

## PRODUCT MONOGRAPH

**PrACUVAIL®**

(ketorolac tromethamine ophthalmic solution 0.45% w/v)

Topical Non-steroidal Anti-inflammatory Agent

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**PrACUVAIL®**

ketorolac tromethamine ophthalmic solution 0.45% w/v

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

| <b>Route of Administration</b> | <b>Dosage Form / Strength</b>                                 | <b>Clinically Relevant Nonmedicinal Ingredients</b>   |
|--------------------------------|---|---|
| Topical Ophthalmic             | Sterile ophthalmic solution, ketorolac tromethamine 0.45% w/v | Not applicable.<br><br><i>For a complete listing see Dosage Forms, Composition and Packaging section.</i> |

**INDICATIONS AND CLINICAL USE**

**ACUVAIL®** (ketorolac tromethamine ophthalmic solution 0.45%) ophthalmic solution is indicated for the treatment of pain and inflammation following cataract surgery.

**Geriatrics (> 65 years of age):**

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

**Pediatrics (< 18 years of age):**

Safety and effectiveness in pediatric patients have not been established.

**CONTRAINDICATIONS**

**ACUVAIL®** is contraindicated in patients who are hypersensitive to ketorolac, to any ingredient in the formulation or component of the container, or to other nonsteroidal anti-inflammatory drugs (NSAIDs).

For a complete listing of ingredients in **ACUVAIL®**, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

- There are no data specific for patients with hepatic or renal impairment and therefore specific dosage recommendations cannot be made.

### **Recommended Dose and Dosage Adjustment**

The recommended dose of **ACUVAIL**<sup>®</sup> is one drop to be applied to the affected eye twice daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first two weeks of the postoperative period.

Approximately two hours prior to surgery, one drop is to be administered approximately every twenty minutes for a total of three drops. Prior to discharge one additional drop is to be administered.

### **Missed Dose**

If a dose of this medication is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the regular dosing schedule resumed. Doses should not be doubled.

### **Administration**

#### **Single-Use Vial**

The solution from one single-use vial is to be used immediately after opening for administration to the affected eye(s), and the remaining contents should be discarded immediately after administration. To avoid contamination, the tip of the unit-dose vial should not touch the eye or any other surface.

#### **Contact Lens Wear**

**ACUVAIL**<sup>®</sup> solution should not be administered while wearing contact lenses.

If contact lens use is recommended by the physician, they should be removed prior to instillation of **ACUVAIL**<sup>®</sup> solution and may be re-inserted 15 minutes following administration.

#### **Concomitant Topical Ocular Therapy**

If more than one topical ophthalmic medication is being used, such as antibiotics, alpha-agonists, beta-blockers, cycloplegics, or mydriatics, the medications must be administered at least 5 minutes apart.

Because the administration of **ACUVAIL**<sup>®</sup> in conjunction with prostaglandin analogues (e.g., Lumigan<sup>®</sup>, Travatan<sup>®</sup>, Xalatan<sup>®</sup>) has not been studied, use only if the benefit outweighs any potential risk.

## **OVERDOSAGE**

There is no data on overdosage with **ACUVAIL**<sup>®</sup> or ketorolac tromethamine. If **ACUVAIL**<sup>®</sup> is accidentally ingested, drink fluids to dilute.

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

## **WARNINGS AND PRECAUTIONS**

### **General**

There exists the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents (see Post-Market Adverse Drug Reactions section). Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Topical NSAIDs may slow or delay healing (see Ophthalmologic section). Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

### **Hematologic**

#### **Bleeding**

With some nonsteroidal anti-inflammatory drugs, 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 hyphemas) in conjunction with ocular surgery.

It is recommended that **ACUVAIL**<sup>®</sup> ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications, which may prolong bleeding time.

### **Ophthalmologic**

#### **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 and should be closely monitored for corneal health.

Topical NSAIDs should be used with caution in 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 as they may be at increased risk for corneal adverse events which may become sight threatening.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

### **Delayed Healing**

All topical NSAIDs may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

### **Eye Injury and Contamination**

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures to avoid injury and contamination of eye drops.

The solution from one single-use vial is to be used immediately after opening for administration to the affected eye(s), and the remaining contents should be discarded immediately after administration. Each vial is intended only for a single treatment in the affected eye(s).

### **Contact Lens Wear**

**ACUVAIL**<sup>®</sup> should not be administered while wearing contact lenses.

If contact lens use is recommended by the physician, they should be removed prior to instillation of **ACUVAIL**<sup>®</sup> solution and may be re-inserted 15 minutes following administration.

### **Special Populations**

#### **Pregnant Women:**

There are no adequate studies in pregnant women. Therefore, **ACUVAIL**<sup>®</sup> should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Ketorolac tromethamine, administered orally during organogenesis, was not teratogenic in rats and rabbits at doses approximately 600 times and 1700 times the typical clinical daily dose of **ACUVAIL**<sup>®</sup>, respectively. Ketorolac tromethamine resulted in dystocia and increased pup mortality in rats, when administered at oral doses up to approximately 300 times the typical clinical daily dose of **ACUVAIL**<sup>®</sup>. See TOXICOLOGY section for more details.

Because of the known nonteratogenic effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system of rats (closure of the ductus arteriosus), the use of **ACUVAIL**<sup>®</sup> during late pregnancy should be avoided.

**Nursing Women:**

Ketorolac tromethamine ophthalmic solutions are not recommended for treatment of nursing mothers.

Secretion of ketorolac tromethamine in human milk after systemic administration is limited. The milk-to-plasma ratio of ketorolac tromethamine concentrations ranged between 0.015 and 0.037 in a study of 10 women.

**Pediatrics (< 18 years of age):** Safety and effectiveness in pediatric patients have not been established.

**Geriatrics (> 65 years of age):** No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

**Driving and Using Machines**

Based on the pharmacodynamic profile, ketorolac is not expected to influence a patient's ability to drive or operate machinery. As with any ocular medication, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

**Carcinogenesis and Mutagenesis**

See TOXICOLOGY section.

**ADVERSE REACTIONS**

**Clinical Trial Adverse Drug Reactions**

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

Two randomized, double-masked, phase 3 studies of identical design (191578-005 and 191578-006) evaluated the efficacy and safety of **ACUVAIL**<sup>®</sup> as compared with vehicle in the treatment of pain and inflammation following cataract surgery. Together in these trials, 511 patients were randomized with only 493 receiving either **ACUVAIL**<sup>®</sup> (N=330) or the vehicle (N=163) starting on the day before surgery. A total of 309 patients were exposed to **ACUVAIL**<sup>®</sup> twice daily for 14 days (93.6% of the 330).

Overall, the incidence of adverse events was statistically significantly higher in the vehicle group (48.5 %, 79/163), as compared to the **ACUVAIL**<sup>®</sup> group (35.2%, 116/330).

IOP increased was the most commonly reported adverse event, and was significantly more frequent in patients treated with **ACUVAIL**<sup>®</sup> (5.8%) as compared to those treated with the vehicle (1.8%, p<0.05). Conjunctival hyperemia, eye pain, photophobia, and anterior chamber inflammation were significantly more frequently reported with the vehicle (p<0.05).

IOP measurements performed during the study revealed that increases in IOP ≥ 10 mm Hg were recorded in 32 patients treated with **ACUVAIL**<sup>®</sup> (9.7%), as compared to 7 patients treated with the vehicle (4.3%). These cases were mostly reported at day 1 (or day 3) and not present afterwards since they were reversible, either spontaneously or after drug treatment. No increased IOP-related complications were reported.

Some of the adverse events may have been the result of the cataract surgical procedure itself. Therefore, the adverse events presented in the following table may or may not be related to the use of **ACUVAIL**<sup>®</sup>.

**Table 1- Adverse Events (occurring in ≥ 3 patients) by Decreasing Incidence (n (%))**

|                                | SOC | <b>ACUVAIL</b> <sup>®</sup><br>(N=330) | Vehicle<br>(N=163) |
|--------------------------------|-----|--|--------------------|
| <b>Overall</b>                 |     | 116<br>(35.2)                          | 79 *<br>(48.5)     |
| <b>Preferred Term</b>          |     |  |                    |
| IOP increased                  | Inv | 19 (5.8)                               | 3 (1.8) †          |
| AC cell                        | Eye | 17 (5.2)                               | 10 (6.1)           |
| Conjunctival hyperaemia        | Eye | 15 (4.5)                               | 23 *<br>(14.1)     |
| Eye pain                       | Eye | 14 (4.2)                               | 25 *<br>(15.3)     |
| Iritis                         | Eye | 14 (4.2)                               | 12 (7.4)           |
| AC flare                       | Eye | 12 (3.6)                               | 8 (4.9)            |
| Corneal oedema                 | Eye | 11 (3.3)                               | 10 (6.1)           |
| Foreign body sensation in eyes | Eye | 11 (3.3)                               | 9 (5.5)            |



|                                 | SOC   | ACUVAIL®<br>(N=330) | Vehicle<br>(N=163) |
|---------------------------------|-------|---------------------|--------------------|
| <b>Overall</b>                  |       | 116<br>(35.2)       | 79 *<br>(48.5)     |
| Headache                        | Nerv  | 10 (3.0)            | 6 (3.7)            |
| Lacrimation increased           | Eye   | 4 (1.2)             | 4 (2.5)            |
| Conjunctival haemorrhage        | Eye   | 4 (1.2)             | 1 (0.6)            |
| Vision blurred                  | Eye   | 4 (1.2)             | 1 (0.6)            |
| Photophobia                     | Eye   | 3 (0.9)             | 16 (9.8) *         |
| Conjunctival oedema             | Eye   | 3 (0.9)             | 4 (2.5)            |
| Eye irritation                  | Eye   | 3 (0.9)             | 4 (2.5)            |
| Eye pruritus                    | Eye   | 3 (0.9)             | 3 (1.8)            |
| Corneal abrasion                | Inj&P | 3 (0.9)             | 1 (0.6)            |
| Vitreous detachment             | Eye   | 3 (0.9)             | 1 (0.6)            |
| Posterior capsule rupture       | Eye   | 3 (0.9)             | 0 (0.0)            |
| Vitreous floaters               | Eye   | 3 (0.9)             | 0 (0.0)            |
| AC fibrin                       | Eye   | 2 (0.6)             | 2 (1.2)            |
| Cataract operation complication | Inj&P | 2 (0.6)             | 1 (0.6)            |
| Macular oedema                  | Eye   | 2 (0.6)             | 1 (0.6)            |
| Nausea                          | Gastr | 2 (0.6)             | 1 (0.6)            |
| Punctate keratitis              | Eye   | 2 (0.6)             | 1 (0.6)            |
| AC inflammation                 | Eye   | 1 (0.3)             | 6 (3.7) *          |
| Iris haemorrhage                | Eye   | 1 (0.3)             | 2 (1.2)            |
| Eyelid oedema                   | Eye   | 0 (0.0)             | 3 (1.8) *          |
| Facial pain                     | Genrl | 0 (0.0)             | 3 (1.8) *          |
| Uveitis                         | Eye   | 0 (0.0)             | 3 (1.8) *          |

SOC = System Organ Class of MedDRA; Eye = eye disorders; Inv = investigations; Nerv = nervous system disorders; Inj&P = injury, poisoning and procedural complications; Gastr = gastrointestinal disorders;

Genrl = general disorders and administration site conditions

\*: statistically significantly higher rate (p<0.05) in the vehicle group

†: statistically significantly higher rate (p<0.05) in the ACUVAIL® group

### **Less Common Clinical Trial Adverse Drug Reactions (≤1%)**

Adverse events observed at an incidence of ≤1% in the 2 pooled phase 3 studies are provided below. Some of the adverse events may have been the result of the cataract surgical procedure itself. Therefore, the adverse events presented below may or may not be related to the use of ACUVAIL®.

**Eye Disorders:** photophobia, conjunctival oedema, eye irritation, eye pruritus, vitreous detachment, posterior capsule rupture, vitreous floaters, anterior chamber fibrin, macular

oedema, punctate keratitis, photopsia, pupillary disorder, visual disturbance, anterior chamber inflammation, iris haemorrhage, erythema of eyelid, maculopathy, asthenopia, conjunctivitis allergic, corneal disorder, Dellen, eyelids pruritus, instillation site irritation, keratoconjunctivitis sicca, lenticular opacities, ocular hyperaemia, pupillary deformity, retinal tear, trichiasis, vitreous disorder, vitreous prolapse

**Injury, poisoning and procedural complications:** corneal abrasion, cataract operation complication, eye operation complication fall, limb injury periorbital haematoma, post procedural haemorrhage, procedural headache, procedural nausea

**Infections and infestations:** urinary tract infection, bronchitis, hypopyon, nasopharyngitis, rhinitis, upper respiratory tract infection

**Cardiac disorders:** atrial fibrillation, angina unstable, bradycardia, cardiac arrest, coronary artery occlusion

**Respiratory, thoracic and mediastinal disorders:** rhinorrhoea, sneezing

**Musculoskeletal and connective tissue disorders:** back pain, pain in extremity

**Psychiatric disorders:** confusional state

**Gastrointestinal disorders:** nausea

**Nervous system disorders:** sinus headache

**Reproductive system and breast disorders:** prostatic pain

### **Abnormal Hematologic and Clinical Chemistry Findings**

Clinical laboratory evaluations were not performed for any of the clinical studies. No laboratory abnormalities were reported as adverse events in any of the clinical studies.

### **Post-Market Adverse Drug Reactions**

The following adverse events have been reported since marketing but due to the expected underreporting from spontaneous sources, the frequencies are unknown:

Eye disorders: eye swelling, eye oedema

Treatment-related eye irritation has been observed following the use of **ACULAR**<sup>®</sup> (ketorolac tromethamine 0.5%).

Post-marketing experiences with **ACULAR**<sup>®</sup> (ketorolac tromethamine 0.5%), suggest that topical NSAIDs used by patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface disease, rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at an increased risk of corneal adverse events. These may include keratitis, epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. There were also case reports of ulcerative keratitis with the use of **ACUVAIL**<sup>®</sup>, some of which were serious.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hour prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

There have been post-marketing reports of bronchospasm or exacerbation of asthma, in patients, who have either a known hypersensitivity to aspirin/non-steroidal anti-inflammatory drugs or a past medical history of asthma, associated with the use of **ACULAR**<sup>®</sup> (ketorolac tromethamine 0.5%) which may be contributory (see WARNINGS AND PRECAUTIONS section).

## **DRUG INTERACTIONS**

### **Drug-Drug Interactions**

There is a potential for cross-sensitivity of ketorolac to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Therefore, caution should be exercised when using **ACUVAIL**<sup>®</sup> in individuals with previously exhibited-sensitivities to these drugs.

Topical NSAIDs may slow or delay healing (see Ophthalmology section). Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

With NSAIDs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied NSAID may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Therefore, It is recommended that **ACUVAIL**<sup>®</sup> ophthalmic solution be used with caution in patients with known bleeding tendencies, or who are receiving other medications, which may prolong bleeding time

**ACUVAIL**<sup>®</sup> ophthalmic solution may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, antibiotics, beta blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics.

## **Others interactions**

Drug-Food, Drug-Herb, and Drug-Laboratory Interactions have not been studied.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Ketorolac tromethamine is a non-steroidal, anti-inflammatory agent with analgesic and anti-inflammatory activity mediated by peripheral effects. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis. Ketorolac tromethamine given systemically does not cause pupil constriction.

Ketorolac tromethamine has demonstrated anti-inflammatory activity when applied topically in several animal models of ocular inflammation. It significantly inhibited the inflammatory responses to silver nitrate-induced cauterization of the corneas of rat eyes at concentrations of 0.25% and 0.5%. Concentrations of ketorolac ranging from 0.02% to 0.5% blocked vascular permeability changes caused by endotoxin-induced uveitis in the eyes of rabbits. Using the same model, ketorolac also blocked endotoxin-induced elevation of aqueous humor PGE<sub>2</sub>. It prevented the development of increased intraocular pressure induced in rabbits with topically applied arachidonic acid. Ketorolac did not inhibit rabbit lens aldose reductase *in vitro*.

### **Pharmacodynamics**

Ketorolac tromethamine ophthalmic solution prevented the development of increased intraocular pressure induced in rabbits with topically applied arachidonic acid. Ketorolac did not inhibit rabbit lens' aldose reductase *in vitro*.

Ketorolac tromethamine ophthalmic solution did not enhance the spread of ocular infections induced in rabbits with *Candida albicans*, *herpes simplex virus type one*, or *Pseudomonas aeruginosa*.

### **Pharmacokinetics**

**Absorption:** In human studies, penetration of the drug is rapid after application to the eye. The relationship between the concentrations of solution administered and the amount of drug that penetrates the cornea is roughly linear.

Two drops (0.1 mL) of 0.5% ketorolac tromethamine ophthalmic solution, instilled into the eyes of patients 12 hours and 1 hour prior to cataract extraction, achieved measurable levels in 8 of 9 patients' eyes. The mean ketorolac concentration was 95 ng/mL in the aqueous humor and

the range was 40 ng/mL to 170 ng/mL. The mean concentration of PGE2 was 80 pg/mL in the aqueous humor of eyes receiving vehicle and 28 pg/mL in the eyes receiving 0.5% ketorolac tromethamine ophthalmic solution.

One drop (0.05 mL) of 0.5% ketorolac tromethamine ophthalmic solution was instilled into one eye and one drop of the vehicle into the other eye t.i.d. for 21 days in 26 healthy subjects. Only 5 of 26 subjects had detectable amount of ketorolac in their plasma (range 10.7 ng/mL and 22.5 ng/mL) when tested 15 minutes after the morning dose on day 10.

When ketorolac is given systemically to relieve pain, the average plasma level following chronic systemic treatment was approximately 850 ng/mL.

**Distribution:** Animal studies have shown that <sup>14</sup>C-labelled ophthalmic solution 0.5% was found to be extensively distributed in ocular tissues with major portions retained in the cornea and sclera.

**Metabolism:** Although no studies have been conducted regarding the sites of metabolism for ophthalmic ketorolac, studies of systemic administration have shown that the drug is metabolized in the liver.

**Excretion:** Results of studies in rabbits and cynomolgus monkeys suggest that the major route of drug elimination from the eye is probably through intraocular blood flow after distribution from the aqueous humor to the iris-ciliary body.

### **Special Populations and Conditions**

**Pediatrics:** Safety and effectiveness in pediatric patients have not been established.

**Geriatrics:** No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

**Hepatic and Renal Insufficiency:** ACUVAIL® has not been studied in patients with hepatic or renal impairment.

### **STORAGE AND STABILITY**

ACUVAIL® should be stored at room temperature (15 to 30°C). Store the vials in the pouch, protected from light. Fold pouch ends closed.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

**ACUVAIL**<sup>®</sup> is available as a sterile preservative-free solution supplied in clear, low density polyethylene, single-use vials as follows:

30 Single-Use Vials, 0.4 mL each

60 Single-Use Vials, 0.4 mL each

The **ACUVAIL**<sup>®</sup> solution has a pH of approximately 6.8, and an osmolality of approximately 285 mOsm/kg.

**ACUVAIL**<sup>®</sup> contains ketorolac tromethamine 0.45% w/v and the following inactive ingredients: Carboxymethylcellulose sodium; sodium chloride; sodium citrate dihydrate; and purified water with sodium hydroxide and/or hydrochloric acid to adjust pH.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

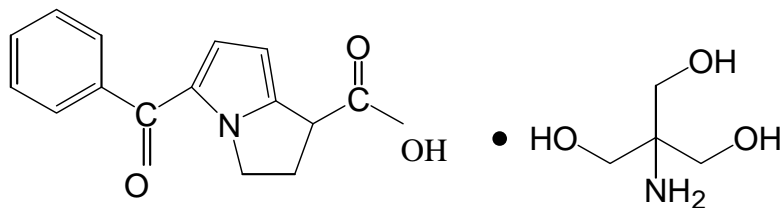
Proper name: ketorolac tromethamine ophthalmic solution 0.45%

Chemical name: ( $\pm$ )-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

2-amino-2-(hydroxymethyl)propane-1,3-diol (1*RS*)-5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylate

Molecular formula and molecular mass:  $C_{19}H_{24}N_2O_6$ ; 376.41

Structural formula:



Physicochemical properties: Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The pKa of ketorolac is 3.5. This white to off-white crystalline substance discolors on prolonged exposure to light.

### CLINICAL TRIALS

#### Study demographics and trial design

Two multicenter, randomized, double-masked, parallel group comparison studies (191578-005 and 191578-006) of identical design including 511 patients assessed the effects of **ACUVAIL**<sup>®</sup> on a summed ocular inflammation score (SOIS) of anterior chamber cell and flare (primary efficacy), ocular pain relief and analysis of pupil size (secondary efficacy endpoints) following cataract extraction with posterior chamber intraocular lens (IOL) implantation. All patients had planned unilateral, single procedure, uncomplicated phacoemulsification extracapsular cataract extraction with posterior chamber IOL implant under topical or intracameral anesthesia at the start of the procedure with no capsular staining during phacoemulsification.

One drop was administered twice daily beginning 1 day prior to cataract surgery and continued on the day of surgery and through the first two weeks post-surgery. On the day of surgery, two hours prior to surgery, one drop was administered every 20 minutes for a total of three drops. Prior to discharge, one additional drop was also administered.

Patient demographics and baseline characteristics were similar across studies and were not significantly different across treatment groups for age, sex, or race (Table 2).

**Table 2 - Summary of patient demographics for studies 191578-005 and 191578-006**

| Study #    | Dosage, route of administration and duration                            | Study patients (entered / completed) | Mean age (Range) | Gender (M/F)            | Race  |
|------------|---|--------------------------------------|------------------|-------------------------|---|
| 191578-005 | <b>ACUVAIL</b> <sup>®</sup><br>ophthalmic BID<br>vehicle BID<br>16 days | 248/201                              | 70 (40-89)       | 107 (43%)/<br>141 (57%) | Caucasians:<br>220 (89%)<br>Others:<br>28 (11%) |
| 191578-006 | <b>ACUVAIL</b> <sup>®</sup><br>ophthalmic BID<br>vehicle BID<br>16 days | 263/222                              | 69 (28-94)       | 111 (42%)/<br>152 (58%) | Caucasians:<br>216 (82%)<br>Others:<br>47 (18%) |

### Study results

Together in these trials, 511 patients were randomized with only 493 receiving either **ACUVAIL**<sup>®</sup> (N=330) or the vehicle (N=163) starting on the day before surgery. A total of 309 patients were exposed to **ACUVAIL**<sup>®</sup> twice daily for 14 days (93.6% of the 330).

For the primary efficacy endpoint in both studies, patients receiving **ACUVAIL**<sup>®</sup> had a statistically significantly higher incidence (46.3% to 58.0%) of clearing of anterior chamber inflammation (SOIS = 0 on day 14) compared with patients receiving vehicle (25.6% to 27.3%). For the secondary efficacy endpoints, **ACUVAIL**<sup>®</sup> was statistically significantly superior to vehicle in resolving ocular pain at day 1 post-cataract surgery in both studies. No significant difference was observed between **ACUVAIL**<sup>®</sup> and vehicle in the inhibition of surgically induced miosis post-I&A (irrigation and aspiration) in either study.



**Table 3 - Results of Efficacy Studies (Modified Intent-to-Treat Population)**

| Study      | Treatment Arm<br>P-Value | #<br>Enrolled/<br>Completed | Primary<br>Endpoint | Secondary Endpoints                         |   |
|------------|--------------------------|-----------------------------|---------------------|---|---|
|            |                          |                             | Day 14<br>SOIS = 0  | Day 1<br>Pain Score = 0<br>( <sup>b</sup> ) | Mean Pupil<br>Area Post-I&A<br>Placement ( <sup>b</sup> ) |
| 191578-005 | Ketorolac 0.45%<br>BID   | 155/144                     | 69/149 (46.3%)      | 114/152<br>(75.0%)                          | 41.8 mm <sup>2</sup>                                      |
|            | Vehicle BID              | 79/57                       | 20/78 (25.6%)       | 32/78 (41.0%)                               | 41.1 mm <sup>2</sup>                                      |
|            | P-value <sup>(a)</sup>   | —                           | 0.002               | < 0.001                                     | 0.706   |
| 191578-006 | Ketorolac 0.45%<br>BID   | 173/163                     | 98/169 (58.0%)      | 119/170<br>(70.0%)                          | 37.9 mm <sup>2</sup>                                      |
|            | Vehicle BID              | 82/59                       | 21/77 (27.3%)       | 30/78 (38.5%)                               | 36.5 mm <sup>2</sup>                                      |
|            | P-value <sup>(a)</sup>   | —                           | < 0.001             | < 0.001                                     | 0.413   |

BID = twice daily; I&A = irrigation and aspiration; SOIS = summed ocular inflammation score.

(a) P-values for SOIS Score and Pain Score are from a 2-sided Pearson's chi-square test. P-values for pupil area are from a 1-way analysis of variance model.

(b) For secondary efficacy variables gate keeping method was employed to address multiple testing.

## DETAILED PHARMACOLOGY

### Animal Pharmacology

Ketorolac tromethamine ophthalmic solution prevented the development of increased intraocular pressure induced in rabbits with topically applied arachidonic acid. Ketorolac did not inhibit rabbit lens' aldose reductase *in vitro*.

Ketorolac tromethamine ophthalmic solution did not enhance the spread of ocular infections induced in rabbits with *Candida albicans*, *herpes simplex virus type one*, or *Pseudomonas aeruginosa*.

### Animal Pharmacokinetics

#### Absorption

Ketorolac tromethamine levels in plasma were measured in four rabbits after administration in one eye, of one drop 5 times daily of 0.45% ketorolac tromethamine formulated in a CMC-based ophthalmic solution. Ketorolac tromethamine was detectable in plasma at relatively low levels (see table below).

**Plasma Ketorolac Pharmacokinetics in NZW rabbits after unilateral topical ocular administration of 0.45% Ketorolac Tromethamine (one drop five times daily), Report PK-07-090**

| Species<br>n/timepoint | Study<br>Day | Dose<br>(%w/v) | Cmax<br>(ng/mL) | Tmax<br>(hr) | AUC0-t<br>(ng·hr/mL) |
|------------------------|--------------|----------------|-----------------|--------------|----------------------|
| 4F                     | 1            | 0.45           | 99.0 (15.0)     | 0.500        | 260 (46)             |
|                        | 28           | 0.45           | 111 (41)        | 0.500        | 372 (125)            |

Cmax: Mean ( $\pm$ SD)

AUC: Composite area under the curve ( $\pm$ SE)

F: Female

Based on indirect comparison, systemic ketorolac exposure levels achieved following ocular administration of **ACUVAIL**<sup>®</sup> solution are probably not significantly different from levels achieved with 0.5% ketorolac tromethamine ophthalmic solution.

Following a single topical ocular instillation of 0.45% ketorolac tromethamine in rabbits (N=2/group), ketorolac was absorbed into the aqueous humor with T<sub>max</sub> occurring 2 hours post-dose. The bioavailability of ketorolac increased in aqueous humor to approximately 200%, as compared with **ACULAR LS**<sup>®</sup> (ketorolac tromethamine 0.4%).

## **TOXICOLOGY**

### *Acute toxicity*

Two single-day studies in New Zealand White (NZW) rabbits were treated with a topical ocular drop of ketorolac tromethamine at 0.45% or its vehicle for up to 6 drops for one day. In one study, no drug-related ocular effects were observed. In another study, slight drug- and pH-related effects on ocular discomfort but no significant drug- or vehicle-related effects were recorded.

Other studies performed with other ketorolac ophthalmic solutions in support of **ACULAR**<sup>®</sup> 0.5% ophthalmic solution are presented below.

| <i>Species Strain Regimen Group Size Preservative</i>  | <i>Route Concentration* (mg/mL)</i> | <i>Clinical Mortality Ophthalmology</i> |     |
|--|-------------------------------------|---|-----|
| Rabbit New Zealand<br>One dose in right eye followed by a 72-hour observation<br>3 females 0.01% BAC   | <b>Ocular</b>                       |   |     |
|  | 2.5                                 | 0/3                                     | NDE |
|  | 5.0                                 | 0/3                                     | NDE |
|  | 10.0                                | 0/3                                     | NDE |
|  | 20.0                                | 0/3                                     | NDE |
| Rabbit New Zealand<br>One dose every 30 min for a total of 12 doses to both eyes. Eyes were examined after the last dose and on days 1, 2, 3 and 6 following dosing<br>6 males 0.01% BAC | <b>Ocular</b>                       |   |     |
|  | Saline control                      | 0/6                                     | NDE |
|  | Vehicle control                     | 0/6                                     |     |
|  | 5.0                                 | 0/6                                     |     |

\*Volume = 0.1 mL/eye

NDE: No drug effect (no indications of irritation or toxicity)

BAC: Benzalkonium chloride

#### *Sub chronic toxicity*

In a 1-month study, NZW rabbits received either ketorolac tromethamine 0.45% or the vehicle in the left eye 5 drops per day for 28 days (with 9 drops per day on day 2 and day 3). No significant treatment-related findings were noted as per the clinical observations, tonometry, ophthalmic examinations, and pathology examinations (study TX07042).

In a 6-day ocular wound healing study (N=10 per group), after anterior keratectomy, NZW rabbits were administered ketorolac tromethamine ophthalmic solutions 0.45% or 0.35%, or **ACULAR LS**<sup>®</sup> (0.40%), up to 4 times daily. Both 0.45% ketorolac tromethamine and **ACULAR LS**<sup>®</sup> resulted in a statistically significant delay in corneal wound healing in comparison with the controls. On day 6, the wound area was 1.3 mm<sup>2</sup> with the blank control (2% of its baseline size), as compared with 6 mm<sup>2</sup> with the 0.45% formulation (11% of its baseline size). Comparable delays were seen with **ACULAR LS**<sup>®</sup>, and the 0.35% ketorolac tromethamine formulation (study TX07062).

#### *Long-term toxicity*

The following studies were performed with other ketorolac tromethamine ophthalmic solutions in support of **ACULAR**<sup>®</sup> 0.5% ophthalmic solution. Note that some of these solutions contained Benzalkonium chloride (BAC).

Ketorolac ophthalmic solution was evaluated in rabbits (pigmented and non-pigmented) in studies up to 6 weeks, and in monkeys in studies lasting up to 6 months.

The results of the preclinical toxicology studies indicate no adverse drug-related effects to ketorolac tromethamine. No adverse effects were observed in monkeys following 6 months of treatment with a thimerosal-preserved formulation. However, in studies with the BAC formulation, corneal fluorescein staining, accompanied by thinning of the epithelium, was seen in vehicle-treated and drug-treated animals. The Dutch Belted rabbit was most sensitive to these effects, with the New Zealand rabbit and the monkey showing decreasing sensitivities. Since the effects were seen primarily in vehicle and low-dose groups and since similar effects have been reported for BAC, the corneal changes were attributed to the preservative. The difference in sensitivity shown by the rabbit compared to the primate may be explained physiologically because of the greater blinking rate and lacrimal response to irritation in primates, including humans. In fact, formulations containing 0.01% BAC are well tolerated by humans and are approved as over-the-counter ophthalmic medications.

### **Carcinogenicity**

Ketorolac tromethamine was not carcinogenic in either rats given up to 5 mg/kg/day orally for 24 months or in mice given 2 mg/kg/day orally for 18 months. These doses are respectively 900 times and 300 times higher than the typical human topical ophthalmic daily dose of 0.324 mg given as BID to an affected eye on a mg/kg basis.

### **Mutagenicity**

Ketorolac tromethamine was not mutagenic *in vitro* in the Ames assay or in forward mutation assays. Similarly, it did not result in an *in vitro* increase in unscheduled DNA synthesis or an *in vivo* increase in chromosome breakage in mice. However, ketorolac tromethamine did result in an increased incidence in chromosomal aberrations in Chinese hamster ovary cells.

### **Reproduction and Teratology**

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 9 mg/kg/day and 16 mg/kg/day, respectively. These doses are respectively 1500 and 2700 times higher than the typical human topical ophthalmic daily dose.

Ketorolac tromethamine, administered orally during organogenesis, was not teratogenic at doses of 3.6 mg/kg/day in rabbits, and 10 mg/kg/day in rats; that is, approximately 600 times and 1700 times higher respectively than the typical human topical ophthalmic daily dose. When administered to rats after Day 17 of gestation at oral doses up to 1.5 mg/kg/day (approximately 300 times the typical human topical ophthalmic daily dose), ketorolac tromethamine resulted in dystocia and increased pup mortality.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE  
PATIENT MEDICATION INFORMATION****PrACUVAIL®****ketorolac tromethamine ophthalmic solution 0.45% w/v**

**Read this carefully before you start using ACUVAIL® and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ACUVAIL®.**

**What is ACUVAIL® used for:**

**ACUVAIL®** is used to treat pain and inflammation (swelling and redness) following cataract eye surgery.

**How does ACUVAIL® work:**

**ACUVAIL®** is a non-steroidal anti-inflammatory drug (NSAIDs). It works by reducing the release of substances called prostaglandins that cause inflammation, and pain.

**What are the ingredients in ACUVAIL®:**

Medicinal ingredients: ketorolac tromethamine

Non-medicinal ingredients: carboxymethylcellulose sodium, sodium citrate, sodium chloride; purified water with hydrochloric acid and/or sodium hydroxide to adjust pH.

**ACUVAIL® comes in the following dosage form:**

Ophthalmic solution 0.45%, w/v in a single-use vial

**Do not use ACUVAIL® if :**

- you are allergic (*hypersensitive*) to ketorolac tromethamine or any of the other ingredients (see “What are the ingredients in **ACUVAIL®**”, above)
- you are allergic to other nonsteroidal anti-inflammatory medicines such as acetylsalicylic acid, difusal, fenoprofen, flurbiprofen, ketoprofen, indomethacin, mefenamic acid, piroxicam, sulindac, tiaprofenic acid or tolmetin.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you use ACUVAIL®. Talk about any health conditions or problems you may have, including if you:**

- have any allergies to acetylsalicylic acid or to any of the other non-steroidal anti-inflammatory drugs (NSAIDs) or have asthma after using NSAIDs
- bruise easily, or if you have bleeding problems, or if you are taking blood thinning medication. **ACUVAIL®** may cause bleeding in the eyes with eye surgery
- have medical conditions such as diabetes mellitus, dry eye syndrome, rheumatoid arthritis or problems with your cornea (the front part of your eye)
- have had recent eye surgery or are planning for eye surgery
- are pregnant or intend to become pregnant
- are breast-feeding or intend to breast-feed

**Other warnings you should know about:**

While using **ACUVAIL**<sup>®</sup> talk to your healthcare professional if you are not getting relief, your symptoms worsen or new eye problems develop.

Do not use **ACUVAIL**<sup>®</sup> more than two weeks unless advised by your doctor. There is risk of corneal problems if you use ophthalmic non-steroidal anti-inflammatory drugs such as **ACUVAIL**<sup>®</sup> beyond 14 days after the surgery.

Use **ACUVAIL**<sup>®</sup> single-use vial immediately after opening and discard the remaining product immediately after use. Do not allow the tip of the vial to touch the eyes or surrounding surfaces to avoid injury and contamination of the eye drops.

**ACUVAIL**<sup>®</sup> eye drop may slow or delay healing of the eyes.

**Driving and Using Machines:** **ACUVAIL**<sup>®</sup> may cause blurred vision. Do not drive or use heavy machinery until your vision clears.

**Contact Lenses:** Do not use **ACUVAIL**<sup>®</sup> drops with your contact lenses in. If your healthcare professional recommends contact lenses use, remove them before using **ACUVAIL**<sup>®</sup> drops. Wait at least 15 minutes after using **ACUVAIL**<sup>®</sup> before putting your contact lenses back in.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with ACUVAIL<sup>®</sup>:**

- blood thinning medication such as warfarin.

**How to use ACUVAIL<sup>®</sup>:**

Follow the following steps to help you use **ACUVAIL**<sup>®</sup> properly:

1. Wash your hands well with soap and water before you start.
2. Tilt your head back or lie down.
3. Gently pull down the lower eyelid to create a small “pocket” between the eyelid and your eye. The drop will go in here.
4. Do not touch your eye or eyelid, surrounding areas or other surfaces with the tip of the unit-dose vial.
5. Hold the unit-dose vial, tip pointing down, While looking up, gently squeeze the vial to release one drop into each eye that needs treatment.
6. Let go of the lower lid, and close your eye for 30 seconds, longer is better (up to 5 minutes). Try not to blink or squeeze your eyelids.
7. Use **ACUVAIL**<sup>®</sup> single-use vials immediately after opening. Discard the remaining content immediately after use.

If you are using more than 1 eye drop medication, wait 5 minutes before applying the other eye drop.

Do not allow the tip of the vial to touch the eyes or eyes lids, eyelashes, fingers, counter surface or anything else. Contact with any surface can contaminate the product which may infect your eyes later on.

**If you wear contact lenses:** Do not use **ACUVAIL**<sup>®</sup> with your contact lenses in. Remove your contact lenses. After using **ACUVAIL**<sup>®</sup>, wait 15 minutes before putting your contact lenses back in.

**Usual adult dose (18 years of age and older):***Patient dosing*

One day before your cataract surgery, apply one drop of **ACUVAIL**<sup>®</sup> to the affected eye twice daily. Continue to apply one drop to the affected eye twice daily on the day of cataract surgery and for as long as your doctor told you. This may be up to two weeks after cataract surgery.

*Dosing on the day of cataract surgery by healthcare professional*

Administer one drop two hours before surgery, then approximately every twenty minutes for a total of three drops. Before discharge administer one additional drop.

**Overdose:**

If you accidentally swallow **ACUVAIL**® eye drops, drink fluids to dilute and contact your local poison centre or doctor.

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

**Missed Dose:**

If you miss a dose of **ACUVAIL**®, use the missed dose as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

**What are possible side effects from using ACUVAIL®?**

These are not all the possible side effects you may feel when using **ACUVAIL**®. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects with treatment of **ACUVAIL**® include eye pain, abnormal sensation in the eye, increased fluid pressure inside the eye(s), and pupil disorder.

| Serious side effects and what to do about them   |                                      |              |   |
|--|--------------------------------------|--------------|---|
| Symptom / effect   | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|  | Only if severe                       | In all cases |   |
| <p><b>Ulcerative keratitis</b> [open sores and swelling of the cornea (clear window in the front of the eye)]:</p> <ul style="list-style-type: none"> <li>• eye redness,</li> <li>• eye pain,</li> <li>• excess tearing,</li> <li>• blurred vision,</li> <li>• decreased vision,</li> <li>• increased sensitivity to light,</li> <li>• a feeling that a foreign object is trapped in your eye</li> </ul> |                                      |              | √   |
| <p><b>Corneal perforation</b> (hole in the cornea):</p> <ul style="list-style-type: none"> <li>• decreased vision,</li> <li>• eye pain,</li> <li>• increased sensitivity to light,</li> <li>• excess tearing</li> </ul>  |                                      |              | √   |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

**Reporting Side Effects**

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

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

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

**Storage:**

Store at room temperature (15 - 30°C). Store the vials in the pouch. Protect from light.

Keep out of reach and sight of children.

**If you want more information about ACUVAIL®:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<http://hc-sc.gc.ca/index-eng.php>); the manufacturer's website [www.allergan.ca](http://www.allergan.ca), or by calling 1-800-668-6424.

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