NOVARTIS

ILEVRO® (nepafenac)

3 mg/ml eye drops suspension

Professional Information

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SCHEDULING STATUS: **S3**

1. NAME OF THE MEDICINE

ILEVRO 3 mg/ml eye drops, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of suspension contains 3 mg nepafenac.

Excipient with known effect

Each ml of suspension contains 0.05 mg benzalkonium chloride

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, suspension

Light yellow to dark orange uniform suspension, pH 6.8 (approximately).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ILEVRO is indicated in adults for:

- Prevention and treatment of pain and inflammation associated with cataract surgery;
- Reduction in risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

4.2 Posology and method of administration

Adults, including the elderly

For the prevention and treatment of pain and inflammation, the dose is 1 drop of ILEVRO in the conjunctival sac of the affected eye(s) once a day beginning 1 day prior to cataract surgery, continued on the day of surgery and for the first 2 weeks of the postoperative period. Treatment can be extended to the first 3 weeks of the postoperative period, as directed by the clinician. An additional drop should be administered 30 to 120 minutes prior to surgery.

In clinical trials, patients were treated for up to 21 days with ILEVRO (see section 5.1).

For the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients, the dose is 1 drop of ILEVRO in the conjunctival sac of the affected eye(s) once daily beginning 1 day prior to cataract surgery, continued on the day of surgery and up to 60 days of the postoperative period as directed by the clinician. An additional drop should be administered 30 to 120 minutes prior to surgery.

Special populations

Patients with renal or hepatic impairment

ILEVRO 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.

Paediatric population

The safety and efficacy of ILEVRO in children and adolescents have not been established. No data are available. Its use is not recommended in these patients.

Geriatric population

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

Method of administration

For ocular use.

Patients should be instructed to shake the bottle well before use. After the cap is removed, if a tamper evident snap collar is present and is loose, remove before using product.

If more than one topical ophthalmic medicine is being used, the medicine must be administered at least 5 minutes apart. Eye ointments should be administered last.

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. Patients should be instructed to keep the bottle tightly closed when not in use.

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 1 missed.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to other nonsteroidal anti-inflammatory drugs (NSAIDs).
- Patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

4.4 Special warnings and precautions for use

The medicine should not be injected. Patients should be instructed not to swallow ILEVRO.

Patients should be instructed to avoid sunlight during treatment with ILEVRO.

Ocular effects

Use of topical (ocular) 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 (see section 4.8). These events may be sight threatening. Therefore, patients with evidence of corneal epithelial breakdown should immediately discontinue use of ILEVRO and should be monitored closely for corneal health.

Topical (ocular) NSAIDs may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. Therefore, it is recommended that caution should be exercised if ILEVRO is administered concomitantly with corticosteroids, particularly in patients at high risk for corneal adverse reactions described below.

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 reactions 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.

There have been reports that ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including hyphaemas) in conjunction with ocular surgery. ILEVRO should be used with caution in patients with known bleeding tendencies or who are receiving other medicines which may prolong bleeding time.

An acute ocular infection may be masked by the topical use of anti-inflammatory medicines. NSAIDs do not have any anti-microbial properties. In case of ocular infection, their use with anti-infectives should be undertaken with care.

Contact lenses

Contact lens wear is not recommended during the postoperative period following cataract surgery. Therefore, patients should be advised not to wear contact lenses unless clearly indicated by their doctor.

Benzalkonium chloride

ILEVRO contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. If contact lenses need to be used during treatment, patients should be advised to remove contact lenses prior to application and wait at least 15 minutes before reinsertion.

Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since ILEVRO contains benzalkonium chloride, close monitoring is required with frequent or prolonged use.

As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations, cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease.

Cross-sensitivity

There is a potential for cross-sensitivity of nepafenac to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs.

4.5 Interaction with other medicines and other forms of interaction

In vitro studies have demonstrated a very low potential for interaction with other medicines and protein binding interactions (see section 5.2).

Prostaglandin analogues

There are very limited data on the concomitant use of prostaglandin analogues and ILEVRO. Considering their mechanism of action, the concomitant use of these medicines is not recommended.

Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. Concomitant use of ILEVRO with medications that prolong bleeding time may increase the risk of haemorrhage (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

ILEVRO should not be used by women of child bearing potential not using contraception.

Pregnancy

There are no adequate data regarding the use of nepafenac in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Since the systemic exposure in non-pregnant women is negligible after treatment with nepafenac, the risk during pregnancy could be considered low. Nevertheless, as inhibition of prostaglandin synthesis may

negatively affect pregnancy and/or embryonal/foetal development and/or parturition and/or postnatal development, ILEVRO is not recommended during pregnancy.

Regular use of non-steroidal anti-inflammatory drugs during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.

Breastfeeding

It is unknown whether nepafenac is excreted in human milk. Animal studies have shown excretion of nepafenac in the milk of rats. However, no effects on the suckling child are anticipated since the systemic exposure of the breastfeeding woman to nepafenac is negligible. ILEVRO can be used during breastfeeding.

Fertility

There are no data on the effect of ILEVRO on human fertility.

4.7 Effects on ability to drive and use machines

ILEVRO has no or negligible influence on the ability to drive and use machines.

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines.

If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies involving over 1900 patients receiving ILEVRO, the most frequently reported adverse reactions were punctate keratitis, keratitis, foreign body sensation in eyes and eye pain which occurred in between 0,4 % and 0,1 % of patients.

Diabetic patients

In the two clinical studies involving 594 patients, diabetic patients were exposed to nepafenac eye drops, suspension treatment for 90 days for the prevention of macular oedema post cataract surgery.

The most frequently reported adverse reaction was punctate keratitis which occurred in 1 % of patients, resulting in a frequency category of common. The other most frequently reported adverse reactions were keratitis and foreign body sensation in eyes which occurred in 0,5 % and 0,3 % of patients, respectively, both adverse reactions with a frequency category of uncommon.

Tabulated list of adverse reactions

The following adverse reactions are classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), or not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions

were obtained from clinical trials or post-marketing reports with ILEVRO and nepafenac 1 mg/ml eye drops, suspension.

System organ classification	**Adverse reactions**
Immune system disorders	*Rare*: hypersensitivity
Nervous system disorders	*Rare*: dizziness, headache
Eye disorders	*Uncommon*: keratitis, punctate keratitis, corneal epithelium defect, foreign body sensation in eyes, eyelid margin crusting *Rare*: iritis, choroidal effusion, corneal deposits, eye pain, ocular discomfort, dry eye, blepharitis, eye irritation, eye pruritus, eye discharge, allergic conjunctivitis, increased lacrimation, conjunctival hyperaemia *Not known*: corneal perforation, impaired healing (cornea), corneal opacity, corneal scar, reduced visual acuity, eye swelling, ulcerative keratitis, corneal thinning, blurred vision
Vascular disorders	*Uncommon*: hypertension *Not known*: blood pressure increased
Gastrointestinal disorders	*Rare*: nausea *Not known*: vomiting
Skin and subcutaneous tissue disorders	*Rare*: cutis laxa (dermatochalasis), allergic dermatitis

Description of selected adverse reactions

Patients with evidence of corneal epithelial breakdown including corneal perforation should immediately discontinue use of ILEVRO and should be monitored closely for corneal health (see section 4.4).

From post-marketing experience with nepafenac 1 mg/ml eye drops, suspension, cases reporting corneal epithelium defect/disorder have been identified. Severity of these cases vary from non serious effects on the epithelial integrity of the corneal epithelium to more serious events where surgical interventions and/or medical therapy are required to regain clear vision.

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 reactions which may become sight threatening.

Paediatric population

The safety and efficacy of ILEVRO in children and adolescents have not been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

No toxic effects are likely to occur in case of overdose with ocular use, nor in the event of accidental oral ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, anti-inflammatory agents, non-steroids, ATC code: S01BC10

Mechanism of action

Nepafenac is a non-steroidal anti-inflammatory and analgesic prodrug. After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, a nonsteroidal anti-inflammatory drug. Amfenac inhibits the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

Secondary pharmacology

In rabbits, nepafenac has been shown to inhibit blood-retinal-barrier breakdown, concomitant with suppression of PGE2 synthesis. Ex vivo, a single topical ocular dose of nepafenac was shown to inhibit prostaglandin synthesis in the iris/ciliary body (85 %-95 %) and the retina/choroid (55 %) for up to 6 hours and 4 hours, respectively.

Pharmacodynamic effects

The majority of hydrolytic conversion is in the retina/choroid followed by the iris/ciliary body and cornea, consistent with the degree of vascularised tissue.

Results from clinical studies indicate that ILEVRO has no significant effect on intraocular pressure.

Clinical efficacy and safety

Prevention and treatment of postoperative pain and inflammation associated with cataract surgery

The efficacy and safety of ILEVRO in the prevention and treatment of postoperative pain and inflammation associated with cataract surgery has been demonstrated in two masked, double blind, placebo-controlled clinical trials in a total of 1339 patients. In these studies in which patients were dosed daily beginning one day prior to cataract surgery, continued on the day of surgery and for the first 14 days of the postoperative period, ILEVRO demonstrated superior clinical efficacy compared to its vehicle in treating postoperative pain and inflammation.

Patients treated with nepafenac were less likely to have ocular pain and measurable signs of inflammation (aqueous cells and flare) in the early postoperative period through to the end of treatment than those treated with its vehicle. In the two studies, nepafenac cleared inflammation at day 14 post operation in 65 % and 68 % of patients compared to 25 % and 35 % of patients on vehicle.

Pain free rates in the nepafenac group were 89 % and 91 % compared to 40 % and 50 % of patients on vehicle.

Efficacy beyond 14 days has not been measured.

Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients

Two studies in diabetic patients were conducted to assess the efficacy and safety of ILEVRO dosed once a day for the prevention of postoperative macular oedema associated with cataract surgery. In these studies, study medication was initiated the day prior to surgery, continued on the day of surgery and for up to 90 days of the postoperative period.

In both double-masked, randomised vehicle-controlled studies, conducted in diabetic retinopathy patients, a significantly greater percentage of patients in the vehicle group developed macular oedema (17,3 % and 14,3 %) compared to patients treated with ILEVRO (2,3 % and 5,9 %). The corresponding percentages in integrated analysis of the 2 studies were 15,9 % in vehicle group and 4,1 % in nepafenac group, p<0,001. A significantly greater percentage of patients achieved improvement of 15 or more letters at Day 14 and maintained the improvement through Day 90 in ILEVRO group (61,7 %) compared to vehicle group (43 %) in one study; the percentage of subjects was similar in the 2 treatment groups for this endpoint in the second study (48,8 % in nepafenac group and 50,5 % in vehicle group). In integrated analysis of the 2 studies, the percentage of subjects with 15 letter improvement at Day 14 and maintained to Day 90 was higher in ILEVRO group (55,4 %) compared to vehicle group (46,7 %, p=0,003).

5.2 Pharmacokinetic properties

Absorption

Following one drop of ILEVRO in both eyes once daily for four days, low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects 2 and 3 hours post-dose, respectively. The mean steady-state plasma C_{max} for nepafenac and for amfenac were 0,847 ± 0,269 ng/ml and 1,13 ± 0,491 ng/ml, respectively, following ocular administration.

Distribution

Amfenac has a high affinity toward serum albumin proteins. In vitro, the percent bound to rat albumin, human albumin and human serum was 98,4 %, 95,4 % and 99,1 %, respectively.

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

Studies in rabbits demonstrated that the topically administered nepafenac is distributed locally from the front of the eye to the posterior segments of the eye (retina and choroid).

Biotransformation

Nepafenac undergoes relatively rapid bioactivation to amfenac via intraocular hydrolases.

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}.

Interactions with other medicines: Neither nepafenac nor amfenac inhibit any of the major human cytochrome P450 (CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4) metabolic activities *in vitro* at concentrations up to 3000 ng/ml. Therefore, interactions involving CYP-mediated metabolism of concomitantly administered medicines are unlikely.

Elimination

After oral administration of ^{14}C-nepafenac to healthy volunteers, urinary excretion was found to be the major route of radioactive excretions, accounting for approximately 85 % while faecal excretion represented approximately 6 % of the dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Boric acid

Propylene glycol

Carbomer

Sodium chloride

Guar

Carmellose sodium

Disodium edetate

Benzalkonium chloride

Sodium hydroxide and/or hydrochloric acid (for pH adjustment)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

Discard 4 weeks after first opening.

6.4 Special precautions for storage

Do not store above 25 °C. Keep bottle in the outer carton in order to protect from light.

For storage conditions after first opening of the medicine, see section 6.3

6.5 Nature and contents of container

Round white low density polyethylene (LDPE) bottle with a LDPE dispensing plug and white polypropylene screw cap containing 3 ml suspension. The bottle may be presented in a pouch.

Carton containing 1 bottle.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBER(S)

52/15.4/0575

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

21 January 2021

10. DATE OF REVISION OF THE TEXT

21 January 2021