125 mm

250 mm

For the use of a Registration Medical Practitioner or a Hospital or a Laboratory

Dorzolamide 2%+Timolol 0.5% Eye Drops

ZOLAMIDOL

DESCRIPTION

ZOLAMIDOL is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decrease elevated intraocular pressure, whether or not associated with glaucoma, by reducing aqueous humor secretion.
It is Clear, colourless to nearly colourless, slightly viscous solution.

COMPOSITION

Each mL contains: Active: 22.3 mg Dorzolamide Hydrochloride equivalent to
20mg dorzolamide. 6.83 mg Timolol Maleate equivalent to 5 mg Timolol
Inactives: Hydroxyethyl cellulose, Mannitol, Sodium citrate,Sodium Hydroxide (to adjust pH) and Water for Injection.
Preservative: 0.075 mg Benzalkonium Chloride

PHARMACOLOGY

Pharmacodynamic Property
ZOLAMIDOL is comprised of two components: dorzolamide hydrochloride and timolol maleate.

Dorzolamide hydrochloride

Dorzolamide hydrochloride is an inhibitor of human carbonic anhydrase II. 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.

Pharmacodynamics
Dorzolamide Hydrochloride

Dorzolamide hydrochloride is a potent inhibitor of human carbonic anhydrase II. 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.

Timolol Maleate

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent. The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that the predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. The combined effect of these two agents results in additional intraocular pressure reduction (IOP) compared to either component administered alone.
Following topical administration, this medicinal product reduces elevated intraocular pressure, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. This medicinal product reduces intra-ocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction

Pharmacokinetics
Dorzolamide Hydrochloride

Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows for the drug to exert its effects directly in the eye at substantially lower doses and therefore with less systemic exposure. In clinical trials, this resulted in a reduction in IOP without the acid-base disturbances or alterations in electrolytes characteristic of oral carbonic anhydrase inhibitors.
When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, drug and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of selective binding to CA-II while extremely low concentrations of free drug in plasma are maintained. The parent drug forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent drug but also inhibits a less active isoenzyme (CA-I). The metabolite also accumulates in RBCs where it binds primarily to CA-I. Dorzolamide binds moderately to plasma proteins (approximately 33%). Dorzolamide is primarily excreted unchanged in the urine; the metabolite is also excreted in urine. After dosing ends, dorzolamide washes out of RBCs nonlinearly, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half-life of about four months.
When dorzolamide was given orally to simulate the maximum systemic exposure after long term topical ocular administration, steady state was reached within 13 weeks. At steady state, there was virtually no free drug or metabolite in plasma; CA inhibition in RBCs was less than that anticipated to be necessary for a pharmacological effect on renal function or respiration. Similar pharmacokinetic results were observed after chronic, topical administration of dorzolamide hydrochloride. However, some elderly patients with renal impairment (estimated CrCl 30-60 milliliter/min) had higher metabolite concentrations in RBCs, but no meaningful differences in carbonic anhydrase inhibition and no clinically significant systemic side effects were directly attributable to this finding.

Timolol Maleate

In a study of plasma drug concentration in six subjects, the systemic exposure to timolol was determined following twice daily topical administration of timolol maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/mL and following afternoon dosing was 0.35 ng/mL.
In a study of plasma drug concentration in six subjects, the systemic exposure to timolol was determined following twice daily topical administration of timolol maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/mL and following afternoon dosing was 0.35 ng/mL.

INDICATIONS

ZOLAMIDOL is indicated for the treatment of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension when concomitant therapy is appropriate.

CONTRAINDICATIONS

ZOLAMIDOL is contraindicated in patients with:
- reactive airway disease, bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease
- sinus bradycardia, sino-atrial block, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock
- hypersensitivity to any component of this product

The above are based on the components and are not unique to the combination.

WARNINGS AND PRECAUTIONS

Cardiovascular/respiratory reactions

Like other topically applied ophthalmic agents timolol is absorbed systemically. Due to beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.

Cardiac disorders

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina, cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.
Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. ZOLAMIDOL should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hepatic impairment

This medicinal product has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

Immunology and hypersensitivity

As with other topically-applied ophthalmic agents, this medicinal product may be absorbed systemically. Dorzolamide contains a ulphonamide group, which also occurs in ulphonamides. Therefore, the same type of adverse reactions found with
systemic administration of ulphonamides may occur with topical administrations, including severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. IF signs of serious reactions or hypersensitivity occur, discontinue use of this preparation.
Local ocular adverse effects, similar to those observed with dorzolamide hydrochloride eye drops, have been seen with this medicinal product. If such reactions occur, discontinuation of this medicinal product should be considered.
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 accidental, diagnostic or therapeutic repeated challenge with such allergens and may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

5 mm
10 mm
5 mm

50 mm

125 mm

250 mm

Concomitant therapy

The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended The use of dorzolamide and oral carbonic anhydrase inhibitors is not recommended.

Withdrawal of therapy

As with systemic beta-blockers, if discontinuation of ophthalmic timolol is needed in patients with coronary heart disease, therapy should be withdrawn gradually.

Additional effects of beta-blockade
Hypoglycaemia/diabetes

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Hyperthyroidism

Therapy with beta-blockers may also mask the signs of hyperthyroidism. Abrupt withdrawal of beta-blocker therapy may precipitate a worsening of symptoms.

Corneal diseases

Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Surgical anaesthesia

Beta-blocking ophthalmic preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthetist should be informed when the patient is receiving timolol. Therapy with beta-blockers may aggravate symptoms of myasthenia gravis.

Additional effects of carbonic anhydrase inhibition

Therapy with oral carbonic anhydrase inhibitors has been associated with urolithiasis as a result of acid-base disturbances, especially in patients with a prior history of renal calculi. Although no acid-base disturbances have been observed with this medicinal product, urolithiasis has been reported infrequently.
Because ZOLAMIDOL contains a topical carbonic anhydrase inhibitor that is absorbed systemically, patients with a prior history of renal calculi may be at increased risk of urolithiasis while using this medicinal product.

Other

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. This medicinal product has not been studied in patients with acute angle-closure glaucoma.
Corneal oedema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery while using dorzolamide. There is an increased potential for developing corneal oedema in patients with low endothelial cell counts. Precautions should be used when prescribing ZOLAMIDOL to these groups of patients.
Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.
As with the use of other antiglaucoma medicines, diminished responsiveness to ophthalmic timolol maleate after prolonged therapy has been reported in some patients. However, in clinical studies in which 164 patients have been followed for at least three years, no significant difference in mean intraocular pressure has been observed after initial stabilisation.

Contact lens use

This medicinal product contains the preservative benzalkonium chloride, which may cause eye irritation. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses.

INTERACTION WITH OTHER MEDICAMENTS

Specific drug interaction studies have not been performed with ZOLAMIDOL. ZOLAMIDOL was used concomitantly with the following systemic medications without evidence of adverse interactions: ACE-inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs including aspirin, and hormones (e.g., estrogen, insulin, thyroxine).
However, the potential exists for additive effects and production of hypotension and/or marked bradycardia when timolol maleate ophthalmic solution is administered together with oral calcium channel blockers, catecholamine-depleting drugs, antiarrhythmics, parasympathomimetics or beta-adrenergic blocking agents.
Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, SSRIs) and timolol.
The dorzolamide component of ZOLAMIDOL is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. In clinical studies, dorzolamide hydrochloride ophthalmic solution was not associated with acid-base disturbances. However, these disturbances have been reported with oral carbonic anhydrase inhibitors and have, in some instances, resulted in drug interactions (e.g., toxicity associated with high-dose salicylate therapy). Therefore, the potential for such drug interactions should be considered in patients receiving ZOLAMIDOL.
Oral -adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

USE IN PREGNANCY AND LACTATION

Pregnancy: ZOLAMIDOL should not be used during pregnancy.
Dorzolamide : No adequate clinical data in exposed pregnancies are available.
Timolol : There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy unless clearly necessary.
Lactation: It is not known whether dorzolamide is excreted in human milk.

ADVERSE REACTIONS

The following adverse reactions have been reported with Zolamidol
Very Common : Burning and stinging of eyes, Dysgeusia
Common : Conjunctival infection, Blurred vision, Corneal erosion, Ocular itching, Tearing, Sinusitis
Uncommon : Urolithias
Rare : Signs and symptoms of systemic allergic reactions, including angioedema, urticarial, pruritus, rash, anaphylaxis, Shortness of breath, Respiratory failure, Rhinitis, Bronchospasm, Contact dermatitis, Stevens- Johnson syndrome, Toxic epidermal necrolysis

OVERDOSAGE

No data are available with regard to human overdosage by accidental or deliberate ingestion of ZOLAMIDOL.
There have been reports of inadvertent overdosage with timolol maleate ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. The most common signs and symptoms to be expected with overdosage of dorzolamide are electrolyte imbalance, development of an acidotic state, and possibly central nervous system effects.
Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol does not dialyze readily.

DOSAGE AND ADMINISTRATION

The dose is one drop of ZOLAMIDOL in the affected eye(s) two times daily.
When substituting ZOLAMIDOL for another ophthalmic antiglaucoma agent(s), discontinue the other agent(s) after proper dosing on one day, and start ZOLAMIDOL on the next day.
If another topical ophthalmic agent is being used, ZOLAMIDOL and the other agent should be administered at least ten minutes apart.
Safety and efficacy in pediatric patients below the age of 2 years have not been established.
When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in an increase in local activity.

PACKING

LDPE bottle with HDPE cap of 5 ml and 10 ml

STORAGE CONDITION

Store below 30°C, Protect from light.

SHELF LIFE

24 months
Use the solution within 28 days after opening the vial.

Manufactured by:
INDOCO REMEDIES LTD.
Plant II, L-32, 33, 34, Verna Industrial Estate, Verna Goa-403 722, INDIA.
Regd. Office: 166, C.S.T. Road, Mumbai 400 098, INDIA.

Name & address of
Product Registration Holder: Arms Pharma Sdn. Bhd.
22-1, Jalan PJU 5/20D, The Strand, 47810 Kota Damansara, Selangor, Malaysia.

Date of Revision: 09.11.2017

G2ZAYLL01AESMY

5 mm
10 mm
5 mm

50 mm

INDOCO REMEDIES LTD.
Packaging Development Department
Packaging Material Specification

Item: Leaflet
A/W Code No.: G2ZAYLL01AESMY
Open Size: 125 x 250 mm
Folding Pattern: H-Unfolded: 250 mm Folded: 20 mm
W-Unfolded: 125 mm Folded: 125 mm
GSM/Paper: 54 Gsm Maplitho Paper
Colour: Pantone 286U
Layout No.: PGB093130089 LF

Approved by:

PDD: _____ HOD: _____

Reason for Preparation: New Development for Singapore registration.

Pharma Code: Front - 282 std.
Back - 283 std.

W:\Art-work\Z\Zolamidol\Export\Malaysia\RA\Zolamidol 5 ml Leaflet G2ZAYLL01AESMY.cdr
06.05.16 / 09.05.16/ 11.04.17/ 18.05.17/ 9.11.17 / 30.07.18