

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**203491Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION**

Application number: 203491  
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CDER stamp date: 12/16/2011  
Product: Nepafenac ophthalmic suspension  
Indication: Treatment of pain and inflammation associated  
with cataract surgery  
Applicant: Alcon Research Ltd  
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# 1 Executive Summary

## 1.1 Introduction

The applicant has submitted an NDA for nepafenac 0.3% for the treatment of pain and inflammation associated with cataract surgery. The proposed formulation is similar to Nevanac® (nepafenac 0.1%) which is currently approved for the same indication. Nepafenac differs from Nevanac in content of the active pharmaceutical ingredient (API) and excipient formulation. The applicant relies on previous studies conducted for the approval of Nevanac for proof of concept, chronic toxicology studies, genotoxicity and safety pharmacology. The applicant has conducted a 1-month bridging study and an ocular distribution study to support approval. No new toxicities were associated with the increased strength and additional excipients in the formulation and ocular pharmacokinetic studies showed dose proportional increases in exposure with no associated toxicity.

## 1.2 Brief Discussion of Nonclinical Findings

The once-per-day dosing regimen with Nepafenac 0.3% is supported by:

- A one month (35-day) toxicity/bridging study and an ocular distribution study to support qualification of the excipients, the total daily exposure levels (cumulative AUC<sub>0-24h</sub>) in rabbits, the *in vitro* COX-1 and COX-2 inhibition data and the *ex vivo* PGE<sub>2</sub> suppression levels in rabbits after a topical ocular dose of a 0.3% nepafenac ophthalmic suspension.

## 1.3 Recommendations

None

### 1.3.1 Approvability

This NDA is approvable from a nonclinical perspective.

### 1.3.2 Additional Non Clinical Recommendations

None.

### 1.3.3 Labeling

(the sponsor proposes the following changes to the current Nevanac label (strikethrough are deletions, red text are insertions/changes).

(b) (4)



Reviewer Recommended Changes to Label (changes in blue italicized text):

## **8.2 Pregnancy**

### **Teratogenic Effects.**

**Pregnancy Category C:** Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately *70 and 630 times* human

plasma exposure at the recommended human topical ophthalmic dose for rats and *20 and 180 times* human plasma exposure for rabbits, respectively. In rats, maternally toxic doses  $\geq 10$  mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Nepafenac Ophthalmic Suspension, 0.3% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### **Non-teratogenic Effects.**

Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of Nepafenac Ophthalmic Suspension, 0.3% during late pregnancy should be avoided.

### **8.3 Nursing Mothers**

Nepafenac is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nepafenac Ophthalmic Suspension, 0.3% is administered to a nursing woman.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed in vitro to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes in vivo in the mouse micronucleus assay in the bone marrow of mice.

Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg.

## **2 Drug Information**

### **2.1 Drug**

CAS Registry Number (Optional): 78281-72-8

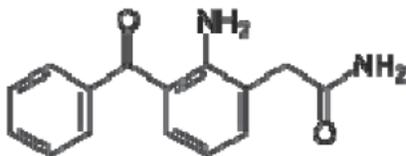
Generic Name: Nepafenac 0.3%

Code Name: AL-6515

Chemical Name: 2-amino-3-benzoylbenzeneacetamide

Molecular Formula/Molecular Weight: C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> / 254.28 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Non-steroidal anti-inflammatory

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

1. NDA 21-862 Nevanac (nepafenac 0.1%)
2. DMF (b) (4)

## 2.3 Drug Formulation

Nepafenac Ophthalmic Solution 0.3% formulation			
Component	Percent w/v	Function	Compendial Status
Nepafenac (AL-6515)	0.3	Active Ingredient	Non-compendial <sup>a</sup>
Benzalkonium Chloride	0.005 <sup>b</sup>	Antimicrobial Agent	NF
Carboxymethylcellulose Sodium	(b) (4)		USP
Guar Gum			NF
Carbomer 974P			NF <sup>c</sup>
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		(b) (4)	USP

Note: FID = Formulation Identification Number  
<sup>a</sup>Meets in-house monograph  
 (b) (4)

## 2.4 Comments on Novel Excipients

Guar gum, (b) (4) and carboxymethylcellulose are not components of the formulation in the approved product, Nevanac®. In the FDA inactive ingredients database, carboxymethylcellulose (CMC) is qualified for ophthalmic use in solution up to 0.5%. Guar gum has not been previously qualified as an excipient for ophthalmic use and it appears that CMC has not been qualified as an excipient in suspension for

ophthalmic use. The applicant has conducted a 1-month (35-day) bridging study using the clinical formulation to qualify guar gum for ophthalmic use (suspension) up to (b) (4) and CMC up to (b) (4). No toxicity was associated with the test article or vehicle in this study.

## 2.5 Comments on Impurities/Degradants of Concern

The total daily intake (TDI) of drug substance is 0.105 mg (assuming 35 µL drop). No impurity exceeds the qualification threshold of 1% or 50µg TDI [ICH Q3B(R2)].

## 2.6 Proposed Clinical Population and Dosing Regimen

Nepafenac 0.3% is indicated for use in patients undergoing cataract surgery for the treatment of pain and inflammation. The recommended dosing regimen is one drop (35 µL) 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. This regimen equates in total daily dose to the approved regimen of Nevanac (nepafenac 0.1%) three times daily.

# 3 Studies Submitted

## 3.1 Studies Reviewed

1. Ocular uptake and tissue distribution of nepafenac and Amfenac following a single topical ocular dose (QD) of NEVANAC® ophthalmic suspension 0.1% to New Zealand White rabbits (Study TDOC-0014023)
2. Ocular Uptake and tissue distribution of Nepafenac and Amfenac following a single topical ocular dose of Nepafenac ophthalmic suspension 0.3% to New Zealand White rabbits (Study TDOC-0014024)
3. One month repeated dose topical ocular toxicity study with a Nepafenac QD ophthalmic suspension containing guar in pigmented rabbits (Study TDOC-0010277)
4. Ocular uptake and tissue distribution following repeated (TID) topical ocular doses of NEVANAC ophthalmic suspension 0.1% and a single (QD) topical ocular dose of Nepafenac ophthalmic suspension 0.3% to New Zealand White rabbits (Study TDOC 0014138)

## 3.2 Studies Not Reviewed/Previously Reviewed:

**Note: Studies highlighted in gray were previously reviewed by Dr. Zhou Chen as part of the NDA review for Nevanac® (NDA 21-862)**

1. AL-6515 (AHR-9434): Summary of preclinical pharmacology evaluation (Study 017:39900:0694)
2. Inhibition of prostaglandin E2 synthesis by AL-6515 in the anterior and posterior portions of the eye (Study 008:39900:0495)
3. Preclinical evaluation of proposed clinical formulations of AL-6515 (Study 008:39900:396)
4. Efficacy of Nepafenac in a model of concanavalin A-mediated pan-retinal inflammation (Study 001:43:0100)
5. Corneal penetration profile of AL-6515 (Study 014:39900:695)
6. Nepafenac: In vitro bioactivation and permeation of external ocular barriers (Study 015:39200:1299)
7. In vitro corneal drug penetration of preserved and unpreserved nepafenac formulations (Study 001:35:1002)
8. PGHS-1 and -2 cyclooxygenase inhibition by nepafenac (AL-6515-01), Amfenac (AL-6295A-02), or ketorolac (AL-15157A-03) (Study TDOC 0006238)
9. PGHS-1 and -2 inhibition by Amfenac (AL-6295A), Bromfenac (AL-3051A), and Nepafenac (AL-6515). A COX-1 and COX-2 study (contract study report from (b) (4)) (Study TDOC-0007966)
10. Effects of NSAID-type compounds on the neural activity of corneal nociceptive units: contract study report from (b) (4) (AL-6515, diclofenac, ketorolac, nepafenac) (Study TDOC-0003301)
11. Assessment of ex vivo PGE2 synthetic capacity of rabbit iris:ciliary body after topical ocular dosing with various formulations of Nepafenac (Study TDOC-0009717)
12. Effects of anecortave acetate (AI-3789) and Amfenac (AL-6295) on BRMEC and HRMEC in vitro angiogenesis and retinal VEGF expression in a rat model of oxygen-induced retinopathy: (b) (4) contract study report (Study TDOC-0001020)
13. Effect of AL-6515 (Nepafenac) on VEGF-induced in vitro angiogenesis: Report from (b) (4) (Study TDOC 0001234)
14. Effect of topical nepafenac (AL-6515) on preretinal neovascularization in the rat model of oxygen induced retinopathy (Study TDOC-0001235)
15. Effect of topical AL-6515 (nepafenac) on preretinal neovascularization in the rat model of oxygen induced retinopathy: Report from (b) (4) (Study TDOC-0002020)
16. Effect of topical AL-6515 on preretinal neovascularization versus marketed topical NSADIS in a rat model of oxygen induced retinopathy (Study TR 097:43:1101)
17. Effect of topical AL-6515 (Nepafenac) on retinal VEGF protein levels in a rat model of oxygen induced retinopathy: Report from (b) (4) (Study TDOC-0002033)
18. Effect of AL-6515 (Nepafenac) on ocular angiogenesis in the mouse model of oxygen induced retinopathy, a mouse model of laser-induced

- CNV, and a transgenic rat model of VEGF overexpression: Report from (b)(4) (Study TDOC-0001491)
19. Peroxide-induced choroidal neovascularization in adult rabbits: Final report from (b)(4), July 2001 (Study TDOC-0001237)
  20. Effect of topical nepafenac (AL-6515) on early nonproliferative diabetic retinopathy in streptazoin-treated adult rats: Report from (b)(4) (Study TDOC-0001238)
  21. 9-month final report: (b)(4) Topical administration of Nepafenac (AL-6515) inhibits diabetes-induced retinal microvascular disease and underlying abnormalities of retinal metabolism and physiology (Study TDOC-0001332)
  22. Effect of topical nepafenac (AL-6515) on VEGF-induced retinal vascular permeability in the adult rabbit (Study TDOC-0000815)
  23. Effect of topical nepafenac (AL-6515) on VEGF-induced retinal vascular permeability in the adult rat model (Study TDOC-0001198)
  24. In vitro receptor binding profile of non-steroidal anti-inflammatory agent, AL-6515 (Study TR 009:39930:1294)
  25. AL-6515: Neuropharmacological profile in mice (Study TR 006:39200:0196)
  26. AL06515: Evaluation of proconvulsant potential in a submaximal electroshock assay (Study TR 017:3920:1196)
  27. AL06515: Effect on phenylquinone-induced writhing in mice (TR 018:39200:1196)
  28. Acute hemodynamic effects of the subcutaneous administration of AL-6515 in the open-chest anesthetized dog (Study TR 010:39200:0196)
  29. Cardiovascular (hemodynamic) and QTc prolongation evaluation of AL-6295A in dogs (Study TDOC-0005097)
  30. Effect of AL-6295A on HERG tail current recorded from stably transfected HEK293 cells (Study TDOC 0005096)
  31. Effect on airway resistance and dynamic lung compliance in the guinea pig (TR 019:3920:1196)
  32. AL06515: Effect on barbiturate induced sleep time in mice (Study TR 021:39200:1196)
  33. AL6515: Determination of electrolyte concentrations and volume diuresis in rats (Study TR 007:3920:0196)
  34. AL-6515: Gastrointestinal propulsion study in male mice (TR 009:39200:0196)
  35. AL6515: Ulcerogenic study in intact rats (TR 008:39200:0296)
  36. AL06515: Evaluation of antagonism to acetylcholine, histamine and barium chloride using the isolated guinea pig ileum (Study TR 020:39200:1196)
  37. Effect of 50 µg and 500 µg AL06515 on corneal reflex in New Zealand Albino rabbits following single topical ocular instillation (Study 049:39500:0795)
  38. Validation of an HPLC/MS/MS method for the determination of nepafenac (AL-6515) and Amfenac in rabbit plasma (Study TDOC-0001750)

39. Pharmacokinetics of Amfenac and Amfenac amide in male rats following 0.5 mg/kg intravenous and 3, 10 and 30 mg/kg oral doses (Study TR 001:38570:0198)
40. Pharmacokinetics of radioactivity in male Sprague Dawley rats following administration of a single 0.5 mg/kg intravenous dose or a single 3 mg/kg oral dose of 14C-AL-6515 (Study TR021:38570:1097)
41. Plasma pharmacokinetics of Amfenac and Amfenac amide in rabbits following intravenous and topical ocular dosing (Study TR 017:38570:0598)
42. Pharmacokinetics of radioactivity in male New Zealand White rabbits following administration of a single 1 mg/kg intravenous or 0.3% topical ocular dose of 14C-AL-6515 (Study TR 018:38570:0797)
43. Pharmacokinetics of AL-6515 and Amfenac following a 0.5 mg/kg intravenous dose of AL-6515 and pharmacokinetics and metabolism of 14C-AL-6515 following a single 0.5 mg/kg intravenous dose to male cynomolgus monkeys (Study TDOC-0001509)
44. Distribution of radioactivity in ocular tissues following a single topical ocular dose of 0.3% 14C-AL-6515 ophthalmic suspension to male New Zealand White and Dutch Belted rabbits (Study TR 022:38570:1097)
45. Distribution of radioactivity in tissues of Sprague Dawley rats following single and multiple oral doses of 14C-AL-6515 (Study TR 012:38570:0299)
46. Distribution of radioactivity in dams and fetal rats following a single oral dose of 14C-AL-6515 (Study TR 014:38570:0299)
47. Secretion of radioactivity in milk of lactating rats following a single oral dose of 14C-AL-6515 (TR 049:38570:1298)
48. The in vitro protein binding of 14C-AL-6515 in rat, monkey and human plasma (Study TDOC-0002142)
49. Metabolism of 14C-Amfenac amide (Nepafenac, AL-6515) in vitro by human precision cut liver slices (Study TDOC-0001077)
50. Chromatographic profiles of radioactivity in ocular tissues following a single bilateral topical ocular dose of 0.3% 14C-Amfenac amide (Nepafenac, AL-6515) ophthalmic suspension to New Zealand White rabbits (Study TDOC-0001353)
51. Chromatographic profiles of radioactivity in plasma and urine following a 0.5 mg/kg intravenous dose of 14C-Amfenac amide (Nepafenac, AL-6515) in Sprague Dawley rats (Study TDOC-0001352)
52. Chromatographic profiles of radioactivity in plasma and urine following a 0.5 mg/kg intravenous dose of 14C-Amfenac amide (Nepafenac, AL-6515) in cynomolgus monkeys (Study TDOC-0001076)
53. Chromatographic profiles of radioactivity in plasma and urine following a an oral dose of 14C-Nepafenac (AL-6515) in healthy human male volunteers from Study C-04-27 (Study TDOC 0003078)
54. The identification of metabolites in human plasma and urine following an oral dose of 14C-Nepafenac (AL-6515) in healthy human male volunteers in Clinical Pharmacology Study C-04-27 (Study TDOC 0003866)

55. The effects of Nepafenac on hepatic microsomal enzyme activities in rats (Study TDOC-0003113)
56. Inhibitory potential of AL-6295 (Amfenac) on human hepatic microsomal cytochrome P450 isozyme activities (Study TDOC-0003114)
57. Evaluation of inhibitory potential of AL-6515 towards metabolic activities of cDNA-expressed (Study TDOC-0002143)
58. Excretion and mass balance of radioactivity in male Sprague Dawley rats following a single intravenous dose of <sup>14</sup>C-AL-6515 (Study TR 011:38570:0299)
59. Acute oral toxicity of AL06515 in mice (up and down procedure) (Study TR 129:38520:0995)
60. Acute oral toxicity of AL06515 in rats (up and down procedure) (Study TR 130:38520:0995)
61. Two-week oral toxicity evaluation of AL06515 in rats (Study TR 131:38520:0995)
62. Three month oral toxicity evaluation of AL06515 in rats (Study TR 025:38520:0196)
63. Six month oral (gavage) toxicity study of AL-6515 in rats (Study TDOC 0001935)
64. Mutagenicity test with AL-6515 in the Salmonella-Escherichia coli/Mammalian microsome reverse mutation assay with a confirmatory assay (Study TR 141:38520:1195)
65. In vitro mammalian cell gene mutation test with an independent repeat assay with AL-6515 (Study TR 007:38520:0298)
66. In vitro mammalian cytogenetic test with an independent repeat assay with AL-6515 (Study TR 008:38520:0298)
67. Micronucleus cytogenetic assay in mice with AL-6515 (Study TR 006:38520:0298)
68. A fertility and general reproduction study in rats with AL-6515 (Study TR 155:30:0801)
69. A range finding developmental toxicity study in rats with AL-6515 (Study TR 153:30:0801)
70. A developmental toxicity study in rats with AL-6515 (Study TR 156:30:0801)
71. A range finding developmental toxicity study in rabbits with AL-6515 (Study 154:30:0801)
72. A developmental toxicity study in rabbits with AL-6515 (Study TR 157:30:0801)
73. A perinatal and postnatal study in rats with AL-6515 (Study TR 158:30:0801)
74. A skin sensitization study of AL-6515 (Nepafenac) in guinea pigs using the maximization method (Study TDOC-0001891)
75. Neutral red uptake phototoxicity assay of Amfenac amide and Amfenac in Balb/c 3T3 fibroblasts (Study TDOC-0004770)

### 3.3 Previous Reviews Referenced

Dr. Zhou Chen: NDA 21-862 [Nevanac® (Nepafenac 0.1%)] review dated 7-19-2005.

## 4 Pharmacology

### 4.1 Primary Pharmacology

Nepafenac (amfenac amide) is an NSAID that rapidly penetrates the cornea and is converted to the active moiety amfenac by ocular tissue hydrolases. Nepafenac and amfenac are thought to inhibit the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production. The cyclooxygenase inhibitory activity of the prodrug nepafenac is relatively weak compared to that of the more potent amfenac. Accordingly, topical administration of nepafenac significantly inhibited trauma-induced prostaglandin production and leakage of the ocular vasculature in rabbits.

### 4.2 Safety Pharmacology

From Dr. Zhou Chen's review:

“In safety pharmacology studies, AL-6515 showed no significant effects on general behavior and body temperature changes, peristalsis, phenylquinone-induced writhing, and electroshock-induced convulsions in mice, GI ulcer potential, urine volume, pH and urinary electrolyte changes in rats, airway resistance and dynamic lung compliance in guinea pigs, cardiac function in beagle dogs, and corneal reflex in NZW rabbits. In *in vitro* studies, AL-6515 did not demonstrate any interaction with 21 receptor and binding sites examined. The drug had no effects on acetylcholine, histamine, and barium chloride-induced contraction in the isolated guinea pig ileum”.

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

#### **Ocular uptake and tissue distribution of nepafenac and Amfenac following a single topical ocular dose (QD) of NEVANAC® ophthalmic suspension 0.1% to New Zealand White rabbits (Study TDOC-0014023)**

This study was reviewed so that comparisons could be made with ocular distribution of the 0.3% nepafenac topical ocular formulation in the current application. The ocular uptake and tissue distribution of AL-6515 (nepafenac) and AL-6295 (amfenac) were determined in New Zealand White rabbits following a single bilateral topical ocular dose of 0.1% NEVANAC® Ophthalmic Suspension (30µg). Plasma and ocular tissue samples were collected at specified time points up to 24 hours post-dose and assayed

for concentrations of AL-6515 and its metabolite AL-6295 using an UPLC tandem mass spectrometry (UPLC-MS/MS) method.

The pharmacokinetics of AL-6515 (nepafenac) and AL-6295 (amfenac) in plasma and ocular tissues are summarized in Tables 1 and 2, respectively. The data indicated that both AL-6515 and AL-6295 were distributed rapidly to the various ocular matrices and plasma. The time taken to reach maximal concentration ( $T_{max}$ ) was 0.5 hour (except the lens, where the  $T_{max}$  was 1 hour) for nepafenac. Amfenac  $T_{max}$  ranged from 0.5 hour to 4 hours. The highest tissue  $C_{max}$  and  $AUC_{0-last}$  values for both nepafenac and amfenac were associated with the bulbar conjunctiva and cornea.

**Table 1. Pharmacokinetic parameters of AL-6515 (nepafenac) in plasma and ocular tissues following topical ocular administration in New Zealand White rabbits**

Matrix	$C_{max}$ (ng/mL or ng/g)	$AUC_{0-8hr}$ (ng·h/mL or ng·h/g)	$AUC_{0-12hr}$ (ng·h/mL or ng·h/g)	$AUC_{0-last}$ (ng·h/mL or ng·h/g)	$T_{last}$	$T_{max}$	$t_{1/2}$ alpha (h)	$t_{1/2}$ beta (h)
Aqueous humor	197 (± 120)	163 (± 26.9)	163 (± 26.9)	163 (± 26.9)	4	0.5	ND	0.413
Bulbar conjunctiva	226 (± 153)	309 (± 36.8)	349 (± 38.8)	483 (± 59.9)	24	0.5	1.89	5.23
Cornea	452 (± 271)	430 (± 59.8)	443 (± 59.9)	513 (± 66.3)	24	0.5	0.550	3.36
Iris-ciliary body	137 (± 55.9)	122 (± 15.5)	122 (± 15.5)	121 (± 15.5)	4	0.5	ND	0.451
Lens	28.3 (± 7.72)	74.2 (± 5.43)	86.7 (± 5.51)	116 (± 6.83)	24	1	0.864	18.3
Plasma	1.12 (± 0.415)	0.800 (± 0.139)	0.800 (± 0.139)	0.639 (± 0.122)	1	0.5	ND	ND

$t_{1/2}$  alpha – denotes the half-life of the decline in concentrations from  $T_{max}$   
 $t_{1/2}$  beta – denotes the half-life of the decline in concentrations from the terminal portion of the curve  
 $t_{last}$  – indicates the last quantifiable timepoint

**Table 2. Pharmacokinetic parameters of AL-6295 (amfenac) in plasma and ocular tissues following topical ocular administration in New Zealand White rabbits**

Matrix	C <sub>max</sub> (ng/mL or ng/g)	AUC <sub>0-8hr</sub> (ng·h/mL or ng·h/g)	AUC <sub>0-12hr</sub> (ng·h/mL or ng·h/g)	AUC <sub>0-last</sub> (ng·h/mL or ng·h/g)	T <sub>last</sub>	T <sub>max</sub>	t <sub>1/2</sub> alpha (h)	t <sub>1/2</sub> beta (h)
Aqueous humor	48.6 (± 14.5)	138 (±6.5)	151 (± 6.56)	151 (± 6.56)	12	1	ND	2.28
Bulbar conjunctiva	886 (± 265)	1674 (± 89.8)	1776 (± 90.4)	1956 (± 90.9)	24	0.5	0.727	9.23
Cornea	895 (± 209)	2271 (± 90.7)	2495 (± 92.9)	2707 (± 101)	24	1	1.90	4.60
Iris-ciliary body	57.9 (± 12.9)	245 (± 8.00)	333 (± 9.96)	548 (± 16.9)	24	1	2.13	24.6
Lens	4.9 (± 2.77)	22.7 (± 1.97)	31.0 (± 2.11)	56 (± 3.88)	24	4	1.70	ND
Plasma	7.19 (± 2.09)	7.88 (± 0.768)	8.15 (± 0.77)	8.15 (± 0.769)	12	0.5	0.560	8.90

t<sub>1/2</sub> alpha – denotes the half-life of the decline in concentrations from T<sub>max</sub>  
t<sub>1/2</sub> beta – denotes the half-life of the decline in concentrations from the terminal portion of the curve  
t<sub>last</sub> – indicates the last quantifiable timepoint

### Ocular Uptake and tissue distribution of Nepafenac and Amfenac following a single topical ocular dose of Nepafenac ophthalmic suspension 0.3% to New Zealand White rabbits (Study TDOC-0014024)

The pharmacokinetics of AL-6515 (nepafenac) and its pharmacologically active amide hydrolysis metabolite, AL-6295 (amfenac), following a single topical ocular, bilateral administration of nepafenac ophthalmic suspension 0.3% was determined in New Zealand White rabbits (n=6). Each animal received a single 30 µL (i.e. 90µg nepafenac) topical ocular administration to the right (OD) followed by the left (OS) eyes for a total dose volume of 60 µL (i.e. 180µg nepafenac). Aqueous humor, cornea, bulbar conjunctiva, iris-ciliary body, whole lens, retina, choroid and vitreous humor were collected at specified time points up to 24 hours post-dose. Concentrations of amfenac amide (nepafenac) and amfenac were determined using an ultra performance liquid chromatography/tandem mass spectrometry (UPLC-MS/MS) analytical method.

Both AL-6515 (nepafenac) and AL- 6295 (amfenac) were detected in ocular anterior segment (aqueous humor, cornea, bulbar conjunctiva, iris-ciliary body and whole lens) and posterior segment (retina, choroid and vitreous humor) tissues, and plasma following a single topical ocular bilateral dose (Table 3 and Table 4, respectively). The data indicate that nepafenac distributes rapidly to the various ocular matrices and systemic circulation, with the time taken to reach maximal concentration (T<sub>max</sub>) being 0.5 hour (except the lens, where the T<sub>max</sub> was 1 hour). The nepafenac concentrations in ocular matrices declined with an initial half-life, denoted as t<sub>1/2</sub> alpha, followed by a more gradual decline, denoted as t<sub>1/2</sub> beta. Exposure in the anterior segment (AUC<sub>0-last</sub>) was greater than for plasma or posterior segments (vitreous humor, retina and choroid) of the eye.

Amfenac (AL-6295) was distributed to the various ocular matrices and systemic circulation, with  $T_{max}$  values ranging from 0.5 hour to 3 hours. The amfenac concentrations in some ocular matrices (bulbar conjunctiva, iris-ciliary body, choroid and vitreous humor) and plasma declined with an initial half-life, denoted as  $t_{1/2}$  alpha, followed by a more gradual decline, denoted as  $t_{1/2}$  beta. For the remaining tissues, a  $t_{1/2}$  alpha was not determined and only a  $t_{1/2}$  beta was calculated from the terminal portion of the curve. The amfenac  $t_{1/2}$  beta was greater at all times than  $t_{1/2}$  alpha due to the gradual decline in concentrations of the terminal portion of the curves. The  $AUC_{0-last}$  in the anterior segment (aqueous humor, cornea, conjunctiva, iris-ciliary body) of the eye was greater than in the plasma and posterior segment (vitreous humor, retina and choroid) of the eye; the exception was the lens which was similar to that of the choroid.

**Table 3. Mean ocular and plasma parameters of nepafenac (AL-6515) following single topical ocular dose of Nepafenac Ophthalmic Suspension 0.3%**

Matrix	C <sub>max</sub> (ng/mL or ng/g)	AUC <sub>0-8h</sub> (ng·h/mL or ng·h/g)	AUC <sub>0-12h</sub> (ng·h/mL or ng·h/g)	AUC <sub>0-last</sub> (ng·h/mL or ng·h/g)	t <sub>last</sub> (h)	T <sub>max</sub> (h)	t <sub>1/2α</sub> (h)	t <sub>1/2β</sub> (h)
Aqueous humor	410 (± 154)	352 (± 33.1)	354 (± 33.1)	354 (± 33.1)	12	0.5	0.369	5.08
Bulbar conjunctiva	619 (± 228)	1484 (± 135)	1946 (± 193)	2718 (± 344)	24	0.5	1.46	7.74
Cornea	903 (± 299)	1660 (± 133)	1827 (± 141)	2149 (± 175)	24	0.5	0.604	15.3
Iris-ciliary body	554 (± 218)	505 (± 47.5)	514 (± 47.6)	523 (± 47.6)	24	0.5	0.418	5.36
Lens	48.4 (± 9.24)	224 (± 24.5)	288 (± 27.1)	411 (± 31.8)	24	1	10.8	19.3
Choroid	61.3 (± 12.3)	63.8 (± 3.86)	67.4 (± 3.97)	67.4 (± 3.97)	12	0.5	0.43	ND
Retina	33.7 ± (5.24)	37.3 (± 2.70)	38.1 (± 2.71)	39.6 (± 2.74)	24	0.5	0.501	19.0
Plasma	3.55 ± (2.62)	2.88 (± 0.763)	2.88 (± 0.76)	2.78 (± 0.759)	2	0.5	ND	0.351
Vitreous humor	5.92 ± (8.08)	5.92 (± 1.80)	6.79 (± 1.82)	8.52 (± 1.96)	24	0.5	1.17	6.6
t <sub>1/2α</sub> –denotes the half-life of the decline in concentrations from the T <sub>max</sub> t <sub>1/2β</sub> –denotes the half-life of the decline in concentrations from the terminal portion of the curve t <sub>last</sub> –indicates last quantifiable time point								

**Table 4. Mean ocular and plasma parameters of amfenac (AL-6295) following single topical ocular dose of Nepafenac Ophthalmic Suspension 0.3%**

Matrix	C <sub>max</sub> (ng/mL or ng/g)	AUC <sub>0-8h</sub> (ng·h/mL or ng·h/g)	AUC <sub>0-12h</sub> (ng·h/mL or ng·h/g)	AUC <sub>0-last</sub> (ng·h/mL or ng·h/g)	t <sub>last</sub> (h)	T <sub>max</sub> (h)	t <sub>1/2α</sub> (h)	t <sub>1/2β</sub> (h)
Aqueous humor	59.3 ± 9.53	296 ± 15.3	344 ± 18.1	388 ± 19	24	3	ND	4.11
Bulbar conjunctiva	1500 ± 446	2966 ± 187	3172 ± 190	3483 ± 193	24	0.5	1.26	7.41
Cornea	1080 ± 256	4264 ± 192	4986 ± 232	5839 ± 249	24	1	ND	4.19
Iris-ciliary body	93.5 ± 23.4	371 ± 16.0	443 ± 16.4	562 ± 17	24	1	2.42	9.07
Lens	11.4 ± 2.61	64.8 ± 4.38	96.5 ± 10.4	166 ± 12.7	24	3	ND	37
Choroid	30.2 ± 15.3	111 ± 6.17	132 ± 6.32	167 ± 7.26	24	1	2.31	9.04
Retina	4.66 ± 0.456	10.2 ± 0.712	10.7 ± 0.714	10.2 ± 0.712	8	0.5	ND	2.37
Plasma	19.2 ± 6.67	26.6 ± 3.45	27.6 ± 3.46	29.2 ± 3.46	24	0.5	0.63	8.95
Vitreous humor	0.6 ± 0.228	1.81 ± 0.123	2.00 ± 0.129	2.43 ± 0.141	24	0.5	1.73	40.4

t<sub>1/2α</sub> –denotes the half-life of the decline in concentrations from the T<sub>max</sub>  
t<sub>1/2β</sub> –denotes the half-life of the decline in concentrations from the terminal portion of the curve  
t<sub>last</sub> –indicates last quantifiable time point

**Reviewer’s note:** In a cross study comparison, in the anterior segment tissues (bulbar conjunctiva, cornea, iris-ciliary body, and lens), exposure to nepafenac and amfenac (AUC<sub>last</sub>) was increased by approximately 4 – 5X following a single dose of 0.3% nepafenac compared to 0.1% nepafenac, while C<sub>max</sub> was increased 2 – 4X. Amfenac exposure in anterior segment tissues was increased by 1 – 2.5 X and C<sub>max</sub> by 1 – 1.7 X. Plasma exposure to both nepafenac and amfenac following a single dose of 0.3% nepafenac was approximately dose proportional with an increase of ~3.5X compared to 0.1% nepafenac. Exposure remained within limits established from the NOAELs observed in the previously reviewed ocular and systemic studies for Nevanac approval (NDA 21-862).

**Ocular uptake and tissue distribution following repeated (TID) topical ocular doses of NEVANAC ophthalmic suspension 0.1% and a single (QD) topical ocular dose of Nepafenac ophthalmic suspension 0.3% to New Zealand White rabbits (Study TDOC 0014138)**

This study determined the ocular tissue and plasma concentrations of AL-6515 (nepafenac) and AL-6295 (amfenac) following a single, once a day (QD), bilateral topical ocular dose of Nepafenac Ophthalmic Suspension 0.3% (Treatment Group 1) and a three times a day (TID) bilateral topical ocular dosing of NEVANAC® Ophthalmic Suspension 0.1% (Treatment Group 2) for one day in New Zealand White rabbits

(n=3/group/timepoint). Dose volume was 30 $\mu$ L/eye. Ocular tissues and plasma were collected at specified time points up to 24 hours post dose. Concentrations of AL-6515 and AL-6295 were analyzed using an ultra high performance liquid chromatography mass spectrometry method (UPLC-MS/MS).

Nepafenac levels were highest in the cornea and lowest in the plasma for both treatment groups (Table 5). In rabbits treated with nepafenac ophthalmic suspension 0.3% the highest amfenac levels were observed in conjunctiva while the lowest were in lens (Table 6). In the Nevanac treatment group [TID (single day)], bilateral topical ocular dosing resulted in the highest amfenac levels in conjunctiva while the lowest were in plasma. With the exception of lens, exposure of AL-6515 and AL-6295 were greater for Nepafenac 0.3% QD than Nevanac 0.1% TID in all ocular tissues [i.e.  $AUC_{0-last}$  (2 – 3X),  $C_{max}$  (~1 – 4X)]. Increases in plasma exposure ( $C_{max}$  and AUC) were apparent with plasma exposure to nepafenac and amfenac ~6 – 8X greater in rabbits administered nepafenac 0.3% QD compared to Nevanac 0.1%.

**Table 5. Mean PK parameters of AL-6515 (nepafenac) following the administration of either a single topical ocular dose of nepafenac ophthalmic suspension 0.3% or Nevanac ophthalmic suspension 0.1% TID (single day) to New Zealand White rabbits**

Treatment Group	Matrix	C <sub>max</sub> (ng/mL or ng/g)	AUC <sub>0-8h</sub> (ng·h/mL or ng·h/g)	AUC <sub>0-12h</sub> (ng·h/mL or ng·h/g)	AUC <sub>0-last</sub> (ng·h/mL or ng·h/g)	t <sub>last</sub> (h)	T <sub>max</sub> (h)	t <sub>1/2α</sub> (h)	t <sub>1/2β</sub> (h)
1. Nepafenac 0.3% QD	Aqueous humor	637 (± 245)	400 (± 51.0)	400 (± 50.9)	400 (± 50.9)	8	0.5	0.237	2.37
	Bulbar conjunctiva	1460 (± 878)	2020 (± 255)	2332 (± 294)	3109 (± 338)	24	0.5	0.702	28.7
	Cornea	2620 (±1320)	2470 (± 309)	2735 (± 325)	3215 (± 357)	24	0.5	0.436	49.0
	Iris-ciliary body	816 (± 310)	492 (± 63.8)	497 (± 63.8)	504 (± 63.9)	24	0.5	0.452	28.5
	Lens	42.9 (±6.37)	150 (± 15.8)	189 (± 17.3)	238 (± 20.3)	24	0.5	ND	6.79
	Plasma	9.78 (± 2.24)	7.01 (± 0.768)	7.01 (± 0.768)	6.97 (± 0.766)	3	0.5	ND	0.424
2. Nevanac 0.1% TID	Aqueous humor	367 (± 239)	236 (± 49.9)	235 (± 49.9)	235 (± 49.9)	6	0.5	0.196	1.53
	Bulbar conjunctiva	358 (± 248)	575 (± 79.4)	690 (± 85.4)	989 (± 107)	24	0.5	0.441	19.7
	Cornea	1040 (± 697)	835 (± 152)	911 (± 154)	1120 (± 162)	24	0.5	0.263	19.7
	Iris-ciliary body	380 (± 231)	247 (± 48.4)	248 (± 48.4)	247 (± 48.4)	8	0.5	0.215	2.03
	Lens	36.9 (± 24)	144 (± 8.60)	180 (± 10.9)	245 (± 15.2)	24	0.5	ND	10.7
	Plasma	1.54 (± 0.758)	1.03 (± 0.223)	1.03 (± 0.223)	1.02 (± 0.223)	2	0.5	ND	0.253
t <sub>1/2α</sub> –denotes the half-life of the decline in concentrations from the T <sub>max</sub> t <sub>1/2β</sub> –denotes the half-life of the decline in concentrations from the terminal portion of the curve t <sub>last</sub> –indicates last quantifiable time point									

**Table 6. Mean PK parameters of AL-6295 (amfenac) following the administration of either a single topical ocular dose of nepafenac ophthalmic suspension 0.3% or Nevanac ophthalmic suspension 0.1% TID (single day) to New Zealand White rabbits**

Treatment Group	Matrix	C <sub>max</sub> (ng/mL or ng/g)	AUC <sub>0-8h</sub> (ng·h/mL or ng·h/g)	AUC <sub>0-12h</sub> (ng·h/mL or ng·h/g)	AUC <sub>0-last</sub> (ng·h/mL or ng·h/g)	t <sub>last</sub> (h)	T <sub>max</sub> (h)	t <sub>1/2α</sub> (h)	t <sub>1/2β</sub> (h)
1. Nepafenac 0.3% QD	Aqueous humor	42.2 (± 15.2)	192 (± 15.6)	222 (± 16.8)	222 (± 16.8)	12	2	ND	1.91
	Bulbar conjunctiva	2080 (± 643)	3454 (± 214)	3803 (± 258)	4165 (± 262)	24	0.5	1.65	9.12
	Cornea	747 (± 150)	3119 (± 225)	3494 (± 230)	3733 (± 235)	24	0.5	ND	4.11
	Iris-ciliary body	56.5 (± 11.2)	288 (± 16.4)	363 (± 17.5)	574 (± 32.1)	24	0.5	ND	24.6
	Lens	9.12 (± 7.97)	47.9 (± 5.72)	69.9 (± 7.09)	102 (± 8.2)	24	4	ND	10.3
	Plasma	55.7 (± 15.1)	53.7 (± 5.86)	54.6 (± 5.86)	56.1 (± 5.87)	24	0.5	1.06	7.71
2. Nevanac 0.1% TID	Aqueous humor	35.9 (± 9.5)	143 (± 7.99)	156 (± 8.13)	167 (± 8.62)	24	1	ND	3.28
	Bulbar conjunctiva	905 (380)	1405 (± 96.7)	1529 (± 97.9)	1792 (± 109)	24	0.5	1.54	10.8
	Cornea	671 (± 360)	2088 (± 118)	2326 (± 122)	2578 (± 135)	24	0.5	ND	3.57
	Iris-ciliary body	49.4 (± 23.4)	221 (± 8.10)	277 (± 9.48)	426 (± 15.1)	24	0.5	ND	19.7
	Lens	12.4 (± 4.73)	76.3 (± 4.61)	108 (± 747)	169 (± 12.3)	24	4	ND	13.3
	Plasma	6.68 (± 2.84)	7.55 (± 1.11)	8.30 (± 1.12)	9.83 (± 1.16)	24	0.5	0.904	8.52

t<sub>1/2α</sub> –denotes the half-life of the decline in concentrations from the T<sub>max</sub>  
t<sub>1/2β</sub> –denotes the half-life of the decline in concentrations from the terminal portion of the curve  
t<sub>last</sub> –indicates last quantifiable time point

**Reviewer’s note:** Nepafenac total exposure levels in anterior segment tissues (bulbar conjunctiva, cornea, iris-ciliary body) are ~2 to 3-fold higher with Nepafenac 0.3% dosed once-per-day compared to levels achieved following nepafenac 0.1% dosed three-times-per-day. However, it is important to note that exposure to nepafenac in the lens is similar following 0.1% nepafenac TID and 0.3% nepafenac QD dosing regimens.

Total exposure levels of amfenac after nepafenac 0.3% QD were ~ 1.3 – 2.3X higher than those attained following nepafenac 0.1% TID. Exposure to amfenac in the lens was higher with nepafenac 0.1% TID than nepafenac 0.3% QD. It is notable that measurements of nepafenac and amfenac in the lens in the nepafenac 0.1% TID were made following the last dose and were still approximately equal to the levels achieved following a single dose of 0.3% nepafenac. Additionally, increases in amfenac/nepafenac t<sub>1/2</sub> in the lens were reported at 0.1% TID, as compared to 0.3% nepafenac. Overall, these data may suggest accumulation of nepafenac and amfenac

in the lens whereas, for other parts of the eye, exposure was decreased following nepafenac 0.1% TID regimen suggesting elimination of the drug over time.

## 6 General Toxicology

### 6.1 Single-Dose Toxicity

From Dr. Zhou Chen's review (dated 7-19-2005):

"In single dose acute toxicity studies using ip or oral (gavage) route, the oral and ip LD<sub>50</sub> values in rats were greater than 0.1 g/kg, the oral LD<sub>50</sub> value in mice was greater than 2 g/kg, and the ip LD<sub>50</sub> value in mice was greater than 1 g/kg."

### 6.2 Repeat-Dose Toxicity

#### Study title: One-month repeated dose topical ocular toxicity study with Nepafenac QD ophthalmic suspension containing guar in pigmented rabbits

Study no.: TDOC-0010277  
 Study report location: EDR S0000 (12-16-2011) Section 2.2.3.2.1  
 Conducting laboratory and location: Alcon Research Ltd  
 6201 South Freeway  
 Fort Worth, TX 76134  
 Date of study initiation: 7-21-2010  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity:

Test/Control Article	FID No.	Batch/Lot No.
Carbopol-Guar Vehicle with (b) (4) CMC	115856	09-56127-1
0.3% Nepafenac in Carbopol-Guar Vehicle with (b) (4) CMC	115535	09-56128-1
0.6% Nepafenac in Carbopol-Guar Vehicle with (b) (4) CMC	115868	09-56129-1
1.0% Nepafenac in Carbopol-Guar Vehicle with (b) (4) CMC	115869	09-56130-1
1.5% Nepafenac Carbopol-Guar Vehicle with (b) (4) CMC	115907	09-56131-1

#### Key Study Findings

- Cataracts were noted in 1 of 4 low dose animals (0.3% QD) and 1 of 4 mid-dose animals (1.0% QD) but not noted in the high dose group. The applicant concludes these as incidental since they were not dose related and only occurred in a single animal in a treatment group. However, given that ocular distribution studies suggest report an increased t<sub>1/2</sub> of amfenac/nepafenac in the lens (see

study TDOC 0014138 above) as compared to other anterior segment tissues, and potential for accumulation in the lens, a treatment-related effect can not be excluded.

- No other treatment or vehicle related effects were noted.
- The data qualify the novel excipients guar gum up to (b) (4) and carboxymethylcellulose (b) (4) up to (b) (4) for ophthalmic topical suspension.

## Methods

Doses:	0.3%, 0.6%, 1.0%, 1.5%
Frequency of dosing:	Once daily (QD) administered to both eyes for 35 days
Route of administration:	Topical ocular drop per eye
Dose volume:	60 µL (vehicle); 67µL (0.3%); 73µL (0.6%); 73µL (1.0%); 74µL (1.5%) (see Table 6, below)
Formulation/Vehicle:	Nepafenac in carbopol-guar vehicle ( (b) (4) guar gum w/v)
Species/Strain:	New Zealand White x Red rabbit (F1); pigmented
Number/Sex/Group:	4 animals/sex/group
Age:	4 – 4.5 months
Weight:	2.9 – 3.2 kg
Satellite groups:	No
Unique study design:	No
Deviation from study protocol:	Enrollment of one rabbit into Group 3 with conjunctival congestion score of 2 at prescreen. This deviation did not impact study results.

**Table 7. Treatment groups and treatment regimens**

Group No.	Treatment	No. of Animals		Total Daily Volume (µL) <sup>a,b</sup>	Total Daily Dose <sup>b</sup> (mg)	Observation/Treatment Duration (Days)
		M	F			
1	Untreated Control	4	4	-	-	35
2	Carbopol-Guar Vehicle with (b) (4) CMC	4	4	60	0	35
3	0.3% Nepafenac in Carbopol-Guar Vehicle with (b) (4) CMC	4	4	67	0.20	35
4	0.6% Nepafenac in Carbopol-Guar Vehicle with (b) (4) CMC	4	4	73	0.44	35
5	1.0% Nepafenac in Carbopol-Guar Vehicle with (b) (4) CMC	4	4	73	0.73	35
6	1.5% Nepafenac in Carbopol-Guar Vehicle with (b) (4) CMC	4	4	74	1.11	35

<sup>a</sup> Each treatment consisted of 1 drop administered to both eyes, via droptainer, 1 time per day for Groups 2 – 6.

<sup>b</sup> Drop sizes for each formulation provided in Table 3.4.-1 were used to calculate the total daily treatment volume.

## Observations and Results

### Mortality

Morbidity and mortality were checked once daily in the morning on days that clinical observations were performed and twice daily (morning and afternoon) on all other days. No animals died on study nor were any animals found in moribund condition.

### Clinical Signs

Clinical observations were made at prescreening, twice weekly during the study and the morning of necropsy (day 36). No treatment-related clinical observations were reported.

### Body Weights

Body weight was determined at prescreening, once weekly during the study and the morning of necropsy (day 36; fasted). No statistically significant or treatment-related effects on body weights were noted.

### Feed Consumption

No treatment related differences were reported.

## Ophthalmoscopy

### Slit-lamp

The final acceptance of an animal for study was based on the prescreen biomicroscopic (slit-lamp) examination of the right (OD) and left (OS) eyes. Normal limits [0 scores for all parameters except for conjunctival congestion where a score of 0 or +1 was acceptable] were defined according to the ocular scoring system described by Hackett and McDonald (1996). The conjunctiva, cornea, anterior chamber, light reflex, lens, and iris were examined by biomicroscopy at each evaluation on Study Days 2/3, 6/7, 13/14, 20/21, and 34/35 (F/M). Lenses were scored as a 0 for normal and 1 for abnormal. The eyes of each animal were dilated with Mydracyl 1% (Tropicamide, Alcon) at pre-screening and on study day 34/35 (F/M) to allow for better examination of the lens after the iris and light reflexes were evaluated.

Vehicle treated and animals treated with varying concentrations of nepafenac did not have an increase in conjunctival congestion or discharge as compared to untreated controls. Sporadic and transient increases in conjunctival congestion up to Grade 1 (hyperemia) were noted across all treatment groups and considered within normal range.

There were two incidences of unilateral posterior capsular cataracts, one in the 0.3% nepafenac group noted beginning on Day 7 of dosing and for the remainder of the observation period (male #3002; OS) and one in the 1.0% nepafenac group noted on Day 6 of dosing and for the remainder of the observation period (female #5504; OD). The sponsor claims the cataracts were likely present at prescreen, but were missed (at prescreen and study day 2/3). According to the sponsor, these findings are likely not related to nepafenac treatment as the cataracts occurred unilaterally, only occurred in a single animal in the affected treatment groups, occurred relatively early in the study and did not increase in frequency over time or with increasing dose.

**Reviewer's note:** In the original NDA application for Nevanac® (NDA 21-862), posterior axial capsular and subcapsular cataracts was observed beginning on Day 41 until study completion in both eyes of one male cynomolgus monkey treated with 0.1% nepafenac QID (TDOC-0001434: *Three-month topical ocular irritation and systemic toxicity evaluation of nepafenac ophthalmic suspension in nonhuman primates*). The cataract in this instance was not attributed to treatment with nepafenac for similar reasons. Given that similar findings occurred in two species, along with the potential for accumulation of amfenac/nepafenac in the lens tissues, the possibility that the observed cataracts are treatment-related cannot be entirely excluded.

### Indirect Ophthalmoscopy

The right and left eye of each animal were examined ophthalmoscopically, utilizing a Heine Indirect Ophthalmoscope at prescreening and on study day 34/35 (F/M). Mydracyl 1% (Tropicamide, Alcon) was used to dilate the pupil of each eye prior to examination. The fundus of each eye was evaluated with respect to characteristics of the optic nerve head (ONH), fundic vascular pattern (retinal and choroidal), and pigmentation/coloration characteristics. At each observation, the ONH, major retinal

vessels, and the choroidal vessels of each examined eye were indicated to be Within Normal Limits (WNL) or Abnormal (ABN). No treatment related differences between untreated, vehicle treated and Nepafenac treated eyes were noted, and all eyes appeared within normal limits.

### **Pachymetry**

A DGH-550 Ultrasonic ultrasound pachymeter was used to measure the central corneal thickness from the right and left eyes of each animal at prescreening, and on study days 6/7, 13/14, and 33/34 (F/M). Three readings were obtained from each eye at each observation. No significant differences in corneal thickness were noted for any treatment group.

### **Intraocular pressure**

Intraocular pressure (IOP) measurements were obtained from both the right and left eye of each animal on study using a Mentor Model 30 Classic pneumatonometer at prescreening and on Study Days 13/14 and 33/34 (F/M). Pressure measurements were taken at approximately the same time of day throughout the study. No trends or significant differences were noted across treatment groups.

Specular microscopy and photography of the central corneal endothelium were obtained from both the right and left eye of each animal using a Topcon Specular 2000P at prescreening and on Study Day 33/34 (F/M). There were no statistically significant or treatment-related findings associated with specular microscopic parameters.

### **ECG**

Not performed.

### **Hematology**

Samples of whole blood were collected from a blood vessel in the ear of all animals for the determination of hematological parameters On Study Day 34/35 (F/M). Animals were bled in a counterbalance order (randomly selected from each group such that an animal was selected from Group 1 then Group 2 and so on) to minimize temporal bias. Animals were fasted overnight prior to blood collection. The following parameters were measured:

**Table 8. Hematological parameters in rabbits administered nepafenac 0.3% QID for 35 days**

<ul style="list-style-type: none"> <li>• White blood cell count</li> <li>• Red blood cell count</li> <li>• Hemoglobin</li> <li>• Hematocrit</li> <li>• Mean corpuscular volume</li> <li>• Mean cell hemoglobin concentration</li> <li>• Red cell distribution width percent</li> <li>• Platelets</li> <li>• Mean platelet volume</li> <li>• Absolute neutrophils</li> </ul>	<ul style="list-style-type: none"> <li>• Absolute lymphocytes</li> <li>• Absolute monocytes</li> <li>• Absolute eosinophils</li> <li>• Absolute basophils</li> <li>• Percentage neutrophils</li> <li>• Percentage lymphocytes</li> <li>• Percentage monocytes</li> <li>• Percentage eosinophils</li> <li>• Percentage basophils</li> </ul>
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There were no test article-related hematology findings following the necropsy. Red blood cell distribution width percent was statistically lower in females administered the vehicle (Group 2; 88% of untreated) and 1.0% Nepafenac (Group 5; 92% of untreated) than the untreated control group (Group 1). These results appear consistent with normal biologic variation and likely incidental because the values were inconsistent between the sexes, and did not occur in a dose-dependent manner.

### Clinical Chemistry

Clinical chemistry parameters and coagulation were measured on samples obtained for hematological analysis on Study Day 34/35 (F/M). There were no test article-related clinical chemistry changes observed. Calcium concentrations were significantly elevated in females administered 0.3% (Group 3) and 1.5% (Group 6) Nepafenac compared to the untreated control females (Group 1). These results were consistent with normal biologic variation and were considered incidental because the differences in values were of small magnitude, transient in nature, inconsistent between the sexes and were not dose-related.

**Table 9. Clinical chemistry parameters measured during the study**

Prothrombin time	Glucose
Activated partial thromboplastin time	Gamma-glutamyl transferase
Albumin	Potassium
Alkaline phosphatase	Sodium
Alanine aminotransferase	Phosphorus
Amylase	Total bilirubin
Aspartate aminotransferase	Total protein
Blood urea nitrogen	Triglycerides
Calcium	BUN-Creatinine ratio
Cholesterol	Albumin-globulin ratio
Creatinine kinase	Globulin
Creatinine	

**Urinalysis**

Not performed.

**Gross Pathology**

Following 35 days of treatment and observation all surviving animals were euthanized by intravenous injection of a sodium pentobarbital based euthanasia solution. Animals were fasted overnight prior to necropsy. No treatment related differences were reported.

**Organ Weights**

Organ weights were obtained for adrenal glands, brain, heart, kidney, liver, ovary, spleen, and testes. No treatment related differences were reported.

**Histopathology**

Adequate Battery: The eyes and adnexa were examined histopathologically.

Peer Review: Not reviewed

Histological Findings:

**Toxicokinetics**

Serial blood samples were obtained from all animals Study Days 1 and 29. Serial blood samples were obtained from all animals in Groups 3 – 6 on Study Day 15. Quantifiable exposures to amfenac (AL-6295) and nepafenac (AL-6515) in plasma were demonstrated and mean plasma  $C_{max}$  and  $AUC_{0-3h}$  values are presented in Table 9. Amfenac exposure increased as the total daily dose was increased from 0.20 to 1.1 mg, a 5.5- fold increase in dose. For  $C_{max}$ , this increase was not linear across the entire dose range. At the highest dose (1.5% Nepafenac Guar Suspension, 1.1 mg/day), the

additional increase in  $C_{max}$  from that observed following administration of the 1.0% Nepafenac Guar Suspension, (0.73 mg/day) was minimal.  $AUC_{0-3h}$  mean values were less than dose proportional.

For nepafenac, the exposure increased with increasing dose. This increase, however, was less than dose proportional, increasing by only 2.0-fold for  $C_{max}$  and 2.3-fold for  $AUC_{0-3h}$ , as compared with the 5.5-fold increase in total daily dose in the 0.3% and 1.5% nepafenac dose groups. There was no plasma accumulation of amfenac or nepafenac between Day 1 and Day 29.

**Table 10. Toxicokinetic measurements in rabbits administered nepafenac 0.3%**

Group/Treatment	Day	Amfenac		Nepafenac	
		$C_{max}$ (ng/mL)	$AUC_{0-3h}$ (ng·h/mL)	$C_{max}$ (ng/mL)	$AUC_{0-3h}$ (ng·h/mL)
0.3% Nepafenac/Guar Suspension (Group 3)	1	42.6 (± 12.1)	47 (±16.2)	14.1 (±5.72)	9.08 (±4.79)
	15	34.1 (±6.28)	43.2 (±14.0)	14.1 (±5.71)	8.90 (±4.26)
	29	38.1 (±4.70)	48.6 (±12.1)	12.9 (±5.50)	8.35 (±47.21)
0.6% Nepafenac/Guar Suspension (Group 4)	1	57.8 (±12.2)	70.6 (±31.9)	20.2 (±6.00)	13.1 (±5.12)
	15	50.2 (±13.1)	62.3 (±36.0)	15.8 (±7.70)	9.51 (±5.06)
	29	56.0 (±20.9)	72.0 (±21.0)	17.4 (±4.67)	11.9 (±2.92)
1.0% Nepafenac/Guar Suspension (Group 5)	1	64.3 (±11.3)	94.1 (±36.9)	27.1 (±9.25)	18.4 (±6.58)
	15	69.5 (±19.5)	79.3 (±33.4)	18.4 (±7.82)	11.8 (±4.50)
	29	75.4 (± 19.3)	102 (±39.5)	20.9 (±5.00)	14.8 (±4.96)
1.5% Nepafenac/Guar Suspension (Group 6)	1	74.7 (±18.8)	104 (± 42.3)	34.5 (±9.780)	23.7 (7.03)
	15	81.5 (± 25.3)	118 (±53.7)	26.7 (± 8.33)	20.2 (± 7.38)
	29	77.2 (± 17.3)	119 (± 53.1)	25.2 (± 8.30)	19.1 (± 8.44)

### Dosing Solution Analysis

The results of the pre-study and post-study formulation analyses for strength and identity of nepafenac (AL-6515) were within the pre-specified acceptance limits.

## 7 Genetic Toxicology

From Dr. Zhou Chen's review:

AL-6515 was non-mutagenic in the Ames test and mouse lymphoma TK assay. The drug was also negative in *in vivo* micronucleus assay. AL-6515 was positive for the induction of structural chromosome aberrations in CHO cells.

## 8 Carcinogenicity

No carcinogenicity studies were conducted on AL-6515. A waiver for carcinogenicity studies was granted by the review division in October 2004.

## 9 Reproductive and Developmental Toxicology

Excerpted from Dr. Zhou Chen's review:

"A fertility and early embryonic development study was conducted in Sprague-Dawley rats. At 15 mg/kg group, sperm motility and sperm concentrations were lower than in control males. Histological examination in the 15 mg/kg group showed slightly decreased spermatozoa in the duct of the epididymis and slightly more intraluminal single necrotic cells in the epididymis in two of three animals examined. In females, there were no toxicologically significant differences in copulation and fertility indices between control and treated groups. However, a decrease in the number of viable fetuses and an increase in the early resorption and post-implantation loss were noted in animals at 10 and 15 mg/kg. Oral administration of AL-6515 in rats at 3.0 mg/kg showed no developmental toxicity in this study.

In the embryo-fetal development study in pregnant rats, animals were treated orally (by gavage) with AL-6515 at 3, 10, and 30 mg/kg/day from gestation Day 6 to Day 17. Mortality and clinical signs were noted in animals at 30 mg/kg. Decreased body weight gain and food consumption were noted at doses > 10 mg/kg. Necropsy examinations showed GI lesions in all dead animals and a few scheduled sacrifice HD animals. For reproductive evaluation, a slight decrease in fetal body weight ( $3.3 \pm 0.5$  g vs. control's  $3.5 \pm 0.2$  g) was seen in HD group. One HD animal had 9 dead fetuses, 6 resorptions, and no viable fetuses. The observed malformations were not considered treatment-related due to the low incidence and lack of dose-dependence. Regarding developmental variations, the incidences of unossified 5th and 6th sternbrae and 7th cervical ribs were significantly higher in the HD group than in the control group. Based on the study results, the dose of 3 mg/kg was considered a NOEL for maternal toxicity and a dose of 10 mg/kg was considered a NOEL for developmental toxicity in rats.

In the embryo-fetal development study in pregnant rabbits, animals were treated orally (by gavage) with AL-6515 at 3, 10, and 30 mg/kg/day from gestation Day 6 to Day 18. Maternal toxicity was seen in the 10 and 30 mg/kg groups. Abortion occurred in one MD

animal and one HD animal. One HD animal had a premature delivery on gestation Day 29. Clinical signs seen in these animals prior to abortion or premature delivery included labored breathing, decreased activity, cool to touch, few or no feces, and soft or mucoid stools. HD animals showed a decrease in body weight gain and food consumption. Regarding reproductive evaluation, HD animals showed an increase in post-implantation loss which was mainly due to an increase in early resorptions. There was a statistically significant increase in the number of litters with skeletal malformations and in the number of litters with total malformations in the 30 mg/kg/day group when compared to the controls. Low incidences of malformations were seen in the MD and LD groups and were not considered drug-related with respect to control. Based on the study results, the dose of 3 mg/kg was considered a NOEL for maternal toxicity and a dose of 10 mg/kg was considered a NOEL for developmental toxicity in rats”.

## 10 Integrated Summary and Safety Evaluation

The applicant has submitted an NDA for nepafenac 0.3% for the treatment of pain and inflammation associated with cataract surgery. Nepafenac 0.3% differs from Nevanac® (nepafenac 0.1%) in content of the active pharmaceutical ingredient (API) and excipient formulation. All excipients are similar except nepafenac 0.3% contains the novel excipient guar gum (b) (4) and the previously qualified excipient carboxymethylcellulose (b) (4). The applicant conducted a one-month (35-day) toxicity/bridging study and an ocular distribution study to support qualification of the excipients. In the 35-day toxicity toxicity/bridging study, no treatment-related toxicities were reported in any dose group (0.3% to 1.5% QD, bilateral), and toxicokinetic results showed a less than dose proportional increase in exposure (amfenac and nepafenac) across doses. As such, no new toxicities were associated with the increased strength and additional excipients in the formulation, and the NDA is approvable from a pharmacology/toxicology standpoint.

The clinical dosing regimen in the current IND is similar in total daily exposure to the approved regimen of Nevanac (nepafenac 0.1%) three times daily. The following safety margins are calculated from NOAELs established in the original NDA review by Dr. Zhou Chen as part of the NDA review for Nevanac® (NDA 21-862).

**Table 11. Safety Margins based on body surface area (systemic) or total daily topical ocular dose**

Toxicity	Species	NOAEL	Safety Margin based on mg/m <sup>2</sup> or clinical ocular total daily dose (0.105mg)
Renal papillary necrosis at 15 mg/kg/day	Rat (oral)	10 mg/kg/day	926×
None	Rabbit (ocular)	1.5% TID (highest dose tested)	>15× *
None	NHP (ocular)	1.0% QID (highest dose tested)	>13× *

\*assumes 35µL drop size

**Table 12. Systemic - safety margins based on pharmacokinetic parameters**

AUC (ng•hr/mL)	Rats (10mg/kg)	Human (0.3%, QD × 4days)	Safety margin
Nepafenac	189 ± 22	1.43 ± 0.533	132 ×
Amfenac	1550 ± 106	3.70 ± 1.44	419×
C <sub>max</sub> (ng/mL)	Rats (10mg/kg)	Human (0.3%, QD × 4days)	Safety margin
Nepafenac	49.5 ± 21.9	0.847 ± 0.269	58×
Amfenac	388 ± 99	1.13 ± 0.419	343×

**Table 13. Developmental and Reproductive safety margins based on pharmacokinetic parameters****Rat**

AUC (ng•hr/mL)	Rat AUC (ng•hr/mL) (10mg/kg dose)	Human AUC <sub>0-∞</sub> : (0.3%, QD × 4days)*	Safety margin
Nepafenac	97 - 207	1.43 ± 0.533	68X
Amfenac	2340 - 4190	3.70 ± 1.44	632
C <sub>max</sub> (ng/mL)	Rats (10mg/kg)	Human (0.3%, QD × 4days)	Safety margin
Nepafenac	69.6 - 242	0.847 ± 0.269	82X
Amfenac	793 - 1710	1.13 ± 0.419	702X

\*Human PK data obtained on Day 4 following daily QD dosing (Study C-09-053)

**Rabbit**

AUC (ng•hr/mL)	Rabbit AUC (ng•hr/mL) (10mg/kg dose)	Human AUC <sub>0-∞</sub> (0.3%, QD × 4days)*	Safety margin
Nepafenac	28.4 – 62.5	1.43 ± 0.533	20X
Amfenac	663 - 3070	3.70 ± 1.44	179X
C <sub>max</sub> (ng/mL)	Rabbit AUC (10mg/kg)	Human AUC (0.3%, QD × 4days)	Safety margin
Nepafenac	39.3 – 70.8	0.847 ± 0.269	46X
Amfenac	666 - 2100	1.13 ± 0.419	589X

*\*Human PK data obtained on Day 4 following daily QD dosing (Study C-09-053)*

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/s/  
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AARON M RUHLAND  
09/13/2012

LORI E KOTCH  
09/13/2012

**PHARMACOLOGY/TOXICOLOGY NDA FILING REVIEW  
MEMORANDUM for MESSAGE TO SPONSOR**

NDA 203491

Drug Name: Nepafenac Ophthalmic Suspension 0.3%

Applicant: Alcon Research, Ltd.

Review Division: Division of Transplant and Ophthalmology Products

Stamp Date: 12-15-2011

Review Date: 1-27-2012

Summary: The filing meeting was held on 1-27-2012. This NDA is filable from the pharmacology/toxicology perspective. However, several review issues (not related to the filability) were identified during the preliminary review.

The following comments should be conveyed to the sponsor as soon as possible.

Comments to the sponsor:

1. For the ease of review, please identify the Study Numbers and locations of additional toxicity studies described in the Question 3 (Toxicology) during the EOP2 meeting for IND 49924 on October 5, 2009.
2. Please comment on the comparative systemic exposure of 0.3% and 0.1% nepafenac ophthalmic suspensions in the animal ocular toxicity studies.
3. In the Pregnancy Section of proposed labeling: Please identify the PK studies and show the calculation of how the multiples of animal dose versus human dose are derived.

Conrad H. Chen, Ph.D.  
Pharmacology Reviewer

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/s/  
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CONRAD H CHEN  
02/01/2012

TERRY J MILLER  
02/01/2012

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 203491    Applicant: Alcon Research, Ltd.    Stamp Date: 12-15-2011**

**Drug Name: Nepafenac    NDA/BLA Type: NDA**  
**Ophthalmic Suspension 0.3%**

On **initial** overview of the NDA/BLA application for filing:

Content Parameter	Yes	No	Comment
Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		The waiver of carcinogenicity study was granted previously.
If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?	X		

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
Has the applicant addressed any abuse potential issues in the submission?			Not applicable.
If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	X		

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Conrad H. Chen, Ph.D. 1-26-2012  
 \_\_\_\_\_  
 Reviewing Pharmacologist Date

Terry Miller, Ph.D. Date  
 \_\_\_\_\_  
 Team Leader (Acting)

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/s/  
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CONRAD H CHEN  
01/27/2012

TERRY J MILLER  
01/27/2012