WARNINGS AND PRECAUTIONS

2.2 Use with Other Topical Ophthalmic Medications

Recommended Dosing

Dosage and Administration

1. INDICATIONS AND USAGE

FULL PRESCRIBING INFORMATION: CONTENTS*

6 ADVERSE REACTIONS

2 DOSAGE AND ADMINISTRATION

11 DESCRIPTION

FULL PRESCRIBING INFORMATION

2 INDICATIONS AND USAGE

4 CONTRAINDICATIONS

17 NONCLINICAL TOXICOLOGY

12 CLINICAL PHARMACOLOGY

5 WARNINGS AND PRECAUTIONS

2.1 Recommended Dosing

2.2 Use with Other Topical Ophthalmic Medications

4 ADVERSE REACTIONS

13 NONCLINICAL TOXICOLOGY

12 CLINICAL PHARMACOLOGY

5.2 Potential for Cross-Sensitivity

5.1 Delayed Healing

5.5 Contact Lens Wear

8 IN USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Nursing Mothers

8.3 Pediatric Use

8.4 Geriatric Use

9 ADVERSE REACTIONS

17.1 Slow or Delayed Healing

17.2 Avoiding Contamination of the Product

17.3 Contact Lens Wear

2.2 Use with Other Topical Ophthalmic Medications

ACUVAIL™ (ketorolac tromethamine ophthalmic solution) 0.45%:

Ketorolac tromethamine, administered during pregnancy, use not teratogenic in rabbits and rats at oral doses of 3.6 mg/kg/day and 10 mg/kg/day, respectively. These doses are approximately 600 times and 1700 times higher respectively than the typical human topical ophthalmic daily dose of 0.35 mg (4.5 mg/mL x 0.04 mL/drop, BID) to an affected eye on a mg/kg basis. Additionally, 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. There are no adequate and well-controlled studies in pregnant women; ACUVAIL™ solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Neonatal Toxicity: Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus) and use of ACUVAIL™ solution during late pregnancy should be avoided.

3.3 Morning Use

Because many drugs are excreted in human milk, caution should be exercised when ACUVAIL™ is administered to a nursing woman.

4.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

4.9 Geriatric Use

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

7.3 Contact Lens Wear

ACUVAIL™ should not be administered while wearing contact lenses.

8.5 Geriatric Use

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of one drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

8.1 Pregnancy

These highlights do not include all the information needed for safe and effective use of ACUVAIL™ safety and effectiveness. See full prescribing information for ACUVAIL™ (ketorolac tromethamine ophthalmic solution) 0.45%.

9.1 Mechanism of Action

17.4 Intercurrent Ocular Conditions

17.3 Contact Lens Wear

Ketorolac tromethamine, administered during ophthalmic procedures, use not teratogenic in rabbits and rats at oral doses of 3.6 mg/kg/day and 10 mg/kg/day, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

13 NONCLINICAL TOXICOLOGY

12 CLINICAL PHARMACOLOGY

5 WARNINGS AND PRECAUTIONS

5.1 Delayed Healing

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) may be slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Topical corticosteroids are also known to slow or delay healing.

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12.1 Mechanism of Action
Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory, and anti-pyretic activity. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis.

12 CLINICAL PHARMACOLOGY
12.2 Pharmacokinetics
ACUVAIL™ solution is supplied as a sterile isotonic aqueous 0.45% preservative-free solution, with a pH of approximately 6.8. ACUVAIL™ solution is a racemic mixture of (S)- and (S)-ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The free ketol of ketorolac is S,S, This free and other crystal forms dissolution studies are performed in glass. The pKa of ACUVAIL™ solution is approximately 6.8.

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The pharmacokinetics of ketorolac tromethamine ophthalmic solution 0.45% have not been assessed in humans.

Five drops of 0.5% ketorolac tromethamine ophthalmic solution instilled into the eyes of patients 10 hours and 1 hour prior to cataract extraction achieved a mean ketorolac concentration 95 ng/mL, in the aqueous humor of 8 of 9 eyes tested (range 40 to 170 ng/mL).

One drop of 0.5% ketorolac tromethamine ophthalmic solution was instilled into 1 eye and 1 drop of vehicle into the other eye TID in 26 normal subjects. Five (5) of 26 subjects had a detectable concentration of ketorolac in their plasma (range 10 to 220 ng/mL). At Day 10 during topical ocular treatment. The range of concentrations following TID dosing of 0.5% ketorolac tromethamine ophthalmic solution are approximately 4 to 8% of the steady state mean minimum plasma concentration observed following four times daily oral administration of 10 mg ketorolac to humans (0.29 to 0.57 ng/mL).

15 NONCLINICAL TOXICOLOGY
15.1 Carcinogenesis, Mutagenesis, Impairment of fertility
Ketorolac tromethamine was not carcinogenic in either rats given up to 5 mg/kg/day orally for 24 months or in mice given 6 mg/kg/day orally for 18 months. Those doses are approximately 500 times and 300 times higher respectively than the typical human topical ophthalmic daily dose given as BID to an affected eye on a mg/gm basis.

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 unselected DNA synthesis or an erythrocyte microinoculation in vitro in cultures of Chinese hamster ovary cells.

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 9 mg/kg/day (10 mg/kg/day, respectively). Those doses are respectively 1900 and 2700 times higher than the typical human topical ophthalmic daily dose.

16 CLINICAL STUDIES
Two multicenter, randomized, double masked, parallel group comparison studies including approximately 100 patients were conducted to evaluate the effects of ACUVAIL™, an eye drops product, and fluocinolone sodium phosphate (NSAID) eye drops product, in anterior chamber and pupil and ocular pain relief following cataract extraction with posterior chamber intraocular lens (IOL) implantation. Results of these studies indicated that patients receiving ACUVAIL™ had a significantly higher incidence of clearing of anterior chamber inflammation 55% (187/339) vs. patients receiving placebo vehicle (85% (158/188) at day 14. ACUVAIL™ was also significantly superior to placebo in resolving anterior chamber. On Day 1 post cataract surgery, 72% (233/330) of patients in the ACUVAIL™ group were pain free compared to 40% (60/156) of patients in the placebo group.

Results from clinical studies indicate that ketorolac tromethamine has no significant effect upon intraocular pressure; however, changes in intraocular pressure may occur following cataract surgery.

16.1 HOW SUPPLIED/STORAGE AND HANDLING
ACUVAIL™ (ketorolac tromethamine ophthalmic solution) 0.45% is available as a sterile solution supplied in clear, LOPR, single-use vials packaged in a foil pouch.

30 Single-Use Vials 0.4 mL each (NDC 0325-3507-30)

Storage: ACUVAIL™ should be stored at 15° to 30°C (59° to 86°F).

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

17 PATIENT COUNSELING INFORMATION
17.1 Scleral or Delayed Healing
Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

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ACUVAIL™ solution.

17.2 Avoiding Contamination of the Product
Patients should be instructed that the solution from one individual single use vial is to be used immediately after opening for administration to the affected eye. The remaining contents should be discarded immediately after administration. Avoid allowing the tip of the vial to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

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

17.3 Contact Lens Wear
ACUVAIL™ solution should not be administered while wearing contact lenses.

17.4 Intercurrent Ocular Conditions
Patients should be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of ACUVAIL™.

17.5 Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, the medications must be administered at least 5 minutes apart.

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