2.2 Use with Other Topical Ophthalmic Medications

One drop of ILEVRO® (nepafenac ophthalmic suspension), 0.3% should be 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.

5.1 Increased Bleeding Time

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO® (nepafenac ophthalmic suspension), 0.3%, 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 problems.

5.5 Contact Lens Wear

ILEVRO* (nepafenac ophthalmic suspension), 0.3% should not be administered while using contact lenses.

8.5 Geriatric Use

Increased bleeding time due to interference with thrombocyte aggregation (5.1) Delayed healing (5.2) Corneal effects including keratitis (5.3)

6.1 Serious and Otherwise Important Adverse Reactions

Most common adverse reactions (5 to 10%) are capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2014

**Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION: CONTENTS**

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

One drop of ILEVRO® (nepafenac ophthalmic suspension), 0.3% should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

2.2 Use with Other Topical Ophthalmic Medications

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.

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

3 DOSAGE FORMS AND STRENGTHS

Sterile ophthalmic suspension 0.3%: 1.7 mL in a 4 mL bottle and 3 mL in a 4 mL bottle.

5.2 Delayed Healing

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 topical NSAIDs including ILEVRO® (nepafenac ophthalmic suspension), 0.3% and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal derangement, corneal epithelial defects, diabetic 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.

Postmarketing 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.

5.4 Contact Lens Wear

ILEVRO® (nepafenac ophthalmic suspension), 0.3% should not be administered while using contact lenses.

6 ADVERSE REACTIONS

6.1 Serious and Otherwise Important Adverse Reactions

The following adverse reactions are described in greater detail in other sections of this label:

- Increased intraocular pressure (Warnings and Precautions 5.1)
- Delayed Healing (Warnings and Precautions 5.2)
- Corneal Effects (Warnings and Precautions 5.3)

6.2 Ocular Adverse Reactions

The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These reactions occurred in approximately 5 to 10% of patients.
Other ocular adverse reactions occurring at an incidence of approximately 1 to 3% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vireous detachment.

Some of these reactions may be the consequence of the cataract surgical procedure.

6.3 Non-Ocular Adverse Reactions

Non-ocular adverse reactions reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects.

Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 70 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 amifuna was approximately 70 and 60 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 100 times human plasma exposure for rabbits, respectively. In rats, maternal toxic doses ≥ 10 mg/kg were associated with dystocia, increased postpartum 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, LEVRO® (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 LEVRO® (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 LEVRO® (nepafenac ophthalmic suspension), 0.3% is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of LEVRO® (nepafenac ophthalmic suspension), 0.3% in pediatric patients below the age of 10 years have not been established.

8.5 Geriatric Use

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

11 DESCRIPTION

LEVRO® (nepafenac ophthalmic suspension), 0.3% is a sterile, topical, nonirritating anti-inflammatory (NSAID) product for ophthalmic use. Each ml of LEVRO® (nepafenac ophthalmic suspension), 0.3% contains 3 mg of nepafenac. Nepafenac is designated chemically as 2-amino-3-naphthoic acid (2-amino-3-naphthalene carboxylic acid) and its empirical formula is C9H7NO2.

The structural formula of nepafenac is:

\[
\text{Nepafenac} = \text{C}_9\text{H}_7\text{NO}_2
\]

Nepafenac is a yellow crystalline powder. The molecular weight of nepafenac is 254.28.

LEVRO® (nepafenac ophthalmic suspension), 0.3% is supplied as a sterile aqueous suspension with a pH approximately of 6.8.

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Nepafenac is a yellow crystalline powder. The molecular weight of nepafenac is 254.28.

LEVRO® (nepafenac ophthalmic suspension), 0.3% is supplied as a sterile aqueous suspension with a pH approximately of 6.8.

The osmolality of LEVRO® (nepafenac ophthalmic suspension), 0.3% is approximately 300 mOsm/kg.

Each ml of LEVRO® (nepafenac ophthalmic suspension), 0.3% contains: Active: nepafenac 0.3% [lactic acid, boric acid, propylene glycol, carbomer 974P, sodium chloride, guar gum, carboxymethylcellulose sodium, edetate disodium, disodium, benzalkonium chloride 0.005% (preservative), sodium hydroxide and/or hydrochloric acid to adjust pH and purified water, USP.]

Inactive: boric acid, propylene glycol, carbomer 974P, sodium chloride, guar gum, carboxymethylcellulose sodium, edetate disodium, disodium, benzalkonium chloride 0.005% (preservative), sodium hydroxide and/or hydrochloric acid to adjust pH and purified water, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amifuna, a nonsteroidal anti-inflammatory drug. Nepafenac and amifuna are thought to exhibit the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

12.2 Pharmacokinetics

Following bilateral topical oculay once-daily dosing of LEVRO® (nepafenac ophthalmic suspension), 0.3%, the concentrations of nepafenac and amifuna peaked at a median time of 0.5 hour and 0.75 hour, respectively on both day 1 and day 4. The mean steady-state Cmax for nepafenac and for amifuna were 0.87 ± 0.269 mg/mL and 1.13 ± 0.479 mg/mL, respectively.

Nepafenac: concentrations up to 3000 ng/mL, and amifuna: concentrations up to 1000 ng/mL did not inhibit the in vitro metabolism of 6 specific marker substrates of cytochrome P450 (CYP) isozymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP2E1), therefore, drug-drug interactions involving CYP mediated metabolism of concomitantly administered drugs are unlikely.

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