

ILEVRO - nepafenac suspension
Alcon Laboratories, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ILEVRO* (nepafenac ophthalmic suspension), 0.3% safely and effectively. See full prescribing information for ILEVRO* (nepafenac ophthalmic suspension), 0.3%.

ILEVRO* (nepafenac ophthalmic suspension), 0.3%, topical ophthalmic
Initial U.S. Approval: 2005

----- **INDICATIONS AND USAGE** -----

ILEVRO* (nepafenac ophthalmic suspension), 0.3% is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery (1).

----- **DOSAGE AND ADMINISTRATION** -----

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)

----- **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. (3)

----- **CONTRAINDICATIONS** -----

Hypersensitivity to any of the ingredients in the formula or to other NSAIDS.(4)

----- **WARNINGS AND PRECAUTIONS** -----

Increased bleeding time due to interference with thrombocyte aggregation (5.1)

Delayed healing (5.2)

Corneal effects including keratitis (5.3)

----- **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: 2/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE SECTION

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

2 DOSAGE AND ADMINISTRATION SECTION

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 SECTION

Sterile ophthalmic suspension 0.3%

1.7 mL in a 4 mL bottle

3 mL in a 4 mL bottle

4 CONTRAINDICATIONS SECTION

ILEVRO* (nepafenac ophthalmic suspension), 0.3% is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

5 WARNINGS AND PRECAUTIONS SECTION

5.1 Increased Bleeding Time

With some nonsteroidal anti-inflammatory drugs including ILEVRO* (nepafenac ophthalmic suspension), 0.3%, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.

It is recommended that ILEVRO* (nepafenac ophthalmic suspension), 0.3% be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

5.2 Delayed Healing

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 steroids may increase the potential for healing problems.

5.3 Corneal Effects

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 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.

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 SECTION

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Serious and Otherwise Important Adverse Reactions

The following adverse reactions are discussed in greater detail in other sections of labeling.

- Increased Bleeding Time (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 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous 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 SECTION

8.1 Pregnancy Section

Teratogenic Effects.

Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥ 10 mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO* (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 ILEVRO* (nepafenac ophthalmic suspension), 0.3% during late pregnancy should be avoided.

8.3 Nursing Mothers Section

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 ILEVRO* (nepafenac ophthalmic suspension), 0.3% is administered to a nursing woman.

8.4 Pediatric Use Section

The safety and effectiveness of ILEVRO* (nepafenac ophthalmic suspension), 0.3% in pediatric

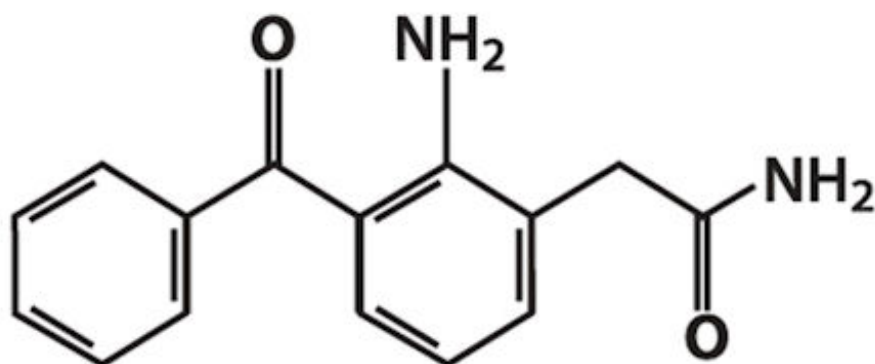
patients below the age of 10 years have not been established.

8.5 Geriatric Use Section

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

11 DESCRIPTION SECTION

ILEVRO* (nepafenac ophthalmic suspension), 0.3% is a sterile, topical, nonsteroidal anti-inflammatory (NSAID) prodrug for ophthalmic use. Each mL of ILEVRO* (nepafenac ophthalmic suspension), 0.3% contains 3 mg of nepafenac. Nepafenac is designated chemically as 2-amino-3-benzoylbenzeneacetamide with an empirical formula of $C_{15}H_{14}N_2O_2$. The structural formula of nepafenac is:



Nepafenac is a yellow crystalline powder. The molecular weight of nepafenac is 254.28. ILEVRO* (nepafenac ophthalmic suspension), 0.3% is supplied as a sterile, aqueous suspension with a pH approximately of 6.8.

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

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

12 CLINICAL PHARMACOLOGY SECTION

12.1 Mechanism of Action Section

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

12.3 Pharmacokinetics Section

Following bilateral topical ocular once-daily dosing of ILEVRO* (nepafenac ophthalmic suspension), 0.3%, the concentrations of nepafenac and amfenac 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 C_{max} for nepafenac and for amfenac were 0.847 ± 0.269 ng/mL and 1.13 ± 0.491 ng/mL, respectively.

Nepafenac at concentrations up to 3000 ng/mL and amfenac at 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, CYP2E1, and CYP3A4). Therefore, drug-drug interactions involving CYP mediated metabolism of concomitantly administered drugs are unlikely.

13 NONCLINICAL TOXICOLOGY SECTION

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Section

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

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

14 CLINICAL STUDIES SECTION

In two double masked, randomized clinical trials in which patients were dosed daily beginning one day prior to cataract surgery, continued on the day of surgery and for the first two weeks of the postoperative period, ILEVRO* (nepafenac ophthalmic suspension), 0.3% demonstrated superior clinical efficacy compared to its vehicle in treating postoperative pain and inflammation.

Treatment effect over vehicle for resolution of ocular pain occurred as early as day 1 post-surgery. Treatment effect over vehicle for resolution of inflammation was significantly better than vehicle in both studies at day 7 and day 14 post-surgery.

Inflammation and Ocular Pain Resolution Results of Nepafenac ophthalmic suspension, 0.3% versus Vehicle at Day 14 Post-surgery (All-Randomized Population)

Studies	Treatment	Inflammation Resolution at Postop Day 14	Ocular Pain Resolution at Postop Day 14
Study 1	Nepafenac ophthalmic suspension, 0.3% (n/N) ⁽¹⁾	552/851 (65%)	734/851 (86%)
	NEVANAC (n/N) ⁽¹⁾	568/845 (67%)	737/845 (87%)
	Vehicle (n/N) ⁽¹⁾	67/211 (32%)	98/211 (46%)
	Difference (95% CI) ⁽²⁾	33% (26%, 40%)	40% (32%, 47%)
Study 2	Nepafenac ophthalmic suspension, 0.3% (n/N) ⁽¹⁾	331/540 (61%)	456/540 (84%)
	Vehicle (n/N) ⁽¹⁾	63/268 (24%)	101/268 (38%)
	Difference (95% CI) ⁽²⁾	38% (31%, 45%)	47% (40%, 54%)

⁽¹⁾n/N is the ratio of those with complete resolution of anterior chamber cell and flare by the postoperative day 14 visit over all randomized subjects.

⁽²⁾Difference is (Nepafenac ophthalmic suspension, 0.3% – vehicle). The 95% confidence interval is derived using asymptotic approximation.

16 HOW SUPPLIED/STORAGE AND HANDLING SECTION

ILEVRO* (nepafenac ophthalmic suspension), 0.3% is supplied in a white, oval, low density polyethylene DROP-TAINER[®] dispenser with a natural low density polyethylene dispensing plug and gray polypropylene cap presented in an overwrap (1.7mL fill only). Tamper evidence is provided with a shrink band around the closure and neck area of the package.

1.7 mL in 4 mL bottle NDC 0065-1750-07
3 mL in 4 mL bottle NDC 0065-1750-14

Storage: Store at 2 - 25°C (36 - 77°F).

Protect from light.

17 PATIENT COUNSELING INFORMATION SECTION

17.1 Slow or Delayed Healing

Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

17.2 Avoiding Contamination of the Product

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

17.3 Contact Lens Wear

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

17.4 Intercurrent Ocular Conditions

Patients should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

17.5 Concomitant Topical Ocular Therapy

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

17.6 Shake Well Before Use

Patients should be instructed to shake well before each use.

U.S. Patent Nos. 5,475,034; 6,403,609; and 7,169,767

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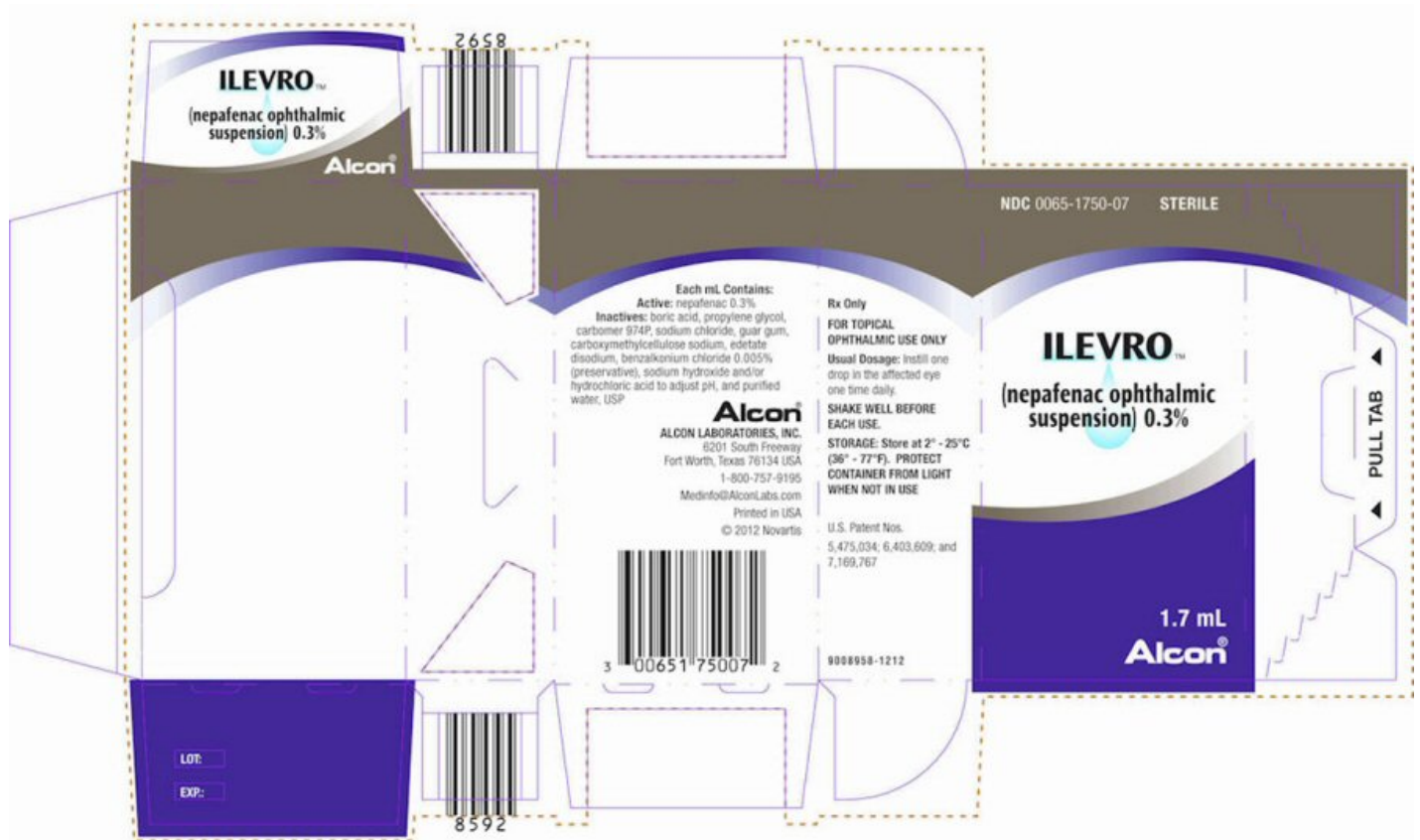
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PRINCIPAL DISPLAY PANEL

NDC 0065-1750-07 STERILE

ILEVRO™
**(nepafenac ophthalmic
suspension) 0.3%**

1.7 mL
Alcon®



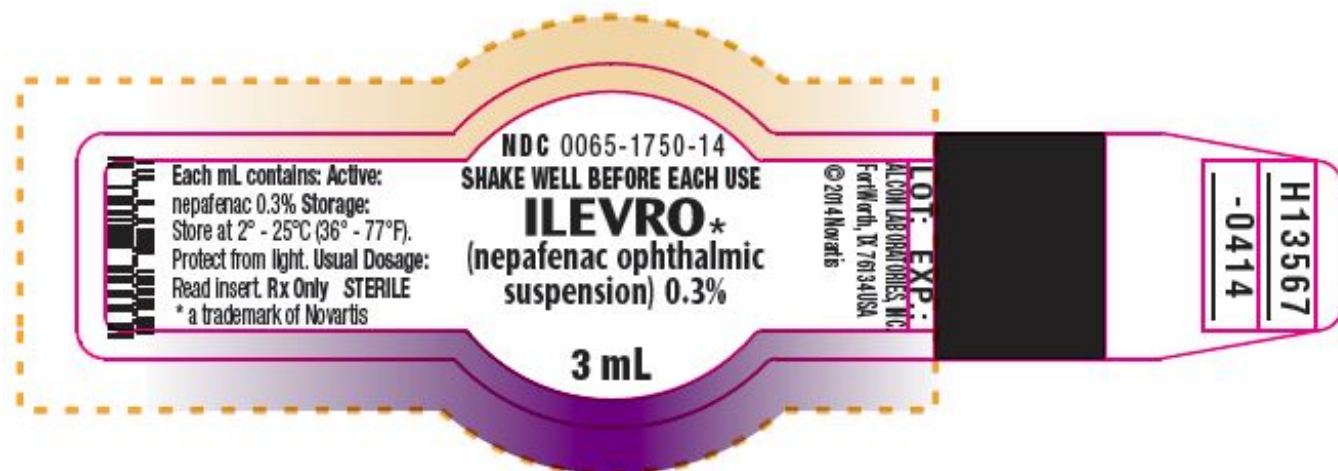


NDC 0065-1750-14 STERILE

ILEVRO*
(nepafenac ophthalmic
suspension) 0.3 %

3 mL

Alcon®
a Novartis company



ILEVRO

nepafenac suspension

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0065-1750
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Nepafenac (UNII: 0J9L7J6V8C) (Nepafenac - UNII:0J9L7J6V8C)	Nepafenac	3 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
Boric Acid (UNII: R57ZHV85D4)	
Propylene Glycol (UNII: 6DC9Q167V3)	
Carbomer Homopolymer Type B (allyl Pentaerythritol Crosslinked) (UNII: HHT01ZNK31)	
Sodium Chloride (UNII: 451W47IQ8X)	
Guar Gum (UNII: E89I1637KE)	
Carboxymethylcellulose Sodium (UNII: K679OBS311)	
Edetate Disodium (UNII: 7FLD91C86K)	
Benzalkonium Chloride (UNII: F5UM2KM3W7)	
Sodium Hydroxide (UNII: 55X04QC32I)	
Hydrochloric Acid (UNII: QTT17582CB)	
Water (UNII: 059QF0K00R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0065-1750-07	1 in 1 CARTON		
1		1.7 mL in 1 BOTTLE, DROPPER; Type 0: Not a Combination Product		
2	NDC:0065-1750-14	1 in 1 CARTON		
2		3 mL in 1 BOTTLE, DROPPER; Type 0: Not a Combination Product		
3	NDC:0065-1750-08	1 in 1 CARTON		
3		.8 mL in 1 BOTTLE, DROPPER; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA203491	12/20/2012	

Labeler - Alcon Laboratories, Inc. (008018525)

Registrant - Alcon Laboratories, Inc. (008018525)

Establishment

Name	Address	ID/FEI	Business Operations
Alcon Research Ltd		007672236	MANUFACTURE(0065-1750)

Establishment

Name	Address	ID/FEI	Business Operations
S.A. Alcon-Couvreur N.V.		370205429	MANUFACTURE(0065-1750)

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Alcon Laboratories, Inc.