

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
203491Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

ONDQA (Biopharmaceutics) Review

505(b)(2) NDA	203-491 (000)
Applicant:	Alcon Research, Ltd.
Trademark:	Not proposed
Stamp Date	December 16, 2011
Established Name:	Nepafenac Ophthalmic Suspension 0.3%
Dosage Form:	Ophthalmic suspension
Route of Administration:	Topical
Indication:	Treatment of pain and inflammation associated with cataract surgery
Reviewer	Tapash Ghosh, Ph.D.

Background: NEVANAC[®] (nepafenac), a non-steroidal anti-inflammatory pro-drug to amfenac, was approved by the FDA in 2005 under NDA 21-862 as a 0.1% ophthalmic suspension.

Submission: The current NDA 203-491 under review provides for an increased concentration (0.3%) of nepafenac. Nepafenac 0.3% dosed once a day is reported to be as efficacious as nepafenac 0.1% dosed 3 times a day.

In this submission the Applicant requested a biowaiver in section 1.12.13. Additionally, in the NDA's filing communication dated Feb 24, 2012, FDA requested the submission of the *in vitro* drug release profile data from the biobatches and stability batches supporting the selection of the proposed acceptance criteria (i.e., specification-sampling time points and specification values). These two (2) issues are the subject of this review.

BIOPHARMACEUTICS EVALUATION:

Biowaiver:

On September 7, 2012, the Applicant was asked to clarify the purpose of their biowaiver request. In a response via e-mail, the applicant confirmed that it was an error from their side. No biowaiver request should have been made in this submission (see E-mail response in Attachment 1).

Reviewer's Comment: *The reviewer acknowledges the applicant's response and therefore evaluation of the biowaiver request is not longer needed.*

In Vitro Drug Release:

The Agency requested in the NDA's filing communication dated Feb 24, 2012, that the Applicant provide the *in vitro* drug release profile data from the biobatches and stability batches supporting the selection of the acceptance criteria for their product. The acceptance criteria will be finalized upon review of the overall *in vitro* drug release data. The Applicant was reminded on September 7, 2012, to respond to the issue. The applicant responded officially on September 12, 2012, with their explanation as excerpted below:

Nepafenac Ophthalmic Solution, 0.3% NDA 203,491

1.11.1. Quality Information Amendment

ISSUE of 07 September 2012:

In addition, we requested in the filing communication dated Feb 24th, that the applicant provide the in vitro drug release profile data from the biobatches and stability batches supporting the selection of the acceptance criteria (i.e., specification-sampling time points and specification values). The acceptance criteria will be finalized upon review of the overall in vitro drug release data.

It is to let you know that for ophthalmic suspension, there can be in-vitro release test and specification for QC purpose where in-vitro release rate is monitored as a function of time and rate (slope) is used as a regulatory specification for release and stability. Therefore it was mentioned in the filing letter. However, as you do not have it, we will not require it for approval purpose of your product. We may require it in future and/or for future products.

Please mention that you do not have it in your amendment to the NDA.

The Applicant's Response:

Alcon acknowledges the request for *in-vitro* drug release data as well as the test and specification. Alcon has not generated *in-vitro* drug release data on Nepafenac Ophthalmic Suspension, 0.3% as it is a topical ophthalmic suspension rather than an injectable ophthalmic suspension. Drug release is not a necessary test to ensure product performance of this product. Product performance for Nepafenac Ophthalmic Suspension, 0.3%, is ensured by setting specifications for drug particle size, suspension redispersibility, and viscosity. In addition, product polymorphism studies indicated that this product showed no change in crystallographic form during stability studies (see Section 3.2.P.2.2, TDOC-0014601).

Reviewer's Comment: *The reviewer acknowledges the Applicant's response and therefore a review of the in-vitro drug release data was not necessary.*

RECOMMENDATION

From the Biopharmaceutics view point NDA 203-491 for Nepafenac Ophthalmic Suspension 0.3% is recommended for APPROVAL.

Tapash K. Ghosh, Ph. D.
Primary Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

ATTACHMENT 1

From: Schafer,Norma,FORT WORTH,Regulatory Affairs [mailto:Norma.Schafer@AlconLabs.com]
Sent: Friday, September 07, 2012 9:42 AM
To: Cuff, Althea
Subject: RE: NDA 203491

Hi Althea,
I am convinced that it is an error. Do you need a document stating that it is in error?
Norma

From: Cuff, Althea [mailto:Althea.Cuff@fda.hhs.gov]
Sent: Friday, September 07, 2012 8:38 AM
To: Schafer,Norma,FORT WORTH,Regulatory Affairs
Subject: NDA 203491

Good Morning Norma,

You requested a biowaiver in section 1.12.13. Please clarify exactly for what purpose you are requesting biowaiver? Please respond as soon as possible.

Thanks
Althea Cuff, MS
Regulatory Health Project Manager
Food & Drug Administration, CDER
Office of New Drugs Quality Assessment II
301-796-4061

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAPASH K GHOSH
09/14/2012

ANGELICA DORANTES
09/14/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	203-491
Submission Date(s):	December 15, 2011
Proposed Brand Name	██████████ (b)
Generic Name	Nepafenac
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DTOP
Applicant	Alcon Research, Ltd.
Submission Type; Code	3S (New formulation ; Standard review)
Formulation; Strength(s)	Nepafenac Ophthalmic Suspension, 0.3%
Indication	Treatment of pain and inflammation associated with cataract surgery
Dosage and Administration	One drop applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30-120 minutes prior to surgery.

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1. EXECUTIVE SUMMARY

Nepafenac (amfenac amide) is a prodrug which is converted to amfenac by intraocular hydrolyses. Amfenac inhibits cyclooxygenase activity, an enzyme required for prostaglandin production. Nepafenac 0.1% ophthalmic suspension (NEVANAC[®]) dosed 3 times daily is currently marketed for treatment of pain and inflammation associated with cataract surgery. In the current submission, the sponsor proposes a once-daily formulation with a higher concentration (i.e., Nepafenac 0.3% ophthalmic suspension) to reduce the dosing frequency and seeks the same indication as Nepafenac ophthalmic suspension, 0.1%.

In support of the NDA, the Applicant submitted clinical studies including:

- One Phase 1 study (C-09-053) to assess the systemic PK of nepafenac and its pharmacologically active metabolite (amfenac) following single and multiple dose of Nepafenac 0.3% Ophthalmic Suspension in healthy subjects.
- One Phase 3 study (C-09-055) to determine whether Nepafenac 0.3% dosed once a day was noninferior to Nepafenac 0.1% dosed 3 times a day for the prevention and treatment of pain and inflammation associated with cataract surgery.
- One Phase 3 study (C-11-003) to determine whether Nepafenac 0.3% dosed once a day had a clinical benefit over Nepafenac 0.1% dosed once a day in a head-to-head comparison.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in the NDA submission is acceptable.

The reviewer's proposed label changes in *Appendix 4.1* will be forwarded to the sponsor.

1.2. Phase IV Commitments

None.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Following bilateral topical ocular dosing of 1 drop of Nepafenac 0.3% Ophthalmic Suspension once daily for 4 days, the mean nepafenac and active metabolite (amfenac) plasma concentration versus time profiles on Day 1 and Day 4 were similar, indicating no accumulation. The mean steady-state C_{max} for nepafenac and amfenac were 0.847 ± 0.269 ng/ml and 1.13 ± 0.491 ng/ml, respectively, following topical ocular administration of Nepafenac 0.3% Ophthalmic Suspension.

In vitro studies suggested that nepafenac at concentrations up to 3000 ng/mL did not inhibit in vitro metabolism of CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Similarly, in vitro studies suggested that amfenac at concentrations up to 1000 ng/mL did not inhibit the metabolism of CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Therefore, drug-drug interactions involving CYP mediated metabolism of concomitantly administered drugs are unlikely following topical ocular administration of Nepafenac 0.3% Ophthalmic Suspension.

Yongheng Zhang, Ph.D.
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

Concurrence:

Philip Colangelo, Pharm.D.; Ph.D.
Team Leader
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

cc:

Division File: NDA 200-740/HFD-520 (CSO/Ng)/HFD-520 (MO/Lloyd)/HFD-520
(Chambers)/HFD-880 (Lazor)

2. QUESTION BASED REVIEW

Nepafenac has been approved for use in NEVANAC® (nepafenac ophthalmic suspension) 0.1% (NDA 21-862) in 2005. Therefore, only relevant questions from the OCP question-based review (QBR) format are addressed below. Please refer to the Clinical Pharmacology Review on NDA 21-862 by Dr. Tapash Ghosh dated 25July2005 for additional information.

2.1. General Attributes of the Drug

2.1.1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

Nepafenac has been approved for use in NEVANAC® (nepafenac ophthalmic suspension) 0.1% (NDA 21-862) in 2005. Nepafenac (AL-6515) is a stable, anti-inflammatory pro-drug substance provided as a yellow crystalline or powder substance.

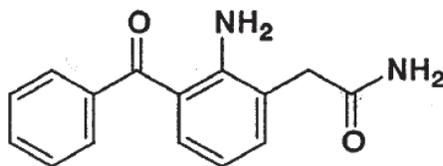
Structural Formula: $C_{15}H_{14}N_2O_2$

Molecular Weight: (b) (4) Dalton

CAS Index Name: 78281-72-8

Chemical Name: 2-Amino-3-benzoylbenzeneacetamide

Chemical Structure:



Drug Product:

The components of Nepafenac Ophthalmic Suspension, 0.3%, their concentration, function and compendial status are listed in **Table 2.1.1-1**.

Table 2.1.1-1: Composition of the Nepafenac Ophthalmic Suspension, 0.3% FID 115535

Component	Percent w/v	Function	Compendial Status		
Nepafenac (AL-6515)	0.3	Active Ingredient	Non-compendial ^a		
Benzalkonium Chloride	0.005 ^b	Antimicrobial Agent	NF		
Carboxymethylcellulose Sodium ^{(b) (4)}			USP		
Guar Gum			NF		
Carbomer 974P			NF ^c		
Boric Acid			NF		
Edetate Disodium			USP		
Propylene Glycol			USP		
Sodium Chloride			USP		
Sodium Hydroxide and/or Hydrochloric Acid			QS for pH adjustment	pH Adjustment	NF
Purified Water					NF
					USP

Note: FID = Formulation Identification Number

^a Meets in-house monograph

(b) (4)

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

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 hydrolyses. The prodrug has relatively weak cyclooxygenase inhibitory activity whereas amfenac exhibits potent cyclooxygenase inhibitory activity.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

One drop of Nepafenac Ophthalmic Suspension, 0.3% applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In support of the NDA, the Applicant submitted clinical studies including:

- One Phase 1 study (C-09-053) to assess the systemic PK of nepafenac and its pharmacologically active metabolite (amfenac) following single and multiple dose of Nepafenac 0.3% Ophthalmic Suspension in healthy subjects.
- One Phase 3 study (C-09-055) to determine whether Nepafenac 0.3% dosed once a day was noninferior to Nepafenac 0.1% dosed 3 times a day for the prevention and treatment of pain and inflammation associated with cataract surgery.
- One Phase 3 study (C-11-003) to determine whether Nepafenac 0.3% dosed once a day had a clinical benefit over Nepafenac 0.1% dosed once a day in a head-to-head comparison.

Based on these studies, the sponsor proposed a once-daily formulation with a higher concentration (i.e., Nepafenac 0.3% ophthalmic suspension) to reduce the dosing frequency and seeks the same indication as Nepafenac ophthalmic suspension, 0.1%.

2.2.2. *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

Yes, the sponsor used validated LC/MS/MS methods to quantitate plasma concentrations of both nepafenac and the active metabolite, amfenac. (Refer to Section 2.6).

2.2.3. *What are the PK characteristics of the drug?*

2.2.3.1 *What are the single dose and multiple dose PK parameters?*

Following bilateral topical ocular dosing of 1 drop of Nepafenac 0.3% Ophthalmic Suspension once daily for 4 days, the mean nepafenac and active metabolite (amfenac) plasma concentration versus time profiles on Day 1 and Day 4 were similar, indicating no accumulation (see Tables below). The mean steady-state C_{max} for nepafenac and amfenac were 0.847 ± 0.269 ng/mL and 1.13 ± 0.491 ng/mL, respectively, following ocular administration of Nepafenac 0.3% Ophthalmic Suspension.

Table 2.2.3.1-1: Comparison of Mean (SD) Pharmacokinetic Parameters of Nepafenac on Day 1 and Day 4 After Once Daily Bilateral Topical Ocular Instillation of 1 Drop of Nepafenac Ophthalmic Suspension, 0.3% in 12 Healthy Subjects (From NDA203491 Section 2.7.2 Page 10)

	C _{max} (ng/mL) (n = 12)	T _{max} ^a (hr) (n = 12)	AUC _{0-t} (ng*hr/mL) (n = 12)	AUC _{0-∞} (ng*hr/mL) (n = 12)	CL/F ^b (L/hr) (n = 12)	k _{el} (1/hr) (n = 12)	t _{1/2} ^a (hr) (n = 12)
Day 1	0.921 (0.326)	0.50 (0.33 – 0.75)	1.50 (0.730)	1.57 (0.721)	1800 (755)	0.824 (0.212)	0.85 (0.54 – 1.63)
Day 4	0.847 (0.269)	0.42 (0.33 – 0.75)	1.34 (0.522)	1.43 (0.533)	1820 (514)	0.873 (0.286)	0.74 (0.49 – 1.85)

^aT_{max} and t_{1/2} are expressed as median with range (minimum to maximum)

^bValues for CL/F converted to L/hr from mL/hr by dividing by 1000 and rounding to 4 digits.

Table 2.2.3.1-2: Comparison of Mean (SD) Pharmacokinetic Parameters of Amfenac on Day 1 and Day 4 After Once Daily Bilateral Topical Ocular Instillation of 1 Drop of Nepafenac Ophthalmic Suspension, 0.3% in 12 Healthy Subjects (*From NDA203491 Section 2.7.2 Page 13*)

	C_{max} (ng/mL) (n = 12)	T_{max}^a (hr) (n = 12)	AUC_{0-t} (ng*hr/mL) (n = 12)	$AUC_{0-\infty}$ (ng*hr/mL) (n = 12)	k_{el} (1/hr) (n = 12)	$t_{1/2}$ (hr) (n = 12)
Day 1	1.15 (0.476)	0.75 (0.50 – 1.00)	3.28 (1.46)	3.60 (1.44)	0.144 (0.0488)	5.49 (2.95 – 7.36)
Day 4	1.13 (0.419)	0.75 (0.50 – 1.00)	3.33 (1.31)	3.70 (1.43)	0.127 (0.0486)	6.26 (3.28 – 10.55)

^a T_{max} and $t_{1/2}$ are expressed as median with range (minimum to maximum)

2.2.3.2. *How does the PK of the drug in healthy volunteers compare to that in patients?*

Nepafenac PK following topical ocular administration was only evaluated in healthy subjects.

2.3. Intrinsic Factors

2.3.1. *What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?*

The effect of the commonly known intrinsic factors including race, gender and age on the PK of nepafenac following topical administration of Nepafenac 0.3% ophthalmic suspension has not been studied. Given the low systemic exposure following topical administration, however, dose adjustment is not warranted in patients based on the commonly known intrinsic factors.

2.4. Extrinsic Factors

2.4.1. *What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?*

Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

The impact of the commonly known extrinsic factors on nepafenac / amfenac dose-exposure and/or exposure–response has not been evaluated. Because of the systemic exposure is low, the impact, if any, would not be clinically significant. Therefore, no dosage adjustments for extrinsic factors are recommended.

2.4.2. *Drug-drug interactions*

2.4.2.1. *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

No. Nepafenac is a prodrug that penetrates the cornea and is converted to the active moiety amfenac by intraocular hydrolases.

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Nepafenac is a prodrug that penetrates the cornea and is converted to the active moiety amfenac by intraocular hydrolayses. It is unknown if amfenac, which is further cyclized into amfenac lactam in vivo, is a susbstrate of CYP enzymes or not. It is also unknown if metabolism of nepafenac and amfenac is influenced by genetics or not.

2.4.2.3. Is the drug an inhibitor and/or an inducer of CYP enzymes?

In vitro studies suggested that nepafenac at concentrations up to 3000 ng/mL did not inhibit in vitro metabolism of CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Similarly, In vitro studies suggested that amfenac at concentrations up to 1000 ng/mL did not inhibit in vitro metabolism of CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4.

2.4.2.4. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No transporter studies were performed by the sponsor, thus, it is unknown if nepafenac or amfenac is an inhibitor and/or substrate of P-glycoprotein transport process.

2.4.2.5. Are there other metabolic/transporter pathways that may be important?

Using radiochromatographic analysis on plasma and urine from healthy subjects after a single 10 mg (98 µCi) oral dose of ¹⁴C-Nevanac (*study not reviewed*), the results showed that nepafenac is metabolized into amfenac and glucuronide conjugates. Therefore, the glucuronidation pathway may be important in metabolism of nepafenac and amfenac in vivo.

2.4.2.6. Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No, the label does not specify co-administration of another drug.

2.4.2.7. What other co-medications are likely to be administered to the target patient population?

No other co-administered drugs can be specified.

2.4.2.8. Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No in vivo drug-drug interaction studies have been conducted.

2.4.2.9. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known mechanistic basis for PD drug-drug interactions.

2.4.2.10. Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no unresolved questions related to active metabolites and metabolic drug interactions.

2.4.3. *What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?*

No issues related to dose, dosing regimens, or administration remain unresolved.

2.5. **General Biopharmaceutics**

Not applicable. Nepafenac is formulated as an ophthalmic solution for topical ocular administration.

2.6. **Analytical Section**

2.6.1. *How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?*

Plasma concentrations for nepafenac and amfenac were determined using validated HPLC/MS/MS methods. The nepafenac and amfenac assay methods were validated with respect to accuracy, precision, and sample stability consistent with the sample collection and storage procedures. The (b)(4) of nepafenac and amfenac were used as internal standards.

2.6.2. *Which metabolites have been selected for analysis and why?*

Amfenac was selected for analysis because it is the primary and pharmacologically active metabolite of nepafenac.

2.6.3. *For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?*

Total nepafenac and amfenac concentrations in the plasma were measured. Free concentrations in the plasma are not considered clinically relevant following ocular topical administration.

2.6.4. *What bioanalytical methods are used to assess concentrations?*

Refer to Section 2.6.1. for further information.

2.6.4.1. *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

The standard curve in plasma ranges from 0.05 ng/mL to 20 ng/mL and from 0.025 ng/mL to 20 ng/mL for nepafenac and amfenac, respectively. The ranges of standard curve are adequate for purposes of determining plasma concentrations of nepafenac and amfenac in the clinical studies.

2.6.4.2. *What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

The LLOQ and ULOQ for nepafenac are 0.05 ng/mL and 20 ng/mL in the undiluted plasma sample, respectively. The LLOQ and ULOQ for amfenac are 0.025 ng/mL and 20 ng/mL in the undiluted plasma sample, respectively.

2.6.4.3. *What are the accuracy, precision, and selectivity at these limits?*

The assay accuracy and precision were determined from the assay standards and QCs. For both nepafenac and amfenac, the accuracy and precision values are satisfactory. Assay selectivity was confirmed by analyzing individual or pooled human plasma samples and none yielded interfering peaks when concentrations were above LLOQ.

2.6.4.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Both analytes were stable: in reconstituted sample extracts, for at least 193 hours at room temperature and for at least 195 hours re-injected against the original calibration curves, and for > 69 hours under refrigeration. Long-term frozen storage stability demonstrated at -20°C and -70°C for at least 156 days and 297 days for nepafenac and amfenac, respectively. Stock solution stability demonstrated at 4°C for at least 353 days for nepafenac and for at least 342 days for amfenac. Stock solution stability demonstrated at room temperature for up to 26 hours for both nepafenac and amfenac.

2.6.4.5. What is the QC sample plan?

QCs prepared in plasma at concentrations of 0.075, 8.00, 15.0 ng/mL of nepafenac or amfenac were included in each analysis. Between-run and within-run accuracy and precision were evaluated using replicates from each of these concentrations were included in each analysis.

3. LABELING RECOMMENDATIONS

See Appendix 4.1. for detail.

4. APPENDICES

4.1. Proposed Package Insert (Original and Annotated) with Clinical Pharmacology edits (noted as underline and strikethrough) as of 19July2012

1 Page of Draft Labeling has been Withheld in Full as b4(CCI/TS) immediately following this page.

4.2. Individual Study Reviews

4.2.1. Pharmacokinetics of Nepafenac in healthy subjects: Study C-09-053

Study Number: C-09-053

A Pharmacokinetic and Safety Study of Nepafenac Ophthalmic Suspension, 0.3% in Healthy Subjects

Dates: 29 June, 2010 to 19 July, 2010

Study Director: C. James Kissling, MD, Covance Clinical Research Unit Inc.

Analytical site: (b) (4)

OBJECTIVES:

The objective was to assess the systemic pharmacokinetics of nepafenac and its pharmacologically active metabolite (amfenac) after a single dose and at steady-state following once daily topical ocular dosing of Nepafenac Ophthalmic Suspension, 0.3% for 4 days in healthy subjects. The secondary objective was to assess the safety of Nepafenac Ophthalmic Suspension, 0.3% following once daily dosing for 4 days in healthy subjects.

FORMULATION & ADMINISTRATION

Nepafenac Ophthalmic Suspension, 0.3% and vehicle control (Lot no. 10-501170-1); One drop in each eye in the morning on Days 1 through 4.

STUDY DESIGN:

This study was a single center, randomized, double-masked, vehicle-controlled, parallel-group study designed to evaluate the pharmacokinetics and safety of Nepafenac Ophthalmic Suspension, 0.3% and its pharmacologically active metabolite (amfenac) following bilateral, topical, ocular administration once daily for 4 days in healthy subjects ≥ 18 years of age (Total $n=20$; $n=12$ for nepafenac group; $n=8$ for control group).

Blood samples for pharmacokinetic analysis:

- A predose sample collected prior to administration of the first dose;
- Serial samples collected at 0.17 (10 min), 0.33 (20 min), 0.5 (30 min), 0.75 (45 min), 1, 2, 3, 4, 5, 8, 12, and 24 hours after the dose On Days 1 and 4;
- Predose samples collected within 30 minutes prior to dosing on Day 3 and Day 4 for determination of steady-state.

Demographic characteristics are summarized in **Table 1**.

Table 1: Demographic Characteristics by Treatment Groups

	Total		Nepafenac 0.3%		Vehicle	
	N	%	N	%	N	%
Total	20	100.0	12	100.0	8	100.0
Age						
Adults (18 to 64 years)	20	100.0	12	100.0	8	100.0
Elderly (65 years or older)	0	0.0	0	0.0	0	0.0
Sex						
Male	10	50.0	7	58.3	3	37.5
Female	10	50.0	5	41.7	5	62.5
Ethnicity						
Hispanic, Latino, or Spanish	10	50.0	6	50.0	4	50.0
Not Hispanic, Latino, or Spanish	10	50.0	6	50.0	4	50.0
Race						
White	14	70.0	9	75.0	5	62.5
Black or African American	4	20.0	2	16.7	2	25.0
Asian	2	10.0	1	8.3	1	12.5
Iris Color						
Brown	16	80.0	10	83.3	6	75.0
Hazel	1	5.0	1	8.3	0	0.0
Green	1	5.0	0	0.0	1	12.5
Blue	2	10.0	1	8.3	1	12.5

ASSAY METHODOLOGY:

Plasma concentrations for nepafenac (AL-6515) and amfenac (AL-6295) were determined using validated HPLC/MS/MS methods. The nepafenac and amfenac assay methods were validated with respect to accuracy, precision, and sample stability consistent with the sample collection and storage procedures. The (b)(4) analogs of nepafenac and amfenac were used as internal standards. The plasma C_{max}, area under the concentration-time curves (AUC_{0-t}, AUC_{0-∞}) and t_{1/2} for both nepafenac and amfenac were estimated using a non-compartmental analysis.

Following solid-phase extraction, for the mass spectral detection, the multiple reaction monitoring (MRM) transitions of m/z 255.2 → 210.2, 260.2 → 215.2, 254.1 → 210.0 and 259.1 → 215.0 were for nepafenac, (b)(4), amfenac and (b)(4), respectively.

This assay was calibrated using a standard curve generated from nine non-zero nepafenac (0.025, 0.035, 0.050, 0.100, 0.500, 1.00, 5.00, 10.0 and 20.0) and seven non-zero amfenac standards (0.050, 0.100, 0.500, 1.00, 5.00, 10.0 and 20.0). In addition, QCs prepared in plasma at concentrations of 0.075, 8.00, 15.0 ng/mL of nepafenac or amfenac were included in each analysis.

Criterion	Nepafenac	Amfenac	Comments
Conc. range, ng/mL	0.05-20.0 (0.5 mL sample)	0.025-20.0 (0.5 mL sample)	satisfactory
LLOQ, ng/mL	0.05	0.025	satisfactory
Linearity, r ²	>0.99	>0.99	satisfactory
Accuracy, % RE	94.2% – 105% ^a At least 67% of samples in 4 of 5 runs ≤ 15% ^b At least 67% of all samples ≤ 15% ^c	94.4% – 102% ^a At least 67% of samples in 3 of 5 runs ≤ 15% ^b At least 67% of all samples ≤ 15% ^c	Satisfactory

Precision, % CV	2.26% – 6.91 % ^a ≤ 15 % ^b ≤ 15 % ^c	2.83% – 9.43% ^a ≤ 15 % ^b ≤ 15 % ^c	Satisfactory
Selectivity	Control plasma from 10 individual donors and three lots of pooled control human plasma samples yielded no interfering peaks when ≥ 0.0250 ng/mL	Control plasma from 10 individual donors and three lots of pooled control human plasma samples yielded no interfering peaks when ≥ 0.0500 ng/mL	Satisfactory
Recovery	Low and high QC samples: 50.4% – 65.4%	Low and high QC samples: 54.0% – 77.1%	Satisfactory
Stability	In reconstituted sample extracts, stable for at least 193 hours at room temperature and for at least 195 hours re-injected against the original calibration curve for both analytes; Stable for > 69 hours under refrigeration for both analytes; Long-term frozen storage stability demonstrated at -20°C and -70°C for at least 156 days and 297 days for nepafenac and amfenac, respectively; Stock solution stability demonstrated at 4°C for at least 353 days for nepafenac and for at least 342 days for amfenac; Stock solution stability demonstrated at room temperature for up to 26 hours for both nepafenac and amfenac.		Satisfactory

^a, Inter- and Intra assay for standards; ^b, Intra-assay for QCs; ^c, Inter-assay for QCs

From Document TDOC-0001752

DATA ANALYSIS

Descriptive statistics were used to summarize the systemic pharmacokinetic parameters of nepafenac and amfenac including C_{max} , T_{max} , AUC_{0-t} , AUC_{0-inf} , $t_{1/2}$, k_{el} , and CL/F (nepafenac only).

RESULTS:

Pharmacokinetics

Following bilateral topical ocular dosing of 1 drop of Nepafenac 0.3% Ophthalmic Suspension once daily for 4 days, the mean nepafenac (AL-6515) and amfenac (AL-6295) plasma concentration versus time profiles on Day 1 and Day 4 were similar, indicating no accumulation (**Figure 1**). PK parameters Day 1 vs. Day 4 are comparable for both nepafenac and amfenac (**Table 1** and **Table 2**, respectively).

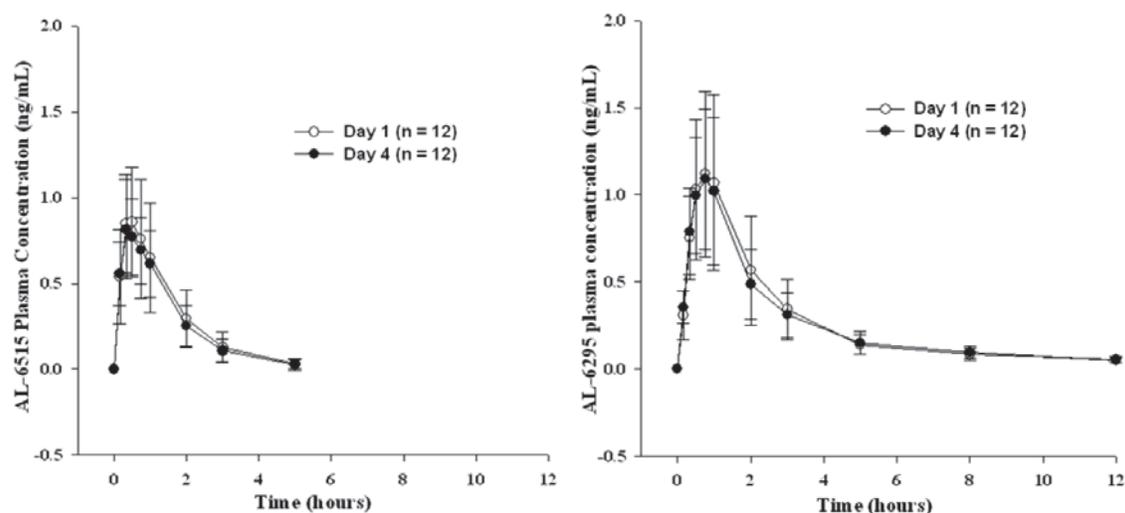


Figure 1: Plasma-Concentration Time Profile of Nepafenac (AL-6515) and Amfenac (AL-6295) After Once Daily Bilateral Topical Ocular Instillation of 1 Drop of Nepafenac Ophthalmic Suspension, 0.3% in 12 Healthy Subjects (From NDA203491 Section 2.7.2 Page 8 and 11)

Table 1: Comparison of Mean (SD) Pharmacokinetic Parameters of Nepafenac on Day 1 and Day 4 After Once Daily Bilateral Topical Ocular Instillation of 1 Drop of Nepafenac Ophthalmic Suspension, 0.3% in 12 Healthy Subjects (From NDA203491 Section 2.7.2 Page 10)

	C_{max} (ng/mL) (n = 12)	T_{max}^a (hr) (n = 12)	AUC_{0-t} (ng*hr/mL) (n = 12)	$AUC_{0-\infty}$ (ng*hr/mL) (n = 12)	CL/F^b (L/hr) (n = 12)	k_{el} (1/hr) (n = 12)	$t_{1/2}^a$ (hr) (n = 12)
Day 1	0.921 (0.326)	0.50 (0.33 – 0.75)	1.50 (0.730)	1.57 (0.721)	1800 (755)	0.824 (0.212)	0.85 (0.54 – 1.63)
Day 4	0.847 (0.269)	0.42 (0.33 – 0.75)	1.34 (0.522)	1.43 (0.533)	1820 (514)	0.873 (0.286)	0.74 (0.49 – 1.85)

^a T_{max} and $t_{1/2}$ are expressed as median with range (minimum to maximum)

^bValues for CL/F converted to L/hr from mL/hr by dividing by 1000 and rounding to 4 digits.

Table 2: Comparison of Mean (SD) Pharmacokinetic Parameters of Amfenac on Day 1 and Day 4 After Once Daily Bilateral Topical Ocular Instillation of 1 Drop of Nepafenac Ophthalmic Suspension, 0.3% in 12 Healthy Subjects (From NDA203491 Section 2.7.2 Page 13)

	C_{max} (ng/mL) (n = 12)	T_{max}^a (hr) (n = 12)	AUC_{0-t} (ng*hr/mL) (n = 12)	$AUC_{0-\infty}$ (ng*hr/mL) (n = 12)	k_{el} (1/hr) (n = 12)	$t_{1/2}$ (hr) (n = 12)
Day 1	1.15 (0.476)	0.75 (0.50 – 1.00)	3.28 (1.46)	3.60 (1.44)	0.144 (0.0488)	5.49 (2.95 – 7.36)
Day 4	1.13 (0.419)	0.75 (0.50 – 1.00)	3.33 (1.31)	3.70 (1.43)	0.127 (0.0486)	6.26 (3.28 – 10.55)

^a T_{max} and $t_{1/2}$ are expressed as median with range (minimum to maximum)

SAFETY RESULTS:

A total of 3 adverse events were reported in 2 (16.7%) subjects in the Nepafenac 0.3% Ophthalmic Suspension group, while 5 adverse events were reported in 3 (37.5%) subjects in the

Vehicle group (**Table 3**). Across both treatment groups, none of the reported adverse events were considered drug-related and all were considered nonocular.

Table 3: Summary of Adverse Events

Adverse Event Category	Nepafenac 0.3%		Vehicle	
	N = 12		N = 8	
	N	%	N	%
Deaths	0	0.0	0	0.0
Serious adverse events	0	0.0	0	0.0
Subjects discontinued due to an adverse event	0	0.0	0	0.0
Subjects with at least 1 treatment emergent adverse event	2	16.7	3	37.5
Subjects with at least 1 ocular adverse event related to treatment	0	0.0	0	0.0
Subjects with at least 1 nonocular adverse event not related to treatment	2	16.7%	3	37.5%

Nepafenac 0.3% Treatment: 1 drop/eye of Nepafenac Ophthalmic Suspension, 0.3% once daily for 4 days.

Vehicle Treatment: 1 drop/eye of Nepafenac Ophthalmic Suspension Vehicle once daily for 4 days.

SPONSORS CONCLUSIONS:

Minimal exposure and a lack of accumulation of nepafenac (AL-6515) and its pharmacologically active metabolite, amfenac (AL-6295), were observed following 4 days of once daily bilateral topical ocular dosing of Nepafenac Ophthalmic Suspension, 0.3% in healthy subjects.

No safety concerns were identified in a limited population of healthy adult subjects administered Nepafenac Ophthalmic Suspension, 0.3% once daily (QD) for 4 days based upon a review of adverse events and an assessment of clinical laboratory measurements and ocular parameters. No safety issues were identified that would preclude further clinical development of Nepafenac Ophthalmic Suspension, 0.3%.

REVIEWER'S ASSESSMENT & RECOMMENDATION:

Results from C-09-053 adequately assessed the systemic pharmacokinetics of nepafenac and its pharmacologically active metabolite, amfenac, following repeated topical ocular administrations of nepafenac 0.3 % ophthalmic suspension. The sponsor's conclusions are valid. The reviewer has one additional note as follows:

- From NAVANAC[®] label, following bilateral topical ocular three-times-daily dosing of nepafenac 0.1% ophthalmic suspension, “*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.*” Therefore, it is not surprising to observe a higher exposure on Day 4 in current PK study (nepafenac C_{max} 0.847 ± 0.269 ng/ml; amfenac C_{max} 1.13 ± 0.491 ng/ml), considering a higher dose strength administered (0.3% vs. 0.1%).

4.2.2. Inhibition potential of Nepafenac towards CYP450s

Study Number: N-04-095

Dates: 29 July 2004 to 22 August 2004

Study Location: (b) (4)

Title: Evaluation of Inhibitory Potential of Nepafenac (AL-6515) Towards Metabolic Activities of cDNA-expressed Human Cytochrome P450 Isozymes

Objectives:

To characterize the inhibitory potential of AL-6515 towards specific isozymes of human cytochrome P450 (CYP450) in vitro.

Methods:

Assays specific to six human hepatic microsomal CYP isozymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) were performed. Each CYP isozyme-specific assay, including controls, was performed using a single probe substrate concentration that approximated the K_m (the concentration of substrate generating one-half the maximum reaction velocity) in the presence of AL-6515. Final concentrations of AL-6515 were 0.3, 1, 3, 10, 30, 100, 300, 1000, and 3000 ng/mL (1.18 to 11800 nM AL-6515). All standard curve, QC and study sample, and control incubations and analyses were performed in duplicate. The CYP isozymes and probe substrate specific to each enzyme used in this study are given in Table 1. The positive control inhibitors and concentrations used are given in Table 2.

Table 1: CYP450s and probe substrates used in the study

Enzyme	Source of Enzyme ¹	(b) (4)	
		Cat. No.	Probe substrate
CYP1A2	cDNA-expressed	455103	Phenacetin
CYP2C9	cDNA-expressed	455118	Diclofenac
CYP2C19	cDNA-expressed	456259	(S)-Mephenytoin
CYP2D6	cDNA-expressed	455117	Bufuralol
CYP2E1	cDNA-expressed	456206	p-Nitrophenol
CYP3A4	cDNA-expressed	455107	Testosterone
CYP3A4	cDNA-expressed	455107	Midazolam
Control Microsomes	Lymphoblastoid cell line	455302	Added to standardize protein concentration

Table 2: Positive controls used in the study

Enzyme	Positive Control	Concentrations (uM)
CYP1A2	7,8-Benzoflavone	0.3
CYP2C9	Sulfaphenazole	3
CYP2C19	Tranlycypromine	100
CYP2D6	Quinidine	1
CYP2E1	4-Methylpyrazole	50
CYP3A4	Ketoconazole	1

Results:

The inhibitory potentials of AL-6515 on the in vitro activities of six human CYP450 isozymes, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4, were summarized in Table 1.

Table 1: Summary of inhibition of cDNA-expressed CYP450s activities by AL-6515 *in vitro*.

Cytochrome P450	Probe Substrate	Concentrations of AL-6515 (ng/mL)								
		0.3	1.0	3.0	10	30	100	300	1000	3000
		Percent Inhibition ^a								
CYP1A2	Phenacetin	3	3	3	0	4	2	0	0	9
CYP2C9	Diclofenac	0	0	3	4	8	1	0	0	10
CYP2C19	(S)-Mephenytoin	0	6	2	0	0	0	6	0	18
CYP2D6	Bufuralol	3	0	0	0	0	1	0	1	2
CYP2E1	p-Nitrophenol	7	3	2	7	3	9	9	20	36
CYP3A4	Testosterone ^{bc}	4	0	0	0	0	0	ND ^b	ND ^b	ND ^b
CYP3A4	Midazolam ^c	0	5	6	6	5	2	4	4	3

^a Percent inhibition observed at 0.3 to 3000 ng/mL AL-6515. Zero percent refers to no inhibition observed and reported as zero or negative values by the contract laboratory (Appendix B).

^b ND refers to not determined, since AL-6515 at 300 ng/mL and higher concentrations exhibited interference in the testosterone-assay, which could not be resolved.

^c Two assays were used, CYP3A4 - testosterone and –midazolam assays, in order to overcome the interference of AL-6515 in the testosterone assay and obtain results over the entire concentration range.

Sponsor's Conclusion

Results indicate that AL-6515 at concentrations up to 1000 ng/mL is not an inhibitor of any of the major human cytochrome P450 (CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4) catalytic activities *in vitro*. AL-6515 at a concentration of 3000 ng/mL showed 36% inhibition of only CYP2E1 but no meaningful inhibition of any of the other major human CYP450s. The results indicate that AL-6515 at plasma concentrations up to 1,000 ng/mL, which is approximately 3,000-fold higher than the observed mean plasma C_{max} in humans (i.e., 0.310 ± 0.104 ng/mL following administration of 0.1% dose), is not likely to elicit any clinical drug-drug interaction involving cytochrome P450 mediated metabolism of concomitantly administered drugs.

Reviewer's assessment and Recommendations:

Study N-04-095 adequately assessed the inhibitory potential of Nepafenac (AL-6515) towards major CYP450s *in vitro*. The sponsor's conclusions are valid.

4.2.3. Inhibition potential of Amfenac towards CYP450s

Study Number: (b) (4)

Dates: April 2005 to September 2005

Study Location: (b) (4)

Title: Evaluation of Inhibitory Potential of Amfenac (AL-6295) on Human Hepatic Microsomal Cytochrome P450 Isozyme Activities

Objectives:

To characterize the inhibitory potential of Amfenac (AL-6295) towards specific isozymes of human cytochrome P450 (CYP450) in vitro.

Methods:

Assays specific to six human hepatic microsomal CYP isozymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) were performed. Each CYP isozyme-specific assay, including appropriate controls, was performed using a single substrate concentration that approximated the K_m (concentration of substrate generating one-half the maximum reaction velocity) in the presence of amfenac (1 to 1000 ng/mL). All sample and control incubations were performed in triplicate. All standard curve and QC samples were analyzed in duplicate. The CYP isozymes, probe substrate specific to each enzyme, and positive control inhibitors and concentrations used in this study are listed in Table 1.

Table 1: CYP450s, probe substrates and positive controls used in the study

Enzyme	Marker Substrates	Positive Control Inhibitors
CYP1A2	Phenacetin	Fluvoxamine (0.5 uM)
CYP2C9	Diclofenac	Sulfaphenazole (5 uM)
CYP2C19	(S)-Mephenytoin	Omeprazole (50 uM)
CYP2D6	Bufuralol	Quinidine (0.125 uM)
CYP2E1	Chlorzoxazone	Diethyldithiocarbamate (250 uM)
CYP3A4	Midazolam	Ketoconazole (0.5 uM)

Human hepatic microsomes, pooled from fifteen individuals, ten males and five females, characterized for total protein and selected cytochrome P450 activities, were incubated with marker substrates in the presence of amfenac at concentrations 0 (control), 1, 5, 10, 50, 100, 500 and 1000 ng amfenac/mL. These concentrations of amfenac are equivalent to 0 (control), 0.0039, 0.0196, 0.0392, 0.196, 0.392, 1.96 and 3.92 uM, respectively. The metabolic activities of each CYP isozyme towards its marker substrate were measured as rates of metabolism (pmol/mg protein/minute) in the presence and absence of amfenac. Metabolic activities remaining in presence of amfenac were then expressed as percentage of metabolic activities of respective control incubation.

Results:

The inhibitory potentials of amfenac on the in vitro activities of six human CYP450 isozymes, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4, were listed in Table 1-6.

Table 1: Effect of Amfenac on Phenacetin O-Deethylase (CYP1A2) Activity

Test Article Conc. ^a		Activity			
(ng/mL)	(uM)	Mean ^b (pmol/minute/mg protein)	SD	Mean ^b Percent of Activity Remaining	SD
0 ^c	0	511	2	100	NA
1	0.0039	522	7	102	1
5	0.0196	525	2	103	1
10	0.0392	528	9	103	2
50	0.196	538	18	105	3
100	0.392	521	5	102	1
500	1.96	525	7	103	2
1000	3.92	518	6	101	2
Inhibitor					
Assay Buffer Control		514	5	100	NA
Fluvoxamine (0.5 uM)		178	5	34.6	1

^a Conc. = Concentration.^b Mean and SD (n = 3).^c Assay buffer only.

NA = Not applicable.

Table 2: Effect of Amfenac on CYP2C9 (Diclofenac 4'-Hydroxylase) Activity

Test Article Conc. ^a		Activity			
(ng/mL)	(uM)	Mean ^b (pmol/minute/mg protein)	SD	Mean ^b Percent of Activity Remaining	SD
0 ^c	0	1140	40	100	NA
1	0.0039	1120	100	97.9	9
5	0.0196	1090	70	95.3	6
10	0.0392	1160	20	102	2
50	0.196	1210	60	106	5
100	0.392	1150	140	101	12
500	1.96	1120	60	98.7	5
1000	3.92	1170	80	102	7
Inhibitor					
Acetonitrile Control		1390	10	100	NA
Sulfaphenazole (5 uM)		137	9	9.85	1

^a Conc. = Concentration.^b Mean and SD (n = 3).^c Assay buffer only.

NA = Not applicable.

Table 3: Effect of Amfenac on CYP2C19 (S-Mephenytoin 4'-Hydroxylase) Activity

Test Article Conc. ^a		Activity			
(ng/mL)	(uM)	Mean ^b (pmol/minute/mg protein)	SD	Mean ^b Percent of Activity Remaining	SD
0 ^c	0	34.1	0.3	100	NA
1	0.0039	34.0	0.5	99.6	2
5	0.0196	32.6	2.2	95.8	6
10	0.0392	34.0	0.3	99.7	1
50	0.196	33.2	0.4	97.4	1
100	0.392	32.6	0.5	95.6	1
500	1.96	32.5	0.8	95.4	2
1000	3.92	32.9	0.1	96.4	0
Inhibitor					
Methanol Control		27.2	0.2	100	NA
Omeprazole (50 uM)		5.45	0.10	20.0	0

^a Conc. = Concentration.^b Mean and SD (n = 3).^c Assay buffer only.

NA = Not applicable.

Table 4: Effect of Amfenac on CYP2D6 (Bufuralolol 1'-Hydroxylase) Activity

Test Article Conc. ^a		Activity			
(ng/mL)	(uM)	Mean ^b (pmol/minute/mg protein)	SD	Mean ^b Percent of Activity Remaining	SD
0 ^c	0	96.6	0.5	100	NA
1	0.0039	106	4	110	4
5	0.0196	97.7	6.5	101	7
10	0.0392	98.5	1.8	102	2
50	0.196	97.1	2.5	101	3
100	0.392	101	4	104	5
500	1.96	99.2	0.7	103	1
1000	3.92	104	9	108	10
Inhibitor					
Acetonitrile Control		86.6	3.4	100	NA
Quinidine (0.125uM)		26.6	0.1	30.7	0

^a Conc. = Concentration.^b Mean and SD (n = 3).^c Assay buffer only.

NA = Not applicable.

Table 5: Effect of Amfenac on CYP2E1 (Chlorzoxazone Hydroxylase) Activity

Test Article Conc. ^a		Activity			
(ng/mL)	(uM)	Mean ^b (pmol/minute/mg protein)	SD	Mean ^b Percent of Activity Remaining	SD
0 ^c	0	875	24	100	NA
1	0.0039	875	23	100	3
5	0.0196	884	27	101	3
10	0.0392	880	12	101	1
50	0.196	845	42	96.5	5
100	0.392	870	36	99.4	4
500	1.96	847	24	96.8	3
1000	3.92	840	25	96.0	3
Inhibitor					
Assay Buffer Control		853	37	100	NA
DEDC ^d (250 uM)		258	11	30.3	1

^a Conc. = Concentration.^b Mean and SD (n = 3).^c Assay buffer only.^d Diethyldithiocarbamate

NA = Not applicable.

Table 6: Effect of Amfenac on CYP3A4 (Midazolam 1'-Hydroxylase) Activity

Test Article Conc. ^a		Activity			
(ng/mL)	(uM)	Mean ^b (pmol/minute/mg protein)	SD	Mean ^b Percent of Activity Remaining	SD
0 ^c	0	1890	40	100	NA
1	0.0039	1820	50	96.5	3
5	0.0196	1830	60	96.8	3
10	0.0392	1770	60	93.8	3
50	0.196	1830	70	96.8	4
100	0.392	1790	80	94.7	4
500	1.96	1710	20	90.5	1
1000	3.92	1710	60	90.5	3
Inhibitor					
Methanol Control		1700	60	100	NA
Ketoconazole (0.5 uM)		71.5	4.3	4.21	0

^a Conc. = Concentration.^b Mean and SD (n = 3).^c Assay buffer only.

NA = Not applicable.

Sponsor's Conclusions

Amfenac did not inhibit the metabolism of any of the CYP isozyme specific marker substrates tested in this study. The maximal human plasma concentration (C_{max}) of amfenac observed following bilateral three-times-a-day topical ocular administrations of nepafenac ophthalmic suspension (0.1%) was 0.422 ± 0.121 ng/mL. The highest concentration of amfenac used in this study (1000 ng/mL, 3.92 uM) is approximately 2,370-times the C_{max} observed in humans. The results demonstrate that amfenac is not likely to elicit drug-drug interactions involving cytochrome P450 mediated metabolism of concomitantly administered drugs.

Reviewer's assessment and Recommendations:

Study 6208-174 adequately assessed the inhibitory potential of amfenac towards major CYP450s in vitro. The sponsor's conclusions are valid.

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/s/

YONGHENG ZHANG
08/28/2012

PHILIP M COLANGELO
08/28/2012

CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA: 203491
 Drug Name: Nepafenac Ophthalmic Suspension, 0.3%
 Indication: Treatment of pain and inflammation associated with cataract surgery
 Applicant: Alcon Research, Ltd.
 Submission Date: December 15, 2011
 Filing Date: February 14, 2012
 PDUFA Date: October 16, 2012
 OCP Primary Reviewer: Yongheng Zhang Ph. D.
 OCP Team Leader: Philip Colangelo Pharm. D., Ph.D.

<i>QUESTION</i>	<i>YES</i>	<i>NO</i>	<i>NA</i>	<i>COMMENTS</i>
<i>Fileability:</i> <i>Is the Clinical Pharmacology section of the application fileable?</i> <i>(if 'NO', please comment as to why it is not fileable)</i>	<i>YES</i>			
<i>Fileability Review Components</i>				
1. Is the clinical pharmacology section of the NDA organized in a manner to allow substantive review to begin (including a table of contents, proper pagination, reference links, etc.)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2. Are the clinical pharmacology studies of appropriate design and breadth of investigation to meet the basic requirements for approvability of this product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Phase 1 multi-dose PK study (C-09-053) submitted
3. If multiple formulations were used in the clinical development of the product, does the NDA contain appropriate biopharmaceutics information to allow comparison between the clinical development and to-be-marketed product(s) (i.e. pivotal BE)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The formulation used in all clinical studies is the same as the TBM.
4. If unapproved products or altered approved products were used as active controls, was bioequivalence to the approved product demonstrated?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Commercially available Nepafenac (0.1% QD or TID) was used as the active control in clinical trials.
5. Are complete and relevant bioanalytical reports included in the NDA submission?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
6. If applicable, was the sponsor's request for a waiver of the requirement for submission of in vivo bioavailability data included in the NDA submission?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7. Are complete datasets supporting the clinical pharmacology studies included in the NDA submission?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

OCP Primary Reviewer

Date

OCP Team Leader

Date

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/s/

YONGHENG ZHANG
01/24/2012

PHILIP M COLANGELO
01/24/2012