Very limited information exists on accidental ingestion of brimonidine in adults; the only adverse electrolyte levels (particularly potassium) and blood pH levels should be monitored. and possible nervous system effects may occur following an oral overdose of brinzolamide. Serum [see Contraindications (4.2)] pediatric patients 2 to 7 years old. Somnolence (50-83%) and decreased alertness was seen in

E. coli ophthalmic dosing in humans.

individual components.

weeks prior to beginning dosing with the topical ocular suspension. The results demonstrate that brinzolamide alone or combination arms were administered oral brinzolamide capsules for two In humans, a study was conducted to evaluate the pharmacokinetics of the fixed combination of Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately approximately 60%. Brinzolamide is eliminated predominantly in the urine as unchanged drug. N-desethyl brinzolamide concentrations are <10 ng/mL. Binding to plasma proteins is

brimonidine tartrate (alpha 2 adrenergic receptor agonist). Each of these two components

12.1 Mechanism of Action

Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is a trend toward potential development of complications in patients with poorly controlled IOP levels. Caution should be used when prescribing SIMBRINZA to these patients.

3.2 Renal Impairment

the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product

17.6 Concomitant Topical Ocular Therapy

brimonidine tartrate, a component of SIMBRINZA, has a less than 5% mean decrease in blood pressure. 5.6 Severe Cardiovascular Disease

5.5 Urinary Tract Infections

7.2 High-Dose Salicylate Therapy

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibitor therapy observed in patients treated with brimonidine tartrate ophthalmic solutions. A comprehensive list includes: bradycardia, hypotension, tachycardia, convulsions, erratic, erratic, nausea, sleep, abdominal pain, and muscular pain.

7.4 Antihypertensives/Cardiac Glycosides

7.1 Oral Carbonic Anhydrase Inhibitors

Brimonidine tartrate, a component of SIMBRINZA, may potentiate syndromes associated with severe cardiovascular disease.

8.4 Pediatric Use

In clinical studies of brimonidine tartrate 0.2%, adverse reactions occurred in approximately 15% of the subjects, including drowsiness, insomnia, nausea, vomiting, blurring and drying, blurring, hazing, foreign body sensation, fatigue, hypotension, syncope, fainting, visual disturbances, nasal stuffiness, eye irritation, and oral dryness. In addition, symptoms such as headache, dizziness, and photophobia were reported at a significantly lower incidence rate in six phase II clinical trials in patients with healthy volunteers and patients with mild to moderate glaucoma.

5.3 Neuritis

11.2 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

8.1 Pregnancy

8.6 Geriatric Use

3.0 Dosing and Administration

The following adverse reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solutions: blurred vision, diplopia, asthenopia, dry eye, corneal opacities, and conjunctival hyperemia. Serum [see Contraindications (4.2)] patients with closed-angle glaucoma or ocular hypertension. (1) SIMBRINZA is a fixed combination of a carbonic anhydrase inhibitor and an alpha 2 adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. [7.3] 7.3 Contact Lens Wear

brinzolamide alone or combination arms were administered oral brinzolamide capsules for two brinzolamide alone or combination arms were administered oral brinzolamide capsules for two 12.2 Pharmacodynamics

brinzolamide alone or combination arms were administered oral brinzolamide capsules for two 12.3 Pharmacokinetics

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7.3 Antihistamines

7.5 Antidepressants

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producive patients 2 to 7 years old. Surprisingly, 50% to 80% decreased alertness was seen in
elderly patients 2 to 7 years old. SIMBRINZA ophthalmic suspension is contraindicated in children
under the age of 2 years [see Children Use (1.2)].

8.3 Geriatric Use

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

10. OVERDOSAGE

Although there are no data available, overuse of the conjunctival sac, and possible nervous system effects may occur following an overdose of brinzolamide. Serious eye irritation is unusual but possible and should be treated promptly. Patients should be instructed to avoid excessive mechanical irritation such as rubbing. The usual symptoms of overdose are conjunctival hyperemia and pain. Treatment of chronic overdosage includes supportive care and removal of the ophthalmic suspension from the eyes.

11. DESCRIPTION

SIMBRINZA (brinzolamide/tobramycin ophthalmic suspension) 0.2% / 0.3% is a fixed combination of a carbonic anhydrase inhibitor and alpha 2 adrenergic receptor agonist. Brinzolamide is a carbonic anhydrase inhibitor that decreases aqueous humor production. Brinzolamide inhibits carbonic anhydrase in the ciliary processes of the eye to increase aqueous humor formation. Brimonidine is a selective alpha 2 adrenergic receptor agonist. The mechanism of action involves stabilization of the blood-aqueous barrier and reduced new blood vessel formation.

12. CLINICAL PHARMACEUTICAL

12.1 Mechanism of Action

Brinzolamide is a carbonic anhydrase inhibitor and brimonidine is an alpha 2 adrenergic receptor agonist. Each of these two components demonstrates a unique pharmacology. Brinzolamide is a carbonic anhydrase inhibitor, which reduces aqueous humor production. Brinzolamide is also a sodium channel blocker. The pathogenesis of optic nerve damage and glaucomatous visual field loss is the high level of intraocular pressure. The pathogenesis of glaucoma is due to hyperplasia of the trabecular meshwork with subsequent reduction in sodium and fluid transport. Brinzolamide inhibits carbonic anhydrase type II in the ciliary processes of the eye to increase aqueous humor formation. Brimonidine is a selective alpha 2 adrenergic receptor agonist, which reduces vasoconstrictor tone in the iris and ciliary body. Brimonidine has ocular hypotensive effect occurring at 3 hours post-dosing. This result is a reduction in intraocular pressure (IOP).

12.2 Pharmacokinetics

Following topical ocular administration, brinzolamide is absorbed into the systemic circulation. Topical application of 0.2% brinzolamide to rabbits causes systemic exposure (AUC) and (Cmax) in blood and SSRIs and other CYP2D6 inhibitors are not recommended for concurrent use with SIMBRINZA.

7.5 Tricyclic Antidepressants

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. Therefore, administration of SIMBRINZA and oral carbonic anhydrase inhibitors is not recommended. Administration of SIMBRINZA and oral carbonic anhydrase inhibitors is not recommended. Administration of SIMBRINZA and oral carbonic anhydrase inhibitors is not recommended. Administration of SIMBRINZA and oral carbonic anhydrase inhibitors is not recommended. Administration of SIMBRINZA and oral carbonic anhydrase inhibitors is not recommended.

13. NURSING MOTHERS

Brinzolamide caused urinary bladder tumors in female rats at doses of 10 mg/kg/day and its oral route of administration in 2-year studies. Brinzolamide was not carcinogenic in male or female mice tested for up to 2 years. The carcinogenicity studies are conducted exclusively in female rats. These studies were not conducted with the topical solutions during nursing. Exposures that exceed the normal daily human exposure would be expected to be lower than approximately 8% of the recommended human exposure in adult studies.

13.3 Carcinogenesis, Mutagenesis, Impairment of fertility

Brinzolamide caused urinary bladder tumors in male rats at doses of 10 mg/kg/day and its oral route of administration in 2-year studies. Brinzolamide was not carcinogenic in male or female mice tested for up to 2 years. The carcinogenicity studies are conducted exclusively in female rats. These studies were not conducted with the topical solutions during nursing. Exposures that exceed the normal daily human exposure would be expected to be lower than approximately 8% of the recommended human exposure in adult studies.

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13.7 Temporary Vasodilation

This long-acting effect of SIMBRINZA is in part due to a dilating effect of brinzolamide on small vessels to increase local blood flow. The dilating effect of brinzolamide on small vessels is dose-related and may be clinically significant at higher doses. Therefore, brinzolamide is more likely to be associated with a dose-related increase in intraocular pressure.

13.8 Temporary Vasodilation

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14. ADVERSE REACTIONS

14.1 General Adverse Reactions

The following tests for mutagenic potential of brinzolamide were negative: (1) chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and (2) in vivo micronucleus assay; (2) reproductive toxicity. These levels of exposure cannot be achieved with topical ocular suspension. The results demonstrate that brinzolamide is formed, which also binds to CA and accumulates in RBCs. This metabolite binds to carbonic anhydrase type II in the ciliary processes of the eye to increase aqueous humor formation. Brimonidine is a selective alpha 2 adrenergic receptor agonist, which reduces vasoconstrictor tone in the iris and ciliary body. Brimonidine has ocular hypotensive effect occurring at 3 hours post-dosing. This result is a reduction in intraocular pressure (IOP).