Glucotim®-LA

1. Generic Names

Timolol Maleate

2. Qualitative and Quantitative Composition

Timolol Maleate 0.5%w/v

3. Dosage form and strength

Topical ophthalmic solution containing Timolol Maleate 0.5%.

4. Clinical particulars

4.1 Therapeutic indication

Primary open angle glaucoma.

4.2 Posology and method of administration

One drop once in a day.

4.3 Contraindication

GLUCOTIM-LA is contraindicated in patients with

- bronchial asthma
- a history of bronchial asthma
- severe chronic obstructive pulmonary disease
- sinus bradycardia
- second or third degree atrioventricular block
- overt cardiac failure (see WARNINGS);
- cardiogenic shock or
- Hypersensitivity to any component of this product

4.4 Special warnings and precautions for use

- 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.
- 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 GLUCOTIMLA administration

4.5 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, quinidine and clonidine have been reported

4.6 Use in special population

- Paediatric: Safety and effectiveness in paediatric patients have not been established
- Geriatric: No overall differences in safety or effectiveness have been observed between elderly and younger patients
- Liver impairment: No data available
- Renal failure: No data available
- Pregnancy and lactation: Teratogenic Effects —Pregnancy Category C. 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.

4.7 Effects on ability to drive and use machine

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to GLUCOTIM-LA is known.

4.8 Undesirable effects

The adverse reactions are Eye pain, Eye irritation, Visual impairment, Ocular hyperaemia, Vision blurred, Eye pruritus

4.9 Overdose

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, and shortness of breath, bradycardia, bronchospasm, and cardiac arrest. An in vitro haemodialysis 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.

5. Pharmacological properties

5.1 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 counter ion. 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).

5.2 Pharmacodynamic properties

Timolol maleate combines reversibly with a part of the cell membrane, the beta-adrenergic receptor, and thus inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the beta-adrenergic receptors by catecholamines having beta-adrenergic stimulating (agonist) activity, whether these originate from an endogenous or exogenous source. Reversal of this blockade can be accomplished by increasing the concentration of the agonist, which will restore the usual biologic response.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

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.

5.3 Pharmacokinetic properties

Timolol is almost completely absorbed from the gastrointestinal tract but is subject to moderate first-pass metabolism. Peak plasma concentrations occur about 1 to 2 hours after a dose. Low concentrations are also found in plasma after use as eye drops. Timolol has low to moderate lipid solubility. Protein binding is reported to be low. Timolol crosses the placenta and is distributed into breast milk. A plasma half-life of 4 hours has been reported. Timolol is extensively metabolised in the liver, the metabolites being excreted in the urine with some unchanged Timolol. Timolol is not removed by haemodialysis.

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

Preparation	**Tmax (h)**	**Cmax (mcg/ml)**	**$AUC_{0-->3}$ (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 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)

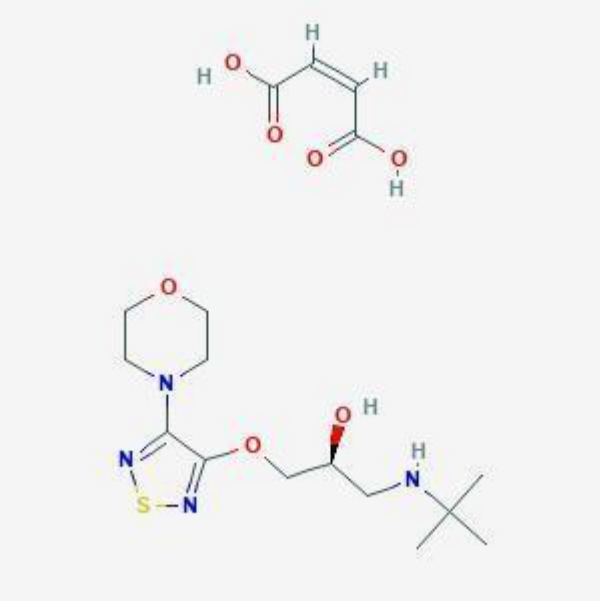
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

No adverse ocular effects were observed in rabbits and dogs administered with timolol maleate topically in studies lasting one and two years, respectively. The oral LD50 of the medicine is 1190 and 900mg/kg in female mice and female rats, respectively.

7. Description

Timolol Maleate is the maleate salt form of timolol, a propanolamine derivative and a non-selective beta-adrenergic antagonist with antihypertensive property. Chemical name is (*Z*)-but-2-enedioic acid;(2*S*)-1-(*tert*-butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol. Molecular weight is 432.5 g/mol. The structure formula is:



The empirical formula is $C_{17}H_{28}N_4O_7S$. Timolol maleate is a white odourless, crystalline powder which is soluble in water, methanol and alcohol and has a melting point of 201.5° C to 202.5° C.

8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

24 months.

8.3 Packaging Information

Sterile Ophthalmic Solution GLUCOTIM-LA is available in clear LDPE bottle with white cap in 5 ml.

8.4 Storage and handling instructions

Store below 30 °C, protect from light. Do not freeze. Keep out of reach of children

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. Manufactured by CENTAUR PHARMACEUTICALS PVT. LTD. and DCI Pharmaceuticals

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158(419)/MFG/DFDA/2020/877 dated. 06.07.2020 for domestic.

12. Date of revision: January 2022.