

## PRODUCT MONOGRAPH

<sup>Pr</sup>ACUVAIL™

(ketorolac tromethamine ophthalmic solution 0.45% w/v)

Topical Non-steroidal Anti-inflammatory Agent

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## Pr ACUVAIL™

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.  <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

#### INDICATIONS AND CLINICAL USE

ACUVAIL™ 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.

## **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™ 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 nonsteroidal anti-inflammatory drugs (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.

### **Contact Lens Wear**

ACUVAIL™ 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™ solution and may be re-inserted 15 minutes following administration.

### **Special Populations**

#### **Pregnant Women:**

There are no adequate studies in pregnant women. Therefore, ACUVAIL™ 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™, 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™. See TOXICOLOGY 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™ 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™ 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™ (N=330) or the vehicle (N=163) starting on the day before surgery. A total of 309 patients were exposed to ACUVAIL™ 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™ group (35.2%, 116/330).

IOP increased was the most commonly reported adverse event, and was significantly more frequent in patients treated with ACUVAIL™ (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  $\geq$  10 mm Hg were recorded in 32 patients treated with ACUVAIL™ (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™.

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

	SOC	ACUVAIL (N=330)	Vehicle (N=163)
<b>Overall</b>		116 (35.2)	79 (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 (14.1) *
Eye pain	Eye	14 (4.2)	25 (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)
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 ( $\leq 1\%$ )**

Adverse events observed at an incidence of  $\leq 1\%$  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:

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 non-steroidal anti-inflammatory drugs (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>, four 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 nonsteroidal anti-inflammatory drugs (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.

## **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™ 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™ 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™ 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™ in conjunction with prostaglandin analogues (e.g., Lumigan®, Travatan®, Xalatan®) has not been studied, use only if the benefit outweighs any potential risk.

## **OVERDOSAGE**

There is no data on overdose with ACUVAIL™ or ketorolac tromethamine. If ACUVAIL™ is accidentally ingested, drink fluids to dilute.

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

## **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™ 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™ solution has a pH of approximately 6.8, and an osmolality of approximately 285 mOsm/kg.

ACUVAIL™ 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

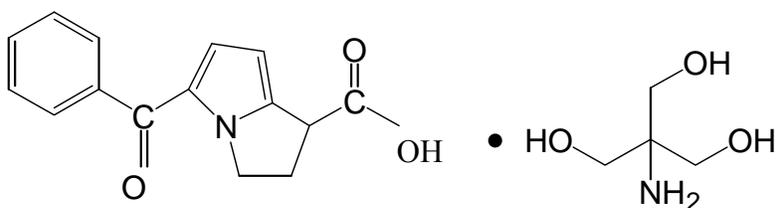
Proper name: ketorolac tromethamine ophthalmic solution 0.45%

Chemical name: (±)-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<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>; 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™ 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	ACUVAIL ophthalmic BID vehicle BID 16 days	248/201	70 (40-89)	107 (43%)/ 141 (57%)	Caucasians: 220 (89%) Others: 28 (11%)
191578-006	ACUVAIL ophthalmic BID vehicle BID 16 days	263/222	69 (28-94)	111 (42%)/ 152 (58%)	Caucasians: 216 (82%) Others: 47 (18%)

## Study results

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

For the primary efficacy endpoint in both studies, patients receiving ACUVAIL™ 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™ 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™ 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 P-Value	# Enrolled/ Completed	Primary Endpoint	Secondary Endpoints	
			Day 14 SOIS = 0	Day 1 Pain Score = 0 <sup>(b)</sup>	Mean Pupil Area Post-I&A Placement <sup>(b)</sup>
191578-005	Ketorolac 0.45% BID	155/144	69/149 (46.3%)	114/152 (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% BID	173/163	98/169 (58.0%)	119/170 (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 n/timepoint	Study Day	Dose (%w/v)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC <sub>0-t</sub> (ng·hr/mL)
4F	1	0.45	99.0 (15.0)	0.500	260 (46)
	28	0.45	111 (41)	0.500	372 (125)

C<sub>max</sub>: Mean (±SD)

AUC: Composite area under the curve (±SE)

F: Female

Based on indirect comparison, systemic ketorolac exposure levels achieved following ocular administration of ACUVAIL™ 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® (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™ 0.5% ophthalmic solution are presented below.

<i>Species Strain Regimen Group Size Preservative</i>	<i>Route Concentration* (mg/mL)</i>	<i>Mortality</i>	<i>Clinical Ophthalmology</i>
Rabbit New Zealand One dose in right eye followed by a 72-hour observation 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 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 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 day3). 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 (0.40%), up to 4 times daily. Both 0.45% ketorolac tromethamine and ACULAR LS 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, 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>TM</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 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.

## PART III: CONSUMER INFORMATION

Pr ACUVAIL™

ketorolac tromethamine ophthalmic solution 0.45% w/v

This leaflet is part III of a three-part "Product Monograph" published when ACUVAIL™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ACUVAIL™. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION****What the medication is used for:**

ACUVAIL™ is used for treatment of pain and inflammation (swelling and redness) following cataract eye surgery.

**What it does:**

ACUVAIL™ (ketorolac tromethamine) is a non-steroidal anti-inflammatory drug (NSAIDs). It works by reducing the production of certain substances (such as prostaglandins) that cause inflammation, and pain.

**When it should not be used:**

ACUVAIL™ should not be used if you are allergic (*hypersensitive*) to ketorolac tromethamine or any of the other ingredients listed below or to other nonsteroidal antiinflammatory medicines such as acetylsalicylic acid, difusal, fenoprofen, flurbiprofen, ketoprofen, indomethacin, mefenamic acid, piroxicam, sulindac, tiaprofenic acid or tolmetin.

**What the medicinal ingredient is:**

Ketorolac tromethamine

**What the important nonmedicinal ingredients are:**

None.

Other nonmedicinal ingredients in the product include: carboxymethylcellulose sodium, sodium citrate, sodium chloride; purified water with hydrochloric acid and/or sodium hydroxide to adjust pH.

**What dosage forms it comes in:**

ACUVAIL™ is a sterile solution packaged in 0.4 mL single-use plastic vials.

**WARNINGS AND PRECAUTIONS**

**BEFORE** you use ACUVAIL™ talk to your doctor or pharmacist if:

- you have any allergies to ACUVAIL™ or any of its ingredients (see **What the important nonmedicinal ingredients are**)
- you bruise easily, or if you have bleeding problems, or if you are taking blood thinning medication

- you are allergic to acetylsalicylic acid or to any of the other non-steroidal anti-inflammatory drugs (NSAIDs)
- you wear contact lenses
- you are pregnant or intend to become pregnant
- you are breast-feeding or intend to breast-feed
- you drive or use heavy machinery. You may find that your vision is blurred for a time just after you use ACUVAIL™

**WHILE** taking ACUVAIL™ talk to your doctor if:

- you are not getting relief, your symptoms worsen or new eye problems develop.

Do not use Acuvail more than two weeks unless advised by your doctor. There is risk of corneal problems if ophthalmic non-steroidal anti-inflammatory drugs such as Acuvail are used beyond 14 days after the surgery.

**INTERACTIONS WITH THIS MEDICATION**

If you are allergic to acetylsalicylic acid or to any of the other non-steroidal anti-inflammatory drugs (e.g. diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, sulindac, tiaprofenic acid, tolmetin) used to treat arthritis or other muscle and joint conditions, discuss with your doctor before using ACUVAIL™.

Talk with your doctor or pharmacist if you are taking any blood thinning medication.

Tell your doctor or pharmacist if you are taking any other prescription or nonprescription (over-the-counter [OTC]) medicine, vitamins, herbals products.

**PROPER USE OF THIS MEDICATION****Usual adult dose (18 years of age and older):***Patient dosing*

One day before your cataract surgery, apply one drop of Acuvail™ 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 maybe up to two weeks after cataract surgery.

*Dosing on the day of cataract surgery by medical personnel*

Two hours before surgery, one drop is to be administered approximately every twenty minutes by medical personnel for a total of three drops. Before discharge one additional drop is to be applied.

Use the medication in the 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 eyes lids, eyelashes, fingers, counter surface or anything else. Contact with any surface can contaminate the product which may infect your eyes later on.

**How to Use:**

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. Discard the remaining content immediately after administration.

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

ACUVAIL™ should not be administered while wearing contact lenses. If contact lens use is determined safe by your doctor, they should be removed before you instill the drops and may be re-inserted 15 minutes following administration.

**Overdose:**

If accidentally ingested, 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 a dose of this medication has been missed, it should be taken 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.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

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.

Acuvail may blur your vision after you instil the drops. Do not drive or perform hazardous task until you can see clearly again.

Acuvail eye drop may slow or delay healing of the eyes

*This is not a complete list of side effects. For any unexpected effects while taking ACUVAIL™, contact your doctor or pharmacist.*

**HOW TO STORE IT**

Store at room temperature (15 - 30°C). Protect from light.

**REPORTING SUSPECTED SIDE EFFECTS**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

- **Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: **Canada Vigilance Program  
Health Canada  
Postal Locator 0701D  
Ottawa, Ontario  
K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Allergan, Inc. at: 1-877-255-2746

This leaflet was prepared by Allergan, Inc.

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