Contains Nonbinding Recommendations

Draft Guidance on Nepafenac

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Suspension; ophthalmic

Recommended Studies: Three options

I. Option One: In vitro studies

To qualify for the in vitro option for nepafenac ophthalmic suspension (0.1%) all of the following criteria should be met:

i. The test and reference listed drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2).
ii. Acceptable comparative physicochemical characterizations of the test and RLD formulations. The characterization study should be performed on at least three exhibit batches of both the test and RLD products[1], and should include:

- Comparative appearance, pH, specific gravity, osmolality, surface tension, buffer capacity, and viscosity as a function of applied shear. Viscosity measurement should also be conducted at the tear pH.
- Comparative re-dispersibility (time required to re-disperse the formulation and sedimentation time).
- Comparative soluble fraction of nepafenac in the final drug product.
- Comparative unit dose content (one drop per unit dose). Provide data for the amount of unit dose (one drop) with assay for nepafenac from a minimum of ten units from three batches each of the test and reference products. The unit dose content should be compared using population BE (95% upper confidence bound).
- Comparative drug particle size distribution. The particle size distribution should be compared using population BE (95% upper confidence bound) based on D50 and SPAN [(D90-D10)/D50]. The applicant should provide no fewer than ten data sets from three different batches each of the test and reference products for the population BE analysis. Full profiles of the particle size distributions should also be submitted for all samples tested.

iii. Acceptable comparative in vitro drug release of nepafenac from the test and RLD formulations. The methodology used for in vitro drug release testing should be able to discriminate the effect of process and variability in the production of the test formulation.

II. Option two: Pharmacokinetic BE studies

[1] All three exhibit batches should be at least 1/10 the size of the commercial batch and the manufacturing process used for the three exhibit batches should be reflective of the process used for the commercial batch.

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

Analytes to measure (in appropriate biological fluid): Nepafenac and amfenac in aqueous humor

Bioequivalence based on (90% CI): Nepafenac

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 NSAIDs just prior to their eye surgery. A single dose of the test or reference product 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.

   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 of 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 nepafenac absorption is needed.

   The following statistical model is recommended:

3. 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:

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

4. 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.

5. 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 in the abbreviated new drug application (ANDA).

6. 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) regulations for abbreviated new drug applications (ANDAs), 21 CFR 314.94(a)(9)(iv)], the applicant should identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

7. 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 nepafenac 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.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

III. Option three: Comparative clinical endpoint study

Type of study: Bioequivalence (BE) Study with Clinical Endpoint

Design: Randomized, double-masked, parallel, placebo controlled, in vivo

Strength: 0.1%

Subjects: Males and nonpregnant females who have a cataract and are planning to undergo cataract extraction.

Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Not applicable (N/A)

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: N/A

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Additional comments regarding the BE study with clinical endpoint:

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with clinical endpoint in the treatment of pain and inflammation associated with cataract surgery comparing the test

product versus the RLD and vehicle control, each administered as one drop to the operative eye one time 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. A placebo (vehicle) control arm is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.

3. 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 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

4. 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 pseudoexfoliation 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.

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]. While stratification is usually not necessary, the treatment groups should be checked for approximate balance.

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 primary endpoint is the proportion of subjects with cure at Post-Op Day 14 defined as a score of 0 for aqueous cells, a score of 0 for aqueous flare and a score of no more than 3 for pain (see Table 1).

10. The protocol should clearly define the per-protocol (PP), modified Intent to Treat (mITT) and safety populations.
    a. The PP population includes all randomized subjects who met all inclusion/exclusion criteria, administered a pre-specified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned product for the specified duration of the study, did not miss the scheduled administrations for more than 3 consecutive days, and completed evaluations at Test of Cure Visit at the Post-Op Day 14 visit within the designated visit window (+/- 2 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries.
    b. The mITT population includes all randomized subjects who met the inclusion/exclusion criteria, administered at least one dose of study product and returned for at least one post-baseline evaluation visit.
    c. The safety population includes all randomized subjects who receive study product.

11. Subjects who discontinue because of lack of treatment effect after completing two days of treatment should be analyzed in the mITT and PP populations as a treatment failure. Subjects discontinued for other reasons, including drug-related adverse events, should be excluded from the PP population, but included in the mITT population using Last Observation Carried Forward (LOCF).

12. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both. The use of analgesics should be compared between treatment groups.

13. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

14. Generally, a drug product intended for ophthalmic use shall contain the same inactive ingredients and in the same concentration 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) regulations 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.

15. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

16. A detailed description of the masking procedure is to be provided in the protocol. The packaging of the test and reference products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate masking of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. If the two treatments differ in appearance, evaluators should not be in the room whenever the treatment is taken out of the external packaging or the subject is dosed with study treatment.

17. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of ICH E6, “Good Clinical Practice: Consolidated Guideline”, for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

18. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

19. To establish bioequivalence for the primary endpoint (proportion of subjects with “cure” at the Day 14 visit), the 90% confidence interval of the test-reference difference between products must contained within [-0.20, +0.20] for dichotomous variables (cure versus failure), using the PP population.

20. As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo/vehicle control ($p<0.05$; two-sided) for the primary endpoint using the mITT study population and Last Observation Carried Forward (LOCF).

21. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (cure versus failure):

    Equivalence Analysis

    Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment must be contained within [-0.20, +0.20] in order to establish equivalence.

    The compound hypothesis to be tested is:

    H_0: $p_T - p_R < -0.20$ or $p_T - p_R > 0.20$

    versus

    H_A: $-0.20 \leq p_T - p_R \leq 0.20$

    Where p_T = success rate of test treatment and p_R = success rate of reference treatment.

    Let
    n_T = *sample size of test treatment group*
    cn_T = *number of successes in test treatment group*
    n_R = *sample size of reference treatment group*
    cn_R = *number of successes in reference treatment group*

    $$\hat{p}_T = cn_T/n_T, \ \hat{p}_R = cn_R/n_R,$$

    $$and\ se = (\hat{p}_T\ (1-\hat{p}_T)/n_T + \hat{p}_R\ (1-\hat{p}_R)/n_R)^{1/2}.$$

    The 90% confidence interval for the difference in proportions between test and reference was calculated as follows. Using Yates' correction:

    $$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2.$$

    $$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2.$$

    We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$.

    Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

22. Study data should be submitted to the OGD in electronic format.
    a. A list of file names, with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the datasets.
    b. Provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
    c. All SAS transport files, covering all variables collected in the Case Report Forms (CRFs) per subject, should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.

d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
e. Please provide a separate dataset for variables such as demographics, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.

23. Please provide a summary dataset containing a separate line listing for each subject (if data exist) 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): test product, RLD, 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)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of a summary dataset containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	Iris_c	EXTRT	EXDUR	completed	disc_is	add_trt	pp	pp_rs	mitt	mitt_rs	safety	safe_rs
101	1	01	54	YEARS	F	1	L	A	16	Y		N	Y		Y		Y	
101	2	01	58	YEARS	F	1	D	B	16	Y		N	Y		Y		Y	

ac_s	af_s	op_s	ac_1	af_1	op_1	ac_7	af_7	op_7	va_7	ac_14	af_14	op_14	va_14	cure	complian	CM	AE
0	0	0	2	1	2	1	0	1	30	1	0	1	30	N	0	Y	Y
0	0	0	1	2	2	0	0	1	20	0	0	0	20	Y	0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID:	Study Identifier
SUBJID:	Subject Identifier for the Study
SITEID:	Study Site Identifier
AGE:	Age
AGEU:	Age units (years)
SEX:	Sex, e.g., M=Male, F=Female, U=Unknown
RACE:	Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
iris_c:	Iris Color, e.g., L=Light (blue, grey, hazel), D=Dark (brown)
EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B= RLD, C=placebo
EXDUR:	Duration of Treatment (total exposure in days)
completed:	Subject completed the study, e.g., Y=Yes, N=No
disc_rs:	Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unmasked, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
add_trt:	Subject required additional treatment for inflammation associated with cataract surgery due to unsatisfactory treatment response, e.g., Y=Yes, N=No
pp:	Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
mitt:	Modified intent to treat (mITT) population inclusion, e.g., Y=Yes. N=No
mitt_rs:	Reason for exclusion from mITT population, A=never treated, etc.
safety:	Safety population inclusion, e.g., Y=Yes, N=No

safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
ac_s:	Aqueous Cells Grade for operative eye at Screening Visit, e.g., 0, 1, 2, 3 or 4
af_s:	Aqueous Flare Grade for operative eye at Screening Visit, e.g., 0, 1, 2, or 3
op_s:	Ocular Pain Grade for operative eye at Screening Visit, e.g., 0, 1, 2, 3, 4, or 5
ac_1:	Aqueous Cells Grade for operative eye at Post-Op Day 1 Visit, e.g., 0, 1, 2, 3 or 4
af_1:	Aqueous Flare Grade for operative eye at Post-Op Day 1 Visit, e.g., 0, 1, 2, or 3
op_1:	Ocular Pain Grade for operative eye at Post-Op Day 1 Visit, e.g., 0, 1, 2, 3, 4, or 5
ac_7:	Aqueous Cells Grade for operative eye at Post-Op Day 7 Visit, e.g., 0, 1, 2, 3 or 4
af_7:	Aqueous Flare Grade for operative eye at Post-Op Day 7 Visit, e.g., 0, 1, 2, or 3
op_7:	Ocular Pain Grade for operative eye at Post-Op Day 7 Visit, e.g., 0, 1, 2, 3, 4, or 5
va_7:	Corrected Visual Acuity for operative eye at Post-Op Day 7 Visit, e.g., 20/xx equivalent
ac_14:	Aqueous Cells Grade for operative eye at Post-Op Day 14 Visit, e.g., 0, 1, 2, 3 or 4
af_14:	Aqueous Flare Grade for operative eye at Post-Op Day 14 Visit, e.g., 0, 1, 2, or 3
op_14:	Ocular Pain Grade for operative eye at Post-Op Day 14 Visit, e.g., 0, 1, 2, 3, 4, or 5
va_14:	Corrected Visual Acuity for operative eye at Post-Op Day 14 Visit, e.g., 20/xx equivalent
cure:	Cure at Post-Op Day 14 Visit, e.g., Y=Yes, N=No
complian:	Treatment compliance, e.g., number of missed doses per subject
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

24. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of nepafenac.