Protocol Number: [redacted]
Protocol Version: Version 2.0, Amendment 2
Protocol Date: 25 JUNE 2018

CLINICAL PROTOCOL

A randomized, multicenter, double masked, placebo controlled, parallel group, bioequivalence study to evaluate the clinical equivalence and safety of Nepafenac 0.3% ophthalmic suspension [redacted] Actavis LLC) with Ilevro™ (Nepafenac ophthalmic suspension), 0.3% of Alcon Laboratories, Inc. for the treatment of pain and inflammation associated with cataract surgery.

SPONSOR

Actavis LLC
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Parsippany, NJ 07054

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SPONSOR SIGNATURE PAGE

Protocol Number: [redacted]

Protocol Version Number & Date: Version 2.0, Amendment 2 dated 25 JUNE 2018

Study Title: A randomized, multicenter, double masked, placebo controlled, parallel group, bioequivalence study to evaluate the clinical equivalence and safety of Nepafenac 0.3% ophthalmic suspension [redacted] Actavis LLC) with Ilevro™ (Nepafenac ophthalmic suspension), 0.3% of Alcon Laboratories, Inc. for the treatment of pain and inflammation associated with cataract surgery.

Signatures of the noted individuals ensure that all designated persons have agreed this version is final:

[redacted]

Director, Clinical R&D (Signature)
Actavis LLC

[redacted]

Associate [redacted] ector, Clinical R&D (Signature)
Actavis LLC

CRO SIGNATURE PAGE

Protocol Number: [redacted]

Protocol Version Number & Date: Version 2.0, Amendment 2 dated 25 JUNE 2018

Study Title: A randomized, multicenter, double masked, placebo controlled, parallel group, bioequivalence study to evaluate the clinical equivalence and safety of Nepafenac 0.3% ophthalmic suspension ([redacted] Actavis LLC) with Ilevro™ (Nepafenac ophthalmic suspension), 0.3% of Alcon Laboratories, Inc., for the treatment of pain and inflammation associated with cataract surgery.

Signatures of the noted individuals ensure that all designated persons have agreed this version is final:

[redacted]

Project Manager (Signature) Date

[redacted]

ical Monitor (Signature) Date

STUDY ACKNOWLEDGMENT / DISCLOSURE

Protocol Number: [redacted]

Protocol Version Number & Date: Version 2.0, Amendment 2 dated 25 JUNE 2018

Study Title: A randomized, multicenter, double masked, placebo controlled, parallel group, bioequivalence study to evaluate the clinical equivalence and safety of Nepafenac 0.3% ophthalmic suspension [redacted] Actavis LLC) with Ilevro™ (Nepafenac ophthalmic suspension), 0.3% of Alcon Laboratories, Inc. Fort Worth, Texas 76134 USA, for the treatment of pain and inflammation associated with cataract surgery.

I have carefully read and understand the foregoing protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH guidelines for Good Clinical Practice, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA), if applicable, the World Medical Association Declaration of Helsinki and local regulatory guidelines. I will attempt to complete the study within the time designated.

I will ensure that the rights, safety and welfare, of study subjects under my care are protected. I will ensure control of the drugs under investigation in this study.

I will provide access to the protocol and all other study-related information supplied by the Sponsor to all personnel responsible to me & who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all study subject information (case report forms, shipment and drug return forms and all other information collected during the study) and drug disposition in accordance with FDA regulations. I agree to retain and maintain strict accountability of the Investigational Products supplied to the study site.

I will not enroll any subjects into this study until applicable Regulatory approval & IRB approval are obtained.

_____ _____

Principal Investigator's Signature **Date**

_____

Principal Investigator's Name

CONTACT DETAILS

CRO
[redacted]
BIOSTATISTICS & DATA MANAGEMENT
[redacted]
CLINICAL LABORATORY
[redacted]
MEDICAL MONITOR
[redacted]
IWRS
[redacted]
IRB
[redacted]
MONITORING
[redacted]

RETENTION SAMPLES STORAGE FACILITY
[redacted]

TABLE OF CONTENTS

SPONSOR SIGNATURE PAGE 2
CRO SIGNATURE PAGE 3
STUDY ACKNOWLEDGMENT / DISCLOSURE 4
CONTACT DETAILS 5
TABLE OF CONTENTS 7
LIST OF ABBREVIATIONS 10
PROTOCOL SYNOPSIS 11
1.0 INTRODUCTION AND BACKGROUND 15
2.0 OBJECTIVES 16
3.0 STUDY OVERVIEW 17
4.0 STUDY POPULATION 17
4.1 Number of Study Subjects 17
4.2 Inclusion Criteria 17
4.3 Exclusion Criteria 19
4.4 Prohibitions 21
4.5 Allowable Co-Administrations 21
5.0 SAFETY AND TOLERABILITY EVALUATIONS 21
5.1 General Safety Evaluations 21
6.0 EVALUATIONS OF EFFICACY 23
7.0 EVALUATION OF SAFETY 23
8.0 STUDY VISITS 23
8.1 Visit 1: Day -21 to Day -1 (Screening/Baseline/Randomization Visit) 23
Pre-Operative Call: Day -1
8.2 Visit 2: Day 0 (The Day of Cataract Surgery) 25
8.3 Visit 3: Day 1 (One Day After the Cataract Surgery) 25
8.4 Visit 4: Day 7± 2 Days (Follow up Visit) 26
8.5 Visit 5: Day 14 ±2 Days (End of Study Visit/Early Discontinuation) 26
8.6 Unscheduled Visits and Early Discontinuation Visit 27
9.0 STUDY SUBJECT DISPOSITION AND DISCONTINUATION 27
10.0 STUDY SUBJECT INSURANCE 28
11.0 INVESTIGATIONAL MEDICINAL PRODUCT 29
11.1 Description 29
11.2 Storage Conditions 29
11.3 Packaging, Masking, and Labeling 29

11.4 Masking 30
11.5 Treatment Assignment 30
11.6 Administration of Investigational Product 31
11.7 Assessment of Compliance 31
11.8 Investigational Medicinal Product Accountability 31
11.9 Retention of Study Drug Samples 32
11.10 Return of Clinical Supplies 32
12.0 STATISTICAL METHODS 32
12.1 Sample Size Rationale 32
12.2 Randomization Procedures 33
12.3 Significance Level 33
12.4 Datasets to be analyzed 33
12.5 Comparability of Study Groups at Baseline 34
12.6 Safety Assessment 34
12.7 Efficacy Assessment 34
12.8 Primary Efficacy Criteria 34
12.9 Test of Bioequivalence 35
12.10 Test of Superiority 35
13.0 ADVERSE EVENTS REPORTING 35
13.1 Definitions 35
13.2 Severity 37
13.3 Relationship to Adverse Event to the Study Drug 38
13.4 Expectedness 38
13.5 Recording and Reporting of Adverse Events 39
13.6 Reporting of Serious Adverse Events 39
13.7 Submission of AEs 43
13.8 Early Termination 43
13.9 Pregnancy 43
13.10 Medication Error and Special Situations 44
13.11 Follow-Up of Subjects after AE 45
14.0 ETHICS 45
14.1 Informed Consent 45
14.2 Institutional Review Board 46
14.3 Study Subject Confidentiality 46

15.0 DOCUMENTATION 47
15.1 Site Regulatory Documents Required for Initiation 47
15.2 Maintenance and Retention of Records 47
15.3 Case Report Forms (CRFs) 48
15.4 Primary Source Documents 48
15.5 Study Monitoring 49
15.6 Audits and Inspections 50
15.7 Modifications to the Protocol 50
15.8 Completion of Study 50

16.0 CONFIDENTIALITY, USE OF INFORMATION AND PUBLICATION 50
REFERENCES 52
APPENDIX I: SCHEDULE OF EVENTS 53
APPENDIX II: INSTRUCTIONS FOR THE SUBJECT 54
APPENDIX III: PRESCRIBING INFORMATION 56

LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse Event
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
DCF	Data Clarification Forms
EC	Ethics Committee
ED	Early Discontinuation Visit
EDC	Electronic Data Capture
EOT	End of Treatment Visit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEENT	Head, Eyes, Ears, Nose and Throat
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonization
ID	Identification
IEC	Institutional Ethics Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board
IU	International Unit
IUD	Intrauterine Device
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
mITT	Modified Intent to Treat
NA	Not Applicable
NSAID	Non-Steroidal Anti-Inflammatory Drug
SAE	Serious Adverse Event
UPT	Urine Pregnancy Test
US	United States
USV	Unscheduled Visit
WOCBP	Women of child bearing potential

Protocol Synopsis

Sponsor: Actavis LLC	**Name of Medical Products:** Nepafenac and Ilevro™ (Nepafenac ophthalmic suspension)	**Active Ingredient(s):** Nepafenac

Study Title, Design and Methodology:
A randomized, multicenter, double masked, placebo controlled, parallel group, bioequivalence study to evaluate the clinical equivalence and safety of Nepafenac 0.3% ophthalmic suspension ([redacted] Actavis LLC) with Ilevro™ (Nepafenac ophthalmic suspension), 0.3% of Alcon Laboratories, Inc. for the treatment of pain and inflammation associated with cataract surgery.

Number of Subjects to be Enrolled and Randomized (Planned):
Approximately 450 subjects [redacted], who have a cataract and are planning to undergo cataract surgery will be enrolled and randomized [redacted].

Study Sites:
This multicenter study will be conducted at approximately **17** study sites in the U.S.

Indication:
Pain and inflammation associated with cataract surgery

Study Phase:
Bioequivalence study with clinical endpoint

Study Objectives:
- To demonstrate the clinical equivalence of Nepafenac 0.3% ophthalmic suspension [redacted] Actavis LLC.) with Ilevro™ (Nepafenac ophthalmic suspension), 0.3% of Alcon Laboratories, Inc. for the treatment of pain and inflammation associated with cataract surgery.
- To demonstrate the superiority of the efficacy of the test and reference products over the placebo control in the treatment of pain and inflammation associated with cataract surgery.

Study Duration:
Total study duration will be of 16 days i.e. the treatment duration. A Screening period of up to 21 days is acceptable.

Diagnosis/Target Population and Key Inclusion Criteria:
Study will be conducted on subjects who have a clinical diagnosis of cataract and are planning to undergo cataract surgery.

The study is designed to be only monocular (only one eye per subject).

Other inclusion and exclusion criteria are mentioned in sections 4.2 and 4.3 of the protocol.

Sponsor: Actavis LLC	**Name of Medical Products:** Nepafenac and Ilevro™ (Nepafenac ophthalmic suspension)	**Active Ingredient(s):** Nepafenac

Investigational Products:

TEST PRODUCT:
Name of the product: Nepafenac
Pharmaceutical dosage form: Ophthalmic suspension
Strength: 0.3%
Manufactured by: [redacted] Actavis LLC.

REFERENCE PRODUCT:
Name of the product: Ilevro™ (Contains Nepafenac)
Pharmaceutical dosage form: Ophthalmic suspension
Strength: 0.3%
Manufactured by: Alcon Laboratories, Inc

PLACEBO:
Name of the product: Sterile ophthalmic suspension
Pharmaceutical dosage form: Ophthalmic suspension
Strength: NA
Manufactured by: [redacted] Actavis LLC.

Dose and Mode of Administration:

A drop of the study drug suspension should be instilled into the affected eye one-time daily, beginning a day prior to the planned cataract surgery, on the day of the cataract surgery and for 14 days thereafter. The study drug should be instilled once daily. On the day of cataract surgery (Day 0) a drop should be added 30-120 minutes prior to the surgery and once following cataract surgery prior to the subject leaving the surgery center.

Note: As the study drug will be administered twice on the day of cataract surgery (Day 0) once prior to cataract surgery and once following cataract surgery prior to the subject leaving the surgery center. The dose and mode of treatment chosen in this study is the dosage approved by US FDA for the treatment of pain and inflammation associated with cataract surgery.

At least 5 minutes between all ophthalmic drop administrations should be maintained throughout the study.

Clinical Evaluations will be performed at:

- Visit 1: Day -21 to Day -1 (Screening/Baseline/Randomization Visit)
  Pre-Operative Call: Day -1
- Visit 2: Day 0 (The Day of Cataract Surgery)
- Visit 3: Day 1 (One Day After Cataract Surgery)
- Visit 4: Day 7± 2 Days (Follow-up Visit)
- Visit 5: Day 14 ± 2 Days (End of Study Visit/ Early Discontinuation)

Sponsor: Actavis LLC	**Name of Medical Products:** Nepafenac and Ilevro™ (Nepafenac ophthalmic suspension)	**Active Ingredient(s):** Nepafenac

Clinical Endpoints:

Evaluation of Efficacy:

Proportion of subjects with cure at Day 14 defined as a score of 0 for aqueous cells, a score of 0 for aqueous flare and a score of no more than 3 for pain.

Evaluation of Safety:

- The incidence of treatment emergent adverse events.
- Ocular parameters (visual acuity, intraocular pressure measurement, slit lamp evaluation and dilated fundus examination)

Table No. 1:

Grade	**Aqueous Cells:** Determined using a narrow slit beam (0.5 mm width at least 8mm length) at maximum luminance. Pigment and red blood cells are to be
0	None
1	1 to 5 cells
2	6 to 15 cells
3	16 to 30 cells
4	Greater than 30 cells
Grade	**Aqueous Flare:** Determined using a narrow slit beam (0.5 mm width at least 8mm length) at maximum luminance.
0	No visible flare when compared with the normal eye.
1	Mild-Flare visible against dark pupillary background but not visible against iris background.
2	Moderate-Flare is visible with the slit-lamp beam aimed onto the iris surface as well as the dark pupillary background.
3	Severe-Very dense flare. May also present as a "hazy" appearance of anterior segment structures when viewed with low power magnification of the slit-lamp. Present as pronounced Tyndall effect.
Grade	**Ocular Pain:** A positive sensation of the eye, including foreign body sensation, stabbing, throbbing or aching.
0	None- absence of positive sensation
1	Patient reports presence of mild sensation or discomfort typical of post-operative ocular surgery, e.g., diffuse or focal foreign body sensation, mild transient burning or stinging.
2	Mild- mild, tolerable aching of the eye.
3	Moderate- moderate or more prolonged aching sufficient to require the use of over-the-counter analgesics (e.g. acetaminophen).
4	Moderately Severe- More prolonged aching requiring the use of any over-the-counter analgesics other than acetaminophen.
5	Severe- Patient reports intense ocular, periocular, or radiating pain (e.g., constant or nearly constant sharp stabbing pain, throbbing or aching, etc.) requiring prescription analgesics.

STATISTICAL METHODS:

SAMPLE SIZE ESTIMATION:

[redacted] To establish bioequivalence for the primary endpoint (proportion of subjects with "cure" at the Day 14), the 90% confidence interval of the test - reference difference between products must be contained within [-0.20, +0.20] for dichotomous variables (cure versus failure), using the PP population.

TEST OF EQUIVALENCE:

- The PP population includes all randomized subjects who meet all inclusion and exclusion criteria, [redacted]
- The mITT population includes all randomized subjects who met the inclusion and exclusion criteria, administered at least one dose of study drug and returned for at least one post-baseline evaluation visit.
- The safety population includes all randomized subjects who receive study drug.

Subjects who discontinue because of lack of treatment effect after completing two days of treatment should be analyzed in the mITT and PP populations as a treatment failure. Subjects discontinued for other reasons, including drug-related adverse events, should be excluded from the PP population, but included in the mITT population using Last Observation Carried Forward (LOCF).

The recommended primary endpoint is the proportion of subjects with cure at Visit 5 (end of the study on day 14 +/- 2 days) defined as a score of 0 for aqueous cells, a score of 0 for aqueous flare and a score of no more than 3 for pain.

SAFETY PARAMETERS:

Incidence of all adverse events reported during the study will be summarized using the current version of MedDRA dictionary by treatment group, body system, severity and relationship to study drug. No inferential statistical analyses are planned.

1.0 INTRODUCTION AND BACKGROUND

Rationale for the Study

This study is designed to determine clinical equivalence of an ophthalmic suspension in order to facilitate the registration of a generic version of Nepafenac 0.3% suspension. The reference listed drug for this suspension is Ilevro™ (Nepafenac Ophthalmic Suspension 0.3%). This study will be conducted in male and female subjects with cataract.

Overview of Study Indication

Some degree of post-operative ocular inflammation remains a predictable consequence of a cataract surgery and intraocular lens implantation. Ocular inflammation is characterized by redness, swelling, and/or pain associated with irritation or trauma to the eye. Surgical trauma causes a trigger of the arachidonic acid cascade which in turn generates prostaglandins by activation of Cyclo-oxygenase-1 and Cyclo-oxygenase-2.

Clinical symptoms of prostaglandin production include hyperemia, miosis, impaired vision, pain and diminished visual acuity secondary to cystoid macular edema (CME).

Clinically, iritis is the hallmark of intra-ocular inflammation, characterized by perilimbal injection and anterior chamber cell and flare. If not treated appropriately, this inflammation can result in significant discomfort for subjects and impede the recovery of the vision. Cystoid macular edema is another vision reducing complication that can occur as a consequence of the post-operative ocular inflammatory response.

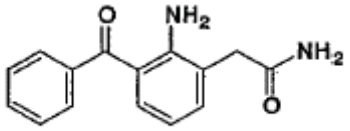
Topical NSAIDs reduce inflammation by inhibiting prostaglandin synthesis and have been shown to be clinically effective in controlling inflammation after cataract surgery. Several clinical studies have shown that NSAIDs are as effective as steroids in the treatment of post-operative pain and inflammation.

Current Treatment for Study Indication

Topical NSAIDs which are used commonly for ocular pain and inflammation are Diclofenac, Ketorolac, Bromfenac, and Nepafenac. Topical steroids used commonly for the same are Loteprednol, Triamcinolone, Rimexolone, Medrysone, Prednisolone, and Dexamethasone.

Reference Product Information (ILEVRO™)

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 C15H14N2O2. 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.

Mechanism of Action/Pharmacodynamics

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.

Pharmacokinetics

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 Cmax 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.

2.0 OBJECTIVES

- To demonstrate the clinical equivalence of Nepafenac 0.3% ophthalmic suspension ([redacted] Actavis LLC) with Ilevro™ (Nepafenac ophthalmic suspension), 0.3% of Alcon Laboratories, Inc. Fort Worth, Texas 76134 USA, for the treatment of pain and inflammation associated with cataract surgery.

- To demonstrate the superiority of the efficacy of the test and reference products over the placebo control in the treatment of pain and inflammation associated with cataract surgery.

3.0 STUDY OVERVIEW

Approximately 450 subjects [redacted], subjects who have a cataract and are planning to undergo cataract surgery will be enrolled and randomized in this investigational study. [redacted]

One drop of the suspension should be instilled into the affected eye one-time daily, beginning a day prior to the planned cataract surgery, on the day of the cataract surgery, and for 14 days thereafter. On the day of cataract surgery (day 0) a drop should be added 30-120 minutes prior to the surgery and an additional drop will be administered following cataract surgery prior to the subject leaving the surgery center. The study is designed to be only monocular (only one eye per subject).

The dose and mode of treatment chosen in this study is the dosage approved by US FDA for the treatment of pain and inflammation associated with cataract surgery.

The study subjects will undergo clinical evaluations throughout the study in order to assess efficacy and safety. Study subject primary endpoint evaluation will be assessed on Visit 1 (-21 to -1 Days prior to cataract surgery), Visit 3 (Day after the cataract surgery), Visit 4 (Follow up Visit Day 7 ± 2 days) and Visit 5 (End of study Day 14 ± 2 days).

If the Investigator determines that the study subject's condition has worsened to the degree that it is unsafe for continuation in the study, the study subject may be discontinued and will be evaluated as a treatment failure.

4.0 STUDY POPULATION

4.1 Number of Study Subjects

This multicenter study will be comprised of subjects who have cataract and are planning to undergo cataract surgery.

Approximately 450 subjects aged 18 years and above, male or female, of any race, who meet all the inclusion and none of the exclusion criteria, will be enrolled into the study.

4.2 Inclusion Criteria

1. Males or non-pregnant, non-lactating females, 18 years of age or older who have a cataract and are expected to undergo cataract extraction.

2. No aqueous cells, no visible aqueous flare and no significant ocular pain in the selected eye noted during the Screening visit by slit-lamp examination.

No aqueous cells	Grade 0
No visible aqueous flare	Grade 0
No significant ocular pain	Grade 0 or 1
For details See Table 1 on page 13	

3. Study subjects must have provided IRB approved written informed consent using the latest version of the IRB informed consent form. In addition, study subjects must sign a HIPAA authorization, if applicable.

4. Study subjects should be literate and willing to complete the subject diary regularly as directed.

5. Study subjects must be in good health and free from any clinically significant disease apart from indication under study.

6. Females of child bearing potential (WOCBP*) must not be pregnant or lactating at baseline visit (as documented by a negative urine pregnancy test).
All female subjects will be considered to be of childbearing potential unless they are postmenopausal. Female subjects of childbearing potential (WOCBP) are defined as sexually mature women without prior hysterectomy, or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for the past 12 or more months are still considered to be of childbearing potential, if the amenorrhea is possibly due to other causes, including prior chemotherapy, anti-estrogens, or ovarian suppression. Postmenopausal women (defined as women who have been amenorrheic for at least 12 consecutive months, in the appropriate age group, without other known or suspected primary cause) or women who have been sterilized surgically or who are otherwise proven sterile (i.e., total hysterectomy, or bilateral oophorectomy with surgery at least 4 weeks prior to randomization) are not considered WOCBP. Subjects who have undergone tubal ligation are **NOT considered as surgically sterile.*

7. Female subjects of childbearing potential must be willing to use an acceptable form of birth control from the day of the first dose administration to 30 days after the last administration of IP. For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, Depo-Provera® (Medroxyprogesterone acetate-stabilized for at least 3 months); vaginal contraceptive; contraceptive implant; double barrier methods (e.g. condom and spermicide); Nuvaring vaginal hormonal birth control, IUD, or abstinence with a second method of birth control should the subject become sexually active. A

sterile sexual partner is NOT considered an adequate form of birth control.

8. All male subjects must agree to use accepted methods of birth control with their partners, from the day of the first dose administration (to 30 days after the last administration of study drug). Please see acceptable forms for "Female" birth control above. Abstinence is an acceptable method of birth control for males.

9. Study subjects must be willing and able to understand and comply with the requirements of the protocol, including attendance at the required scheduled study visits.

10. Study subjects must be willing to refrain from using any other treatments other than the investigational product.

4.3 Exclusion Criteria

1. Females who are pregnant, breast feeding, or planning a pregnancy during the course of the study and for 30 days after last study dose.

2. Females of childbearing potential who do not agree to utilize an adequate form of contraception.

3. Current or past history of severe hepatic or renal impairment, uncontrolled diabetes mellitus, rheumatoid arthritis or bleeding tendencies.

4. Current or history within two months prior to baseline of clinically significant ocular disease, e.g., corneal denervation, corneal epithelial defects, severe dry eye syndrome, ocular trauma to the operative eye, corneal edema, proliferative diabetic retinopathy in the operative eye or ocular infection.

5. In the operative eye, history of chronic or recurrent inflammatory disease, e.g., iritis, scleritis, uveitis, iridocyclitis or rubeosis iritis, lens pseudoexfoliation syndrome with glaucoma or zonular compromise.

6. Congenital ocular anomaly, e.g., aniridia or congenital cataract in the operative eye.

7. Iris atrophy in the operative eye in the operative eye.

8. Current corneal abnormalities that would prevent accurate IOP readings with the Goldmann applanation tonometer in the operative eye.

9. Nonfunctional nonoperative eye (visual acuity of 20/200 or worse Snellen).

10. Known hypersensitivity to any component of nepafenac therapy or to other nonsteroidal anti-inflammatory drug (NSAID).

11. Use within one week prior to baseline in either eye of: Topical, ophthalmic, e.g. cyclosporine (Restasis®), or systemic NSAID.

12. Use within one month prior to baseline in either eye of: 1) systemic corticosteroid, 2) high-dose salicylate therapy, or 3) topical ophthalmic prostaglandin analogs, e.g., bimatoprost, latanoprost, or travoprost.

13. Use of systemic analgesic medications, e.g. narcotics, tramadol, Neurontin® within 48 hours of baseline. Exceptions are salicylate therapy 81mg or less per day, and acetaminophen not within 8 hours of any visit from Visit 1 until V5.

14. Use within six months prior to baseline of intravitreal or subtenon injection of ophthalmic corticosteroid in either eye.

15. Underwent within six months prior to baseline any complicated intraocular surgery or repeat ocular surgeries (e.g., cataract surgery) in the operative eye.

16. Underwent within twelve months prior to baseline: refractive surgery, filtering surgery or laser surgery for IOP reduction in the operative eye.

17. History or presence of significant alcoholism or drug abuse in the past one year.

18. History or presence of significant smoking (more than 20 cigarettes or any other equivalent tobacco product/day). Discretion will be left to the Principal Investigator as to whether a patient with a history or presence of significant smoking will be included in the study.

19. History of hematologic disorders other than mild anemia.

20. Severe, unstable, or uncontrolled cardiovascular or pulmonary disease.

21. Therapy with an investigational agent within the past 30 days prior to screening.

22. Clinically significant hematologic and/or biochemical abnormalities based on laboratory testing.

23. Subjects who are in the investigator's best judgment at risk of visual field or visual acuity worsening as a consequence of participation in trial in either eye.

24. Use of any prescribed medication during last two weeks or OTC medicinal products during the last one week preceding the first dosing that results in drug-drug interaction with the study drug.

25. Major illness, as per investigator discretion, during 3 months before screening.

26. Subjects who are employees of site or CRO or sponsor or immediate family of employees.

4.4 Prohibitions:

The following are prohibited during the study:

a. Ophthalmic prostaglandin analogs, e.g., bimatoprost (Lumigan®), latanoprost (Xalatan®) or travoprost (Travatan®, Travatan Z®).
b. Topical, ophthalmic, e.g. cyclosporine (Restasis®) and lifitegrast (Xiidra®), inhaled or systemic NSAIDs, other than the assigned study drug.
c. Topical, ophthalmic, or systemic corticosteroid.
d. Use of systemic analgesic medications, e.g. narcotics, tramadol, Neurontin®Intraocular corticosteroid implant.
e. Intravitreal or subtenon injection of ophthalmic corticosteroid.
f. High-dose salicylate therapy (>81mg/day).
g. Medications which may prolong bleeding time (e.g. Warfarin®, Eliquis®) should be evaluated on a case-by-case basis by the investigator to determine if the subject is eligible to participate.
h. Contact lenses in the operative eye. Contact lens use in the non-operative eye is acceptable.
i. Ocular surgery in the study eye, other than study surgery.

45 Allowable Co-Administrations:

The following are allowable drugs to be co-administered during the study:

a. Coadministration of beta-blocker, carbonic anhydrase inhibitor, alpha-agonist, cycloplegic, mydriatic, and topical ophthalmic medications is permitted. When more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.
b. Coadministration of antibiotics, artificial tears, and low dose aspirin (less than or equal to 81 mg) is permitted.
c. Subjects will be permitted to take acetaminophen as needed for ocular pain. Any use of acetaminophen will be recorded by the subject in the subject diary including Date (DD/MMM/YYYY), Dose (Mg), and Time (HH:MM).
   Note: Adults and Adolescents Weighing 50kg or 110lbs and Over: 1,000mg every 6 hours or 650mg every 4 hours to a maximum of 4,000mg per day. Minimum dosing interval of 4 hours.
   Adults and Adolescents Weighing under 50kg or 110lbs: the recommended dosage of acetaminophen injection is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of acetaminophen injection of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day.
   A minimum of 8 hours between the last dose of acetaminophen and assessment of ocular pain and aqueous cells and flare should be maintained.

At least 5 minutes between all ophthalmic drop administrations should be maintained throughout the study.

5.0 SAFETY AND TOLERABILITY EVALUATIONS

5.1 General Safety Evaluations

Adverse Events
Safety will be determined by monitoring adverse events (AEs), which will be classified using MedDRA terminology.

Medical History
A complete medical history, including a complete review of all current and past diseases and their respective treatments, must be done prior to starting the study drug.

Physical Examination
Physical examination at the time of screening and on Day 14±2.

Vital Signs
Vital signs (blood pressure, pulse, respiratory rate and body temperature) at each study visit.

Ophthalmic Evaluation (To be performed on both the operative and non-operative eye.)
Following examinations will be performed during study visits:

Best Corrected Visual Acuity: Subjects visual acuity will be measured during Visit 1, 4 & 5. Visual acuity will be tested using the subjects best-available spectacle correction with a Snellen chart. Best Corrected Visual Acuity will be recorded in Snellen units. Pinhole correction is acceptable method of correction to use for post-surgical visit measurements.

Assessment of Ocular Pain: When using the scale, the investigator should describe the meaning of pain to the subject. Then, verbally the subject should be asked to choose one of the six descriptors (provided in table no. 1 on page no. 13) that best represent the level of pain intensity a subject is experiencing.

Slit Lamp Examination: Complete slit-lamp evaluation including evaluation of the anterior eye segment for presence of aqueous cells and flare, lids, cornea, Anterior Chamber, iris and conjunctiva. Anterior Chamber evaluation is to be administered using a narrow slit beam (0.5 width at least 8 mm length) at maximum luminance. Pigment and red blood cells are to be ignored.

Intraocular Pressure Measurement by Goldmann Applanation Tonometry: Measurement of intraocular pressure will be recorded in millimeters of mercury (mmHg) by using Goldman applanation tonometry (manual version) during all visits except Visit 2 (On the day of cataract surgery).

Dilated Fundus Examination: A dilated fundus examination will be administered on the day of screening and at the end of the study visit (Visit 5 or early exit). In it, appropriate eye drops will be used to dilate or enlarge the pupil in order to obtain better view of the fundus of the eye. Once the pupil is dilated, an ophthalmoscope or indirect lens will be used to view the eye structures:

Lens	For opacities and other challenges
Vitreous	Normal or Abnormal. Any changes, character or location

Retina	Any pathological finding
Optic Nerve Head	Normal/ glaucomatous, horizontal and vertical cup/disc ratio

Laboratory Tests

The following laboratory tests will be performed at screening and at end of the study:

Serum Chemistry	ALT	AST	BUN
	Total Bilirubin	Glucose	Creatinine
Hematology	Hemoglobin	Total WBC count with differential	
Urinalysis	Appearance	Specific Gravity	Protein
	pH	Microscopic examination	

If warranted, other tests or examinations may be performed at the discretion of the investigator. Approximately 15 ml of blood will be withdrawn during screening visit and at the end of the study visit to perform above mentioned clinical laboratory test.

Pregnancy Test

Females of child bearing potential must have a negative urine pregnancy test performed during screening visit, at Visit 2, and at end of study or early termination visit (Visit 5).

All female study subjects are considered to be of childbearing potential unless they have been surgically sterilized or have been postmenopausal for at least 1 year.

Vital signs, including blood pressure, pulse rate, respiratory rate and body temperature will be documented at each visit.

Prior medication/Concomitant medications will be assessed at screening, baseline and at each subsequent study visit.

6.0 EVALUATION OF EFFICACY

Proportion of subjects with cure at Visit 5 (End of study at day 14 $\pm$ 2 days defined as a score of 0 for aqueous cells, a score of 0 for aqueous flare and a score of no more than 3 for pain.

7.0 EVALUATION OF SAFETY:

- The incidence of treatment emergent adverse events.
- Ocular parameters (visual acuity, intraocular pressure measurement, slit lamp evaluation and dilated fundus examination).

8.0 STUDY VISITS

8.1 Visit 1: Screening/Baseline/Randomization Visit (Day-21 to day -1):

The following procedures will be performed at Visit 1:

1. Informed consent will be obtained from all participants who have confirmation on the

diagnosis of cataract and are planning to undergo cataract surgery. The latest version of IRB approved Informed Consent Form will be used for consenting process. The study subject will be allowed as much time as needed to read and understand the information presented in the informed consent form. Appropriate study personnel will be available to answer any questions the study subject might have regarding the study or study-related procedures. If the study subject chooses to participate in the study, he or she will be asked to sign and date the consent form and will be provided with a copy of the signed and dated consent form for his or her reference.

2. A complete medical history will be recorded. Information regarding the subject's current and past medical conditions will be captured including surgical procedures.

3. Review of prior medications which have been stopped/ongoing within 30 days prior to screening.

4. Demographics (Height, Weight, Age, Sex, Race/Ethnicity).

5. Physical Examination and Vital signs. At a minimum, the physical examination will include the following: assessment of general appearance, skin, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, gastrointestinal system, genitourinary system and extremities.

6. Assessment of ocular pain.

7. The study subject will be evaluated for iris color and complete slit lamp examination including a grading of the aqueous cells and aqueous flare.

8. Visual Acuity.

9. Intraocular pressure.

10. Fundus Examination.

11. A urine pregnancy test will be conducted for all females of childbearing potential.

12. The laboratory evaluation for routine hematology, biochemistry and urine analysis tests.

13. Assessment of any concomitant medications.

14. When the study subject has completed all screening procedures, the available data will be verified with the inclusion and exclusion criteria. Subject will be excluded from the study if any eligibility criterion is not satisfactory by the available information.

15. If eligibility criteria are satisfactory with the available information, the cataract surgery will be scheduled.

16. Randomize the patient in the study.

17. The patient should be instructed on how to administer the study medication, and be instructed to administer the study medication one day prior to the surgical day. To ensure that the study subject does administer the study medication one day prior to surgery the subject will be called the day before surgery and reminded to apply the study medication in the operative eye and bring both the subject diary and study drug on the day of surgery.

18. The study subject will be given a subject diary and instructed to document any medical events and any new medication used during the study.

Note: ***One Day Prior to Cataract Surgery (Day -1):***
Subject should be called and reminded to administer study medication in operative eye and bring both the subject diary and study drug on the day of surgery. At least 5 minutes between all ophthalmic drop administrations should be maintained throughout the study.

8.2 Visit 2: The Day of Cataract Surgery (Day 0):

1. Verification of study drug administration one day prior to surgery as required. Failure to comply with Day -1 study drug administration will result in the subject either proceeding with cataract surgery as scheduled but being withdrawn from the study, rescheduling of cataract surgery within 7 days of Screening/Baseline/Randomization Visit and proceeding on study, or cancellation of surgery and withdrawal from study.

2. Vital signs

3. Urine Pregnancy Test (for all females of childbearing potential)

4. Assessment of any concomitant medication

5. Assessment of Adverse Events

6. Administration of study drug to the operative eye should be administered 30-120 minutes prior to cataract surgery. (Administration of study drug should only be performed by the patient, caregiver, independent study drug administrator or unmasked personnel that are not assigned any other study duties). No masked members of staff should be involved in drug administration.

   An additional drop of study drug should be administered post cataract surgery prior to the subject leaving the surgery center. (Administration of drug should only be performed by the patient, caregiver, independent study drug administrator or unmasked site personnel that are not assigned any other study duties). No masked members of staff should be involved in drug administration. The study is designed to be only monocular (only one eye per subject).

7. Investigator should use the standard surgical methods, regimen of pre-operative and post-operative medication with the exception of NSAIDs and/or steroidal usage.

8.3 Visit 3: One day after the Cataract Surgery (Day 1)

1. Vital signs
2. Assessment of Adverse Events
3. Assessment of any concomitant medication
4. Assessment of ocular pain
5. Slit Lamp Examination
6. Assessment of intraocular pressure
7. Administration of the study drug to the operated eye (Administration of study drug should only be performed by the patient, caregiver, independent study drug administrator or unmasked site personnel that are not assigned any other study duties)
8. Re-dispense the subject diary to the subject with instructions to document the administration of the study drug, adverse events, and any concomitant medication used. Also, the patient should be instructed to administer the study medication before visiting the clinical facility for next scheduled visit.
9. Schedule Visit 4

8.4 Visit 4: Follow-up Visit (Day 7 ± 2 Days)

1. Review the subject diary to assess for any adverse events, changes in concomitant medication & compliance to study drug.
2. Retrieve the subject diary pages for completed visit and keep in the source file of the patient
3. Vital signs
4. Assessment of ocular pain
5. Visual acuity assessment
6. Slit Lamp Examination
7. Assessment of Intraocular pressure
8. Re-dispense the subject diary to the subject with instructions to document the administration of the study drug, adverse events, and any concomitant medication

used. Also, the patient should be instructed to administer the study medication before visiting the clinical facility for next scheduled visit.

9. Schedule Visit 5

8.5 Visit 5: End of Study Visit/Early Discontinuation Visit (Day 14 ± 2 Days)

1. Review of subject diary card to assess if any adverse events, changes in concomitant medication & compliance to study drug.

2 Retrieve the subject diary pages for completed visit and keep in the source file of the patient

3. Collect the study medication container from the subject.

4. Physical Examination and Vital signs. At a minimum, the physical examination will include the following: assessment of general appearance, skin, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, gastrointestinal system, genitourinary system and extremities.

5. Assessment of ocular pain

6. Visual acuity assessment

7. Slit Lamp Examination

8. Assessment of Intraocular pressure

9. Fundus Examination

10. Urine Pregnancy Test (for females of child bearing potential)

11. The laboratory evaluation for routine hematology, biochemistry and urine analysis.

12. A standard of care treatment may be advised at the Investigator's discretion.

8.6 Unscheduled Visits and Early Discontinuation Visit:

An Unscheduled Visit is allowed at any time, for any reason, if in the Investigator's opinion it is warranted. If the Unscheduled Visit is due to an AE, the Investigator will determine whether additional visits are needed.

If a study subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Visit 5 will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the study subject will continue to take part in the study), then the reason for unscheduled visit is documented and required procedures at the discretion of

investigator considering the reason for visit, will be performed.

If the study subject's condition has worsened to the degree that it is unsafe for the study subject to continue in the study, the study subject may be discontinued from the study as treatment failure and a standard of care treatment may be advised at the Investigator's discretion.

9.0 STUDY SUBJECT DISPOSITION AND DISCONTINUATION

Study subjects will be discontinued from the study for any of the following reasons:

- If the study subject withdraws his or her consent for any reason
- Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of inflammation and pain the subject should be discontinued, excluded from the PP population analysis, and provided with effective treatment
- If the study subject's drug code is unmasked
- If an adverse event occurs for which the study subject desires to discontinue treatment or the Investigator determines that it is in the study subject's best interest to be discontinued
- If there is a protocol violation*
- If a concomitant therapy is reported or required which is prohibited or may interfere with the results of the study
- If the study subject misses 3 consecutive days' IP applications or has made less than 14 or more than 20 product administrations in the study
- If the study subject is lost to follow-up
- If the study subject becomes pregnant
- Administrative reasons
- Any other reason that may affect the outcome of the study or the safety of study subjects

*A protocol violation is defined as any study subject or Investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy that affects the rights, well-being or safety of the subject or the scientific integrity of the study data.

The reasons for a study subject discontinuation will be documented. If a study subject is discontinued from the study for any reason, the procedures scheduled for Visit 5 will be completed and any outstanding data and study drug will be collected if possible. Data, in addition to the reason for discontinuation and the date of removal, will be documented on the End of Study Case Report Form.

Before a study subject is considered to be lost to follow-up, the Investigator will document all attempts to reach the study subject twice by telephone and will send a certified follow-up letter.

In the event that a study subject discontinues from the study at any time due to an adverse event, the reason for discontinuation, the nature of the event and its clinical course must be fully documented. For such a study subject, the Investigator must strive to follow the study

subject until the adverse event has resolved, become clinically insignificant, is stabilized or the study subject is lost to follow-up. Should a Serious Adverse Event be noted, procedures stated in section 13.2 must be followed.

When a study subject discontinues the study due to any of the above reasons, the study subjects should be prescribed appropriate treatment that he/she can continue to use as per the Investigators clinical judgment.

10.0 STUDY SUBJECT INSURANCE

All study subjects will be covered by adequate insurance for any trial related injuries. This insurance covers cost of medical treatment, discomfort or injury to the study subject as a result of drug administration or any of the procedures carried out during the study.

11.0 INVESTIGATIONAL PRODUCT

11.1 Description

The investigational product supplied by the Sponsor will consist of the following:

TEST PRODUCT:
Name of the product: Nepafenac
Pharmaceutical dosage form: Ophthalmic suspension
Strength: 0.3%
Manufactured by: [redacted] Actavis LLC

REFERENCE PRODUCT:
Name of the product: Ilevro™ (Contains Nepafenac)
Pharmaceutical dosage form: Ophthalmic suspension
Strength: 0.3%
Manufactured by: Alcon Laboratories, Inc

PLACEBO:
Name of the product: Sterile ophthalmic suspension
Pharmaceutical dosage form: Ophthalmic suspension
Strength: NA
Manufactured by: [redacted] Actavis LLC

11.2 Storage Conditions

Investigational Medicinal Product should be stored at 2-25 ^{0}C (36-77 ^{0}F), in a secured, authorized access area at the investigative site.

11.3 Packaging, Masking and Labeling

The study product will be randomized, packaged and masked by an independent packaging company (Actavis, SLC site). The randomization will be pre-planned according to a computer-generated randomization schedule. The study product will be masked, packaged

[redacted] An accurate inventory of the study product will be maintained in accordance with federal regulations.

The IP at the study site will be completely handled by independent dispenser who is unmasked to the treatment received by the subject as described in the latest version of the IP manual. These personnel will not be involved in any activities or procedures where assessment of efficacy and safety of the subject is performed. Once the study drug is dispensed on day of discharge from the clinical facility, the subject will be instructed not to open the container at the clinical trial site and open the container only after reaching home and administer the drug.

11.4 Masking

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be masked to the patient assignment. Each study site will have at least one Independent Dispenser. The role of the Independent Dispenser is to dispense and collect study product to/from the patients, maintain dispensing records, and ensure the study product logs are complete and accurate. The patient will be requested not to discuss the appearance of the study product with the Investigator or study staff outside of the Independent Dispenser. To ensure that information that could potentially bias handling of data is not disclosed, the packaging company will hold the randomization scheme until after database lock.

In case of an emergency, if the details of the study drug are required for management of an emergency as per the opinion of investigator, the investigator can unmask the product that is received by the subject during the study. In case of non-emergency condition that requires study drug information for management of condition as per investigator's opinion, the investigator should obtain sponsor or medical monitor approval in writing prior to [redacted] It is recommended that all attempts should be made to maintain the mask of the study. However, in case that unmasking is performed, the reason for breaking the mask must be clearly documented in the source documentation and CRF and the patient must be discontinued from the study.
Whenever possible, the [redacted] Medical Monitor should be contacted before breaking the mask for any patient. Investigative sites can use either one of the above methods to unmask a patient, when unmasking is deemed necessary by the Principal Investigator.
In the event the mask is broken for any reason, Sponsor and [redacted] will be notified as soon as possible in writing of the details of the occurrence.

At the conclusion of the study, after the database has been locked, each site will be sent a sealed envelope containing the full study randomization scheme that should be retained

with the study documents in the event of an FDA inspection.

11.5 Treatment Assignment

The study subject number will correspond to a computer-generated randomization schedule assigning that number to one of the three study treatment groups. [redacted]

11.6 Administration of Investigational Product

One drop of the study drug suspension should be instilled into the affected eye one-time daily, beginning a day prior to the planned cataract surgery, on the day of the cataract surgery and for 14 days thereafter. The study drug should be instilled once daily. On Day 0 a drop should be added 30-120 minutes prior to the cataract surgery. As the study drug will be administered twice on the day of cataract surgery (Day 0) once prior to cataract surgery and once following cataract surgery prior to the subject leaving the surgery center. On Day 0 administration of drug should only be performed by the patient, caregiver, independent study drug administrator or unmasked site personnel that are not assigned any other study duties. The dose and mode of treatment chosen in this study is the dosage approved by US FDA for the treatment of pain and inflammation associated with cataract surgery. The study is designed to be only monocular (only one eye per subject).

11.7 Assessment of Compliance

A subject diary will be provided to all subjects where it is required to document the date and time of administration of the study drug. In the subject diary, subjects will also note any adverse event observed and any concomitant medication taken or changes.

Compliance will be determined from the subject diary, which the subject will be trained and instructed to use to record all doses, as well as all missed doses. The number of missed and additional doses will be captured on the compliance page of the CRF.

Subject who misses 3 consecutive doses of study medication will be considered non-compliant and discontinued from the study. The used kits of study medication will be returned to the study site at appropriate visits or early termination or as applicable.

Subject who will take less than 14 doses of total study drug during the study will be considered non-compliant and discontinued from the study. Subjects who will take more than 20 doses of the study drug are also considered as non-compliant and discontinued from the study.

11.8 Investigational Medicinal Product Accountability

It is the responsibility of the Investigator to ensure that the accountability of the IP is maintained at each study site where study drug is stored and dispensed. When a drug shipment is received at a study site, the Investigator or the Investigator's Designee must

provide an acknowledgement for the receipt of the study drug.

A Drug Accountability Log will assist study site staff in maintaining inventory records of study drug. The Drug Accountability Log should include:

- The amount of the IP received initially / from Sponsor and placed in the storage area
- The amount of the study drug currently in storage area
- The dates and the initials of the person(s) responsible for each IP inventory entry / movement
- The amount of IP dispensed to and returned by each study subject (including the study subject's initials, study subject's number or other unique study subject identifiers)
- The amount of IP remaining at the site at the end of study
- The amount of IP retained by the study site and/or sent to a third party (retention samples)

Study subjects must return used/unused IP to the independent dispenser. Any remaining drug supplies can be accounted for and noted in the Drug Accountability Log. The original Drug Accountability Log must remain at the study site and a copy should be provided to the study monitor after the study.

11.9 Retention of Study Drug Samples

For every study product shipment received at the investigative site, the Investigator (or designee) will randomly select study product kits for retention, unless otherwise instructed by the Sponsor and/or [redacted]. The selection process will ensure a sufficient amount of retention samples are retained as per Sponsor requirement. These kits will be affixed with a label to be clearly marked as retention samples and are not to be used for dispensing to study patients. The selected retention samples will be retained at a third party storage facility [redacted] under FDA regulations as study retention samples.

11.10 Return of Clinical Supplies

With the exception of the retention samples, all remaining IP will be returned by the Investigator or designee to CRO / clinical supply vendor for storage and / or destruction after the close-out visit, following the instructions provided by CRO. At the completion of the study, the reserve samples will be either stored at the clinical investigational site or will be transferred to an independent third party with an adequate facility for storage under conditions consistent with product labeling.

12.0 STATISTICAL METHODS

The sections that follow highlight sample size determinations and planned analyses for this study. SAS Version 9.2 or higher will be used to perform all the statistical analyses. A Statistical Analysis Plan (SAP) will be prepared separately from this protocol which gives descriptions of the statistical methods, hypotheses, and analysis populations to be analyzed. The SAP will serve as a companion to the protocol and will serve as the de facto documentation of the proposed statistical evaluation.

12.1 Sample Size Rationale

The sample size calculation for this study is based on the published literature and FDA's current guidance on the clinical endpoint bioequivalence study of Nepafenac 0.3% [redacted]

Thus, approximately 450 patient(s) ([redacted], who have cataract and are planning to undergo cataract surgery will be enrolled and randomized [redacted]

12.2 Randomization Procedures

Subjects will be randomly assigned [redacted] to receive the Test product or the Reference Product or the Placebo control, respectively. The randomization schedule for this study will be generated by a third-party vendor of the CRO such that a non-study-assigned independent expert will allocate the subjects to one of the three treatment arms using a computer generated automated process i.e. Interactive Web Response System (IWRS). A sealed copy of the randomization scheme (randomization mask cards) will be retained at the study site and should be available to regulatory authority inspectors at the time of site inspection to allow for verification of the treatment identity of each patient.

12.3 Significance Level

All statistical tests will be carried out at a significance level of $\alpha = 0.05$, unless otherwise indicated. No adjustment will be made for multiplicity.

12.4 Datasets to be Analyzed

Three analysis populations will be used in the analysis of the clinical data and they are

defined as follows:

- The PP population includes all randomized subjects who meet all inclusion and none of the exclusion criteria, [redacted]
- The mITT population includes all randomized subjects who met the inclusion and none of the exclusion criteria, administered at least one dose of study drug and returned for at least one post-baseline evaluation visit.
- The safety population includes all randomized subjects who receive study drug.
- [redacted]

12.5 Comparability of Study Groups at Baseline

The comparability of treatment groups, with regard to study subject demographic characteristics and baseline score for aqueous cells, aqueous flare and ocular pain will be evaluated using descriptive statistics. No inferential analyses are planned.

12.6 Safety Assessment

The extent of exposure will be summarized using descriptive statistics. No inferential analyses are planned.

Incidence of all adverse events reported during the study will be summarized using the current version of MedDRA dictionary by treatment group, body system, severity, and relationship to study drug. No inferential analyses are planned.

Incidence of concomitant medications will be summarized by treatment group.

Vital signs at each visit will be summarized using descriptive statistics. No inferential analyses are planned.
Laboratory results will be descriptively summarized for each treatment group (with placebo group separately). Safety analyses will be performed on the safety population. All safety data will be listed by treatment and study subject in data listings.

12.7 Efficacy Assessment

The primary efficacy measure in this study is the proportion of subjects with cure at Visit 5 (end of the study on day 14 $\pm$ 2 days) defined as a score of 0 for aqueous cells, a score of 0 for aqueous flare and a score of no more than 3 for pain.

12.8 Primary Efficacy Criteria

The primary bioequivalence comparison is between the test and reference products for the difference in success proportions at Visit 5 (end of the study on day 14 $\pm$ 2 days) for the scores of aqueous cells, aqueous flare and Ocular Pain.

The primary superiority evaluations are the comparisons between each active treatment and the placebo control for the difference in success proportions at Visit 5 (end of the study on day 14 $\pm$ 2 days) for the scores of aqueous cells, aqueous flare and Ocular Pain.

Success is defined as score of 0 for aqueous cells, a score of 0 for aqueous flare and a score of no more than 3 for pain at Visit 5 (end of the study on day 14 $\pm$ 2 days).

12.9 Test of Bioequivalence

For the primary efficacy parameter, i.e. the proportion of patient(s) in the per protocol population identified as "treatment success" occurring at Visit 5 (end of the study on day 14 $\pm$ 2 days)., a two-sided 90% confidence interval for the difference in success proportions ($P_T - P_R$) between test and reference products should be contained within [- 0.20, +0.20] in order to establish equivalence.

The above analyses of therapeutic equivalence will be performed for the per-protocol population.

The detailed description of the statistical analysis to be used for the statistical evaluation & construction of 90% confidence interval will be elaborated in the Statistical Analysis Plan (SAP).

12.10 Test of Superiority

The primary evaluations of efficacy will also be used to compare each active treatment to the placebo with respect to the primary efficacy measure. Thus, each active arm will be compared to the placebo to establish the superiority of active arms over the placebo for the primary efficacy measure i.e. proportion of patient(s) with "treatment success" at Visit 5 (end of the study on day 14 $\pm$ 2 days). Superiority will be claimed using Fisher's exact test when the proportion of patient(s) with treatment success in the active treatment arm(s) is greater than the placebo and the corresponding two-sided p-value is < 0.05, at 5% level of significance.

The above analyses to demonstrate superiority will be performed on the mITT population. The mITT analyses will be performed using last observation carried forward. (LOCF) approach for missing efficacy results.

13.0 ADVERSE EVENTS REPORTING

13.1 Definitions

Adverse Event (AE)

An adverse event is any untoward medical occurrence in a subject, regardless of whether it has a causal relationship with this treatment.

In this study, any adverse event occurring after the subject has signed the informed consent form until the end of follow-up period should be recorded and reported as an adverse event. An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a preexisting condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other preexisting conditions drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, or require medical treatment or further diagnostic work up, or are considered by the investigator to be clinically significant (Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)
- all events of possible drug induced liver injury with hyperbilirubinemia (defined as aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥3 times the upper limit of the normal range [ULN], plus either bilirubin ≥2 times the ULN or International Normalized Ratio [INR] >1.5) or Hy's Law events require immediate study treatment cessation and reporting as a serious adverse event.

Worsening of the disease under study will be measured by evaluation of pain and inflammation. The evaluation of pain and inflammation should be recorded as an adverse event only if the presentation and/or outcome is more severe than would normally be expected from the normal course of the disease in a particular patient.

A treatment-emergent AE is any AE that occurs after initiation of study medication, or any event already present that worsens in either intensity or frequency following exposure to study medication.

Serious Adverse Event (SAE)

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (i.e., the subject was at immediate risk of death from the event as it occurred; does not include an event that, had it occurred in a more

severe form, might have caused death)

- inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event. Hospitalizations scheduled prior to study entry will not be considered serious adverse events, unless there was worsening of the preexisting condition during the subject's participation in this study.
- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the subject and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event. An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a non-serious adverse event.

  All occurrences of possible drug induced liver injury that meet Hy's law criteria, defined as all of the below, must be reported by the investigator to the sponsor as a serious adverse event:

  - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation of >3x the upper limit of normal (ULN)
  - total bilirubin elevation of >2x ULN or International Normalized Ratio [INR] >1.5
  - absence of initial findings of cholestasis (i.e., no substantial increase of alkaline phosphatase [ALP])

Other Significant Adverse Events

When tested, marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events, should be collected in the CRF and summarized in the clinical study report.

13.2 Severity

The severity of each adverse event must be recorded as 1 of the choices on the following scales.

Mild: No limitation of usual activities
Moderate: Some limitation of usual activities
Severe: Inability to carry out usual activities

13.3 Relationship of an Adverse Event to the Study Drug

Adverse events will be assessed for the relationship to the study drug (causality) according

to the following scale:

TERM	DEFINITION	CLARIFICATION
No Reasonable Possibility (not related)	This category applies to those adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those adverse events, which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	An adverse experience may be considered No Reasonable Possibility if it is clearly due to extraneous causes or when (must have two): • It does not follow a reasonable temporal sequence from the administration of the test drug. • It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • It does not follow a known pattern of response to the test drug. • It does not reappear or worsen when the drug is re-administered.
Reasonable Possibility (related)	This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty or felt with a high degree of certainty to be related to the test drug.	An adverse experience may be considered Reasonable Possibility related if or when (at least two of the following): • It follows a reasonable temporal sequence from administration of the drug. • It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists. • It follows a known pattern of response to the test drug.

13.4 Expectedness

An AE which is not included in the adverse events section of the relevant Safety Information Reference by its specificity, severity, outcome or frequency is considered an unexpected adverse event.
The reference safety information for this study is to be found in Appendix III.
The sponsor's Pharmacovigilance Department will determine the expectedness for all serious adverse events. CRO and investigators will not determine the expectedness.

13.5 Recording and Reporting of Adverse Events

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, clinical laboratory test results, vital signs measurements, physical examination findings (including body weight and height measurements), and use of concomitant medication.

For adverse event recording, the study period is defined for each subject as that time period from signature of the informed consent form through the end of the study (including the follow up period).
All adverse events that occur during the defined study period must be recorded on the source documentation, regardless of the severity of the event or judged relationship to the study drug. For serious adverse events, the Serious Adverse Event Form must also be completed, and the serious adverse event must be reported immediately (see Section 13.8). The investigator does not need to actively monitor subjects for adverse events once the study has ended. However, serious adverse events occurring in a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them.

At each contact with the subject, the investigator or designee must question the subject about adverse events by asking an open-ended question such as, "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings may be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the Serious Adverse Event Form.
The onset and end dates and times, action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation.
The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described above.
The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized or returned to baseline, until the subject is referred for continued care to a health care professional or until a determination of a cause unrelated to the study drug

or study procedure is made.
Adverse events will be coded according to MedDRA (Medical Dictionary for Regulatory Activities) and reported with respect to severity, duration, relationship to study medication(s), seriousness and action taken.

13.6 Reporting of Serious Adverse Events

To satisfy regulatory requirements, all serious adverse events (as described in Section 1.1) that occur during the study period (including the protocol defined follow up period, described in Section 5.7), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor or CRO by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available.

PLEASE NOTE THAT EMAIL IS THE PREFERRED MEANS OF COMMUNICATION.

The CRO should inform PhV if the whole study is early discontinued due to safety reasons.

It is the responsibility of the CRO to report a Serious Adverse Event (SAE) to the FDA within proper time constraints as per the Guidance for Industry and Investigators Safety Reporting Requirements for INDs
and BA/BE Studies- December 2012. Confirmation of submission of this report must then be provided to Actavis, Inc. (Teva)'s study representative as well as their Pharmacovigilance department (contact info below).
The timeliness for submission of expedite reports should be 15 days or 7 days (death cases) or as otherwise specified in local regulations.
All SAE of the study due to safety reasons must be reported in parallel to the following persons:

[redacted]

Sponsor's Contact person for this Biostudy (copy of the SAE details for information purposes only)

Name: [redacted]
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]
These SAE reports must contain the following information, preferably using the template provided by the Sponsor:
A. Study name/number
B. Study Drug
C. Investigator details (name, phone, fax, e-mail)
D. Subject Number
E. Subject Initials when appropriate

F. Subject Demographics
G. Clinical Event
1) Description
2) Date of onset
3) Treatment (drug, dose, dosage form)
4) AE Relationship to study drug
5) Action taken regarding study drug in direct relationship to the AE
H. If the AE was Fatal:
1) Cause of death (whether or not the death was related to study drug)
2) Autopsy findings (if available)

The SAE form and supportive documents should be filled/written in English. The SAE form completion and reporting must not be delayed even if all of the information is not available at the time of the initial contact. Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded within 24 hours of the information becoming available to the same address as the initial report. Subjects who have had an SAE during the treatment period must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor pharmacovigilance to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease.

Pharmacovigilance local safety officer at Actavis Inc. (Teva) USA will take on the responsibility of reporting SAEs to local authorities (except from US). The CRO will take on the responsibility of reporting SAEs to the investigators and/or to the IRB/Ethics Committee.

The investigator does not need to actively monitor subjects for adverse events once the study has ended. Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them.

Submission of SAEs

Any serious adverse event will be reported to competent authority and ethics committee according to the country specific requirements and the responsibilities defined in the abovementioned section. All AEs will be reported in the Clinical Study Report with the complete information named above according to the requirements of the Note for Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95).

Investigator Reporting of SAEs

Adverse events which are evaluated by the Investigator as "Serious" will be reported to the CRO designated below and IRB within 24 hours of notice whether or not they are considered expected or drug-related. All Serious Adverse Events will be reported as per FDA regulations.

Any serious adverse events should be reported to [redacted] within 24 hours to:

[redacted]

[redacted]

*Any Serious Adverse Events emailed to [redacted] should also copy: [redacted]

The Investigator or the Investigator's designee must be prepared to supply minimum details needed in the SAE reporting with the following information:

a. Investigator Name and Site Number
b. Patient I.D. Number
c. Patient initials and date of birth
d. Patient Demographics
e. Clinical Event
    1) Description
    2) Date of onset
    3) Severity
    4) Treatment (including hospitalization)
    5) Relationship to study drug
    6) Action taken regarding study drug
f. If the AE was Fatal or Life-threatening
    1) Cause of death (whether or not the death was related to study drug)
    2) Autopsy findings (if available)
    3) Death Certificate
g. Concomitant medication log
h. AE log
i. Relevant tests with dates
j. IP Unblinding information, if applicable

CRO Reporting of SAEs

[redacted] will report any Serious Adverse Event to Actavis Inc. drug safety team and the medical monitor within 1 business day.

Drug Safety Department:

[redacted]

Sponsor Study Manager:

[redacted]

Medical Monitor:

[redacted]

13.7 Submission of SAEs

The Principal Investigator or the Principal Investigator's Designee must complete the provided Serious Adverse Event (SAE) Form (Attachment 1). Actavis LLC. will be responsible for reporting the SAE to the FDA per regulations. Actavis LLC. will provide [redacted] with a completed MedWatch FDA Form 3500A wherever applicable.

13.8 Early Termination

A subject may terminate from the study early for any reason at any time without any disadvantages. In this case, the investigator should make every effort to have the subject return to the next scheduled visit to perform all required End of Study / Study Completion / Early Termination visit activities and to collect and reconcile all test articles. If the subject does not return for the End of Study / Study Completion / Early Termination visit, the site should fully document the reason for early termination. All data, including the date and primary reason for termination, must be recorded on the End of Study / Study Completion / Early Termination case report form (CRF), and source document.

Any subject who experiences an adverse event may be terminated from the study or from study treatment at any time at the discretion of the investigator. In this case, the subject should be followed at the discretion of the investigator until the resolution or stabilization of the AE. All applicable data should be recorded in the adverse events section of the case report form (CRF). If a subject terminates from the study early for multiple reasons that include adverse events, the End of Study / Study Completion / Early Termination case report form should indicate that early termination was related to an adverse event.
An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant early termination but that requires the use of a prohibited medication, thereby requiring discontinuation of the subject. In such a case, the reason for discontinuation would be the need to take a prohibited medication, not the adverse event.

The investigator must inform the clinical project physician/clinical leader/Principal Investigator as soon as possible of all subjects who are being considered for early termination due to adverse events. Additional reports must be provided when requested. The Sponsor reserves the right to terminate the study at any time for administrative reasons. The study may also be terminated by regulatory authorities or by the investigator for his/her site following consultation with the Sponsor. Following a decision to discontinue the trial, the investigator will immediately inform both the study subjects and the IEC responsible for this trial within 10 working days, stating the reasons for discontinuation of the study and,

furthermore, advise them in writing of any potential risks to the health of study subjects or other persons. It is Sponsor's responsibility to report the premature termination of the study to the regulatory agencies within 15 days providing them with the reasons for the trial discontinuation and advising them in writing of any potential risks to the health of study subjects or other persons. The CRO may notify the regulatory agency on behalf of the Sponsor.

13.9 Pregnancy

All pregnancies of women participating in the study that occur during the study, or within 30 days of completion of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the Sponsor with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event (see 13.8). Any female subject becoming pregnant during the study will discontinue treatment. All subjects who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after termination from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, one of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion not due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

13.10 Medication Error and Special Situations

Any administration of medication that is not in accordance with the study protocol should be reported on the CRF, regardless of whether an adverse event occurs as a result.

Types of medication errors and special situations:

1. Breastfeeding - Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.
2. Unexpected Benefits of Drug
3. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
4. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.

5. Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
6. Abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
7. Off-label use: Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
8. Occupational exposure: Exposure to a medicinal product, as a result of one's professional or non-professional occupation.
9. Lack of efficacy

13.11 Follow Up of Subjects after AE

The staff of the clinical facility has to monitor the clinical trial subject's safety from the occurrence of an AE until satisfactory recovery.

Any AE which remains unresolved at the time point of subject's last visit requires detailed evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence is found; in case of AEs related to the IMPs every effort has to be made to follow-up clinical trial subjects in order to determine the final outcome. If follow-up cannot be completed until release of CRF by the investigator the individual CRF will be released and transferred to the Clinical Data Management. In this case, follow-up information will be documented separately in the subjects' record and outcome including a short description on follow-up procedures performed must be sent to the sponsor.

It is the investigator's responsibility to assure that subjects experiencing adverse reactions will receive definitive treatment for any adverse reaction, if required. Details of follow-up care are to be provided (i.e. if treatment or hospitalization is required). The responsibility to provide adequate follow-up for AEs includes periodically repeating laboratory tests yielding clinically abnormal results at the end of study evaluation.

14.0 ETHICS

This study will be performed in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements. The study will be conducted in compliance with the protocol.

The rights, safety and well-being of the study subjects are the most important considerations and should prevail over interests of society and science.

14.1 Informed Consent

The Investigator must ensure that study subjects are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. The principles of Informed Consent, according to FDA Regulations and ICH GCP will be followed. A copy of the proposed consent form must be submitted to the IRB, together with the protocol, for approval. Prior to beginning of the study, the Investigator must have the IRB's written approval of the written informed consent form and

any other information to be provided to study subjects.

Informed consent will be obtained from all study subjects using the following procedure: Study subjects must have provided IEC/IRB approved written informed consent. Each study subject's signed informed consent must be kept on file by the Investigator. A copy of the signed consent form will be given to the study subject. A notation will be made in the study subject's medical record indicating the date the informed consent was obtained. In addition, the Investigator or the Investigator's Designee will provide a HIPAA authorization form (if applicable) for the study subject to review and sign. Both the ICF and the HIPAA form (if applicable) must be signed by the study subject before any protocol assessments can be undertaken.

14.2 Institutional Review Board

Before study initiation, the Investigator must have, including but not only, written and dated approval from the IEC/IRB for the protocol, consent form, study subject recruitment materials and any other written information to be provided to study subjects. The Investigator or Actavis LLC/CRO will also provide the IRB with a copy of the package insert.

Any changes to the protocol as well as a change of the Investigator, which is approved by the Sponsor, must also be approved by the site's IRB and documentation of this approval provided to the Sponsor/designee. Records of the IRB review and approval of all documents pertaining to this study must be kept on file by the Investigator and are study subject to inspection during or after completion of the study. All SAEs must also be reported to the IRB.

Periodic status reports must be submitted to the IRB at least annually, as well as notification of completion of the study and a final report within one (1) month of study completion or discontinuation. A copy of all reports submitted to the IRB must be sent to the Sponsor/designee.

14.3 Study Subject Confidentiality

As of April 14, 2003, the federal medical Privacy Rule authorized by the Health Insurance Portability and Accountability Act (HIPAA) requires most health care providers to take new measures to protect the privacy of individually identifiable health information. The Privacy Rule's requirements extend to identifiable health information used or disclosed in research.

The HIPAA Privacy Rule reinforces clinical Investigators' existing obligations to protect the privacy of identifiable health information under state law, codes of medical ethics and the federal regulations governing research.

Please be advised that the Privacy Rule compliance obligations include the following:

1. Treating individually identifiable health information as confidential in accordance with HIPAA and other federal, state and local laws and regulations governing the confidentiality and privacy of such information
2. Using or disclosing individually identifiable health information for study subject

recruitment purposes only as permitted by HIPAA, applicable laws and regulations and institutional policies

3. Obtaining each study subject's written authorization for the use or disclosure of individually identifiable health information in research, where applicable, in a form that meets the requirements of HIPAA and identifies all uses, disclosures and data recipients
4. Disclosing identifiable health information created or maintained in connection with the research only for the purposes and to the parties described in the authorization form or as necessary to communicate with the Food and Drug Administration and other regulatory authorities or as otherwise permitted or required by law
5. Employing appropriate physical and technical safeguards to protect the privacy of individually identifiable health information
6. Obtaining a HIPAA waiver of authorization, or where applicable, providing representations and/or entering data use agreements as required under the HIPAA Privacy Rule for any secondary data analyses or activities preparatory to research and referencing these and other research uses and disclosures in your HIPAA notice of privacy practices.

Also, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to the Sponsor, it is required that the Investigator permit the study monitor, Sponsor auditor, IRB and/or FDA representative to review that portion of the study subject's medical record that is directly related to the study. This shall include all study relevant documentation including study subject medical histories to verify eligibility, admission/discharge summaries for hospital stays occurring while the study subject is enrolled in the study and autopsy reports for deaths occurring during the study.

As part of the required content of the informed consent, the study subjects must be informed that his/her medical chart may be reviewed by the Sponsor, the Sponsor's authorized representatives, FDA officials. Should access to the medical record require a separate waiver or authorization, it is the Investigator's responsibility to obtain such permission from the study subject in writing before the study subject is entered into the study.

15.0 DOCUMENTATION

15.1 Site Regulatory Documents Required for Initiation

A minimum of the following set of documents will be received by the CRO prior to the initiation of the study:

1. Fully executed protocol
2. Completed and signed FDA Form 1572
3. Current curricula vitae, signed and dated for the Investigator and each Sub-Investigator named in the FDA Form 1572 (current within 2 years)
4. Current medical licenses of the Investigator and Sub-Investigators named in FDA Form 1572
5. Documentation of "No Objection" to proceed from the local regulatory agency, wherever applicable.
6. Documentation of IRB approval of this study protocol, Investigator and informed consent forms

7. Current IRB membership list or roster and EC SOPs
8. Original Non-disclosure Agreements for the Investigator and Sub-Investigators named in FDA Form 1572
9. Financial Disclosure Statement for the Investigator and each Sub-Investigator named in FDA Form 1572
10. Sites Clinical Laboratory Head's current (within 2 years) curricula vitae and normal reference ranges of laboratory parameters
11. Fully executed Clinical Trial Agreement

15.2 Maintenance and Retention of Records

It is the responsibility of the Investigator to maintain a comprehensive and centralized filing system of all relevant documentation.

Copies of all pertinent records will be retained by the Investigator for at least two years following final approval of the drug and/or notification from the Sponsor. These regulatory documents should be retained for a longer period if required by local regulatory authorities. These records include documents pertaining to the receipt and return of drug supplies, IEC/IRB, informed consent, source documents, as well as CRFs (paper or electronic files). No documents shall be transferred from the site or destroyed without first notifying the Sponsor. The Sponsor will archive the data for the lifetime of the product. If the Investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Notice of such transfer will be given in writing to the Sponsor.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to document all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation. Data reported on the eCRF, which are derived from source documents, must be consistent with the source documents.

15.3 Case Report Forms (CRFs)

Electronic Data Capture (EDC) technology will be utilized. Electronic CRFs (CRFs) will be prepared for all data collection fields. Study subjects will be identified by initials, birth date and subject number, if applicable. Corrections to the CRF will generate an automated audit trail including date and timestamp, full name of the person making the correction and original entry. The user will document the reason for the change which is also maintained in the audit trail. CRFs may be reviewed and signed manually / electronically by properly trained and authorized individuals. The EDC platform will be compliant with 21 CFR part 11 security and audit trail requirements.

CRFs must be kept current to reflect the study subject's status at each phase during the course of the study. Study subjects are not to be identified on CRFs by name; appropriately coded identification (i.e., study subject study number) and the study subject's initials must be used. The Investigator must keep a separate log of the study subject's names and addresses.

Source documents such as the clinic chart are to be maintained separately from the e- CRF (in order to allow data verification. Due to the potential for errors and inaccuracies in entering data into CRFs, originals of laboratory and other test results must be kept on file with the study subject's source document. Source documents and copies of test results must be available at all times for inspection by the study monitor.

15.4 Primary Source Documents

The Investigator must maintain primary source documents supporting significant data for each study subject's medical notes. These documents, which are considered "source data", should include documentation of:

- Demographic information
- Evidence supporting the diagnosis/condition for which the study subject is being studied
- General information supporting the study subject's participation in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any evaluations, relevant findings/notes by the Investigator(s), occurrence (or lack) of adverse events and changes in medication usage, including the date the study drug commenced and completed.
- Any additional visits during the study
- Any relevant telephone conversations with the study subject regarding the study or possible adverse events
- An original, signed informed consent form for study participation
- Subject Diary

The Investigator must also retain all study subject specific printouts/reports of tests/procedures performed as a requirement of the study. During monitoring visits, the monitor will need to validate data in the CRFs against these sources of data.

15.5 Study Monitoring

[redacted] will be responsible for monitoring the study according to Good Clinical Practice and applicable regulations. Monitoring visits are for the purpose of confirming adherence to the protocol and to verify complete and accurate data collection. The clinical site will make all records associated with the study available to [redacted] representative during such visits and audits.

The study may be subject to audit by the Sponsor, Sponsor Representative or by regulatory authorities. If such an audit occurs the Investigator must agree to allow access to required patient records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of study procedures.
The following should also be available for review:

1. Study Subject Screening Log – reflecting the reason any study subject screened for the study was found to be ineligible
2. Delegation of Authority / Study Personnel Signature Log – all site personnel will be listed along with their responsibilities and signatures; to be maintained at the site throughout the study
3. Monitoring Log – the date and purpose of all monitoring visits by the Sponsor/Designee will be documented
4. Enrollment Log – documenting study subject initials and start and end dates for all study subjects enrolled
5. Drug Inventory/Packing Slip – reflecting the total amount of drug shipped to the site and received and signed for by the Investigator
6. Drug Accountability Log – reflecting the total amount of investigational product dispensed to and returned by each study subject
7. Informed Consent Form – which must be available for each study subject and be verified for proper documentation
8. All correspondence

Monitoring visits will be arranged in advance at a mutually acceptable time with site personnel. Sufficient time must be allowed by the site personnel for the monitoring of CRFs and relevant source documents. The Study Coordinator and/or Investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits should be made available by the Investigator.

At the end of the study, a closeout monitoring visit will be performed.

15.6 Audits and Inspections

During the course of the study and/or after it has been completed, one or more site visits may be undertaken by auditors as authorized representatives of the Sponsor. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with the protocol, recognized GCP guidelines and all applicable regulations. Additionally, the study may be inspected by regulatory agencies. These inspections may take place at any time during the study or after the study.

15.7 Modifications to the Protocol

The procedures defined in the protocol and in the eCRF/paper CRF will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. In order to ensure the validity of the data, no deviations from the protocol, with minimal exceptions, may be made unless the issue is broad enough to warrant revision of the protocol. Such revisions must be submitted to and have documented approval from the Sponsor and the IEC/IRB prior to implementation. All amendments to the protocol, which involve substantial changes in study design, procedure or analyses, will be submitted to appropriate regulatory authority for prior approval.
The only circumstance in which an amendment may be initiated without prior IEC/IRB approval is to eliminate apparent immediate hazards to a study subject or study subjects. However, the Investigator must notify the Sponsor and the IEC/IRB as soon as possible.

15.8 Completion of Study

The Investigator is required to forward CRFs and all other relevant data and records to CRO. The Investigator will complete and report (submission of CRFs) his/her study in satisfactory compliance with the protocol as soon as possible after the completion of the study.

The Investigator must submit a final report to the IEC/IRB and CRO within one (1) month of study completion or discontinuation.

16.0 CONFIDENTIALITY, USE OF INFORMATION AND PUBLICATION

All information supplied by the Sponsor in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, data, materials (i.e., the clinical protocol, CRFs), equipment, experience (whether of a scientific, technical, engineering, operational or commercial nature), designs, specifications, know-how, product uses, processes, formulae, costs, financial data, marketing plans and direct selling systems, customer lists and technical and commercial information relating to customers or business projections used by the Sponsor in its business. Any data, inventions or discoveries collected or developed, as a result of this study is considered confidential. This confidential information shall remain the sole property of the Sponsor, shall not be disclosed to any unauthorized person or used in any unauthorized manner without written consent of the Sponsor and shall not be used except in the performance of the study.

The information developed during the course of this clinical study is also considered confidential and will be used by the Sponsor in connection with the development of the drug. The information may be disclosed as deemed necessary by the Sponsor. To allow the use of the information derived from this clinical study, the Investigator is obliged to provide the Sponsor with complete test results and all data developed in the study. The information obtained during this study may be made available to other Investigators who are conducting similar studies.

REFERENCES

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- Nepafenac draft guidance available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM428231.pdf
- http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf
- http://www.drugs.com/acetaminophen.html
- http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019872Orig1s042lbl.pdf

APPENDIX I: SCHEDULE OF EVENTS

Visit Details	**Visit 1**	**Telephone Call**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Study Activities	**Day -21 to -1 Screening/ Baseline/ Randomization**	**Day -1 Pre-Operative Telephone Call**	**Day 0 The Day of Cataract Surgery**	**Day 1 One Day After Cataract Surgery**	**Day 7 ± 2 days Follow-up visit**	**Day 14 ± 2 days (End of Study / Early Discontinuation)**
Informed Consent Process	×					
Medical History & Demographics	×					
Pre-Operative Call		×				
Physical Examination	×					×
Vital Signs	×		×	×	×	×
Inclusion/Exclusion Review	×					
Schedule the day for Cataract Surgery	×					
Assessment of Ocular Pain	×			×	×	×
Visual Acuity	×				×	×
Slit Lamp Examination	×			×	×	×
Intraocular Pressure	×			×	×	×
Fundus Examination	×					×
Laboratory Assessments (hematology, biochemistry and urine analysis)	×					×
Urine Pregnancy Test	×		×			×
Dispense/Administer Study drug	×		×	×	×	×
Dispense Subject Diary	×			×	×	
Retrieval/Review of Subject Diary					×	×
Retrieval of Study Medication						×
Concomitant Medication Assessment	×		×	×	×	×
Adverse Event Assessment	×	×	×	×	×	×

APPENDIX II: INSTRUCTIONS FOR THE SUBJECT

1. The proper way to instill the drop-in eye is detailed in your subject diary. The study medication should be applied in the operative/operated eye as one drop once daily for 16 days starting from a day before the surgery, continued on the day of surgery and then 2 weeks thereafter. On Day 0 a drop should be added 30-120 minutes prior to the cataract surgery. As the study drug will be administered twice on the day of cataract surgery (day 0) once prior to cataract surgery and once following cataract surgery prior to the subject leaving the surgery center. The study is designed to be only monocular (only one eye per subject).
2. During Visit 2, administration of drug should only be performed by the patient, caregiver, independent study drug administrator or unmasked site personnel that are not assigned any other study duties. At your visit today, you were instructed how to use study medication.
3. How to apply the eye drops: Shake the bottle well just before you use it. To apply the eye drops:
   a. Tilt your head back slightly and pull down your lower eyelid to create a small pocket. Hold the dropper above the eye with the dropper tip down. Look up and away from the dropper as you squeeze out a drop and then close your eyes.
   b. Gently press your finger to the inside corner of the eye (near your nose) for about 1 minute to keep the liquid from draining into your tear duct or gently close eyes for 15-30 seconds.
   c. Do not allow the dropper tip to touch any surface, including the eyes or hands. If the dropper becomes contaminated it could cause infection in your eye, which can lead to vision loss or serious damage to the eye.
   d. At least 5 minutes between all ophthalmic drop administrations should be maintained throughout the study.
4. You have to complete the subject diary after each instillation in the eye. You will be allowed to take acetaminophen as needed for ocular pain. You will record any use of acetaminophen in your subject diary. Adults and Adolescents Weighing 50kg and Over: 1,000mg every 6 hours or 650mg every 4 hours to a maximum of 4,000mg per day. Minimum dosing interval of 4 hours. Adults and Adolescents Weighing under 50kg: the recommended dosage of acetaminophen injection is 15 mg/kg every 6 hours or 12.5 mg/kg every 4 hours, with a maximum single dose of acetaminophen injection of 15 mg/kg, a minimum dosing interval of 4 hours, and a maximum daily dose of acetaminophen of 75 mg/kg per day. A minimum of 8 hours between the last dose of acetaminophen and assessment of ocular pain and aqueous cells and flare should be maintained.
5. Do not use any other ophthalmic treatments or start any new medications during your study participation without prior approval from your study doctor.
6. If you miss any dose during the study on a day, then continue the instillation as directed from the next day on.
7. Avoid any contact with affected eye during your day-to-day activities.
8. Slow or delayed healing may occur while using the study medication.
9. Please avoid allowing the tip of the bottle to touch your eye or surrounding structures because this could contaminate the tip and cause infection. Serious damage to the eye and subsequent loss of vision may result after using such contaminated solution.
10. If you develop any condition like infection, are thinking of having ocular surgery, or suffer trauma you should contact your study doctor right away.
11. Do not use the eye drops when wearing contact lens.
12. For Visit 3 (Post-Op Day 1), please follow the Subject Diary's instructions for the Subject to administer the study medication at the doctor's office following your exam.
13. On Visit 4 and Visit 5, the study medication will be administered prior to visiting the site for scheduled

assessments at respective visits.

14. It is important that you bring your study medication with you at each visit in order to determine if you are using the study medication properly. You will be given additional bottles, if needed. All used and unused study medication must be returned to your doctor's clinic during Visit 5.
15. If you see a doctor for another medical problem while you are participating in the study, please have him/her call your physician.
16. The study coordinator will attempt to remind you of your next scheduled visit.

APPENDIX III: PRESCRIBING INFORMATION

NDA 203-491/S-001
Page 3

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. (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: 12/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing
2.2 Use with Other Topical Ophthalmic Medications
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Increased Bleeding Time
5.2 Delayed Healing
5.3 Corneal Effects
5.4 Contact Lens Wear
6 ADVERSE REACTIONS
6.1 Serious and Otherwise Important Adverse Reactions
6.2 Ocular Adverse Reactions
6.3 Non-Ocular Adverse Reactions
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Slow or Delayed Healing
17.2 Avoiding Contamination of the Product
17.3 Contact Lens Wear
17.4 Intercurrent Ocular Conditions
17.5 Concomitant Topical Ocular Therapy
17.6 Shake Well Before Use

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

Reference ID: 3231062

FULL PRESCRIBING INFORMATION

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

4 CONTRAINDICATIONS

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

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

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

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

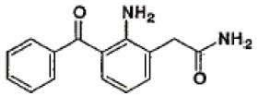
8.3 Nursing Mothers
Nepafenac is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO™ (nepafenac ophthalmic suspension), 0.3% is administered to a nursing woman.

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

11 DESCRIPTION

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

12.1 Mechanism of Action
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
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 Cmax 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

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

14 CLINICAL STUDIES

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

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. 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

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

Protect from light.

17 PATIENT COUNSELING INFORMATION

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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