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was diarrhea, which was generally of mild to moderate intensity.

Drug-related clinical adverse experiences of moderate or severe intensity in ≥2% of patients treated with VIRACEPT coadministered with ZDV plus 3TC (Study 511) or in combination with d4T (Study 506) for up to 24 weeks are presented in Table 3.

[See table 3 at top of previous page]

Adverse events occurring in less than 2% of patients receiving VIRACEPT in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment and of at least moderate severity are listed below.

Body as a Whole: accidental injury, allergic reaction, back pain, fever, headache, malaise, and pain.

Digestive System: anorexia, dyspepsia, epigastric pain, gastrointestinal bleeding, hepatitis, mouth ulceration, pancreatitis and vomiting.

Hemic/Lymphatic System: anemia, leukopenia and thrombocytopenia.

Metabolic/Nutritional System: increases in alkaline phosphate, amylase, creatine phosphokinase, lactic dehydrogenase, SGOT, SGPT and gamma glutamyl transpeptidase; hyperlipemia, hyperuricemia, hyperglycemia, hypoglycemia, dehydration, and liver function tests abnormal.

Musculoskeletal System: arthralgia, arthritis, cramps, myalgia, myasthenia and myopathy.

Nervous System: anxiety, depression, dizziness, emotional lability, hyperkinesia, insomnia, migraine, paresthesia, seizures, sleep disorder, somnolence and suicide ideation.

Respiratory System: dyspnea, pharyngitis, rhinitis, and sinusitis.

Skin/Appendages: dermatitis, folliculitis, fungal dermatitis, maculopapular rash, pruritus, sweating, and urticaria.

Special Senses: acute iritis and eye disorder.

Urogenital System: kidney calculus, sexual dysfunction and urine abnormality.

Laboratory Abnormalities

Few patients experienced significant laboratory abnormalities while receiving VIRACEPT. The percentage of patients with marked laboratory abnormalities in Studies 511 and 506 are presented in Table 4. Marked laboratory abnormalities are defined as a Grade 3 or 4 abnormality in a patient with a normal baseline value or a Grade 4 abnormality in a patient with a Grade 1 abnormality at baseline.

[See table 4 on previous page]

OVERDOSAGE

Human experience of acute overdose with VIRACEPT is limited. There is no specific antidote for overdose with VIRACEPT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. Since nelfinavir is highly protein bound, dialysis is unlikely to significantly remove drug from blood.

DOSAGE AND ADMINISTRATION

Adults: The recommended dose is 750 mg (three 250 mg tablets) three times daily. VIRACEPT should be taken with a meal or light snack. Antiviral activity is enhanced when VIRACEPT is administered in combination with nucleoside analogues. Therefore, it is recommended that VIRACEPT be used in combination with nucleoside analogues.

Pediatric patients (2–13 years): The recommended oral dose of VIRACEPT for pediatric patients 2 to 13 years of age is 20–30 mg/kg per dose, three times daily with a meal or a light snack. For children unable to take tablets, VIRACEPT Oral Powder may be administered. The oral powder may be mixed with a small amount of water, milk, formula, soy formula, soy milk or dietary supplements; once mixed, the entire contents must be consumed in order to obtain the full dose. The recommended use period for storage of the product in these media is 6 hours. Acidic food or juice (e.g., orange juice, apple juice or apple sauce) are not recommended to be used in combination with VIRACEPT, because the combination may result in a bitter taste. VIRACEPT Oral Powder should not be reconstituted with water in its original container. The recommended pediatric dose of VIRACEPT to be administered three times daily is described in Table 5:

[See table 5 on previous page]

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Surgical: (800) 862-5266
(Instrumentation/Surgical Meds)
Systems: (800) 289-1991
(Medical Management Information Systems)
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OPHTHALMIC PRODUCTS

For information on Alcon ophthalmic products, consult the PDR For Ophthalmology. See a complete listing of products in the Manufacturers' Index section of this book. For information, literature, samples or service items contact Alcon at the phone numbers listed above.

AZOPT™ ℞
(brinzolamide ophthalmic suspension) 1%

DESCRIPTION

AZOPT™ (brinzolamide ophthalmic suspension) 1% contains a carbonic anhydrase inhibitor formulated for multidose topical ophthalmic use. Brinzolamide is described chemically as: (R)-(+)-4-Ethylamino-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno [3,2-e]-1,2-thiazine-6-sulfonamide-1,1-doxide. Its empirical formula is $C_{12}H_{21}N_3O_5S_3$.

Brinzolamide has a molecular weight of 383.5 and a melting point of about 131°C. It is a white powder, which is insoluble in water, very soluble in methanol and soluble in ethanol.

AZOPT 1% is supplied as a sterile, aqueous suspension of brinzolamide which has been formulated to be readily suspended and slow settling, following shaking. It has a pH of approximately 7.5 and an osmolality of 300 mOsm/kg. Each mL of AZOPT 1% contains 10 mg brinzolamide. Inactive ingredients are mannitol, carbomer 974P, tyloxapol, edetate disodium, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water. Benzalkonium chloride 0.01% is added as a preservative.

CLINICAL PHARMACOLOGY

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. It catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In humans, carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II), found primarily in red blood cells (RBCs), but also in other tissues. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport.

The result is a reduction in intraocular pressure (IOP).

AZOPT 1% contains brinzolamide, an inhibitor of carbonic anhydrase II (CA-II). Following topical ocular administration, brinzolamide inhibits aqueous humor formation and reduces elevated intraocular pressure. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.

Following topical ocular administration, brinzolamide is absorbed into the systemic circulation. Due to its affinity for CA-II, brinzolamide distributes extensively into the RBCs and exhibits a long half-life in whole blood (approximately 111 days). In humans, the metabolite N-desethyl brinzolamide is formed, which also binds to CA and accumulates in RBCs. This metabolite binds mainly to CA-I in the presence of brinzolamide. In plasma, both parent brinzolamide and N-desethyl brinzolamide concentrations are low and generally below assay quantitation limits (<10 ng/mL). Binding to plasma proteins is approximately 60%. Brinzolamide is eliminated predominantly in the urine as unchanged drug.

IOP reductions are equivalent to the reductions observed with TRUSOPT* (dorzolamide hydrochloride ophthalmic solution) 2% dosed TID in the same studies.

In two clinical studies in patients with elevated intraocular pressure, AZOPT 1% was associated with less stinging and burning upon instillation than TRUSOPT* 2%.

INDICATIONS AND USAGE

AZOPT™ Ophthalmic Suspension 1% is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

AZOPT™ is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

AZOPT™ is a sulfonamide and although administered topically it is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of AZOPT. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

PRECAUTIONS

General:

Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. The effect of continued administration of AZOPT on the corneal endothelium has not been fully evaluated. The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. AZOPT has not been studied in patients with acute angle-closure glaucoma.

AZOPT has not been studied in patients with severe renal impairment (CrCl <30 mL/min). Because AZOPT and its metabolite are excreted predominantly by the kidney, AZOPT is not recommended in such patients.

AZOPT™ has not been studied in patients with hepatic impairment and should be used with caution in such patients. There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and AZOPT. The concomitant administration of AZOPT and oral carbonic anhydrase inhibitors is not recommended.

Information For Patients:

AZOPT™ is a sulfonamide and although administered topically, it is absorbed systemically; therefore, the same type of adverse reactions attributable to sulfonamides may occur with topical administration. Patients should be advised that if serious or unusual ocular or systemic reactions or signs of hypersensitivity occur, they should discontinue the use of the product and consult their physician (see **Warnings**).

Vision may be temporarily blurred following dosing with AZOPT. Care should be exercised in operating machinery or driving a motor vehicle.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures or other surfaces, since the product can 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.

Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart. The preservative in AZOPT™ Ophthalmic Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of AZOPT, but may be reinserted 15 minutes after instillation.

Drug Interactions:

AZOPT™ Ophthalmic Suspension 1% contains a carbonic anhydrase inhibitor. Acid-base and electrolyte alterations were not reported in the clinical trials with brinzolamide.

receiving AZOPT.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenicity data on brinzolamide are not available. The following tests for mutagenic potential were negative: (1) *in vivo* mouse micronucleus assay; (2) *in vivo* sister chromatid exchange assay; and (3) Ames *E. coli* test. The *in vitro* mouse lymphoma forward mutation assay was negative in the absence of activation, but positive in the presence of microsomal activation.

In reproduction studies of brinzolamide in rats, there were no adverse effects on the fertility or reproductive capacity of males or females at doses up to 18 mg/kg/day (375 times the recommended human ophthalmic dose).

Pregnancy:

Teratogenic Effects: Pregnancy Category C. Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3, and 6 mg/kg/day (20, 62, and 125 times the recommended human ophthalmic dose) produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, such as accessory skull bones, which was only slightly higher than the historic value at 1 and 6 mg/kg. In rats, statistically decreased body weights of fetuses from dams receiving oral doses of 18 mg/kg/day (375 times the recommended human ophthalmic dose) during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. Increases in unossified sternebrae, reduced ossification of the skull, and unossified hyoid that occurred at 6 and 18 mg/kg were not statistically significant. No treatment-related malformations were seen. Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and was present in the fetal tissues and blood.

There are no adequate and well-controlled studies in pregnant women. AZOPT™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

In a study of brinzolamide in lactating rats, decreases in body weight gain in offspring at an oral dose of 15 mg/kg/day (312 times the recommended human ophthalmic dose) were seen during lactation. No other effects were observed. However, following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from AZOPT, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

In clinical studies of AZOPT (brinzolamide ophthalmic suspension) 1%, the most frequently reported adverse events associated with AZOPT 1% were blurred vision and bitter, sour or unusual taste. These events occurred in approximately 5–10% of patients. Blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis were reported at an incidence of 1–5%.

The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing and urticaria.

OVERDOSAGE

Although no human data are available, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur following oral administration of an overdose. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

DOSAGE AND ADMINISTRATION

Shake well before use. The recommended dose is 1 drop of AZOPT™ Ophthalmic Suspension in the affected eye(s) three times daily.

AZOPT may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

HOW SUPPLIED

AZOPT™ Ophthalmic Suspension 1% is supplied in plastic DROP-TAINER® dispensers with a controlled dispensing-tip as follows:

NDC 0065-0275-24	2.5 mL
NDC 0065-0275-05	5 mL
NDC 0065-0275-10	10 mL
NDC 0065-0275-15	15 mL

Storage: Store AZOPT Ophthalmic Suspension 1% at 4–30°C (39–86°F).

Rx Only

DESCRIPTION

BETOPTIC S Ophthalmic Suspension 0.25% contains betaxolol hydrochloride, a cardioselective beta-adrenergic receptor blocking agent, in a sterile resin suspension formulation. Betaxolol hydrochloride is a white, crystalline powder, with a molecular weight of 343.89.

Chemical Name:

(±)-1-[p-[2-(cyclopropylmethoxy)ethyl] phenoxy]-3-(isopropylamino)-2-propanol hydrochloride.

Each mL of BETOPTIC S Ophthalmic Suspension contains: **Active:** betaxolol HCl 2.8 mg equivalent to 2.5 mg of betaxolol base. **Preservative:** benzalkonium chloride 0.01%. **Inactive:** Mannitol, Poly(Styrene-Divinyl Benzene) sulfonic acid, Carbomer 934P, edetate disodium, hydrochloric acid or sodium hydroxide (to adjust pH) and purified water.

CLINICAL PHARMACOLOGY

Betaxolol HCl, a cardioselective (beta-1-adrenergic) receptor blocking agent, does not have significant membrane-stabilizing (local anesthetic) activity and is devoid of intrinsic sympathomimetic action. Orally administered beta-adrenergic blocking agents reduce cardiac output in healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor antagonists may inhibit the sympathetic stimulatory effect necessary to maintain adequate cardiac function. When instilled in the eye, BETOPTIC S Ophthalmic Suspension 0.25% has the action of reducing elevated intraocular pressure, whether or not accompanied by glaucoma. Ophthalmic betaxolol has minimal effect on pulmonary and cardiovascular parameters.

Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Betaxolol has the action of reducing elevated as well as normal intraocular pressure and the mechanism of ocular hypotensive action appears to be a reduction of aqueous production as demonstrated by tonography and aqueous fluorophotometry. The onset of action with betaxolol can generally be noted within 30 minutes and the maximal effect can usually be detected 2 hours after topical administration. A single dose provides a 12-hour reduction in intraocular pressure. In controlled, double-masked studies, the magnitude and duration of the ocular hypotensive effect of BETOPTIC S Ophthalmic Suspension 0.25% and BETOPTIC Ophthalmic Solution 0.5% were clinically equivalent. BETOPTIC S Suspension was significantly more comfortable than BETOPTIC Solution.

Ophthalmic betaxolol solution at 1% (one drop in each eye) was compared to placebo in a crossover study challenging nine patients with reactive airway disease. Betaxolol HCl had no significant effect on pulmonary function as measured by FEV_1, Forced Vital Capacity (FVC), FEV_1/FVC and was not significantly different from placebo. The action of isoproterenol, a beta stimulant, administered at the end of the study was not inhibited by ophthalmic betaxolol.

No evidence of cardiovascular beta adrenergic-blockade during exercise was observed with betaxolol in a double-masked, crossover study in 24 normal subjects comparing ophthalmic betaxolol and placebo for effects on blood pressure and heart rate.

INDICATIONS AND USAGE

BETOPTIC S Ophthalmic Suspension 0.25% has been shown to be effective in lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma and ocular hypertension. It may be used alone or in combination with other intraocular pressure lowering medications.

CONTRAINDICATIONS

Hypersensitivity to any component of this product. BETOPTIC S Ophthalmic Suspension 0.25% is contraindicated in patients with sinus bradycardia, greater than a first degree atrioventricular block, cardiogenic shock, or patients with overt cardiac failure.

WARNING

Topically applied beta-adrenergic blocking agents may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported with topical application of beta-adrenergic blocking agents.

BETOPTIC S Ophthalmic Suspension 0.25% has been shown to have a minor effect on heart rate and blood pressure in clinical studies. Caution should be used in treating patients with a history of cardiac failure or heart block. Treatment with BETOPTIC S Ophthalmic Suspension 0.25% should be discontinued at the first signs of cardiac failure.

PRECAUTIONS

General:

Diabetes Mellitus. Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetics who are receiving insulin or oral hypoglycemic agents because beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis. Beta-adrenergic blocking agents may mask clinical signs of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents, which might precipitate a thyroid storm.

Muscle Weakness. Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g , diplopia, ptosis and generalized weakness).

Major Surgery. Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli.

Pulmonary. Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. There have been reports of asthmatic attacks and pulmonary distress during betaxolol treatment. Although rechallenges of some such patients with ophthalmic betaxolol has not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta blockers cannot be ruled out.

Information for Patients: Do not touch dropper tip to any surface, as this may contaminate the contents. Do not use with contact lenses in eyes.

Drug Interactions: Patients who are receiving a beta-adrenergic blocking agent orally and BETOPTIC S Ophthalmic Suspension 0.25% should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia.

Betaxolol is an adrenergic blocking agent; therefore, caution should be exercised in patients using concomitant adrenergic psychotropic drugs.

Risk from anaphylactic reaction: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Ocular: In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Betaxolol has little or no effect on the pupil. When BETOPTIC S Ophthalmic Suspension 0.25% is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime studies with betaxolol HCl have been completed in mice at oral doses of 6, 20 or 60 mg/kg/day and in rats at 3, 12 or 48 mg/kg/day; betaxolol HCl demonstrated no carcinogenic effect. Higher dose levels were not tested.

In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, betaxolol HCl was nonmutagenic.

Pregnancy: Pregnancy Category C. Reproduction, teratology, and peri- and postnatal studies have been conducted with orally administered betaxolol HCl in rats and rabbits. There was evidence of drug related postimplantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol HCl was not shown to be teratogenic, however, and there were no other adverse effects on reproduction at subtoxic dose levels. There are no adequate and well-controlled studies in pregnant women. BETOPTIC S should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether betaxolol HCl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BETOPTIC S Ophthalmic Suspension 0.25% is administered to nursing women.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Ocular: In clinical trials, the most frequent event associated with the use of BETOPTIC S Ophthalmic Suspension 0.25% has been transient ocular discomfort. The following other conditions have been reported in small numbers of patients: blurred vision, corneal punctate keratitis, foreign body sensation, photophobia, tearing, itching, dryness of eyes, erythema, inflammation, discharge, ocular pain, decreased visual acuity and crusty lashes.

Additional medical events reported with other formulations of betaxolol include allergic reactions, decreased corneal sensitivity, corneal punctate staining which may appear in dendritic formations, edema and anisocoria.

Systemic: Systemic reactions following administration of BETOPTIC S Ophthalmic Suspension 0.25% or BETOPTIC Ophthalmic Solution 0.5% have been rarely reported. These include:

Cardiovascular: Bradycardia, heart block and congestive failure.

Pulmonary: Pulmonary distress characterized by dyspnea, bronchospasm, thickened bronchial secretions, asthma and

No data are available on the extent of systemic absorption from TOBRADEX® Ophthalmic Suspension or Ointment; however, it is known that some systemic absorption can occur with ocularly applied drugs. If the maximum dose of TOBRADEX® Ophthalmic Suspension is given for the first 48 hours (two drops in each eye every 2 hours) and complete systemic absorption occurs, which is highly unlikely, the daily dose of dexamethasone would be 2.4 mg. The usual physiologic replacement dose is 0.75 mg daily. If TOBRADEX® Ophthalmic Suspension is given after the first 48 hours as two drops in each eye every 4 hours, the administered dose of dexamethasone would be 1.2 mg daily. The administered dose for TOBRADEX Ophthalmic Ointment in both eyes four times daily would be 0.4 mg of dexamethasone daily.

INDICATIONS AND USAGE

TOBRADEX® Ophthalmic Suspension and Ointment are indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product is active against the following common bacterial eye pathogens:

Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae.*

Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii, most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

CONTRAINDICATIONS

Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and many other viral diseases of the cornea and conjunctiva. Mycobacterial infection of the eye. Fungal diseases of ocular structures. Hypersensitivity to a component of the medication.

WARNINGS

NOT FOR INJECTION INTO THE EYE. Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction does occur, discontinue use.

Prolonged use of steroids may result in glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation. Intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

PRECAUTIONS

General. The possibility of fungal infections of the cornea should be considered after long-term steroid dosing. As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. When multiple prescriptions are required, or whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Cross-sensitivity to other aminoglycoside antibiotics may occur; if hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

Information for Patients: Do not touch dropper or tube tip to any surface, as this may contaminate the contents.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No studies have been conducted to evaluate the carcinogenic or mutagenic potential. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at doses of 50 and 100 mg/kg/day.

Pregnancy Category C. Corticosteroids have been found to be teratogenic in animal studies. Ocular administration of 0.1% dexamethasone resulted in 15.6% and 32.3% incidence of fetal anomalies in two groups of pregnant rabbits. Fetal growth retardation and increased mortality rates have been observed in rats with chronic dexamethasone therapy. Reproduction studies have been performed in rats and rabbits with tobramycin at doses up to 100 mg/kg/day parenterally

oids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when TOBRADEX® Ophthalmic Suspension or ointment is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination. Exact incidence figures are not available. The most frequent adverse reactions to topical ocular tobramycin (TOBREX®) are hypersensitivity and localized ocular toxicity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration. The reactions due to the steroid component are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing.

Secondary Infection. The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used. Secondary bacterial ocular infection following suppression of host responses also occurs.

OVERDOSAGE

Clinically apparent signs and symptoms of an overdose of TOBRADEX Ophthalmic Suspension or Ointment (punctate keratitis, erythema, increased lacrimation, edema and lid itching) may be similar to adverse reaction effects seen in some patients.

DOSAGE AND ADMINISTRATION

Suspension: One or two drops instilled into the conjunctival sac(s) every four to six hours. During the initial 24 to 48 hours, the dosage may be increased to one or two drops every two (2) hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely. **Ointment:** Apply a small amount (approximately $^1/_2$ inch ribbon) into the conjunctival sac(s) up to three or four times daily.

Not more than 20 mL or 8 g should be prescribed initially and the prescription should not be refilled without further evaluation as outlined in PRECAUTIONS above.

HOW SUPPLIED

Sterile ophthalmic suspension in 2.5 mL (NDC 0065-0647-25), 5 mL (NDC 0065-0647-05) and 10 mL (NDC 0065-0647-10) DROP-TAINER® dispensers. Sterile ophthalmic ointment in 3.5 g ophthalmic tube (NDC 0065-0648-35).

STORAGE

Store at 8° to 27°C (46° to 80°F).

Store suspension upright and shake well before using.

Rx Only.

U.S. Patent No. 5,149,694

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OPHTHALMIC PRODUCTS

For information on Allergan, Inc., prescription, OTC, and ophthalmic products, consult the Physicians' Desk Reference for Ophthalmology. For literature, service items, or sample material, contact Allergan directly. See a complete listing of products in the Manufacturers' Index section of this book.

ACULAR® ℞
(ketorolac tromethamine ophthalmic solution) 0.5%
Sterile

ACULAR® relieves the ocular itch associated with seasonal allergic conjunctivitis and inflammation following cataract surgery due in part to its ability to inhibit prostaglandin biosynthesis.

In two double-masked, paired studies (N=241), ACULAR® Solution was found to be superior to placebo in relieving the ocular itch of seasonal allergic conjunctivitis.[1]

Two controlled clinical studies showed that patients treated for two weeks with ACULAR® ophthalmic solution were less likely to have measurable signs of inflammation (cell and flare) than patients treated with its vehicle.

ACULAR® Solution is also proven safe in clinical trials, and avoids steroid-like side effects (e.g., no significant effect upon IOP).[1] There is no significant ocular toxicity reported in clinical studies to date with ACULAR®.

The most frequently reported adverse events have been transient stinging and burning on instillation (approximately 40%). Caution should be used in patients with sensitivities to other NSAIDs.

ACULAR® Solution is available in 3 mL, 5 mL and 10 mL plastic bottles with a controlled-dropper tip.

Please see full prescribing information included.

1. Data on file, Syntex (U.S.A.) Inc.

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ACULAR® is marketed by Allergan, Inc.

PRESCRIBING INFORMATION

ACULAR® ℞
(ketorolac tromethamine ophthalmic solution) 0.5%
Sterile

DESCRIPTION

ACULAR® (ketorolac tromethamine ophthalmic solution) is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use. Its chemical name is (±)-5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).

ACULAR® is supplied as a sterile isotonic aqueous 0.5% solution, with a pH of 7.4. ACULAR® is a racemic mixture of R-(+)- and S-(-)- ketorolac tromethamine. 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. The molecular weight of ketorolac tromethamine is 376.41. Each mL of ACULAR® ophthalmic solution contains: Active: ketorolac tromethamine 0.5%. Preservative: benzalkonium chloride 0.01%. Inactives: edetate disodium 0.1%; octoxynol 40; sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH; and purified water. The osmolality of ACULAR® is 290 mOsmol/kg.

ANIMAL PHARMACOLOGY

Ketorolac tromethamine 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.*

CLINICAL PHARMACOLOGY

Ketorolac tromethamine is 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, in part, to its ability to inhibit prostaglandin biosynthesis. Ketorolac tromethamine given systemically does not cause pupil constriction.

Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure. Prostaglandins also appear to play a role in the miotic response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms.

Two drops (0.1 mL) of 0.5% ACULAR® 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 (mean ketorolac concentration 95 ng/mL aqueous humor, range 40 to 170 ng/mL). Ocular administration of ketorolac tromethamine reduces prostaglandin E_2 (PGE_2) levels in aqueous humor. The mean concentration of PGE_2 was 80 pg/mL in the aqueous humor of eyes receiving vehicle and 28 pg/mL in the eyes receiving ACULAR® 0.5% ophthalmic solution.

One drop (0.05 mL) of 0.5% ACULAR® ophthalmic solution was instilled into one eye and one drop of vehicle into the other eye TID in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of ketorolac in their plasma (range

rary relief of ocular itching due to seasonal allergic conjunctivitis. ACULAR® is also indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

CONTRAINDICATIONS

ACULAR® ophthalmic solution is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

WARNINGS

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

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.

PRECAUTIONS

General: It is recommended that ACULAR® ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Information for Patients: ACULAR® should not be administered while wearing contact lenses.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: An 18-month study in mice at oral doses of ketorolac tromethamine equal to the parenteral MRHD (Maximum Recommended Human Dose) and a 24-month study in rats at oral doses 2.5 times the parenteral MRHD, showed no evidence of tumorigenicity.

Ketorolac tromethamine was not mutagenic in Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1590 ug/mL (approximately 1000 times the average human plasma levels) and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg and 16 mg/kg respectively.

Pregnancy:

Pregnancy Category C. Reproduction studies have been performed in rabbits, using daily oral doses at 3.6 mg/kg and in rats at 10 mg/kg during organogenesis. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac tromethamine at 1.5 mg/kg, which was half of the human oral exposure, administered after gestation day 17 caused dystocia and higher pup mortality in rats. There are no adequate and well-controlled studies in pregnant women. Ketorolac tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ACULAR® ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers: Caution should be exercised when ACULAR® is administered to a nursing woman.

Pediatric Use: Safety and efficacy in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS

In controlled clinical studies, the most frequent adverse events reported with the use of ACULAR® ophthalmic solution have been transient stinging and burning on instillation. These events were reported by up to 40% of patients treated with ACULAR® ophthalmic solution. In all development studies conducted, other adverse events occurring less than 5% of the time during treatment with ACULAR® included ocular irritation, allergic reactions, superficial ocular infections, and superficial keratitis.

Other adverse events reported rarely with the use of ACULAR® ophthalmic solution include: eye dryness, corneal infiltrates, corneal ulcer, and visual disturbance (blurry vision).

***Information will be superseded* by supplements and subsequent editions**

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ALLERGAN

Irvine, CA 92612

Shown in Product Identification Guide, page 303

ACULAR® PF ℞

(ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free

DESCRIPTION

ACULAR® PF (ketorolac tromethamine ophthalmic solution) Preservative-Free is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use. Ketorolac tromethamine's chemical name is (±)-5-benzoyl-2,3-dihydro-1*H* pyrrolizine-1-carboxylic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).

ACULAR® PF is a racemic mixture of R-(+) and S-(-)-ketorolac tromethamine. 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. The molecular weight of ketorolac tromethamine is 376.41. The osmolality of ACULAR® PF is 290 mOsmol/kg. Each ml of ACULAR® PF contains: Active ingredient: ketorolac tromethamine 0.5%. Inactives: sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH to 7.4; and purified water.

CLINICAL PHARMACOLOGY

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. Ketorolac tromethamine given systemically does not cause pupil constriction.

One drop (0.05 mL) of ketorolac tromethamine (preserved) was instilled into one eye and one drop of vehicle into the other eye TID 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.

In two double-masked, multi-centered, parallel-group studies, 340 patients who had undergone incisional refractive surgery received ACULAR® PF or its vehicle QID for up to 3 days. Significant differences favored ACULAR® PF for the treatment of ocular pain and photophobia.

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

INDICATIONS AND USAGE

ACULAR® PF ophthalmic solution is indicated for the reduction of ocular pain and photophobia following incisional refractive surgery.

CONTRAINDICATIONS

ACULAR® PF is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

WARNINGS

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

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.

µg/mL (approximately 1000 times the average human plasma levels) and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.

Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg and 16 mg/kg, respectively.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Reproduction studies have been performed in rabbits, using daily oral doses at 3.6 mg/kg and in rats at 10 mg/kg during organogenesis. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac tromethamine at 1.5 mg/kg, which was half of the human oral exposure, administered after gestation day 17 caused dystocia and higher pup mortality in rats. There are no adequate and well-controlled studies in pregnant women. Ketorolac tromethamine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ACULAR® PF during late pregnancy should be avoided.

Nursing Mothers: Caution should be exercised when ACULAR® PF is administered to a nursing woman.

Pediatric Use: Safety and efficacy in pediatric patients below the age of 12 years have not been established.

ADVERSE REACTIONS

The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by approximately 20% of patients participating in clinical trials.

Other adverse events occurring 1%–10% of the time during treatment with ketorolac tromethamine ophthalmic solutions included ocular irritation, allergic reactions, superficial ocular infections, superficial keratitis, ocular inflammation, corneal edema, and iritis.

Other adverse events reported rarely with the use of ketorolac tromethamine ophthalmic solutions include: eye dryness, corneal infiltrates, corneal ulcer, visual disturbance (blurry vision), and headaches.

DOSAGE AND ADMINISTRATION

The recommended dose of ACULAR® PF Preservative-Free is one drop (0.25 mg) four times a day in the operated eye as needed for pain and photophobia for up to 3 days after incisional refractive surgery.

HOW SUPPLIED

ACULAR® PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free is available as a sterile solution supplied in single-use vials as follows: ACULAR® PF 12 Single-Use Vials 0.4 mL each - NDC 0023-9055-04. Store ACULAR® PF between 15°C–30°C (59°F–86°F) with protection from light.

Rx only

U.S. Patent Nos. 4,089,969; 4,454,151; 5,110,493

ALLERGAN

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Shown in Product Identification Guide, page 303

ALPHAGAN® ℞

(brimonidine tartrate ophthalmic solution) 0.2%

DESCRIPTION

ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It is an off-white, pale yellow to pale pink powder. In solution, ALPHAGAN® has a clear, greenish-yellow color. It has a molecular weight of 442.24 as the tartrate salt and is water soluble (34 mg/mL). The molecular formula is $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$.