SCHEDULING STATUS
Schedule 4

PROPRIETARY NAME (and dosage form)
ACULAR 0,4% Ophthalmic solution

COMPOSITION
ACULAR 0,4% ophthalmic solution contains:
Ketorolac tromethamine: 4 mg/ml
Preservative: Benzalkonium chloride 0,006% m/v.

PHARMACOLOGICAL CLASSIFICATION
A 15.4. Ophthalmic preparations. Other.

PHARMACOLOGICAL ACTION

Mechanism of action:
Ketorolac tromethamine is a non-steroidal anti-inflammatory agent demonstrating analgesic and anti-inflammatory activity. It is believed to inhibit the cyclo-oxygenase enzyme essential for biosynthesis of prostaglandins.

Pharmacokinetics:
One drop (0,05 ml) of 0,5% ketorolac tromethamine ophthalmic solution was instilled into one eye and one drop of vehicle into the other eye 3 times a day in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of ketorolac in their plasma (range 10,7 to 22,5 ng/ml) at day 10 during topical ocular treatment. When ketorolac tromethamine 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/ml.

Clinical Studies:
Results from clinical studies indicate that ketorolac tromethamine has no significant effect upon intraocular pressure.

INDICATIONS
ACULAR 0,4% ophthalmic solution is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery.

CONTRA-INDICATIONS

ACULAR 0,4% ophthalmic solution is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

ACULAR 0,4% ophthalmic solution should not be administered while wearing contact lenses.

Safety and efficacy of ACULAR 0,4% in children have not been established.

Safety and efficacy in pregnancy and lactation have not been established.

WARNINGS

As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations, cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication, like ACULAR 0,4%, over an extended period in patients with extensive ocular surface disease.

There is the potential for cross-sensitivity to acetylsalicylic acid, phenyl acetic derivatives and other non-steroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these agents.

With some non-steroidal anti-inflammatory agents, like ACULAR 0,4%, there exists 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 ACULAR 0,4%, may cause increased bleeding of ocular tissue (including hyphemas) in conjunction with ocular surgery.

It is recommended that ACULAR 0,4% ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medication which may prolong bleeding time.

INTERACTIONS

Medication containing anticoagulants, coumarin- or indandione-derivative, heparin or platelet aggregation inhibitors may interact with ACULAR 0,4%. Concurrent use with these agents may increase the risk of post-operative bleeding.

All topical non-steroidal anti-inflammatory agents (NSAIDs), including ACULAR 0,4% ophthalmic solution, may slow or delay healing. Topical corticosteroids are also known to slow

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

PREGNANCY AND LACTATION

Because of the known effects of prostaglandin-inhibiting agents on the foetal cardiovascular system of rats (closure of the ductus arteriosus), ACULAR 0,4% ophthalmic solution should not be used during pregnancy (see CONTRA-INDICATIONS).

Nursing Mothers: It is not known whether ketorolac tromethamine is excreted in human milk following administration of ACULAR 0,4%. Therefore, ACULAR 0,4% should not be administered to nursing women (see CONTRA-INDICATIONS).

DOSAGE AND DIRECTIONS FOR USE

The recommended dose for ACULAR 0,4% ophthalmic solution is one drop four times a day in the operated eye. It can be instilled for up to 4 days following corneal refractive surgery.

Avoid touching the dropper tip against the eye or any other surface.
ACULAR 0,4% ophthalmic solution has been safely administered in conjunction with other ophthalmic medications such as antibiotics, beta-blockers, carbonic anhydrase inhibitors, cycloplegics and mydriatics.

No dosage adjustment is required for elderly patients.

ACULAR 0,4% ophthalmic solution should not be administered while wearing contact lenses (see CONTRA-INDICATIONS).

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects

Eye disorders

Very common (>1/10):	Stinging or burning on instillation
Common (>1/100, <1/10):	Conjunctival hyperaemia, corneal infiltrates, ocular oedema, ocular pain, iritis, ocular inflammation, corneal oedema, ocular irritation, superficial keratitis and superficial ocular infections

The following side effects have been reported during post marketing use but the frequencies are unknown: corneal erosion, corneal perforation, corneal thinning and epithelial breakdown (see PRECAUTIONS).

Nervous system disorders
Common (>1/100, <1/10): Headache

Skin and subcutaneous tissue disorders
Common (>1/100, <1/10): Allergic reactions (itching, rash, redness or swelling of skin)

Precautions
General: All topical non-steroidal anti-inflammatory agents (NSAIDs), including ACULAR 0,4%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs, such as ACULAR 0,4%, 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 cornea perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of ACULAR 0,4% and should be closely monitored for corneal health.

Post marketing experience with topical NSAIDs such as ACULAR 0,4% suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g. dry eye syndrome), rheumatoid arthritis or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs such as ACULAR 0,4% should be used with caution in these patients.

Post marketing experience with topical NSAIDs such as ACULAR 0,4% also suggest 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.
It is recommended that ACULAR 0,4% ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medication which may prolong bleeding time (see WARNINGS).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See Side-Effects and Special Precautions. In the event of topical overdose, wash the eye with water. Treatment is symptomatic and supportive.

IDENTIFICATION

ACULAR 0,4% is a clear, colourless to pale yellow solution.

PRESENTATION

ACULAR 0,4% is supplied in a sterile, white, low density polyethylene (LDPE) bottle with a controlled dropper tip and high impact polystyrene (HIPS) cap. The pack size is 5 ml in a 10 ml bottle.

STORAGE INSTRUCTIONS

Store below 25ºC. Keep well closed.
KEEP OUT OF REACH OF CHILDREN.
Do not use more than 30 days after opening.
Discard any unused portion.

REGISTRATION NUMBER

A40/15.4/0282

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