CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-862

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Nepafenac Ophthalmic Suspension, 0.1%
PRODUCT (Proposed Brand Name):	Nevanac
NDA:	21-862
THERAPEUTIC CLASS:	NSAID
PROPOSED INDICATIONS:	— treatment of pain and inflammation associated with cataract surgery
SUBMISSION DATE:	February 27, 2005
SPONSOR:	Alcon Research, Ltd. Ft. Worth. TX
REVIEWER:	Tapash K. Ghosh, Ph.D.
TEAM LEADER:	Edward D. Bashaw, Pharm.D.
OCPB DIVISION:	DPE III, HFD 880
OND DIVISION:	HFD 550

EXECUTIVE SUMMARY

This NDA application is for Nepafenac ophthalmic suspension, 0.1%, a Nonsteroidal Anti-Inflammatory Drug (NSAID). The proposed indication of the drug product is for the — treatment of pain and inflammation associated with cataract surgery. Nepafenac also known as amfenac amide, is a prodrug that penetrates the cornea and is converted to the active moiety amfenac by intraocular hydrolases. The prodrug has very weak cyclooxygenase inhibitory activity whereas amfenac exhibits potent cyclooxygenase activity.

Although nepafenac (amfenac amide) is a new molecular entity, amfenac sodium (AHR 5850) has been on the Japanese market since 1986 (as FENAZOX®, Meiji) in an oral dosage form (50 mg, four-times-daily) indicated for the treatment of pain and inflammation associated with rheumatoid and osteoarthritis and low back pain, as well as the treatment of pain and inflammation following surgery, injury or tooth extraction.

There are currently three topical nonsteroidal anti-inflammatory drugs (NSAIDs) and two topical ophthalmic steroids approved for the treatment of postoperative inflammation:

bromfenac sodium 0.1% (Xibrom), ketorolac tromethamine ophthalmic solution 0.5% (Acular), diclofenac sodium ophthalmic solution 0.1% (Voltaren), loteprednol etabonate ophthalmic solution 0.5% (Lotemax) and rimexolone ophthalmic suspension 1% (Vexol).

There are currently no available topical treatments available for the treatment of pain and inflammation associated with cataract surgery. The sponsor submitted for approval this new drug/dosage form (nepafenac ophthalmic suspension, 0.1%) for treatment of pain and inflammation associated with cataract surgery. The clinical pharmacology and biopharmaceutics review of this NDA 21-862 consists of 1 pivotal study to evaluate the multiple-dose, safety and pharmacokinetics of 0.1% Nepafenac Ophthalmic Suspension TID in healthy subjects. Following bilateral topical ocular TID dosing of Nepafenac Ophthalmic Suspension, 0.1%, low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects. The mean steady-state C_{max} (0.422 ± 0.121 ng/ml) for amfenac following ocular administration is approximately 1,659 times lower than the mean C_{max} (0.7 µg/ml) observed in subjects who received multiple 50 mg oral doses of amfenac. Minimal accumulation in plasma of nepafenac and amfenac was seen following TID dosing of Nepafenac Ophthalmic Suspension, 0.1%.

Overview of Efficacy and Safety: According to the sponsor, Nepafenac ophthalmic suspension has demonstrated superiority to vehicle in two adequate and well controlled trials in its ability to clear ocular inflammation and eliminate pain following cataract surgery. The safety profile of this drug product is consistent with other products in the topical NSAID class. There are no new unexpected adverse events associated with the topical ocular use of this product.

Recommendation:

The Clinical Pharmacology and Biopharmaceutics section of NDA 21-862 is acceptable with the suggested labeling changes as described below.

CPB Labeling: The sponsor did not mention any word about systemic exposure in the pharmacokinetics section of the proposed labeling. The following section is suggested to be included in the final labeling.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

Following bilateral topical ocular TID dosing of Nepafenac Ophthalmic Suspension, 0.1%, low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects out to 2 and 3 hours postdose, respectively. The mean steady-state C_{max} for nepafenac and for amfenac were (0.310 ± 0.104 ng/ml) and (0.422 ± 0.121 ng/ml) respectively, following ocular administration.

Primary Reviewer: Tapash K. Ghosh, Ph.D.

Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation III

Team Leader: Edward D. Bashaw, Pharm.D.

III. QUESTION-BASED REVIEW

1. General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

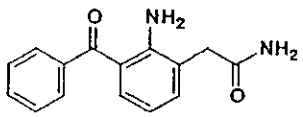
Trade name: Nevanac™

Generic name: Nepafenac ophthalmic suspension, 0.1%

Chemical name: 2-amino-3-benzoylbenzeneacetamide

Molecular formula/molecular weight: $C_{15}H_{14}N_2O_2$ /254.28

Chemical Structure:



Formulation: NEVANAC™ 0.1% is a sterile, topical, ophthalmic suspension of nonsteroidal anti-inflammatory prodrug nepafenac with the following composition:

Composition of Nepafenac Ophthalmic Suspension, 0.1%

FID[a] 105022

Component	Percent w/v	Function	Compendial Status
Nepafenac (AL-6515)	0.1	Active Ingredient	Non-compendial[b]
Benzalkonium Chloride	0.005		NF
Carbomer 974P	—		NF[c]
Tyloxapol	—		USP
Edetate Disodium	—	Preservative	USP
Mannitol	—		USP
Sodium Chloride	—		USP
Sodium Hydroxide and/or Hydrochloric Acid	QS for pH to —	pH adjustment	NF NF
Purified Water	QS 100	Vehicle	USP

a FID = Formulation Identification Number
b Meets in-house monograph
c Meets NF Monograph for Carbomer 934P

Nepafenac is a member of the nonsteroidal anti-inflammatory drug (NSAID) class. The drug is presented as a suspension formulation applied by the topical ocular route, and is indicated for the treatment of pain and inflammation associated with cataract surgery. Nepafenac also known as amfenac amide, is a prodrug that penetrates the cornea and is converted to the active moiety amfenac by intraocular hydrolases. The prodrug has very weak cyclooxygenase inhibitory activity whereas amfenac exhibits potent cyclooxygenase activity.

2. General Clinical Pharmacology

What is the pharmacokinetics of proposed Nepafenac Ophthalmic Suspension, 0.1%?

Following bilateral topical ocular TID dosing of Nepafenac Ophthalmic Suspension, 0.1%, low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects out to 2 and 3 hours postdose, respectively. The mean steady-state C_{max} for nepafenac and for amfenac were (0.310 ± 0.104 ng/ml) and (0.422 ± 0.121 ng/ml) respectively, following ocular administration.

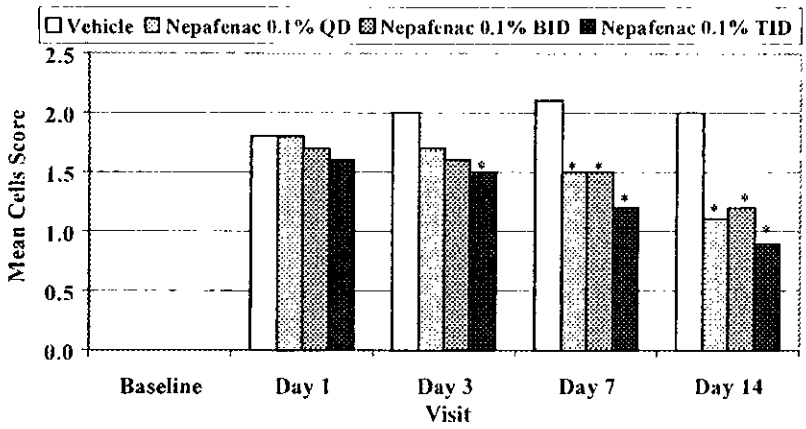
What is the basis for selecting the dose in Nepafenac Ophthalmic Suspension? What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

There were 2 dose-response studies (C-95-93 and C-97-30) in which Nepafenac was dosed four-times-daily beginning the day after surgery and continuing through the first 2 weeks of the postoperative period. Concentrations of Nepafenac ranged from 0.003% to 0.3%. Two additional studies (C-02-53 and C-03-32) were conducted using the final concentration (0.1%) and dosing regimen (three-times-daily beginning 1 day prior to surgery, and continuing the day of surgery and through the first 2 weeks of the postoperative period). In C-02-53, the primary efficacy endpoint was treatment failures based on aqueous cells and flare scores, which are the hallmark of ocular inflammation. In C-03-32, the primary efficacy endpoint was percent cures, wherein cures were defined as the absence of inflammation.

Subjective assessment of ocular pain, rated on a 6-point scale, was evaluated in the 2 efficacy studies (C-02-53 and C-03-32). All 4 studies were placebo-controlled and were conducted in adult patients requiring cataract extraction, the target patient population for the indication being pursued.

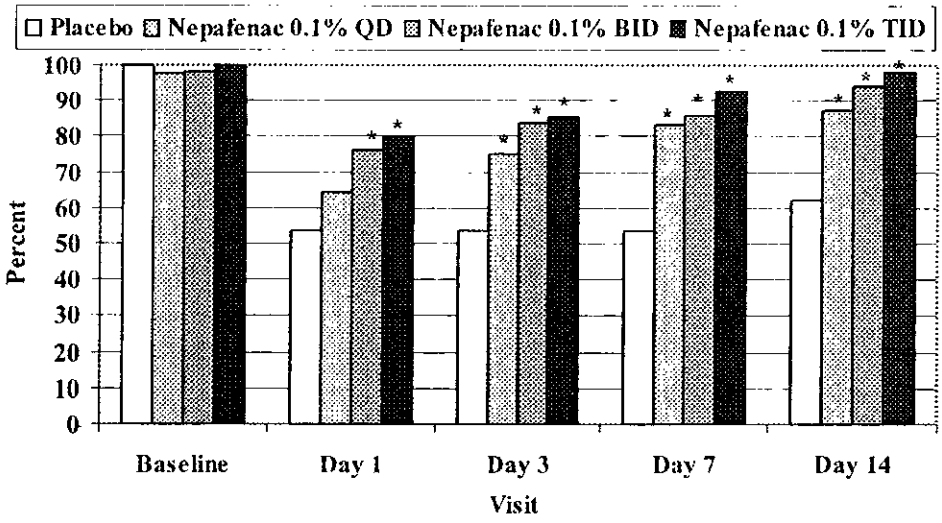
According the clinical review, Nepafenac Ophthalmic Suspension, 0.1% (QD, BID and TID) in study C-02-53 was superior to placebo in the treatment of inflammation and pain associated with cataract surgery based upon clinical assessments of aqueous cells and pain. Study C-02-53 also demonstrated that Nepafenac Ophthalmic Suspension, 0.1% was superior to placebo for the prevention of inflammation and pain at the early postoperative visit Day 3. Efficacy findings based on study C-02-53 results is presented in the following figures. The TID dosing regimen was shown to be the optimal dosing regimen rather than the QD or BID regimens. Therefore, in the final stage phase 3 study (C-03-32) all patients received TID dosing.

Mean Aqueous Cells Scores by Visit
(C-02-53, Intent-to-Treat)



*LSMeans p-value ≤ 0.0098
RM ANOVA treatment by visit interaction p-value < 0.0001

Percent of Patients with No Ocular Pain by Visit
(C-02-53, Intent-to-Treat)



*Chi-square test p-value ≤ 0.0220

The efficacy of Nepafenac Ophthalmic Suspension, 0.1% for — reatment of pain and inflammation following cataract surgery has not been investigated in pediatric patients.

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? How are the active moieties identified and measured in the blood in the clinical pharmacology and biopharmaceutics studies? What bioanalytical methods are used to assess concentrations?

Yes. Plasma concentrations of nepafenac and its hydrolysis product amfenac were determined using a validated [redacted]

Intrinsic Factors

What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

With the enrollment of 8 males and 8 females in study C-04-08, analyses were done to examine the effects of gender on the steady-state pharmacokinetics of nepafenac and amfenac. Two-sample t-test analysis showed statistically significant gender difference in C_{max} ($p = 0.0256$) and $AUC_{0\text{-}8}$ ($p = 0.0022$) for nepafenac, but not for amfenac. When these pharmacokinetic parameters were normalized to 70 kg body weight ($C_{max,\,norm}$ and $AUC_{0\text{-}8,\,norm}$), no statistically significant ($p \geq 0.1912$) differences were seen for nepafenac in these parameters between males and females. There was no gender difference in T_{max} or $t_{1/2}$ for either nepafenac or amfenac (see the individual study C-04-08 report on Sub-Group analysis).

Appendix A

Package Insert (annotated)

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___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Appendix B

Clinical Pharmacology and Biopharmaceutics
Individual Study Review

- Study C-04-08

NDA: 21-862/Study C-04-08 **Study Dates: June '04 – Jul '04**

A Double-Masked, Multiple-Dose, Safety and Pharmacokinetic Study of 0.1% Nepafenac Ophthalmic Suspension TID in Healthy Subjects

Objective: The primary objective of this study was to determine the steady-state pharmacokinetics of nepafenac and the active metabolite amfenac following TID dosing of Nepafenac Ophthalmic Suspension, 0.1%.

Overall Study Design: This was a single-center, placebo-controlled, double-masked, randomized, parallel-group comparison in 20 healthy subjects (18 – 64 years, 10 M and 10 F) who were randomly assigned to receive Nepafenac Ophthalmic Suspension, 0.1% or vehicle during a 4-day period. Sixteen received Nepafenac Ophthalmic Suspension, 0.1% and 4 received vehicle. The plasma samples from the vehicle group were not assayed. Therefore, data from 16 subjects were available for pharmacokinetic analysis, and 20 subjects were available for safety analyses.

Subjects received TID dosing (one drop of test article in each eye) on Days 1, 2, and 3. On Day 4, subjects received test article only once in the morning. On the morning of Days 1 and 4, predose plasma PK samples were collected. Plasma PK samples were then collected 10, 20, 30, 45 minutes and 1, 2, 3, 5, and 8 hours after the dose. On the morning of the Days 2 and 3, trough plasma PK samples were collected before the morning administration of test article. After the 8-hour sample collection on Day 4, exit procedures were performed, and the subjects were discharged.

Nepafenac and amfenac plasma concentrations were determined using a validated method with a limit of quantitation of ng/ml for nepafenac and ng/ml for amfenac.

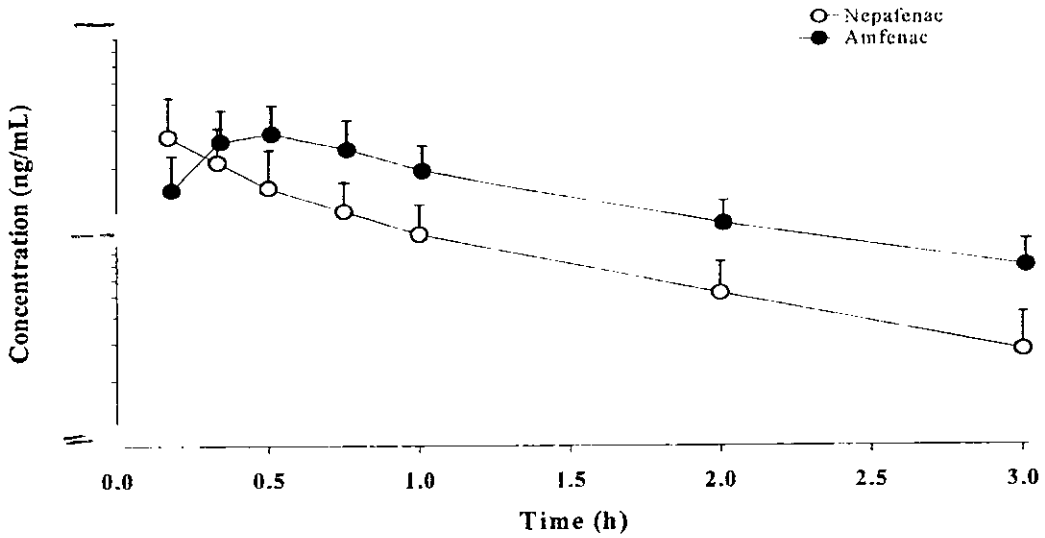
Results:

Nepafenac Data Set: Quantifiable nepafenac plasma concentrations (ng/mL) on Days 1 and 4 were available for all 16 subjects receiving Nepafenac Ophthalmic Suspension, 0.1% out to the 2-hour post-dose timepoint except for Subject # 103. Subject # 103 had quantifiable plasma concentrations only out to the 1-hour timepoint after dosing on Day 1. There were 11 subjects on Day 1 (Subjects 101, 102, 104, 107, 108, 201, 202, 206, 207, 208, and 210) and 8 subjects on Day 4 (Subjects 104, 201, 202, 203, 205, 206, 207, and 210) for whom the nepafenac concentrations were quantifiable out to 3-hours post-dose. Additionally, there was 1 subject on Day 4 (Subject # 208) for whom the nepafenac concentrations were measurable out to the 5-hour timepoint. Pharmacokinetic parameters (C_{max}, T_{max}, $t_{1/2}$, AUC_{0-2}, and AUC_{0-inf}) were reported for all subjects, with one exception being, that $t_{1/2}$, AUC_{0-2}, and AUC_{0-inf} were not determined for Subject # 103 after the first dose on Day 1. The AUC over the 8-hour dosing interval

(AUC_{0-8}) was estimated based on the interpolated concentrations from the area to the infinity extrapolation.

Amfenac Data Set: Quantifiable amfenac plasma concentrations (≥ — ng/mL) on Days 1 and 4 were available for all 16 subjects receiving Nepafenac Ophthalmic Suspension, 0.1% out to the 3-hour postdose timepoint, except for Subjects 106 and 208. Subject # 106 had quantifiable plasma concentrations out to the 1-hour timepoint on Day 1 and out to the 2-hour timepoint on Day 4. Subject # 208 had quantifiable plasma concentrations out to the 2-hour timepoint on Day 1 and out to the 3-hour timepoint on Day 4. There were 6 subjects on Day 4 (Subjects 101, 107, 110, 202, 203, and 210) and 5 subjects on Day 4 (Subjects 102 103, 104 108, and 201) for whom amfenac concentrations were quantifiable up to 5-hours and 8-hours postdose, respectively. Pharmacokinetic parameters (C_{max}, T_{max}, $t_{1/2}$, AUC_{0-t}, AUC_{0-8}, and AUC_{0-inf}) were reported for all subjects, with two exceptions. For Subject # 106, Day 1 $t_{1/2}$, AUC_{0-3}, and AUC_{0-inf} values and Day 4 AUC_{0-3} were not calculated because of limited data. For Subject # 208, AUC_{0-3} was not calculated after the first dose on Day 1. The AUC over the 8-hour dosing interval (AUC_{0-8}) was estimated based on the interpolated concentrations from the area to the infinity extrapolation.

Single Dose Pharmacokinetics: Following first administration of Nepafenac Ophthalmic Suspension, 0.1%, measurable plasma concentrations of nepafenac (≥ — ng/mL) and amfenac (≥ — ng/mL) were seen at the first sampling time (10 minutes) in the majority of subjects. Mean (± SD) Day 1 Nepafenac and Amfenac Plasma Profiles After a Single Dose of Nepafenac Ophthalmic Suspension, 0.1% in Healthy Subjects is presented in the following Figure: (Semi-log scale, sample times are offset for clarity; N = 16)



* Nepafenac and amfenac concentrations below the limit of quantitation (— ıg/mL and — ıg/mL, respectively) were replaced with one half the limit of quantitation for the calculation of mean plasma concentrations. Mean concentrations beyond 3 hours were BLQ and therefore are not presented.

Plasma concentrations of nepafenac and amfenac reached maximal levels, on average within 0.21 ± 0.08 hours (range 0.17 to 0.37 hours) and 0.48 ± 0.10 hours (range 0.33 to 0.75 hours) after dosing, respectively (Table 1). Following the peak, plasma concentrations of nepafenac and amfenac declined monophasically with mean $t_{1/2}$ values of 1.1 ± 0.4 hours (range 0.4 to 2.1 hours) for nepafenac and 1.5 ± 0.5 hours (range 0.9 to 3.0 hours) for amfenac.

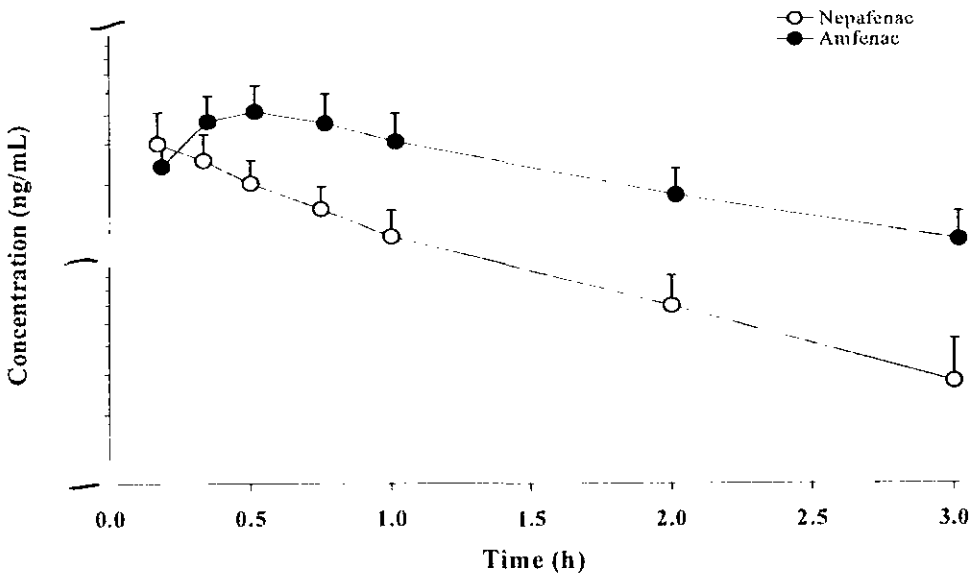
The mean peak plasma concentration (C_{max}) for nepafenac was 0.276 ± 0.146 ng/mL (range 0.077 to 0.608 ng/mL) and for amfenac was 0.293 ± 0.107 ng/mL (range 0.106 to 0.504 ng/mL) (Table 1).

Table 1: Mean ± SD (range) Day 1 Nepafenac and Amfenac Pharmacokinetic Parameters After a Single Dose of Nepafenac Ophthalmic Suspension, 0.1% in Healthy Subjects

Pharmacokinetic Parameters	Nepafenac (N = 16)	Amfenac (N = 16)
C_{max} (ng/mL)	0.276 ± 0.146 (0.077 – 0.608)	0.293 ± 0.107 (0.106 – 0.504)
T_{max} (h)	0.21 ± 0.08 (0.17 – 0.37)	0.48 ± 0.10 (0.33 – 0.75)
AUC_{0-t} (ng*h/mL)	0.241 ± 0.090[a, b] (0.111 – 0.406)	0.487 ± 0.117[c, d] (0.267 – 0.706)
AUC_{0-inf} (ng*h/mL)	0.323 ± 0.126 (0.080 – 0.597)	0.611 ± 0.164 (0.214 – 0.837)
$t_{1/2}$ (h)	1.1 ± 0.4 (0.4 –2.1)	1.5 ± 0.5 (0.9 – 3.0)

[a] = AUC_{0-2}; [b] N = 15; [c] = AUC_{0-3}; [d] N = 14

Multiple Dose Pharmacokinetics: Mean (± SD) plasma profiles of nepafenac and amfenac after multiple TID bilateral topical ocular dosing of Nepafenac Ophthalmic Suspension, 0.1% from the 16 subjects are presented in the following Figure (Semi-log scale, sample times are offset for presentation; N = 16) (semi-log).



* Nepafenac and amfenac concentrations below the limit of quantitation — ng/mL and — ng/mL, respectively) were replaced with one half the limit of quantitation for the calculation of mean plasma concentrations. Mean concentrations beyond 3 hour time BLQ and therefore are not presented.

Peak plasma concentrations (C_{max}) of nepafenac and amfenac after multiple topical dosing of Nepafenac Ophthalmic Suspension, 0.1% averaged 0.310 ± 0.104 ng/mL (range 0.140 to 0.523 ng/mL) and 0.422 ± 0.121 ng/mL (range 0.179 to 0.651 ng/mL), respectively (See Table 2).

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Table 2: Mean ± SD (range) Day 4 Nepafenac Plasma Pharmacokinetic Parameters After Multiple Dosing of Nepafenac Ophthalmic Suspension, 0.1% in Healthy Subjects

Pharmacokinetic Parameters	Nepafenac (N = 16)	Amfenac (N = 16)
C_{max} (ng/mL)	0.310 ± 0.104 (0.140 – 0.523)	0.422 ± 0.121 (0.179 – 0.651)
T_{max} (h)	0.25 ± 0.10 (0.17 – 0.50)	0.55 ± 0.14 (0.33 – 0.83)
AUC_{0-8} (ng*h/mL)	0.368 ± 0.106 (0.200 – 0.546)	0.976 ± 0.284 (0.382 – 1.41)
AUC_{0-inf} (ng*h/mL)	0.371 ± 0.109 (0.201 – 0.548)	1.03 ± 0.314 (0.390 – 1.45)
$t_{1/2}$ (h)	0.9 ± 0.2 (0.7 – 1.6)	1.6 ± 0.3 (1.2 – 2.3)

Sub-Group Analysis

Although the study was not designed to assess gender differences, with the enrollment of 8 males and 8 females, additional analyses were done to examine the effects of gender on the steady-state pharmacokinetics of nepafenac and amfenac. The mean pharmacokinetic parameters for nepafenac and amfenac by gender are presented in Tables 3 and 4, respectively. Two-sample t-test analysis showed statistically significant gender difference in C_{max} ($p = 0.0256$) and AUC_{0-8} ($p = 0.0022$) for nepafenac, but not for amfenac. When these pharmacokinetic parameters were normalized to 70 kg body weight ($C_{max, norm}$ and $AUC_{0-8, norm}$), no statistically significant ($p \geq 0.1912$) differences were seen for nepafenac in these parameters between males and females. There was no gender difference in T_{max} or $t_{1/2}$ for either nepafenac or amfenac.

Table 3: Mean ± SD (range) Nepafenac Plasma Pharmacokinetic Parameters by Gender After Multiple Dosing of Nepafenac Ophthalmic Suspension, 0.1% in Healthy Subjects

Pharmacokinetic Parameters	Male (N = 8)	Female (N = 8)	P values[a]
C_{max} (ng/mL)	0.254 ± 0.089 (0.140 – 0.381)	0.366 ± 0.090 (0.254 – 0.523)	0.0256
$C_{max,\ norm}$ (ng/mL)	0.305 ± 0.095 (0.190 – 0.432)	0.351 ± 0.093 (0.245 – 0.481)	0.3416
T_{max} (h)	0.27 ± 0.12 (0.17 – 0.5)	0.23 ± 0.08 (0.17 – 0.33)	0.4790
AUC_{0-8} (ng*h/mL)	0.295 ± 0.091 (0.200 – 0.459)	0.440 ± 0.062 (0.364 – 0.546)	0.0022
$AUC_{0-8,\ norm}$ (ng*h/mL)	0.357 ± 0.105 (0.224 – 0.538)	0.426 ± 0.097 (0.280 – 0.580)	0.1912
$t_{1/2}$ (h)	0.9 ± 0.3 (0.7 – 1.6)	1.0 ± 0.1 (0.8 – 1.2)	0.2623

[a] Two-sample t-test

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Table 4: Mean ± SD (range) Amfenac Plasma Pharmacokinetic Parameters by Gender After Multiple Dosing of Nepafenac Ophthalmic Suspension, 0.1% in Healthy Subjects

Pharmacokinetic Parameters	Male (N = 8)	Female (N = 8)	P values [a]
C_{max} (ng/mL)	0.376 ± 0.122 (0.179 – 0.537)	0.469 ± 0.107 (0.354 – 0.651)	0.1268
$C_{max,\ norm}$ (ng/mL)	0.455 ± 0.145 (0.242 – 0.648)	0.455 ± 0.134 (0.281 – 0.679)	0.9951
T_{max} (h)	0.52 ± 0.13 (0.35 – 0.83)	0.57 ± 0.16 (0.33 – 0.75)	0.5069
AUC_{0-8} (ng*h/mL)	0.963 ± 0.327 (0.382 – 1.34)	0.989 ± 0.257 (0.698 – 1.41)	0.8622
$AUC_{0-8,\ norm}$ (ng*h/mL)	1.17 ± 0.39 (0.517 – 1.52)	0.959 ± 0.310 (0.570 – 1.47)	0.2595
$t_{1/2}$ (h)	1.7 ± 0.4 (1.2 – 2.3)	1.5 ± 0.3 (1.2 – 2.0)	0.2084

[a] Two-sample t-test

Discussion: Following bilateral topical ocular TID dosing of Nepafenac Ophthalmic Suspension, 0.1%, low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects out to 2 and 3 hours postdose, respectively. The mean steady-state C_{max} (0.422 ± 0.121 ng/ml) for amfenac following bilateral topical TID administration of Nepafenac Ophthalmic Suspension, 0.1% is approximately 1,659 times lower than the mean C_{max} (0.7 µg/ml) observed in subjects who received multiple 50 mg oral doses of amfenac. Based on very limited numbers of quantifiable trough samples for nepafenac and amfenac and elimination half-lives, it is predicted that steady-state will be achieved by Day 2. Given quantifiable plasma concentrations of both nepafenac and amfenac were obtained only out to the 3-hour timepoint after dosing, no accumulation is expected.

Reviewer's comments:

Based on pharmacokinetic data available from healthy subjects, Nepafenac ophthalmic suspension, 0.1% has demonstrated low systemic exposure following topical ocular TID dosing. However, this study was conducted in healthy volunteers. It is expected that patients with cataract surgery will not have much of a difference in terms of systemic exposure of this drug product.

Appendix C

OCPB Filing Form

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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-862	Brand Name	Nevanac
OCPB Division (I, II, III)	III	Generic Name	1%Nepafenac Suspension
Medical Division	HFD-540	Drug Class	NSAID
OCPB Reviewer	Tapash K. Ghosh, Ph.D.	Indication(s)	Treatment of cataract pain
OCPB Team Leader	Edward D. Bashaw, Pharm.D.	Dosage Form	Ophthalmic suspension
		Dosing Regimen	TID
Date of Submission	2/27/05	Route of Administration	Topical
Estimated Due Date of OCPB Review	6/27/05	Sponsor	Alcon
PDUFA Due Date	8/27/05	Priority Classification	3S
Division Due Date	7/27/05		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
eers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X			
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference.				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	1			

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included) FDA letter date if applicable.
QBR questions (key issues to be considered)	• **Systemic exposure of nepafenac and amfenac from ophthalmic suspension compared to oral administration**	
Other comments or information not included above		
Primary reviewer Signature and Date	*Tapash K. Ghosh 03-15-05*	
Secondary reviewer Signature and Date	*Edward D. Bashaw 03-15-05*	

CC: NDA 21-862, HFD-850 (Electronic Entry or Lee), HFD-540(F. Cross), HFD-880 (TL, DD, DDD),

CDR (B. Murphy)

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/s/

Tapash Ghosh
7/21/05 05:16:19 PM
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Dennis Bashaw
7/25/05 03:27:55 PM
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