PRESCRIBING INFORMATION

For the use of a registered Medical Practitioner or a Hospital or a Laboratory only.

℞

Timolol LA Ophthalmic Solution

Glucotim®-LA

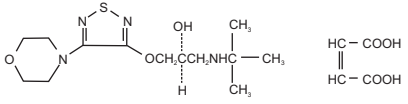
STERILE EYE DROPS

ग्लुकोटीम-एल ए

DESCRIPTION

GLUCOTIM-LA ophthalmic solution 0.5% is a non-selective beta-adrenergic receptor blocking agent. Its chemical name is (-)-1-(*tert*-butylamino) –3- [(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt).

Its molecular formula is $C_{13}H_{24}N_4O_3S$-$C_4H_4O_4$ and its structural formula is:



Timolol maleate long-acting has a molecular weight of 432.49. It is a white, odorless, crystalline powder, which is soluble in water, methanol, and alcohol. **GLUCOTIM-LA** ophthalmic solution is stable at room temperature and is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate in a single strength. It has a pH of 6.5- 7.5 and an osmolality of 275-330 mOsm/kg.

Each mL of **GLUCOTIM-LA** contains 5 mg of timolol (6.8 mg of timolol maleate). Inactive ingredients: monobasic sodium phosphate monohydrate, potassium sorbate 0.47%, sodium chloride, sodium hydroxide, and purified water. Benzalkonium chloride 0.005% is added as preservative.

CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism of the ocular hypotensive action of **GLUCOTIM-LA** is not clearly established at this time. Tonography and fluorophotometry studies in man suggest that its predominant action may be related to reduce aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

GLUCOTIM-LA ophthalmic solution, when applied topically on the eye, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. The onset of reduction in intraocular pressure following administration of **GLUCOTIM-LA** can usually be detected within one-half hour after a single dose. The maximum effect usually occurs in one to two hours and significant lowering of intraocular pressure can be maintained for periods as long as 24 hours with a single dose. Repeated observations over a period of one year indicate that the intraocular pressure lowering effect of **GLUCOTIM-LA** is well maintained. In considering the physicochemical property of timolol as a cationic drug it was found that lipophilicity increased in the presence of an appropriate counterion. **GLUCOTIM-LA** is formulated with potassium sorbate that increases the lipophilicity of Timolol due to ion -pair formation. **GLUCOTIM-LA** thus shows improved permeability into cornea epithelium, which is a lipophilic layer resulting in better bioavailability than Timolol alone (i.e. without sorbic acid).

Pharmacokinetics

GLUCOTIM-LA concentrations were measured up to 3 hr after instillation. The C max of Glucotim LA was 3.1-fold higher than that of Timolol 0.5.

Preparation	Tmax (h)	Cmax (mcg/ml)	$AUC_{0\to3}$ (mcg h/ml)
Glucotim-LA	0.5	9.398	12.799
Timolol 0.5%	1.0	2.986	5.899
Timolol 0.5% (Gel)	0.5	8.382	13.127

The $AUC_{0\to3}$ of **GLUCOTIM-LA** was similar to that of Timolol 0.5% (Gel), and the AUCs of both (**GLUCOTIM-LA** & Timolol 0.5% (Gel)) were 2.2-fold higher than that of Timolol 0.5%. Thus the bioavailability of the **GLUCOTIM-LA** is almost same as that of Timolol 0.5% (Gel)

Reference: International Journal of Pharmaceutics 272(2001) 91-98

INDICATIONS AND USAGE

GLUCOTIM-LA ophthalmic solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

GLUCOTIM-LA 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 (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

GLUCOTIM-LA is absorbed systemically. 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 & rarely death in association with cardiac failure have been reported following systemic or ophthalmic administration of Timolol Maleate. **GLUCOTIM-LA** should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic.

Information for Patients
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 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.

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.

Patients should be advised that **GLUCOTIM-LA** contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following **GLUCOTIM-LA** administration.

Drug Interactions
Although **GLUCOTIM-LA** used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with **GLUCOTIM-LA** and epinephrine has been reported occasionally.
Interactions with *Beta-adrenergic blocking agents, Calcium antagonists, Catecholamine-depleting drugs, Digitalis and calcium antagonist, Quinidine, Clonidine have been reported.*

Pregnancy:
Teratogenic Effects —Pregnancy Category C.

Nursing Mothers
Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from **GLUCOTIM-LA** 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.

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

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS
The most frequently reported adverse experiences have been burning and stinging upon instillation in 38% of patients treated with TIMOLOL MALEATE LA. Additional events reported with **GLUCOTIM-LA** at a frequency of 4 to 10% include: blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity.

OVERDOSAGE
There have been reports of inadvertent overdosage with **GLUCOTIM-LA** 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.

An *in vitro* hemodialysis study, using 14C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSAGE AND ADMINISTRATION
GLUCOTIM-LA ophthalmic solution is available in a concentration of 0.5 percent. The starting dose is one drop of 0.5 percent **GLUCOTIM-LA** in the affected eye(s) once a day in the AM. If the patient's intraocular pressure is not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

PRESENTATION
Sterile Ophthalmic Solution **GLUCOTIM-LA** is a clear, colourless to light yellow solution. **GLUCOTIM-LA** Ophthalmic Solution, 0.5% supplied in clear LDPE bottle with white cap in 5 ml size.

STORAGE
Store below 30^{0} C, protect from light.
Do not freeze.
Keep out of reach of childrens.

Technology licensed from:
SENJU Pharmaceutical Co., Ltd.
Japan

Centaur
Manufactured by:
CENTAUR PHARMACEUTICALS PVT. LTD.
Plant 1, Plot No. 3, Tivim Indl. Estate, Karaswada, Mapusa, Goa - 403 526.
Regd. Off.: Centaur House, Santacruz (E), Mumbai - 400 055.

TVDJ10H100

®Registered Trade Mark