CLEAN PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ACUVAIL 4,5 mg/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 4,5 mg of ketorolac tromethamine.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution

Clear, colourless to pale yellow solution with a pH of approximately 6,8 and an osmolality of approximately 285 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ACUVAIL is indicated in adults for the treatment of pain and inflammation following cataract surgery.

4.2 Posology and method of administration

Posology

Patient dosing

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 post-operative period.

Dosing on the day of cataract surgery by healthcare professional

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.

Special populations

Elderly population

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

Hepatic or renal impairment

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

Paediatric population

Safety and effectiveness in paediatric patients have not been established. No data available.

Method of administration

If more than one topical ophthalmic medication is being used the medicines must be

administered at least 5 minutes apart**.**

4.3 Contraindications

ACUVAIL is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

For a complete listing of ingredients in ACUVAIL, see Section 6.1.

4.4 Special warnings and precautions for use

Cross-Sensitivity or Hypersensitivity

There is the potential for cross-sensitivity to aspirin, phenylacetic acid derivatives, and other non-steroidal anti-inflammatory drugs (NSAIDs) [see Section 4.5]. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these medicines.

There have been 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 ketorolac tromethamine 0,5 % ophthalmic solution which may be contributory. Caution is recommended in the use of ACUVAIL in these individuals.

Bleeding

With some non-steroidal anti-inflammatory agents, like ketorolac tromethamine as in ACUVAIL, there is the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied non-steroidal anti-inflammatory medication, like ketorolac tromethamine, as in ACUVAIL, may cause increased

bleeding of ocular tissues (including hyphaemas) 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.

Delayed Healing

Topical non-steroidal anti-inflammatory agents, like ketorolac tromethamine as in ACUVAIL, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical non-steroidal anti-inflammatory agents and topical steroids may increase the potential for healing problems.

Corneal Effects

Use of topical non-steroidal anti-inflammatory agents, like ketorolac tromethamine as in ACUVAIL, may result in keratitis. In some susceptible patients, continued use of topical non-steroidal anti-inflammatory agents, like ketorolac tromethamine as in ACUVAIL, 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 ACUVAIL and should be closely monitored for corneal health.

ACUVAIL 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 non-steroidal anti-inflammatory agents, like ketorolac

tromethamine as in ACUVAIL, 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.

Eye Injury and Contamination

Patients should be instructed to avoid allowing the tip of the vial 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 should not be administered while wearing contact lenses. If contact lens use is recommended by the doctor, they should be removed prior to instillation of ACUVAIL solution and may be re-inserted 15 minutes following administration.

4.5 Interaction with other medicines and other forms of interaction

There is a potential for cross-sensitivity of ketorolac to aspirin, phenylacetic acid derivatives, and other non-steroidal anti-inflammatory agents (NSAIDs). Therefore, caution should be exercised when using ACUVAIL in individuals with previously exhibited sensitivities to these medicines (see Section 4.4).

Topical non-steroidal anti-inflammatory agents may slow or delay healing (see Section 4.4). Concomitant use of ACUVAIL and topical steroids may increase the potential for healing problems.

With non-steroidal anti-inflammatory agents, there is the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied non-steroidal anti-inflammatory agents, like ACUVAIL, may cause increased bleeding of ocular tissues (including hyphaemas) in conjunction with ocular surgery. Therefore, 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.

ACUVAIL may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, antibiotics, beta blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well controlled studies in pregnant women.

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.

Because of the known non-teratogenic effects of prostaglandin-inhibiting medicines on the foetal cardiovascular system of rats (closure of the ductus arteriosus), the use of ACUVAIL during late pregnancy should be avoided.

Breastfeeding

ACUVAIL is 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.

Fertility

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses of 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.

4.7 Effects on ability to drive and use machines

If transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Summary of safety profile

In clinical trials the most common adverse reactions were increased intra-ocular pressure, conjunctival haemorrhage, eye pain, and blurred vision.

Tabulated list of adverse reactions

The following adverse reactions were reported during clinical trials with ACUVAIL or in the post-marketing period.

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare

(≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	**Adverse Reaction**
Eye disorders	Common	Increased intra-ocular pressure, eye pain, conjunctival haemorrhage, blurred vision
	Unknown	Ulcerative keratitis, eye swelling, eye oedema, eyelid oedema, ocular hyperaemia

Additional side effects reported for preserved 0,4 % and 0,5 % ketorolac tromethamine formulations which may potentially occur with ACUVAIL are tabulated below:

System Organ Class	**Adverse Reaction**
Eye disorders	Stinging or burning on instillation, conjunctival hyperaemia, corneal infiltrates, iritis, ocular inflammation, corneal oedema, eye irritation, superficial keratitis and superficial ocular infections, corneal erosion, corneal perforation, corneal thinning, epithelial breakdown, keratic precipitates, hem retinal, cystoid macular oedema, eye burning, eye pruritus, eye trauma
Nervous system disorders	Headache
Skin and subcutaneous tissue disorders	Allergic reactions (itching, rash, redness or swelling of skin)
Immune system disorders	Hypersensitivity

Description of selected adverse reactions

Treatment-related eye irritation has been observed following the use of ketorolac tromethamine 0,45 % ophthalmic solution.

Post-marketing experiences with ketorolac tromethamine 0,45 % ophthalmic solution, 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 (see Section 4.4). There were also case reports of ulcerative keratitis with the use of ACUVAIL, some of which were serious.

Post-marketing experience with topical non-steroidal anti-inflammatory agents, such as ACUVAIL, 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.

There have been post-marketing reports of bronchospasm or exacerbation of asthma, in patients, who have either a known hypersensitivity to aspirin or non-steroidal anti-inflammatory agents (NSAIDs) or a past medical history of asthma, associated with the use of ketorolac tromethamine 0,45 % ophthalmic solution which may be contributory (see Section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers

are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

You can also report side effects to AbbVie (Pty) Ltd by sending an e-mail to MEAPV@abbvie.com

4.9 Overdose

In the event of topical overdose, wash the eye with water. If ACUVAIL is accidentally ingested, drink fluids to dilute. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A. 15.4 Ophthalmic preparations. Others.

Pharmacotherapeutic group: Anti-inflammatory agents, non-steroids

ATC code: S01BC05

Mechanism of action

Ketorolac tromethamine is a non-steroidal, anti-inflammatory agent with analgesic and anti-inflammatory activity. It is thought to exert its effects by inhibiting the cyclo-oxygenase enzyme essential for prostaglandin biosynthesis. Ketorolac tromethamine given systemically does not cause pupil constriction. Ketorolac tromethamine ophthalmic solution has no significant effect on intraocular pressure.

5.2 Pharmacokinetic properties

Absorption

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

Two drops 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 humour and the range was 40 ng/ml to 170 ng/ml. The mean concentration of PGE2 was 80 pg/ml in the aqueous humour of eyes receiving vehicle and 28 pg/ml in the eyes receiving 0,5 % ketorolac tromethamine ophthalmic solution.

One drop of 0,5 % ketorolac tromethamine ophthalmic solution was instilled into one eye and one drop of the vehicle into the other eye three times a day 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 ^{14}C-labelled ketorolac tromethamine ophthalmic solution was found to be extensively distributed in ocular tissues with major portions retained in the cornea and sclera.

Biotransformation

Although no studies have been conducted regarding the sites of metabolism for ophthalmic ketorolac, studies of systemic administration have shown that the medicine is metabolised in the liver.

Elimination

Results of studies in rabbits and cynomolgus monkeys suggest that the major route of medicine elimination from the eye is probably through intra-ocular blood flow after distribution from the aqueous humour to the iris-ciliary body.

Special Populations and Conditions

Paediatric population

Safety and effectiveness in paediatric patients have not been established.

Geriatric population

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

Hepatic and Renal Insufficiency

Ketorolac tromethamine has not been studied in patients with hepatic or renal impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carboxymethylcellulose sodium

Sodium chloride

Sodium citrate dihydrate

Hydrochloric acid and/or sodium hydroxide (to adjust pH)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years, unopened

Discard the opened single-dose vial immediately after use.

6.4 Special precautions for storage

Store at or below 25 ºC.

Store the vials in the pouch, protected from light. Fold pouch ends closed.

6.5 Nature and contents of container

Clear single-dose low-density polyethylene (LDPE) vials with a twist-off tab. Each single-dose vial contains 0,4 ml solution.

The following pack size is available:

Carton containing 30 single-dose vials in three foil pouches. Each pouch contains 10 single-dose vials.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

AbbVie (Pty) Ltd

Building 7, Waterfall Corporate Campus

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Waterfall City

Midrand, 1685

South Africa

8. REGISTRATION NUMBER

47/15.4/0336

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

16 November 2021

10. DATE OF REVISION OF THE TEXT

21 April 2023