PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrACUVAIL®

ketorolac tromethamine ophthalmic solution

solution, 0.45% w/v, for ophthalmic use

Non-Steroidal Anti-inflammatory Agent (ATC code: S01BC05)

AbbVie Corporation

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St-Laurent, QC H4S 1Z1

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RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ACUVAIL® (ketorolac tromethamine ophthalmic solution) is indicated for:

- the treatment of pain and inflammation following cataract surgery.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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

2 CONTRAINDICATIONS

- Ketorolac tromethamine ophthalmic solution is contraindicated in patients who are hypersensitive to ketorolac, to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, component of the container, or to other nonsteroidal anti-inflammatory drugs (NSAIDs). For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

4.2 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.

Health Canada has not authorized an indication for pediatric use.

4.4 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. Each vial is intended only for a single treatment in the affected eye(s). To avoid injury and contamination of the eye drops, 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.

4.5 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.

5 OVERDOSAGE

There is no data on overdosage 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/ Composition	Non-medicinal Ingredients
Ophthalmic	Solution Ketorolac tromethamine 0.45% w/v	Carboxymethylcellulose sodium, sodium chloride, sodium citrate dihydrate and purified water with sodium hydroxide and/or hydrochloric acid to adjust pH.

ACUVAIL is available as a sterile preservative-free solution supplied in clear, low density polyethylene, single-use vials as follows: follows: 30 single-use vials, 0.4 mL each.

The ACUVAIL solution has a pH of approximately 6.8, and an osmolality of approximately 285 mOsml/kg.

7 WARNINGS AND PRECAUTIONS

General

There exists the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. See 8.5 Post-Market Adverse Reactions. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Topical NSAIDs may slow or delay healing (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic). Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY section.

Driving and Operating Machinery

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.

Hematologic

Bleeding

With some NSAIDs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that ACUVAIL 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.

7.1 Special Populations

7.1.1 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 16 NON-CLINICAL TOXICOLOGY.

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.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reactions Overview

In the two Phase 3 clinical studies conducted with ACUVAIL, the most frequently occurring adverse drug reactions were IOP increased (5.8%) and AC cell (5.2%). Most treatment-related adverse events were ocular and were mild or moderate. All serious adverse events were non-ocular and none were related to treatment. Twelve patients (3.6%) discontinued from the studies. The most common adverse event leading to study discontinuation was anterior chamber inflammation.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, 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 reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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).

Intraocular pressure (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 ≥ 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 2 may or may not be related to the use of ACUVAIL.

Table 2 – Adverse Events (occurring in ≥ 3 patients) by Decreasing Incidence (n [%]) organized by System Organ Class (SOC) of MedDRA

	ACUVAIL n = 330 (%)	**Placebo n = 163 (%)***
Eye disorders		
AC cell	17 (5.2)	10 (6.1)
Conjunctival hyperaemia	15 (4.5)	23 (14.1)*
Eye pain	14 (4.2)	25 (15.3)*
Iritis	14 (4.2)	12 (7.4)
AC flare	12 (3.6)	8 (4.9)
Corneal oedema	11 (3.3)	10 (6.1)
Foreign body sensation in eyes	11 (3.3)	9 (5.5)
Lacrimation increased	4 (1.2)	4 (2.5)
Conjunctival haemorrhage	4 (1.2)	1 (0.6)
Vision blurred	4 (1.2)	1 (0.6)
Photophobia	3 (0.9)	16 (9.8)*
Conjunctival oedema	3 (0.9)	4 (2.5)
Eye irritation	3 (0.9)	4 (2.5)
Eye pruritus	3 (0.9)	3 (1.8)
Vitreous detachment	3 (0.9)	1 (0.6)
Posterior capsule rupture	3 (0.9)	0 (0.0)
Vitreous floaters	3 (0.9)	0 (0.0)
AC fibrin	2 (0.6)	2 (1.2)
Macular oedema	2 (0.6)	1 (0.6)
Punctate keratitis	2 (0.6)	1 (0.6)

	ACUVAIL n = 330 (%)	Placebo n = 163 (%)*
AC inflammation	1 (0.3)	6 (3.7)*
Iris haemorrhage	1 (0.3)	2 (1.2)
Eyelid oedema	0 (0.0)	3 (1.8)*
Uveitis	0 (0.0)	3 (1.8)*
Gastrointestinal		
Nausea	2 (0.6)	1 (0.6)
General disorders and administration site conditions		
Facial pain	0 (0.0)	3 (1.8)*
Injury, poisoning and procedural complications		
Cataract operation complication	3 (0.9)	1 (0.6)
Corneal abrasion	2 (0.6)	1 (0.6)
Investigations		
IOP increased	19 (5.8)	3 (1.8)†
Nervous system disorders		
Headache	10 (3.0)	6 (3.7)

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

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

8.3 Less Common Clinical Trial Adverse 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.

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

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

Gastrointestinal disorders: nausea

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

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

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

Nervous system disorders: sinus headache

Psychiatric disorders: confusional state

Reproductive system and breast disorders: prostatic pain

Respiratory, thoracic and mediastinal disorders: rhinorrhoea, sneezing

8.4 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.

8.5 Post-Market Adverse 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 (ketorolac tromethamine 0.5%).

Post-marketing experiences with ACULAR (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, 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/NSAIDs or a past medical history of asthma, associated with the use of ACULAR (ketorolac tromethamine 0.5%) which may be contributory (see 7 WARNINGS AND PRECAUTIONS of the ACULAR/ACULAR LS Product Monograph).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No interaction studies were conducted.

9.3 Drug-Behavioural Interactions

No formal drug-behavioural interaction studies were conducted.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 – Summary of Effect of Co-administered Drugs on Exposure to ACUVAIL

Co-administered drug	Source of Evidence	Effect	Clinical comment
Acetylsalicylic acid	T	Potential for cross-sensitivity	Caution should be exercised when using ketorolac tromethamine in individuals with previously exhibited sensitivities to these drugs.
Phenylacetic acid derivatives	T	Potential for cross-sensitivity	Caution should be exercised when using ketorolac tromethamine in individuals with previously exhibited sensitivities to these drugs.
Other NSAIDs	T	Potential for cross-sensitivity	Caution should be exercised when using ketorolac tromethamine in individuals with previously exhibited sensitivities to other NSAIDs.
Topical steroids	T	Potential for healing problems	Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. (See 7 WARNINGS AND PRECAUTIONS, Ophthalmologic)
NSAIDs	T	Potential for increased bleeding time due to interference with thrombocyte aggregation	Recommended that ketorolac tromethamine ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications, which may prolong bleeding time. (See 7 WARNINGS AND PRECAUTIONS, Hematologic)

Co-administered drug	Source of Evidence	Effect	Clinical comment
NSAIDs	T	Potential for increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery	Recommended that ketorolac tromethamine ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications, which may prolong bleeding time. (See 7 WARNINGS AND PRECAUTIONS, Hematologic)
Legend: T = Theoretical			

Ketorolac tromethamine 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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 PGE2. 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.

10.2 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*.

10.3 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 three times daily. 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.

In animal studies, 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 4).

Table 4 – 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_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (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_{max}: 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_{max} 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%).

Distribution

Animal studies have shown that ^{14}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 Insufficiency:** Ketorolac tromethamine has not been studied in patients with hepatic impairment.
- **Renal Insufficiency:** Ketorolac tromethamine has not been studied in patients with renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

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

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

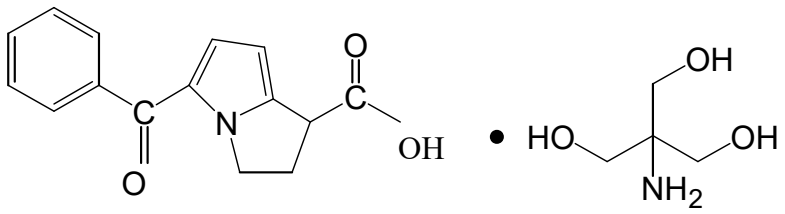
Proper name: ketorolac tromethamine ophthalmic solution 0.45%

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 (1RS)-5-benzoyl-2,3-dihydro-1H-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.

14 CLINICAL TRIALS

14.1 Clinical Trial by Indication

Pain and Inflammation Following Cataract Surgery

Table 5 – Summary of patient demographics for clinical trials in treatment of pain and inflammation following cataract surgery

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n) (entered / completed)	Mean age (range)	Sex (M/F)	Race
191578-005	Multicenter, randomized, double-masked, parallel group comparison study	**ACUVAIL** ophthalmic BID vehicle BID 16 days	248/201	68 (40-89)	107 (43%) / 141 (57%)	Caucasians: 220 (89%) Others: 28 (11%)

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n) (entered / completed)	Mean age (range)	Sex (M/F)	Race
	in patients with cataract surgery					
191578-006	Multicenter, randomized, double-masked, parallel group comparison study in patients with cataract surgery	**ACUVAIL** ophthalmic BID vehicle BID 16 days	263/222	68 (28-94)	111 (42%) / 152 (58%)	Caucasians: 216 (82%) Others: 47 (18%)

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 5).

Table 6 – Results of Studies 191579-005 and 191578-006 in Treatment of pain and inflammation following cataract surgery (Modified Intent-to-Treat Population)

			Primary Endpoint	Secondary Endpoints	
Study	**Treatment Arm** **P-Value**	**# Enrolled/ Completed**	**Day 14 SOIS = 0**	**Day 1 Pain Score = 0** [(b)]	**Mean Pupil Area** Post-I&A Placement [(b)]
191578-005	Ketorolac 0.45% BID Vehicle BID P-value[(a)]	155/144 79/57 —	69/149 (46.3%) 20/78 (25.6%) 0.002	114/152 (75.0%) 32/78 (41.0%) < 0.001	41.8 mm^2 41.1 mm^2 0.706

			Primary Endpoint	Secondary Endpoints	
Study	**Treatment Arm** **P-Value**	**# Enrolled/** **Completed**	**Day 14** **SOIS = 0**	**Day 1** **Pain Score = 0** [(b)]	**Mean Pupil Area** Post-I&A Placement [(b)]
191578-006	Ketorolac 0.45% BID Vehicle BID P-value [(a)]	173/163 82/59 —	98/169 (58.0%) 21/77 (27.3%) < 0.001	119/170 (70.0%) 30/78 (38.5%) < 0.001	37.9 mm^2 36.5 mm^2 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.

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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL 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.

Table 7 – Acute Toxicity

Species Strain Regimen Group Size Preservative	Route Concentration* (mg/mL)	Mortality	Clinical Ophthalmology
Rabbit New Zealand One dose in right eye followed by a 72-hour observation 3 females 0.01% BAC	**Ocular**		
	2.5	0/3	NDE
	5.0	0/3	NDE
	10.0	0/3	NDE
	20.0	0/3	NDE
	40.0	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	**Ocular**		
	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^2 with the blank control (2% of its baseline size), as compared with 6 mm^2 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 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 twice daily to an affected eye on a mg/kg basis.

Genotoxicity: 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.

Reproductive and Developmental Toxicology: 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrACUVAIL®

Ketorolac tromethamine ophthalmic solution

Read this carefully before you start taking **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 (NSAID). It works by reducing the release of substances called prostaglandins that cause inflammation, and pain.

What are the ingredients in ACUVAIL?

Medicinal ingredient: ketorolac tromethamine

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

ACUVAIL comes in the following dosage forms:

Ophthalmic solution 0.45% w/v

Do not use ACUVAIL if:

- you are allergic (hypersensitive) to ketorolac tromethamine or any of the other ingredients (see section **What are the ingredients in ACUVAIL?**);
- you are allergic to other nonsteroidal anti-inflammatory medicines such as acetylsalicylic acid, diflunisal, fenoprofen, flurbiprofen, ketoprofen, indomethacin, mefanamic acid, piroxicam, sulindac, tiaprofenic acid or tolmetin.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take 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 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 talk to your healthcare professional if you are not getting relief, your symptoms worsen or new eye problems develop.

Do not use ACUVAIL more that 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 beyond 14 days after the surgery.

ACUVAIL eye drop may slow or delay healing of the eyes.

Driving and Using Machines:

ACUVAIL may cause blurred vision. Do not drive or use heavy machinery until your vision clears.

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:

- blood thinning medication such as warfarin.

How to take ACUVAIL:

- If you use ACUVAIL with other eye drops, wait 5 minutes between using ACUVAIL and the other drops.
- Use ACUVAIL single-use vial immediately after opening.
    - 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.
- Remove your contact lenses before using ACUVAIL. You may put them back in 15 minutes after using ACUVAIL.

Follow the following steps to help you use ACUVAIL properly:

- Wash your hands well with soap and water before you start.
- Tilt your head back or lie down.
- Gently pull down the lower eyelid to create a small “pocket” between the eyelid and your eye. The drop will go in here.

- 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.
- 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.

Usual dose:

Patient dosing (18 years of age and older):

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 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 think you, or a person you are caring for, have taken too much ACUVAIL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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

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 dose.

What are possible side effects from using ACUVAIL?

These are not all the possible side effects you may have when taking ACUVAIL. If you experience any side effects not listed here, tell 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	
UNKNOWN			
Ulcerative keratitis [open sores and swelling of the cornea (clear window in the front of the eye)]: a feeling that a foreign object is trapped in your eye, blurred vision, decreased vision, excess tearing, eye pain, eye redness, increased sensitivity to light			✓
Corneal perforation (hole in the cornea): decreased vision, eye pain, excess tearing, increased sensitivity to light			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.abbvie.ca, or by calling 1-888-704-8271.

This leaflet was prepared by AbbVie Corporation.

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