PRODUCT MONOGRAPH

Pr ILEVRO®

(Nepafenac) Ophthalmic Suspension
0.3% w/v

Nonsteroidal Anti-Inflammatory

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic (topical)	Suspension/ 0.3%	benzalkonium chloride as preservative propylene glycol *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

ILEVRO® (nepafenac) ophthalmic suspension, 0.3% is indicated for management of pain and inflammation associated with cataract surgery.

Geriatrics (≥ 65 years of age):
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

Pediatrics (< 18 years of age):
The safety and effectiveness of ILEVRO in pediatric patients have not been established. The use of ILEVRO in pediatric patients is not recommended.

CONTRAINDICATIONS

ILEVRO (nepafenac) ophthalmic suspension, 0.3% is contraindicated in:

- Patients who are hypersensitive to nepafenac, to any ingredient in the formulation or component of the container (for a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph)
- Patients who are hypersensitive to other nonsteroidal anti-inflammatory drugs (NSAIDs).
- Patients in whom attacks of asthma, urticarial or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDS

WARNINGS AND PRECAUTIONS

General

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of ILEVRO (nepafenac) ophthalmic suspension, 0.3% and should be monitored closely for corneal health.

There is a potential for cross-sensitivity of nepafenac to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drug substances.

Topical NSAIDs, including ILEVRO, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical corticosteroids may increase the potential for healing complications.

The safety of ILEVRO for pre-treatment more than one day before cataract surgery, the total treatment duration greater than two weeks, or treatment with dosing frequency more than once daily, has not been assessed in humans.

Hematologic

With some NSAIDs, including ILEVRO, the potential exists for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that ILEVRO be used with caution in patients with known bleeding tendencies or who are receiving medications which may prolong bleeding time.

Ophthalmologic

Use of topical NSAIDs, including ILEVRO, may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight-threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of ILEVRO and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events, which may become sight-threatening. Topical NSAIDs should be used with caution in these patients. Prolonged use of topical NSAIDs may increase patient risk for occurrence and severity of corneal adverse reactions.

Post-marketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.

Contact lens wear is not recommended during the postoperative period following cataract surgery; therefore, contact lenses should not be worn during treatment with ILEVRO. In addition, ILEVRO contains benzalkonium chloride, which may cause eye irritation and is known to discolour soft contact lenses.

ILEVRO may cause temporary blurred vision or other visual disturbances that can affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until vision clears before driving or using machinery.

Sexual Function/Reproduction

There are no adequate data regarding the use of ILEVRO on human fertility.

Special Populations

Pregnant Women:

No adequate and well-controlled studies have been conducted in pregnant women. Studies in animals with nepafenac have shown reproductive toxicity. The potential risk for humans is unknown.

The inhibition of prostaglandin synthesis may negatively affect pregnancy and/or embryonal/foetal development and/or parturition and/or postnatal development, therefore, the use of ILEVRO during pregnancy is not recommended.

Nursing Mothers: It is unknown whether nepafenac is excreted in human milk after topical ocular administration. Animal studies have shown excretion of nepafenac in the milk of pregnant rats after oral administration. Caution should be exercised when ILEVRO is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of ILEVRO in pediatric patients have not been established. Its use is not recommended in these patients until further data become available.

Geriatric Use: No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In one phase 3 and one phase 2 controlled clinical study including 1339 patients exposed to ILEVRO (nepafenac) ophthalmic suspension, 0.3%, 157 (11.8%) patients exposed to ILEVRO experienced 205 adverse events. Adverse events considered related to ILEVRO were identified in 3 (0.2%) patients. These adverse drug reactions led to discontinuation in 1 (0.1%) patient. No serious adverse drug reactions related to ILEVRO were reported in these studies.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In one phase 3 and one phase 2 controlled clinical study, ILEVRO was administered to 1339 patients at a dose of one drop, once daily for an average of 15 days post cataract surgery.

The most common treatment-emergent adverse events, independent of a causal association, occurring at rates ≥ 1.0% included headache and intraocular pressure increased. Headache was observed in 27 (2.0%) patients treated with ILEVRO compared with 13 (1.6%) patients treated with NEVANAC® (nepafenac) ophthalmic suspension, 0.1% and 5 (1.1 %) patients treated with nepafenac vehicle 0.3%. Intraocular pressure increase was observed in 15 (1.1%) patients treated with ILEVRO compared with 7 (0.9%) patients treated with NEVANAC and 1 (0.2%) patients treated with nepafenac vehicle 0.3%. Intraocular pressure increases typically resolved within 5 days following treatment initiation (3 days following surgery). All adverse events of headache or intraocular pressure increase were considered mild to moderate in intensity.

All adverse drug reactions in patients with exposure to ILEVRO are presented in Table 1. No treatment-related adverse drug reactions were reported at a frequency of >0.1% in patients with exposure to ILEVRO. All adverse drug reactions were considered mild to moderate in intensity.

Table 1: All Treatment-Related Adverse Drug Reactions

MedDRA Preferred Term (Version 14.1)	**Nepafenac 0.3% QD n= 1339 (%)**	**Nepafenac Vehicle 0.3%QD n= 455 (%)**	**NEVANAC 0.1% TID n=819 (%)**	**NEVANAC Vehicle TID n=205 (%)**	**Nepafenac 0.1% QD n= 506 (%)**
Eye Disorders					
eye pain	1 (0.1)			1 (0.5)	
eyelid oedema		1 (0.2)			
foreign body sensation in eyes		1 (0.2)			
punctate keratitis	1 (0.1)				
Immune System Disorders					
hypersensitivity	1 (0.1)				

QD: Once daily; TID: Trice daily.

In 16 clinical studies, NEVANAC was administered to 2309 patients at a dose of one drop (once daily, two-times daily, three-times daily, or four-times daily). The most frequent adverse drug reactions (>0.1%) in patients with exposure to NEVANAC are presented in Table 2. No treatment-related adverse drug reactions were reported at a frequency of ≥1% in patients with exposure to NEVANAC.

Table 2: Treatment-Related Adverse Drug Reactions >0.1%

MedDRA Preferred Term (Version 14.1)	**NEVANAC 0.1% n= 2309 (%)**
Eye Disorders	
punctate keratitis	10 (0.4)
foreign body sensation in eyes	5 (0.2)
eyelid margin crusting	4 (0.2)
eye pain	4 (0.2)

NEVANAC Less Common Clinical Trial Adverse Drug Reactions (≤0.1%)

Eye disorders: blepharitis, blurred vision, conjunctival hyperaemia, conjunctivitis allergic, choroidal effusion, corneal deposits, corneal disorder, corneal epithelium defect, corneal erosion, dry eye, eye discharge, eye pruritus, iritis, keratitis, lacrimation increased, photophobia, ocular discomfort.

Gastrointestinal disorders: dry mouth, nausea

Immune system disorders: hypersensitivity

Investigations: intraocular pressure increased

Nervous system disorders: headache

Skin and subcutaneous tissue disorders: cutis laxa, dermatitis allergic

Abnormal Hematologic and Clinical Chemistry Findings

ILEVRO had no clinically relevant effect on laboratory parameters.

Post Market Adverse Drug Reactions

Adverse reactions identified from postmarketing experience that have not been reported previously in clinical trials with NEVANAC include the following: corneal perforation, ulcerative keratitis, corneal thinning, impaired healing (cornea), reduced visual acuity, corneal scar, corneal abrasion, corneal opacity, eye swelling, eye irritation, ocular hyperaemia, dizziness, vomiting, blood pressure increased.

DRUG INTERACTIONS

Overview

Neither nepafenac nor amfenac inhibits any of the major human cytochrome P450 (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) metabolic activities *in vitro* at concentrations up to 300 ng/mL. Therefore, drug-drug interactions involving CYP-mediated metabolism of concomitantly administered drugs are unlikely. Drug-drug interactions mediated by protein binding are also unlikely.

Drug-Drug Interactions

ILEVRO (nepafenac) ophthalmic suspension, 0.3% may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics.

The administration of ILEVRO in conjunction with prostaglandin analogues was not evaluated in clinical trials. Interactions between ILEVRO and prostaglandin analogues are not anticipated following topical ocular administration.

There is a potential cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents.

Concomitant use of topical NSAIDs and topical corticosteroids may increase the potential for healing complications. Concomitant use of ILEVRO with medications that prolong bleeding time may increase the risk of haemorrhage.

Drug-Food Interactions

Interactions with food are not anticipated following topical ocular administration.

Drug-Herb Interactions

Interactions with herbal products are not anticipated following topical ocular administration.

Drug-Laboratory Interactions

Interactions with laboratory tests are not anticipated following topical ocular administration.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ILEVRO (nepafenac) ophthalmic suspension, 0.3% has not been studied in patients with hepatic disease or renal impairment. Nepafenac is eliminated primarily through biotransformation and the systemic exposure is very low following topical ocular administration. No dose adjustment is warranted in these patients.

Recommended Dose and Dosage Adjustment

Shake well before use. One drop of ILEVRO should be applied to the affected eye(s) once daily beginning 1 day prior to cataract surgery, and continued on the day of surgery for up to 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

The safety and efficacy of ILEVRO for treatment duration greater than 2 weeks, or more frequently than once daily, has not been assessed.

Missed Dose

If a dose is missed, a single drop should be applied as soon as possible before reverting to regular routine. Do not use a double dose to make up for the one missed.

Administration

ILEVRO has been safely administered in conjunction with other ophthalmic medications such as antibiotics, anesthetics, beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. Because the administration of ILEVRO in conjunction with prostaglandin analogues has not been studied, use only if the benefit outweighs any potential risk.

If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

Contact lens wear is not recommended during the postoperative period following cataract surgery; therefore, contact lenses should not be worn during treatment with ILEVRO.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

OVERDOSAGE

A topical overdosage may be flushed from the eye(s) with warm tap water.

There is minimal risk of adverse effects due to accidental ingestion of a 4 mL bottle (3 mL fill size) of ILEVRO (nepafenac) ophthalmic suspension, 0.3% (total dose of 9 mg based on a 3 mL fill size) by a child. The recommended adult dose of amfenac sodium (FENAZOX), marketed in Japan since 1986, is one to four 50 mg tablets daily. This translates to 1 to 4 mg/kg per day for a 50 kg person. If a 20 kg child ingested the entire contents of a 4 mL bottle (3 mL fill size) of ILEVRO, it would translate to a dose of 0.45 mg/kg or only 11% to 45% of the recommended adult dose.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Nepafenac is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits the action of cyclooxygenase (COX) enzymes which are responsible for biosynthesis of prostaglandins and other prostanoids. Ocular hydrolases convert nepafenac to amfenac, also a NSAID. Both nepafenac and amfenac inhibit the action of COX-1 and COX-2 with more selectivity for COX-1. Nepafenac is a reversible, non-time dependent inhibitor of COX enzymes, whereas amfenac is an irreversible, time dependent inhibitor of COX (see Animal Pharmacodynamics subsection in the DETAILED PHARMACOLOGY section). The time-dependent irreversible inhibition of COX enzymes by amfenac may have important clinical implications related to efficacy and safety of ILEVRO (nepafenac) ophthalmic suspension, 0.3%.

Pharmacodynamics

A single topical ocular dose of 0.1% or 0.3% nepafenac in rabbits produced significant and prolonged inhibition of PGE2 synthesis in iris-ciliary body (ICB) with near maximum inhibition between 0.5 hour and 12 hours and about 60% inhibition at 24 hour after dosing. The sustained inhibition of prostaglandin synthesis in ICB is correlated to the irreversible inhibition of COX enzymes by amfenac. Both nepafenac and amfenac have also been shown to produce effective and prolonged inhibition of paracentesis-induced breakdown of the blood-aqueous barrier in rabbits. In retina/choroid, nepafenac has demonstrated a 65%-90% inhibition of PGE2 synthesis at 1.3 hour, but approximately 10% inhibition at 3 hours after a single topical ocular dose of 0.1% nepafenac in rabbits. Therefore, topically administrated nepafenac in rabbit eyes has been shown to inhibit prostaglandin formation in both the anterior and posterior segments of the eye. This observed rate and duration of PGE2 inhibition in retina/choroid are significantly lower and shorter, respectively, compared to those in ICB after a single topical ocular dose of 0.1% nepafenac in the animal (see Animal Pharmacodynamics subsection in DETAILED PHARMACOLOGY section).

Pharmacokinetics

Table 3: Plasma Pharmacokinetic Parameters of Topically Administrated ILEVRO in the Eyes of Healthy Subjects

	C_{max} (ng/mL)	**T_{max} (h)**	**$AUC_{0\text{-}inf}$** (ng•h/mL)	**$t_{½}$ (h)**
Nepafenac	0.847 ± 0.269	0.42 (0.33 – 0.75)	1.43 ± 0.533	0.74 (0.49 – 1.85
Amfenac	1.13 ± 0.419	0.75 (0.5 – 1.00)	3.70 ± 1.43	6.26 (3.28 – 10.55)

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

Systemic Absorption: Following one drop of ILEVRO in both eyes of healthy subjects daily for 4 days, low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects within 30 minutes post-dose, respectively. The mean steady-state plasma C_{max} for nepafenac and for amfenac were 0.847 ± 0.269 ng/ml at 0.42 hr and 1.13 ± 0.491 ng/ml at 0.75 hour, respectively, following ocular administration (Table 3).

Ocular and Systemic Distribution: Ocular half-lives and potential ocular accumulation of nepafenac and amfenac have not been established in humans treated with ILEVRO (see Animal Pharmacokinetics subsection in the DETAILED PHARMACOLOGY section).

Maximal nepafenac and amfenac levels (C_{max}) in most rabbit ocular tissues are achieved within 30 minutes to 1 hour after a single topical ocular dose of ILEVRO. The levels of exposure (C_{max} and $AUC_{0\text{-}last}$) to nepafenac and amfenac in the dosing sites (cornea and conjunctiva) are substantially higher than that in other ocular tissues. A significant amount of amfenac is found in cornea and conjunctiva, indicating a high level of metabolic conversion of nepafenac occurs in these tissues. Internal ocular tissues in the anterior segment of the eye have much higher levels of exposure than those in the posterior segment with the highest exposure level in iris-ciliary body (ICB) in all internal ocular tissues. C_{max} and $AUC_{0\text{-}last}$ of nepafenac or amfenac in retina and vitreous humor was the lowest in the eye and at least 13 fold lower than that in ICB (see Animal Pharmacokinetics subsection in DETAILED PHARMACOLOGY section).

The terminal elimination half-lives ($t_{1/2}$) of nepafenac and amfenac in many ocular tissues of the anterior segment of the eye in rabbits are relatively long (up to 32 hrs) (see Animal Pharmacokinetics subsection in DETAILED PHARMACOLOGY section). The half-lives of nepafenac and amfenac in human plasma are estimated to be 0.74 hour and 6.26 hours, respectively, following topical ocular administration of ILEVRO (Table 3).

Nepafenac has moderate affinity towards plasma protein binding whereas amfenac has a high affinity towards plasma protein binding. *In vitro* the percent binding of nepafenac and amfenac were 83.5% and 99.1%, respectively.

Studies in rats have shown that radioactive drug-related materials distribute widely in the body following single and multiple oral doses of ^{14}C-nepafenac.

Metabolism: Nepafenac topically administrated to the eye is rapidly hydrolyzed to produce the active metabolite, amfenac, by ocular hydrolases, predominantly in cornea and conjunctiva (see DETAILED PHARMACOLOGY section). Subsequently, amfenac undergoes extensive metabolism to more polar metabolites involving hydroxylation of the aromatic ring leading to glucuronide conjugate formation.

Radiochromatographic analyses before and after β-glucuronidase hydrolysis indicated that all metabolites were in the form of glucuronide conjugates, with the exception of amfenac. Amfenac was the major metabolite in plasma, representing approximately 13% of total plasma radioactivity. The second most abundant plasma metabolite was identified as 5-hydroxy nepafenac, representing approximately 9% of total radioactivity at C_{max}.

Excretion: After oral administration of ^{14}C-nepafenac to healthy volunteers, urinary excretion was found to be the major route of radioactivity elimination, accounting for approximately 85.5% of the dose while fecal excretion represented approximately 6.2% of the dose. Nepafenac and amfenac were not quantifiable in the urine.

Special Populations and Conditions

Pediatrics: ILEVRO has not been evaluated in the pediatric population.

Geriatrics: No overall differences in safety and effectiveness have been observed between elderly and younger patients.

Gender: Gender differences in the plasma pharmacokinetics of nepafenac and amfenac were small and not clinically relevant.

Race: A comparison of the single- and steady-state pharmacokinetic data for nepafenac and amfenac in healthy Japanese and non-Japanese subjects indicate that there are no clinically meaningful ethnic differences in the systemic exposure of either nepafenac or amfenac following topical ocular administration of ILEVRO.

Hepatic or Renal Insufficiency: ILEVRO has not been studied in patients with hepatic disease or renal impairment. The systemic exposure is very low following topical ocular administration and no dose adjustment is warranted in these patients.

STORAGE AND STABILITY

Store at 2°C - 25°C and protect from light. Discard 28 days after opening.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ILEVRO (nepafenac) ophthalmic suspension, 0.3% contains the active ingredient nepafenac 0.3% (3 mg/ml), the preservative benzalkonium chloride 0.005%, and the inactive ingredients boric acid, propylene glycol, carbomer 974P, sodium chloride, guar, carmellose sodium, disodium edetate, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

ILEVRO is supplied in a 4 mL round or oval white low density polyethylene bottle with a natural low density polyethylene dispensing plug. The round bottle has a white polypropylene cap and the oval bottle has a white or grey polypropylene cap. For the round bottle, tamper evidence is provided by a closure with an extended skirt that locks to the bottle finish on application and breaks away from the closure on opening. After cap is removed: if tamper evident snap collar is loose, remove before using product. For the oval bottle, tamper evidence is provided by a shrink band around the closure and neck area of the package.

Net contents are 3 mL supplied in a 4 mL bottle.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

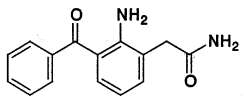
Drug Substance

Common name: nepafenac

Chemical name: 2-amino-3-benzoylbenzeneacetamide
2-(2-amino-3-benzoylphenyl)acetamide

Molecular formula and molecular mass: $C_{15}H_{14}N_2O_2$; 254.28

Structural formula:



Physicochemical properties: Nepafenac drug substance is provided as a yellow crystalline or powder material.

CLINICAL TRIALS

Study demographics and trial design

The clinical development of ILEVRO® (nepafenac) ophthalmic suspension, 0.3% was based on the body of work that had been compiled for the approval of NEVANAC® (nepafenac) ophthalmic suspension, 0.1%, in addition to one phase 3 and one phase 2 pivotal clinical trial and one clinical pharmacokinetic study using ILEVRO.

Two prospective, randomized, double-masked, placebo-controlled, parallel group, multicenter pivotal efficacy studies (C-09-055 and C-11-003) of similar design assessed the effect of ILEVRO on ocular pain and inflammation following cataract extraction with posterior chamber intraocular lens (IOL) implantation. The study population consisted of patients 18 years of age and older, who had a cataract, and were planning to undergo a unilateral, single procedure, cataract extraction by phacoemulsification with the implantation of a posterior chamber intraocular lens. Patients with a history of chronic or recurrent inflammatory eye disease, previous ocular trauma to operative eye, the use of topical ocular, inhaled, or systemic corticosteroids (within 14 days of surgery), nonsteroidal anti-inflammatory drugs (within 7 days of surgery), or prostaglandins (within 4 days of surgery) were not permitted.

ILEVRO was administered once daily beginning 1 day prior to cataract surgery and continued on the day of surgery and through the first two weeks post-surgery. On the day of surgery, one drop was administered approximately 30 minutes to two hours prior to surgery.

Patient demographics and baseline characteristics were similar across studies and were not significantly different across treatment groups for age, sex, or race (Table 4).

Approximately 73% of the patients were over 65 years of age and approximately 86% were Caucasian. There was a slight predominance of female patients (57%), which is typical of an elderly population.

Table 4: Summary of demographics for patients in pivotal clinical trials in cataract surgery patients

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean Age (Range)	Gender	Race
C-09-055 Safety & Efficacy	Prospective, randomized, double-masked, placebo-controlled, parallel group	One drop TID One drop nepafenac 0.1% or placebo One drop QD nepafenac 0.3% or placebo / topical ocular / 16 days[1]	n = 2022 (intent to treat)	68.9 yrs (20–92 yrs)	866 M 1156 F	A=106 B=152 C=1755 H=n/a O=9
C-11-003 Safety & Efficacy	Prospective, randomized, double-masked, placebo-controlled, parallel group	One drop QD nepafenac 0.3% or nepafenac 0.1% or placebo / topical ocular / 16 days[1]	n = 1257 (intent to treat)	69.3 yrs (21-94 yrs)	532 M 725 F	A=78 B=94 C=1081 H=n/a O=4

A=Asian; B=Black; C=Caucasian; H=Hispanic; O=Other
[1]Dosing started 1 day prior to surgery.

Study results

In these two pivotal clinical studies, 3462 patients were randomized with 3324 receiving treatment, including ILEVRO ophthalmic suspension (N=1339), ILEVRO vehicle (N=455), NEVANAC ophthalmic suspension (N=1325), or NEVANAC vehicle (N=206). Overall, 1238 patients (89.0%) were exposed to ILEVRO ophthalmic suspension once daily for 16 days.

In each of the two pivotal efficacy studies (C-09-055 and C-11-003), aqueous cells and flare, which are the hallmark of ocular inflammation, served as the basis for evaluating the efficacy of the drug product. Aqueous cells and flare were evaluated using slit-lamp biomicroscopy. Aqueous cells were graded by the investigator on a 5-point scale and aqueous flare was graded by the investigator on a 4-point scale. The scales were designed to distinguish between the various degrees of anterior segment inflammation encountered following cataract surgery, and to describe when inflammation is cured (i.e., a score of 0 for cells indicates that no cells are observed and a score of 0 for flare indicates that no flare is observed).

Subjective assessment of ocular pain, rated by the investigator on a 6-point scale was evaluated as a secondary efficacy variable in C-09-055 and as a tertiary (supportive) efficacy variable in C-11-003. The scales were designed to differentiate between the various degrees of ocular pain that may be encountered following cataract surgery and also served as an element in determining treatment failures**.**

Table 5: Results of study C-09-055

C-09-055: Clinical Evaluation of Nepafenac Ophthalmic Suspension, 0.3% for Prevention and Treatment of Ocular Inflammation and Pain after Cataract Surgery

Nepafenac 0.3% given once daily is noninferior to NEVANAC given 3 times daily for the management of pain and inflammation following cataract surgery.

Primary Outcome

- Nepafenac 0.3% and NEVANAC are superior to their respective vehicles for the prevention and treatment of ocular inflammation;
- Nepafenac 0.3% is noninferior to NEVANAC based on the percentage of cures at Day 14 postoperatively (lower bound of 95% 2-sided confidence interval for the difference between treatments of -6.42%) (per protocol).

Patients Cured at Day 14 (Intent-to-Treat)

Nepafenac 0.3%		Nepafenac Vehicle 0.3%			NEVANAC		NEVANAC Vehicle		
N	**n (%)**	**N**	**n %**	**p-value**	**N**	**n (%)**	**N**	**n (%)**	**p-value**
807	552 (68.4)	197	67 (34.0)	<0.0001	811	568 (70.0)	205	73 (35.6)	<0.0001

Cure is defined as a patient having a score of 0 for both cells and flare at Day 14 (LOCF).
N is the number of patients with non-missing post-surgery data; n is the number of patients cured.
p-value is based upon Cochran-Mantel-Haenszel test controlling for site.

Non-Inferiority Results – Patients Cured at Day 14 (Per Protocol)

Nepafenac 0.3%		NEVANAC			
N	**n (%)**	**N**	**n %**	**95% CI**	**p-value**
761	531 (69.8)	760	546 (71.8)	(-6.24, 2.64)	<0.0001

Cure is defined as a patient having a score of 0 for both cells and flare at Day 14 (LOCF).
N is the number of patients with non-missing post-surgery data; n is the number of patients cured.
Non-inferiority margin of -10%.
p-value is based upon method of Yanagawa, Tango and Hiejima for demonstrating non-inferiority.

Secondary Outcome

- Nepafenac 0.3% and NEVANAC are superior to their respective vehicles for the prevention and treatment of ocular pain;
- Nepafenac 0.3% is noninferior to NEVANAC based on the percentage of patients who were pain-free at Day 14 postoperatively (lower bound of 95% 2-sided confidence interval for the difference between treatments of -3.63%) (per protocol);

Patients Pain-Free at Day 14 (Intent-to-Treat)

Nepafenac 0.3%		Nepafenac Vehicle 0.3%			NEVANAC		NEVANAC Vehicle		
N	**n (%)**	**N**	**n %**	**p-value**	**N**	**n (%)**	**N**	**n (%)**	**p-value**
807	734 (91.0)	197	98 (49.7)	<0.0001	811	737 (90.9)	205	115 (56.1)	<0.0001

Pain-free is defined as a score of 0 on the Investigator's assessment of ocular pain at Day 14 (LOCF).
N is the number of patients with non-missing post-surgery data; n is the number of patients cured.
p-value is based upon Cochran-Mantel-Haenszel test controlling for site.

Non-Inferiority Results – Patients Pain-Free at Day 14 (Per Protocol)

Nepafenac 0.3%		NEVANAC			
N	**n (%)**	**N**	**n %**	**95% CI**	**p-value**
761	701 (92.1)	760	699 (92.0)	(-3.63, 2.34)	<0.0001

Pain-free is defined as a score of 0 on the Investigator's assessment of ocular pain at Day 14 (LOCF).
N is the number of patients with non-missing post-surgery data; n is the number of patients cured.
Non-inferiority margin of -10%.
p-value is based upon method of Yanagawa, Tango and Hiejima for demonstrating non-inferiority.

Supportive Outcomes

- Nepafenac 0.3% and NEVANAC are superior to their respective vehicles based on cumulative percentage of patients who were cures beginning at Day 7 postoperatively ($p<0.0001$);
- Nepafenac 0.3% and NEVANAC are superior to their respective vehicles based on the cumulative percentage of patients were pain-free at each postoperative visit (Day 1, 3, 7, 14) ($p<0.0001$).

Table 6: Results of study C-11-003

C-11-003: Clinical Evaluation of Nepafenac Ophthalmic Suspension, 0.3% Compared to Nepafenac Ophthalmic Suspension 0.1% and Vehicle for Prevention and Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery

Nepafenac 0.3% is superior to its vehicle with respect to the treatment of postoperative inflammation and pain associated with cataract surgery.

Primary Outcome

- Nepafenac 0.3% is superior to its vehicle for the prevention and treatment of ocular inflammation;

Patients Cured at Day 14 (Intent-to-Treat)

Nepafenac 0.3%		Nepafenac Vehicle 0.3%		
N	**n (%)**	**N**	**n %**	**p-value**
512	331 (64.6)	252	63 (25.0)	<0.0001

Cure is defined as a patient having a score of 0 for both cells and flare at Day 14 (LOCF).
N is the number of patients with non-missing post-surgery data; n is the number of patients cured.
p-value is based upon Cochran-Mantel-Haenszel test controlling for site.

Supportive Outcomes

- Nepafenac 0.3% is superior to its vehicle based upon cumulative percent cures beginning Day 7 postoperatively ($p<0.0001$).
- Nepafenac 0.3% is superior to its vehicle at all visits for the cumulative percentage of patients who were pain-free.

DETAILED PHARMACOLOGY

Animal Pharmacodynamics

Mechanism of action

Inhibition of cyclooxygenase (COXs) is considered as the mechanism for the therapeutic effects of nepafenac and amfenac. *In vitro* studies have demonstrated that nepafenac and amfenac produced instantaneous reversible inhibition of COX enzymes (COX-1 and COX-2). The IC50 values increased in the order: nepafenac (9.7 μM for COX-1 and 85 μM for COX-2) < amfenac (16.9 μM for COX-1 and 180 μM for COX-2) < ketorolac (51 μM for COX-1 and 510 μM for COX-2). The selectivity of the instantaneous inhibition potency toward COX-1 was 5-6 folds with the three compounds. More importantly, amfenac, but not nepafenac, also exhibited time-dependent and irreversible inhibition where the extent of inhibition was proportional to the length of pre-exposure to COX enzyme. Amfenac inhibition is more selective for COX-1 than COX-2 and is sustained due to irreversible binding to COX enzymes. Amfenac appears more potent in such inhibition than ketorolac.

Pharmacodynamic impact on ocular structures of anterior chamber of the eye

Nepafenac administered topically in the eye of animals at a therapeutic dose produced significant and prolonged inhibition of PGE2 synthesis in iris-ciliary body (ICB). After a single topical ocular dose in rabbits, NEVANAC (nepafenac) ophthalmic suspension, 0.1% demonstrated about 85%-95% inhibition of PGE2 synthesis in ICB as assayed *ex vivo* between 0.5 hour and 12 hours, and still remained about 60% inhibition at 24 hours. ILEVRO (nepafenac) ophthalmic suspension, 0.3% also produced about 60% inhibition of PGE2 synthesis in ICB at 24 hours following a single topical ocular dose. The sustained inhibition of prostaglandin synthesis in ICB is correlated with the long half-life of amfenac (about 17 hours) in this ocular tissue and the, irreversible binding to COX enzymes (see Mechanism of Action subsection in ACTION AND CLINICAL PHARMACOLOGY).

Topically administrated nepafenac in the eye of rabbits around the therapeutic dose is shown to produce effective and prolonged inhibition of paracentesis-induced breakdown of blood aqueous barrier. Following a single topical ocular dose of 0.1% nepafenac, the subsequent paracentesis-induced breakdown of blood aqueous barrier was inhibited by about 60% between 15 minutes and 90 minutes with still about 20% inhibition at 24 hours. Such inhibition was dose-dependent between 0.001% and 0.01% nepafenac, but appeared to reach the plateau at about 0.03% nepafenac.

Amfenac administered topically in the eye of rabbits was also shown to inhibit prostaglandin synthesis in ICB and inhibit paracentesis-induced breakdown of blood aqueous barrier as effective as or stronger than nepafenac administrated at the same amount and route, indicating that amfenac may be effectively absorbed into the eye of rabbits.

Pharmacodynamic impact on ocular structures of posterior chamber of the eye

In retina/choroid, nepafenac has demonstrated a 65%-90% inhibition of PGE2 synthesis at 1.3 hour, but approximately 10% inhibition at 3 hours after a single topical ocular dose of 0.1% nepafenac in rabbits. This observed rate and duration of PGE2 inhibition in retina/choroid are significantly lower and shorter, respectively compared to those in ICB after a single topical ocular dose of 0.1% nepafenac in the animal (see under subheading "Pharmacodynamic impact on ocular structures of anterior chamber of the eye" above).

Safety pharmacology studies investigated the effects of nepafenac on the central and autonomic nervous, cardiovascular, pulmonary, gastrointestinal, metabolic and renal systems. In *in vitro* studies, 1, 10 and 100 µM concentrations of nepafenac did not interact with 21 different receptors and binding sites including steroid receptors and 1 µM and 10 µM concentrations had no statistically significant effect on guinea pig ileum (smooth muscle) responses to acetylcholine, histamine and barium chloride. The active metabolite of nepafenac, amfenac, had no effect on the HERG tail current (a measure of cardiac repolarization) at concentrations up to 100 ng/ml.
In vivo studies showed that nepafenac (3 mg/kg) had no effect on general behavior, body temperature, or electroshock-induced convulsions (a measure of nepafenac's ability to alter CNS function). At the same concentration, nepafenac produced a statistically significant increase in barbiturate-induced sleep time, but, the increase was not considered clinically meaningful. Three mg/kg of nepafenac had no effect on phenylquinone-induced writhing (a measure of its analgesic activity) and 1 mg/kg administered subcutaneously had no effect on pulmonary or cardiovascular function including the lead II ECG. Likewise, the sodium salt of amfenac at 1.08 mg/kg IV (cumulative dose 1.55 mg/kg) had no effect on BP, HR or lead II ECG, including QTc interval, in anesthetized dogs. Nepafenac (0.1 to 3 mg/kg) also did not significantly affect gastrointestinal motility, urine output, pH or electrolyte concentrations. Oral doses of 3 mg/kg showed no gastric ulcer potential and topical ocular doses up to 500 µg showed no anesthetic activity in rabbits.

Human Pharmacokinetics

Ocular half-lives and potential ocular accumulation of nepafenac and amfenac have not been established in humans treated with ILEVRO.

In Vitro Studies
Amide hydrolysis of nepafenac to amfenac was demonstrated in the cornea, iris-ciliary body (ICB) and retina-choroidal tissues. In human ocular tissue preparations (obtained within 10 hours post-mortem), the specific activity of hydrolase in the ICB was greater than that in the cornea. The rate of hydrolysis of nepafenac in rabbit cornea at an *in vitro* condition was concentration- and time-dependent in a linear manner. Nepafenac protein binding was moderate and independent of concentration (range 10 to 1000 ng/mL). The mean protein binding of ^{14}C-nepafenac in human plasma was 83.5 ± 0.8%. Amfenac, on the other hand, exhibits high affinity binding to albumin. The percentages bound *in vitro* to human albumin and to human serum were 95.4% and 99.1%, respectively.

^{14}C-Amfenac partitioning into blood cells is minimal. The ratio of radioactivity in the blood to plasma was <0.09 and <0.04 at the 0.2 μg/mL and 2.0 μg/mL concentrations, respectively. The results indicate only slight distribution of radioactivity into blood cells. Given the limited ^{14}C-amfenac concentration range examined, slight partitioning of radioactivity into blood cells did not indicate concentration dependency.

Potential inhibitory effects of nepafenac on the metabolism of isozyme specific substrates of human cytochrome P450 (CYP) enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) were assessed. The results demonstrate that nepafenac up to 1000 ng/ml does not inhibit catalytic activities of the 6 major CYP isozymes studied. Based on these observations, nepafenac plasma concentrations up to 1000 ng/mL, approximately 3,000 fold greater than the mean steady state C_{max} (0.310 ± 0.104 ng/ml) observed in subjects who received TID Nepafenac Ophthalmic Suspension, 0.1%, are unlikely to result in drug-drug interaction involving CYP mediated metabolism of concomitantly administered drugs.

In Vivo Studies

Single-Dose

Following a single topical ocular dose of 1 drop of ILEVRO to both eyes of healthy subjects, the nepafenac C_{max} in plasma was reached by 30 minutes (range 0.33 – 0.75 hours) with a mean concentration of 0.921 ± 0.326 ng/mL. After C_{max}, nepafenac plasma concentrations declined with a median half-life of 0.85 (range 0.54 – 1.63) hours. The amfenac C_{max} in plasma was reached by 45 minutes (range 0.5 – 0.75 hours) with a mean concentration of 1.15 ± 0.476 ng/mL. After C_{max}, amfenac plasma concentrations declined with a median half-life of 5.49 (range 2.95 – 7.36) hours.

Following a single 10 mg oral dose of ^{14}C-radiolabeled nepafenac in healthy subjects, the C_{max} of total radioactivity in plasma was 230 ± 50 ng-equivalents/mL and was reached by 0.80 ± 0.18 hours. Total radioactivity in plasma was eliminated with a half-life of 4.69 ± 2.70 hours. Urinary excretion was found to be the major route of radioactivity elimination, accounting for approximately 85.5% of the dose while fecal excretion represented approximately 6.2% of the dose. Nepafenac and amfenac were not quantifiable in the urine.

Plasma Steady-State

Following bilateral topical ocular daily dosing of 1 drop of ILEVRO to both eyes of healthy subjects for 4 days, the nepafenac C_{max} in plasma was reached by approximately 25 minutes (range 0.33 – 0.75 hours) with a mean concentration of 0.847 ± 0.269 ng/mL. After C_{max}, nepafenac plasma concentrations declined with a median half-life of 0.74 (range 0.49 – 1.85) hours. The amfenac C_{max} in plasma was reached by 45 minutes (range 0.5 – 0.75 hours) with a mean concentration of 1.13 ± 0.419 ng/mL. After C_{max}, amfenac plasma concentrations declined with a median half-life of 6.26 (range 3.28 – 10.55) hours. Steady-state drug levels in human ocular tissues have not been determined for ILEVRO.

Animal Pharmacokinetics

Following a single topical ocular dose of 0.3% nepafenac in male rabbits, nepafenac and amfenac maximal concentrations (C_{max}) were observed in most ocular tissues within 30 minutes to 1 hour, except for amfenac in lens with a T_{max} of 3-4 hours.

After a single topical ocular dose of 0.1% or 0.3% nepafenac, the exposure levels (C_{max} and $AUC_{0\text{-}last}$) of nepafenac and amfenac in cornea and conjunctiva are vastly higher than that in other ocular tissues (Table 7). A significant amount of amfenac is found in cornea and conjunctiva, indicating a high level of metabolic conversion of nepafenac occurs in these tissues. The highest exposure level in internal ocular structures is in iris-ciliary body (ICB) where the C_{max} and $AUC_{0\text{-}last}$ for nepafenac were about 39% and 19% of that in cornea, respectively, while C_{max} and $AUC_{0\text{-}last}$ for amfenac in ICB were about 8% and 12% of that in cornea, respectively. Much lower concentrations are seen in retina where the level of exposure (C_{max} and $AUC_{0\text{-}last}$) to nepafenac and amfenac was below 2% and below 0.5%, respectively, of that in cornea or at least 13 fold lower than that in ICB.

Table 7: Rabbit Ocular Tissue Exposure Levels Following a Single Topical Dose of ILEVRO

	C_{max}		$AUC_{0\text{-}last}$	
	Nepafenac	Amfenac	Nepafenac	Amfenac
Aqueous Humor	524	51	377	305
Conjunctiva	1040	1790	2914	3824
Cornea	1762	914	2682	4786
ICB	685	75	513.5	568
Lens	45.7	10.3	324.5	134
Choroid	61.3	30.2	67.4	167
Retina	33.7	4.66	39.6	10.2
Vitreous	5.92	0.60	8.52	2.43

Nepafenac and amfenac concentrations in most ocular tissues decline in a largely biphasic manner. Following a single topical ocular dose of ILEVRO in rabbits, the following tissue's terminal half-lives of nepafenac were observed: 4 hrs in aqueous humor, 18 hrs in bulbar conjunctiva, 32 hrs in cornea, 17 hrs in iris-ciliary body, and 13 hrs in lens. The terminal half-lives of amfenac were 3 hrs in aqueous humor, 8 hrs in bulbar conjunctiva, 4 hrs in cornea, 17 hrs in iris-ciliary body and 24 hrs in lens. The plasma half-lives of nepafenac and amfenac in rabbits were 0.4 and 8.3 hours, respectively. Twenty-four (24) hours after a topical ocular dose of ILEVRO, the concentrations of nepafenac in conjunctiva, cornea and iris-ciliary body are 6%, 2% and 0.09% of the corresponding C_{max}, respectively. At the same time, the concentrations of amfenac in these same tissues are 1%, 1% and 20% of the corresponding C_{max}, respectively.

Animal studies indicate that biologically significant accumulation of nepafenac and/or amfenac may occur in some ocular tissues after once-daily topical ocular doses of ILEVRO in rabbits, especially for amfenac in ICB and lens.

Long ocular half-lives and potential ocular accumulation of nepafenac and amfenac as well as long effective inhibition (24 hours) of COX enzymes by ILEVRO (see Animal Pharmacodynamics subsection) in ocular tissues in rabbits may lead to unwanted ocular effects after prolonged daily dosing. Since ocular half-lives and potential ocular accumulation of nepafenac and amfenac have not been established in humans treated with ILEVRO, caution should be exercised in patients treated with ILEVRO.

Following an intravenous dose in rats, rabbits and monkeys, plasma levels of nepafenac and amfenac decline rapidly with half-lives of approximately 1 hour or less. The absolute oral bioavailability of nepafenac is relatively low, approximately 6%, and is likely the result of first pass metabolism. However, the percent of dose reaching the systemic circulation as amfenac is higher, estimated to be in the range of 30% to 40%. The percent of a radiolabeled dose of nepafenac absorbed is substantially higher at approximately 85%.

Topical ocular administration of a ^{14}C-nepafenac ophthalmic suspension to non-pigmented New Zealand white rabbits and pigmented Dutch belted rabbits found both C_{max} levels and half-lives in corresponding tissues, such as iris-ciliary body, choroid and retina to be similar between the two rabbit strains, indicating that nepafenac and its metabolites do not bind to melanin pigmented tissues.

Multiple dosing (3 mg/kg daily oral doses for 14 days) show minimal accumulation in normal male rats. Systemic tissue distribution studies in normal male and pregnant female rats show that radioactive drug equivalents distribute widely in the body, including to the fetus.

In rats, approximately 90% of the dose is excreted within the first 24 hours following intravenous administration.

Radioactivity was found in the milk of lactating rats. However, the milk:plasma ratios were less than unity and the concentrations of radioactivity in milk and plasma declined with similar half-lives.

Nepafenac is metabolized to amfenac and to more polar metabolites involving hydroxylation of the aromatic ring and glucuronide conjugate formation. Except for nepafenac and amfenac, the circulating plasma metabolites in human and monkey are primarily in the form of glucuronide conjugates whereas those in rats are not conjugated. The most abundant plasma metabolite in all species is amfenac. In humans, amfenac represented approximately 13% of total plasma radioactivity whereas all other metabolites were <10%. Apart from amfenac, the most abundant human plasma metabolite has been identified as 5-hydroxy amfenac amide which represents about 9.5% of total radioactivity at C_{max}. This metabolite is also observed in rat and monkey plasma. In rat plasma the 5-hydroxy metabolite is not conjugated whereas in monkeys and humans it is conjugated.

MICROBIOLOGY
Not applicable.

TOXICOLOGY
Single Dose Studies
Single dose toxicity studies using the Up and Down procedure to approximate the LD_{50} were conducted in mice and rats by the oral and intraperitoneal routes (see **Table 8**). Rats showed greater lethality than mice and the LD_{50} in this species was similar for the PO and IP routes of administration. Systemic exposure to high dose nepafenac (greater than 50,000-fold the maximum proposed clinical dose) resulted in no evidence of toxicity.

Table 8: Single-Dose Toxicity of Nepafenac

Species	Route / Doses (mg/kg)	LD_{50} (mg/kg)	Findings
Mouse/ICR	Oral 1000 mg/kg 2000 mg/kg	> 2000	None of the animals treated orally with 2.0 g/kg of nepafenac were noted with any significant signs of toxicity during the study.
	Intraperitoneal 1000 mg/kg 2000 mg/kg	> 1000	Clinical signs included decreased activity, hunched gait, and swollen abdomen.
Rat/Sprague Dawley	Oral 100 mg/kg 500 mg/kg 1000 mg/kg	Male LD_{50} > 100 Female LD_{50} > 500	Clinical signs noted include swollen abdomens, red exudates on face, little or no stool and less active behavior.
	Intraperitoneal 100 mg/kg 250 mg/kg 500 mg/kg	Male LD_{50} > 250 mg/kg; Female LD_{50} > 100 mg/kg;	Clinical signs noted include swollen abdomens, red exudates on face, little or no stool and less active behavior.

Repeat-Dose Oral Studies: Oral repeat-dose studies conducted with nepafenac are summarized in **Table 9**. The daily dose levels of nepafenac evaluated in these studies are significantly higher than the recommended daily dose of NEVANAC (nepafenac) ophthalmic suspension, 0.1%.

Table 9: Repeat-Dose Systemic Studies of Nepafenac

Species/No. per Group	Dose/Route[a]	Duration of Treatment	Findings
Sprague-Dawley rats/ 10 male, 10 female	0, 2.5, 7.5, 25 mg/kg/day orally by gavage.	2 weeks	Decreases in RBC, hemoglobin and hematocrit were noted in the 25 mg/kg group. There was no evidence that oral dose levels of 25 mg/kg/day of the test material resulted in histomorphological changes usually associated with NSAID's toxicity.
Sprague Dawley rats/ 10 male, 10 female	0,1 (male), 5 (female), 15 mg/kg/day orally by gavage	3 months	Renal papillary necrosis (a common finding with NSAID) was observed in 2 of 10 females receiving 15 mg/kg/day. For males, a slight decrease in the mean body weight was noted in the mid- and high-dose groups (<10%). The 5 and 1 mg/kg/day were considered to represent the NOEL in female and male Sprague Dawley rats.
Fischer F344 rats / 25 male, 25 female	Vehicle, 1, 3, and 10 mg/kg/day orally by gavage	6 months	The most common finding was alopecia of the forelimbs, discoloration around the nose, eyes, paws and mouth and inguinal area. Red blood cell parameters (red cell counts, haemoglobin and hematocrit) were slightly reduced in the high dose males after 26 weeks of treatment compared to controls, but were within the normal range. Absolute kidney and liver weights were elevated in the high dose female rats compared to vehicle controls. Thymus weights (absolute and relative) were significantly reduced in the low and mid dose females, compared to vehicle controls. No differences in male organ weights. The no observable adverse effect level for nepafenac was greater than 10 mg/kg/day.

[a] Underlined values indicate the no observed adverse effect level or the no observable effect level

Repeat-Dose Ocular Studies: Ophthalmic solutions of nepafenac were evaluated in repeat-dose topical ocular studies in rabbits (NZW/pigmented) and Cynomolgus monkeys (see **Table 10**).

Table 10: Results of Topical Ocular Repeat-Dose Studies of Nepafenac

Species/No. per Group	Dose/Route	Duration of Treatment	Findings
Rabbits (New Zealand white) / 4 male, 4 female	Vehicle, 0.1%, 0.3%, 1.0% or sham. Four drops unilateral per day / topical ocular.	7 days prior to corneal incision and 27 days post incision.	Low ocular irritation potential; no postoperative ocular complications, no ocular irritation or delayed wound healing.
Rabbits (New Zealand white) / 4 male, 4 female	Untreated control, vehicle, 0.1%, 0.3%, 1.0%. Four daily doses bilateral (1 drop/dose) / topical ocular.	1 month	Minimal conjunctival congestion (hyperemia) was noted in all treatment and control groups.
Rabbits (New Zealand white) / 4 male, 4 female	Untreated control, vehicle, 0.1%, 0.3%, 1.0%. Four daily doses bilateral (1 drop/dose) / topical ocular.	3 months	Minimal conjunctival congestion (hyperemia) was noted in all treatment and control groups.
Rabbits (Pigmented) / 7 male, 7 female	Untreated control, vehicle, 0.3%, 1.0% or 1.5%. Three daily doses unilateral (2 drops/dose) / topical ocular.	6 months	Low ocular irritation potential; and did not elicit any signs of ocular or systemic toxicity.
Cynomolgus monkeys / 4 male, 4 female	Vehicle, 0.1%, 0.3% or 1.0% unilateral. Four daily doses (2 drops/dose) / topical ocular.	3 months	Low ocular irritation potential; and did not elicit any signs of ocular or systemic toxicity.

[a] Underlined values indicate the no observed adverse effect level or the no observable effect level

Toxicokinetic Studies

The toxicokinetics of nepafenac and amfenac were characterized in repeat dose oral and topical ocular studies. Maximal plasma concentrations (C_{max}), areas under the concentration-time curves (AUC) and exposure margins were determined (see Table 11 and Table 12).

Table 11: Nepafenac Plasma C_{max} and AUC Values from Highest NOAEL Doses in Toxicology Studies

Species	Route, Frequency, Duration	Dose (Nepafenac)	C_{max} (ng/ml)	AUC_{0-t} (ng*h/ml) (Interval 0-t)	C_{max} Exposure Margin [a]	AUC Exposure Margin [b]
Rat	Oral, QD, 6 months	10 mg/kg/day	118 ± 32	189 ± 22 (0 – 4 hours)	381	509
Rat Segment II	Oral, QD, Gestation days 6-17	10 mg/kg/day (NOEL dose)[c] Data from Day 17	242 ± 196	207 ± 51 (0 - 6 hours)	781	558
Rabbit Segment II	Oral, QD, Gestation days 6-18,	10 mg/kg/day (NOEL dose)[c] Data from Day 18	40.2 ± 59.6	28.4 ± 40.9 (0 – 6 hours)	130	77
Rabbit	Topical Ocular, TID, 6 months	Nepafenac 1.5% Ophthalmic Suspension (3.6 mg/day)	6.01 ± 6.03	6.01 ± 5.98 (0 - 2.25 hours)	19	16
Monkey	Topical Ocular, QID, 3 months (97 days)	Nepafenac 1.0% Ophthalmic Suspension (3.2 mg/day)	17.4 ± 5.8	35.7 ± 12.7 (0 – 3 hours)	56	96

[a] C_{max} divided by clinical C_{max} of 0.310 ng/ml observed at the end of 4 days of TID dosing of Nepafenac 0.1% Ophthalmic Suspension.

[b] AUC divided by clinical AUC_{0-inf} estimated at the end of 4 days of TID dosing of Nepafenac 0.1% Ophthalmic Suspension.

[c] Retrospective TK, no toxicological evaluations were performed during this study.

Table 12: Amfenac Plasma C_{max} and AUC Values from Highest NOAEL Doses in Toxicology Studies

Species	Route, Frequency, Duration	Dose (Nepafenac)	C_{max} (ng/ml)	AUC $_{0-t}$ (ng*h/ml) (interval 0-t)	C_{max} Exposure Margin [a]	AUC Exposure Margin [b]
Rat	Oral, QD, 6 months	10 mg/kg/day	670 ± 137	1550 ± 106 (0 – 4 hours)	1,588	1,505
Rat Segment II	Oral, QD, Gestation Days 6-17	10 mg/kg/day (NOEL dose) [c] Data from Day 17	1710 ± 1620	4190 ± 620 (0 – 6 hours)	4,052	4,068
Rabbit Segment II	Oral, QD, Gestation Days 6-18	10 mg/kg/day (NOEL dose) [c] Data from Day 18	666 ± 608	663 ± 453 (0 – 6 hours)	1,578	644
Rabbit	Topical Ocular, TID, 6 months	Nepafenac 1.5% Ophthalmic Suspension (3.6 mg/day)	45.4 ± 18.0	50.6 ± 21.2 (0 - 2.25hours)	146	49
Monkey	Topical Ocular QID, 3 months (97 days)	Nepafenac 1.0% Ophthalmic Suspension (3.2 mg/day)	26.4 ± 14.5	45.5 ± 16.1 (0 – 3 hours)	63	44

[a] C_{max} divided by clinical C_{max} of 0.422 ng/ml observed at the end of 4 days of TID dosing of Nepafenac 0.1% Ophthalmic Suspension (C-04-08).
[b] AUC divided by clinical AUC_{0-inf} of 1.03 ng*h/ml estimated at the end of 4 days of TID dosing of Nepafenac 0.1% Ophthalmic Suspension (C-04-08).
[c] Retrospective TK, no toxicological evaluations were performed during this study.

Mutagenicity: Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. However, nepafenac was not mutagenic *in vitro* in the Ames assay or in a forward mutation assay. Additionally, 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.

Carcinogenicity: Nepafenac has not been evaluated in long-term carcinogenicity studies.

Reproduction and Teratology: 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 260 and 2400 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 80 and 680 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥ 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.

PART III: CONSUMER INFORMATION

Pr ILEVRO®
Nepafenac Ophthalmic Suspension, 0.3% w/v

This leaflet is part III of a three-part "Product Monograph" published when ILEVRO® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ILEVRO. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ILEVRO (nepafenac) ophthalmic–suspension, 0.3% is used to manage eye pain and inflammation following cataract surgery.

What it does:
ILEVRO is a nonsteroidal anti-inflammatory drug (NSAID), and can reduce formation of prostaglandins by your body, which cause pain and swelling in your eye.

When it should not be used:
Do not use ILEVRO if you:

- are allergic (*hypersensitive*) to nepafenac or any of the other ingredients of this medicine (see What the important nonmedicinal ingredients are).
- are allergic to other NSAIDs.
- have had reactions, such as asthma, itchy or runny nose, after taking acetylsalicylic acid or other NSAIDs.

What the medicinal ingredient is:
Nepafenac, 0.3% w/v

What the important nonmedicinal ingredients are:
Preservative: benzalkonium chloride.
Others: boric acid, propylene glycol, carbomer 974P, sodium chloride, guar, carmellose sodium, disodium edetate. Tiny amounts of hydrochloric acid or sodium hydroxide are sometimes added during the manufacture of the product to adjust to the proper pH.

What dosage forms it comes in:
ILEVRO contains tiny yellow particles suspended in a clear liquid. It is supplied as 3 mL of suspension in a 4 mL plastic bottle with a screw cap.

WARNINGS AND PRECAUTIONS

BEFORE you use ILEVRO ophthalmic suspension, talk to your doctor or pharmacist if you:

- have any allergies to ILEVRO or any of its ingredients (see What the important nonmedicinal ingredients are)
- bruise easily or have or have had bleeding problems.
- take any medicines that may make you bleed more like acetylsalicylic acid or warfarin.
- have an eye disorder called dry eye syndrome, a corneal ulcer, a corneal denervation or a corneal epithelial defect.
- have diabetes.
- have rheumatoid arthritis.
- have had many eye surgeries within a short period of time.
- have had complicated eye surgeries.
- wear contact lenses.
- apply other NSAID or steroid medications to your eye since these may slow the healing of your eye.
- are using other medications in the eye.
- have ever had an allergic reaction to NSAIDs, including acetylsalicylic acid, as you may be allergic to ILEVRO.

Pregnancy or breast-feeding
If you are pregnant, think you may be pregnant or are planning to become pregnant, talk to your doctor before you use ILEVRO. You should not use ILEVRO if you are pregnant. If you are breast-feeding, ILEVRO may get into your milk. Talk to your doctor about breastfeeding.

Other Medications
Please tell your doctor or pharmacist if you are taking (or recently took) any other medicines. Remember to mention also medicines that you bought without prescription, over the counter.

While taking ILEVRO
Tell your doctor if you are not getting any relief or if problems develop.

If you wear contact lenses
There is a preservative in ILEVRO (benzalkonium chloride) that can discolour soft lenses and may cause eye irritation. Additionally, wearing contact lenses is not recommended after cataract surgery. Do not wear contact lenses while using ILEVRO.

Driving and using machines
You may find that your vision is blurred or you may have other vision changes just after you use ILEVRO. Do not drive or use machines until your vision is clear.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all drugs that you are using or planning to use, including those without a prescription.

Do not use acetylsalicylic acid, phenylacetic acid or other nonsteroidal anti-inflammatories with ILEVRO if you have previously developed reactions to the use of these products (See When it should not be used).

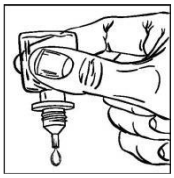
PROPER USE OF THIS MEDICATION

Always use ILEVRO exactly as your doctor has told you.

Usual adult dose:
One drop of ILEVRO should be applied to the affected eye(s) once daily. Begin 1 day before cataract surgery. Continue on the day of surgery. Then use it for as long as your doctor told you to. This may be up to 2 weeks after your operation.

How to Use:


1


2


3

- Get the ILEVRO suspension bottle and a mirror.
- Wash your hands.
- Shake well before use.
- Turn the closed bottle upside down and shake down once before each use
- Twist off the bottle cap.
- After cap is removed: if tamper evident snap collar is loose, remove before using product.
- Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back.
- Pull down your lower eyelid with a clean finger until there is a 'pocket' between the eyelid and your eye. The drop will go in here (picture 1).
- Bring the bottle tip close to the eye. Do this in front of a mirror if it helps.
- Do not touch your eye or eyelid, surrounding areas or other surfaces with the dropper. It could infect the drops.
- Gently squeeze the sides of the bottle until one drop is released into your eye (picture 2).
- After using ILEVRO suspension, press a finger into the corner of your eye, by the nose (picture 3). This helps to stop ILEVRO suspension getting into the rest of the body.
- If you use drops in both eyes, repeat the steps for your other eye.
- Close the bottle cap firmly immediately after use.
- Use up one bottle before opening the next bottle.
- If a drop misses your eye, try again.

If you are using other eye drops wait at least 5 minutes between putting in ILEVRO and the other drops.

Overdose:
If you use more ILEVRO than you should, rinse it all out with warm water. Don't put in any more drops until it's time for your next regular dose. If accidentally ingested, contact your local poison control centre or doctor.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to use ILEVRO, use a single dose as soon as you remember. If it is almost time for the next dose, leave out the missed dose and continue with the next dose of your regular routine. Do not use a double dose to make up for a missed dose. Do not use more than one drop in the affected eye(s) once daily.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

A small number of people who use ILEVRO may get side effects. They can be unpleasant, but most of them disappear rapidly.

Do not stop taking ILEVRO without speaking to your doctor. You can usually continue using ILEVRO, unless the effects are serious. If you're worried, talk to a doctor or pharmacist.

The most common side effects include eye pain, abnormal sensation in the eye, crusty eyelids, and eye surface inflammation.

Less common side effects include eye surface damage with loss of cells, blurred vision, eye itching, dry eye, eye discharge, increased tear production, eyelid inflammation, sensitivity to light, eye allergy, increased allergic symptoms, nausea, skin allergy, headache and allergy.

Additional side effects may also affect people using ILEVRO including inflammation (pain, redness, swelling) of the eye or eyelid, reduced vision, eye irritation, eye redness, dizziness, vomiting and increased blood pressure.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Eyes get redder, eyes become more painful		✓	
Cornea (protective outer layer of the eye) disorder, including corneal disorder, surface changes, and damage including thinning or perforation and impaired healing, eye inflammation, clouding, eye surface scarring: blurred vision, eye pain and redness.		✓	

This is not a complete list of side effects. For any unexpected effects while taking ILEVRO, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 2ºC - 25°C. Protect from light. Discard 28 days after opening. Keep out of the reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: *Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance program does not provide medical advice.*

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.novartis.ca or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at: 1-800-363-8883.

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ILEVRO is a registered trademark.

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