GLANTRIM OPHTHALMIC SOLUTION
Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

GLANTRIM Ophthalmic Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains: Dorzolamide as HCl USP 2%w/v and Timolol as maleate USP 0.5%w/v

Excipient: For a full list of excipients, see section 6.1.

Preservative: Sodium Perborate:

Sodium Perborate is an Oxidative preservative, able to penetrate cell membrane and interfere with cell functions. When combined with water, Sodium Perborate is converted to Hydrogen Peroxide, thus destroying microorganism. Once Sodium Perborate enters eye it is converted to water and oxygen by enzymes present in conjunctival sac.

3. PHARMACEUTICAL FORM

Eye drops (solution)
Clear colorless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glantrim is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP determined after multiple measurements over time).

4.2 Posology and method of administration

The dose is one drop of Glantrim in the affected eye(s) two times daily. If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

4.3 Contraindications

Glantrim is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease; (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure; (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

4.4 Special warnings and precautions for use

General

Since dorzolamide and its metabolite are excreted predominantly by the kidney, Glantrim is not recommended in patients with severe renal impairment (CrCl <30 mL/min).

Dorzolamide should be used with caution in patients with hepatic impairment. While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions 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.

Local ocular adverse effects, primarily conjunctivitis and lid reactions are reported with chronic administration of the solution. Many of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of drug therapy. If such reactions are observed, medication should be discontinued and the patient evaluated before considering restarting the drug. The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. There is no information available about the use of the solution in patients with acute angleclosure glaucoma.

Choroidal detachment after filtration procedures is reported with the administration of aqueous suppressant therapy (e.g., timolol). Beta-adrenergic blockade is reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol is reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms. There are reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers are inadvertently contaminated by patients who, in most cases, have a concurrent corneal disease or a disruption of the ocular epithelial surface.

Information for Patients

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product.

Dorzolamide (which is a sulfonamide), although administered topically, is absorbed systemically. Therefore the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration. Patients should be advised that if serious or unusual reactions or signs of hypersensitivity occur, they should discontinue the use of the product (see WARNINGS).

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should discontinue use and seek their physician's advice. Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, 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 also should 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Either timolol maleate or dorzolamide hydrochloride demonstrated no adverse effect on male or female rat's fertility at doses up to approximately 100 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pediatric Use

The safety and effectiveness of dorzolamide hydrochloride ophthalmic solution and timolol maleate ophthalmic solution have been established when administered individually in pediatric patients aged 2 years and older. Safety and efficacy in pediatric patients below the age of 2 years have not been established.

Geriatric Use

No overall differences in safety or effectiveness are observed between elderly and younger patients.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions

Carbonic anhydrase inhibitors: 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 Glantrim. The concomitant administration of Glantrim and oral carbonic anhydrase inhibitors are not recommended.

Acid-base disturbances: Although acid-base and electrolyte disturbances are not reported with dorzolamide hydrochloride ophthalmic solution, these disturbances are 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 Glantrim.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and Glantrim should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the co-administration of betaadrenergic blocking agents, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, co-administration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a betablocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

CYP2D6 inhibitors: 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.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There are no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

4.6 Pregnancy and lactation

Pregnancy

Since, there is no adequate information available, Glantrim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Lactation

It is not known whether dorzolamide is excreted in human milk. Timolol maleate is detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from Glantrim in nursing infants, 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.

4.7 Effects on ability to drive and use machines

As with any eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient should wait until their vision clears before driving or using machinery.

4.8 Side effects

Other adverse reactions that have been reported with the individual components are listed below:

Dorzolamide — Allergic/Hypersensitivity: Signs and symptoms of local reactions including palpebral reactions and systemic allergic reactions including angioedema, bronchospasm, pruritus, urticaria; Body as a Whole: Asthenia/fatigue; Skin/Mucous Membranes: Contact dermatitis, epistaxis, throat irritation; Special Senses: Eyelid crusting, signs and symptoms of ocular allergic reaction, and transient myopia.

Timolol (ocular administration) — Body as a Whole: Asthenia/fatigue; Cardiovascular: Arrhythmia, syncope, cerebral ischemia, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet; Digestive: Anorexia; Immunologic: Systemic lupus erythematosus; Nervous System/Psychiatric:

Increase in signs and symptoms of myasthenia gravis, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss; Skin: Alopecia, psoriasiform rash or exacerbation of psoriasis; Hypersensitivity: Signs and

symptoms of systemic allergic reactions, including anaphylaxis, angioedema, urticaria, and localized and generalized rash; Respiratory: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease); Endocrine: Masked symptoms of hypoglycemia in diabetic patient; Special Senses: Ptosis, decreased corneal sensitivity, cystoid macular edema, visual disturbances including refractive changes and diplopia, pseudopemphigoid, and tinnitus; Urogenital: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects are reported with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate: Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; Body as a Whole: Extremity pain, decreased exercise tolerance, weight loss; Cardiovascular: Worsening of arterial insufficiency, vasodilatation; Digestive: Gastrointestinal pain, hepatomegaly, mesenteric arterial thrombosis, ischemic colitis; Hematologic: Nonthrombocytopenic purpura; thrombocytopenic purpura, agranulocytosis; Endocrine: Hyperglycemia, hypoglycemia; Skin: Pruritus, skin irritation, increased pigmentation, sweating; Musculoskeletal: Arthralgia; Nervous System/Psychiatric: Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; Respiratory: Rales, bronchial obstruction; Urogenital: Urination difficulties.

4.9 Overdose

There are no human data available on overdosage with Glantrim. Symptoms consistent with systemic administration of beta-blockers or carbonic anhydrase inhibitors may occur, including electrolyte imbalance, development of an acidotic state, dizziness, and headache, shortness of breath, bradycardia, bronchospasm, cardiac arrest and possible central nervous system effects. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. A study of patients with renal failure showed that timolol did not dialyze readily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Glantrim is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intraocular pressure, whether or not associated with glaucoma, by reducing aqueous humor secretion. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure the greater the likelihood of glaucomatous field loss and optic nerve damage.

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. Timolol maleate is a beta1 and beta2 (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane stabilizing) activity. The combined effect of these two agents administered as Glantrim b.i.d. results in additional intraocular pressure reduction compared to either component administered alone, but the reduction is not as much as when dorzolamide t.i.d. and timolol b.i.d. are administered concomitantly.

5.2 Pharmacokinetic properties

Dorzolamide Hydrochloride

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 are measured.

Dorzolamide accumulates in RBCs during chronic dosing as a result of binding to CA-II. The parent drug forms a single N-desethyl metabolite, which inhibits CA-II

less potently than the parent drug but also inhibits CA-I. The metabolite also accumulates in RBCs where it binds primarily to CA-I. Plasma concentrations of dorzolamide and metabolite are generally below the assay limit of quantitation (15nM). Dorzolamide binds moderately to plasma proteins (approximately 33%).

Dorzolamide is primarily excreted unchanged in the urine; the metabolite also is excreted in urine.

After dosing is stopped, 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.

Timolol Maleate

The systemic exposure to timolol is determined following twice daily topical administration of timolol maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing is 0.46 ng/mL.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1. Hypromellose
2. Mannitol
3. Sodium Citrate
4. Sodium Perborate
5. Water for Injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

02 years.

6.4 Special precautions for storage

Keep out of the reach of the children.
Protect from light & heat.
Do not store above 30 ºC.
The content should not be used more than four weeks after first opening the bottle.
Replace cap securely after use.
Use as directed by the physician.
Prescription Only Medicine.

6.5 Nature and contents of container

5 ml bottle with DROP-TAINER dispensing system consisting of a transparent low density polyethylene bottle and dispensing plug and white polypropylene closure. Tamper evidence is provided by a security seal around the closure of the bottle. Pack size: box containing 5ml x 1 bottle

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ATCO Laboratories Limited
B-18, S.I.T.E., Karachi-75700, Pakistan

8. MARKETING AUTHORISATION NUMBER(S)

H2017/CTD4110/137

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

September 12, 2008 / September 11, 2013

10 DATES OF REVISION OF TEXT

12th June 2026