of ophthalmic corticosteroid.
    o. Underwent within six months prior to baseline any complicated intraocular surgery or repeat ocular surgeries (e.g., cataract surgery).
    p. Underwent within twelve months prior to baseline: refractive surgery, filtering surgery or laser surgery for IOP reduction.

4. A subject presenting at any postoperative visit with an aqueous cells score of ≥3, aqueous flare score of ≥3, OR ocular pain score of ≥4 should be considered a treatment failure, discontinued from study treatment, and treated with rescue therapy according to local standard of care as deemed appropriate by the Investigator.

5. The amount of iris pigmentation can affect the speed in which anterior chamber inflammation resolves. It is recommended that treatment groups be balanced with respect to iris pigmentation [light (blue, grey, hazel) or dark (brown) colored irides].

6. Coadministration of beta-blocker, carbonic anhydrase inhibitor, alpha-agonist, cycloplegic, and mydriatic topical ophthalmic medications are permitted. When more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

7. Coadministration of low dose aspirin (less than or equal to 100 mg) is permitted.

8. The protocol should include a list of the prescription and over-the counter drug products, procedures, and activities that are prohibited during the study, such as:
    a. Ophthalmic prostaglandin analogs, e.g., bimatoprost (Lumigan®), latanoprost (Xalatan®) or travoprost (Travatan®, Travatan Z®).
    b. Topical, ophthalmic, inhaled or systemic NSAIDs, other than the assigned study product.
    c. Topical, ophthalmic, inhaled or systemic corticosteroid.
    d. Intraocular corticosteroid implant.
    e. Intravitreal or subtenon injection of ophthalmic corticosteroid.
    f. High-dose salicylate therapy.
    g. Medications that may prolong bleeding time.
    h. Contact lenses.
    i. Ocular surgery, other that study surgery.

9. The recommended co-primary endpoints measured in the operative eye are:
    a. Proportion of subjects with score of 0 for aqueous cells at Post-Op Day 14 AND score of 0 for aqueous flare at Post-Op Day 14
    b. Proportion of subjects with score of 0 for ocular pain at Post-Op Day 1

10. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[a] for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.

11. Study data should be submitted in a standardized format. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

12. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable
    a. Study identifier
    b. Subject identifier
    c. Site identifier: study center
    d. Age

e. Age units (years)
f. Sex
g. Race
h. Iris color (light/dark)
i. Name of Actual Treatment (exposure): T product, RS, placebo
j. Duration of Treatment (total exposure in days)
k. Completed the study (yes/no)
l. Reason for premature discontinuation of subject
m. Subject required additional treatment for ocular inflammation due to unsatisfactory treatment response (yes/no)
n. Per Protocol (PP) population inclusion (yes/no)
o. Reason for exclusion from PP population
p. Modified Intent to Treat (mITT) Population (yes/no)
q. Reason for exclusion from mITT population
r. Safety population inclusion (yes/no)
s. Reason for exclusion from Safety population
t. Aqueous Cells Grade for operative eye at Screening Visit
u. Aqueous Flare Grade for operative eye at Screening Visit
v. Ocular Pain Grade for operative eye at Screening Visit
w. Aqueous Cells Grade for operative eye at Post-Op Day 1 Visit
x. Aqueous Flare Grade for operative eye at Post-Op Day 1 Visit
y. Ocular Pain Grade for operative eye at Post-Op Day 1 Visit
z. Aqueous Cells Grade for operative eye at Post-Op Day 7 Visit
aa. Aqueous Flare Grade for operative eye at Post-Op Day 7 Visit
bb. Ocular Pain Grade for operative eye at Post-Op Day 7 Visit
cc. Visual acuity for operative eye at Post-Op Day 7 Visit
dd. Aqueous Cells Grade for operative eye at Post-Op Day 14 Visit
ee. Aqueous Flare Grade for operative eye at Post-Op Day 14 Visit
ff. Ocular Pain Grade for operative eye at Post-Op Day 14 Visit
gg. Visual acuity for operative eye at Post-Op Day 14 Visit
hh. Cure at Post-Op Day 14 Visit (yes/no)
ii. Treatment compliance: number of missed doses per subject
jj. Concomitant medication (yes/no)
kk. Adverse event(s) reported (yes/no)

Additional information:

Device:
The RLD is presented in a bottle with a dropper tip. The bottle with dropper tip is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the T device.

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[b]
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]

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[a] For the most recent version of a 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/regulatoryinformation/search-fda-guidance-documents.