Summary Product Characteristics

1. Name of the medicinal product: TIMOLOL MALEATE OPHTHALMIC SOLUTION

2. Qualitative and Quantitative composition:

Batch size: 100 Litres

SR. N	Ingredients	Specifi cation	Label Clai per ml	Qty/ml in (mg)	Over ages	Qty. / Vial in mg	Qty/ batch (kg)	Reason f inclusion
ACTIVE								
1.	Timolol Maleate	USP	0.5%w/v	7.00	--	35.00	0.700	Active
EXCIPIENTS								
2.	Boric acid	BP	--	15.00	--	75.00	1.500	Buffering agent.
3.	Borax	BP	--	3.00	--	15.00	0.300	Preservative
4.	Di Sodium EDT.	BP	--	0.5	--	2.5	0.050	Chelating age
5.	Benzalkonium chloride Solution	BP	0.02% v/v	0.0002 ml	--	0.001 ml	20 ml	Preservative
6.	Sodium Metabisulphite	BP	--	1.00	--	5.00	0.100	Preservative
7.	Sodium Hydroxide	BP	--	0.5	--	2.5	0.050	pH adjustmen
8.	Water for Injetio	BP	--	q.s to 1 ml	--	q.s to 5 ml	q.s to 1 Liter	Vehicle

Where,

USP: United State Pharmacopiea; BP: British Pharmacopoeia; q.s: Quantity sufficient.

Note: Quantity of active ingredients to be taken by consideration of their Assay and water contents.

Calculation:

- 432.50 molecular weight of Timolol maleate is equivalent to 316.42 molecular weight of Timolol. Hence 7.00 mg of Timolol maleate is equivalent to 25 mg of Timolol.

3. Pharmaceutical Form: Eye Drops (Ophthalmic Solution)

4. Clinical Particulars:

4.1 Therapeutic Indications

Timolol Eye Drops Solution is a beta-adrenoreceptor blocking agent used topically in the reduction of elevated intra-ocular pressure in various conditions including the following:

- Patients with ocular hypertension
- Patients with chronic open-angle glaucoma including aphakic patients
- Some patients with secondary glaucoma.

4.2 Posology and method of administration:

Posology

Recommended therapy is one drop 0.25% solution in the affected eye twice a day.

If clinical response is not adequate, dosage may be changed to one drop 0.5% solution in each affected eye twice a day. If needed, 'Timoptol' may be used with other agent(s) for lowering intra-ocular pressure. The use of two topical beta-adrenergic blocking agents is not recommended (see 4.4 'Special warnings and precautions for use').

Intra-ocular pressure should be reassessed approximately four weeks after starting treatment because response to 'Timoptol' may take a few weeks to stabilise.

Provided that the intra-ocular pressure is maintained at satisfactory levels, many patients can than be placed on once-a-day therapy.

Transfer from other agents

When another topical beta-blocking agent is being used, discontinue its use after a full day of therapy and start treatment with 'Timoptol' the next day with one drop of 0.25% 'Timoptol' in each affected eye twice a day. The dosage may be increased to one drop of 0.5% solution in each affected eye twice a day, if the response is not adequate.

When transferring a patient from a single anti-glaucoma agent other than a topical beta-blocking agent, continue the agent and add one drop of 0.25% 'Timoptol' in each affected eye twice a day. On the following day, discontinue the previous agent completely, and continue with 'Timoptol'. If a higher dosage of 'Timoptol' is required, substitute one drop of 0.5% solution in each affected eye twice a day.

'Timoptol' Eye Drops Solution is also available as 'Timoptol' Unit dose: The Unit-dose Dispenser of 'Timoptol' is free from preservative and should be used for patients who may be sensitive to the

preservative benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

Paediatric use: is not currently recommended.

Use in the elderly: there has been wide experience with the use of timolol maleate in elderly patients. The dosage recommendations given above reflect the clinical data derived from this experience.

Method of Administration

For ocular use only

4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients.

Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.

Sinus bradycardia, sick sinus syndrome sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker.

Overt cardiac failure, cardiogenic shock.

4.4 Special warnings and precautions for use

Like other topically applied 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.

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and the 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.

Timolol Eye Drops 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.

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.

Beta-blockers may also mask the signs of hyperthyroidism.

Corneal diseases

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

Other beta-blocking agents

The effect on intra-ocular 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

Anaphylactic reactions

While taking beta-blockers, patients with history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Surgical anaesthesia

β-blocking ophthalmological preparations may block systemic β-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

This formulation of Timolol Eye Drops contains benzalkonium chloride as a preservative which may be deposited in soft contact lenses. Hence, Timolol Eye Drops should not be used while wearing these lenses. The lenses should be removed before instillation of the drops and not reinserted earlier than 15 minutes after use.

When Timolol Eye Drops is used to reduce intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

A reduction in ocular hypotensive response has been reported in some patients following prolonged therapy with Timolol maleate eye drops.

Muscle weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis, and generalised weakness). Timolol Eye Drops have been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

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 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 develop any intercurrent ocular condition (e.g. trauma, ocular surgery or infection), they should immediately seek their physician's advice concerning the continued use of present multi-dose container.

There have been reports of bacterial keratitis associated with the use of topical ophthalmic products.

4.5 Interaction with other medicinal products and other forms of interaction:

No specific drug interaction studies have been performed with timolol.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

There is also a potential for AV conduction disturbances or left ventricular failure to occur when oral calcium channel blockers like verapamil and diltiazem are used with the beta blocker

Beta-blockers may increase the hypoglycaemic effect of anti-diabetic agents. Beta-blockers can mask the signs and symptoms of hypoglycaemia.

4.6 Pregnancy and Lactation

Pregnancy

There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy unless clearly necessary.

Epidemiological studies have not revealed malformative effects but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If timolol eye drops is administered until delivery, the neonate should be carefully monitored during the first days of life.

Lactation

Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant.

Fertility

Timolol have not been found to have any effect on male or female fertility in animal studies.

4.7 Effects on the ability to drive and use machines

No studies on the effect of this medicinal product on the ability to drive have been conducted. While driving vehicles or operating different machines, it should be taken into account that occasionally visual disturbances may occur including refractive changes, diplopia, ptosis, frequent episodes of mild and transient blurred vision and occasional episodes of dizziness or fatigue.

4.8 Undesirable effects:

Like other topically applied ophthalmic drugs, timolol maleate is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic betablocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. Listed adverse reactions include reactions seen within the class of ophthalmic betablockers.

Data from clinical studies including frequencies (if available).

Additional adverse reactions have been seen with ophthalmic beta-blockers and may potentially occur with Timolol Eye Drops.

Immune system disorders:

Systemic allergic reactions including angiooedema, urticaria, localized and generalized rash, pruritus, anaphylactic reaction.

Metabolism and nutrition disorders:

Hypoglycaemia.

Psychiatric disorders:

Insomnia, depression, nightmares, memory loss.

Nervous system disorders:

Syncope, cerebrovascular accident, cerebral ischemia, increases in signs and symptoms of myasthenia gravis, dizziness, paraesthesia, and headache.

Eye disorders:

Signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness), blepharitis, keratitis, blurred vision andchoroidal detachment following filtration surgery (see 4.4 Special warnings and special precautions for use), decreased corneal sensitivity, dry eyes, corneal erosion ptosis, diplopia.

Cardiac disorders:

Bradycardia, chest pain, palpitations, oedema, arrhythmia, congestive heart failure, atrioventricular block, cardiac arrest, cardiac failure.

Vascular disorders:

Hypotension, Raynaud's phenomenon, cold hands and feet.

Respiratory, thoracic, and mediastinal disorders:

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnoea, cough.

Gastrointestinal disorders:

Dysgeusia, nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting.

Skin and subcutaneous tissue disorders:

Alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash.

Musculoskeletal and connective tissue disorders:

Myalgia,

Reproductive system and breast disorders:

Sexual dysfunction, libido decreased impotence.

General disorders and administration site conditions:

Asthenia/fatigue.

4.9 Overdose

There have been reports of inadvertent overdosage with Timolol 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.

If overdosage occurs, the following measures should be considered:

1. Gastric lavage, if ingested. Studies have shown that timolol does not dialyse readily.
2. Symptomatic bradycardia: atropine sulphate, 0.25 to 2 mg intravenously, should be used to induce vagal blockade. If bradycardia persists, intravenous isoprenaline hydrochloride should be administered cautiously. In refractory cases, the use of a cardiac pacemaker may be considered.

3. Hypotension: a sympathomimetic pressor agent such as dopamine, dobutamine or noradrenaline should be used. In refractory cases, the use of glucagon has been reported to be useful.
4. Bronchospasm: isoprenaline hydrochloride should be used. Additional therapy with aminophylline may be considered.
5. Acute cardiac failure: conventional therapy with digitalis, diuretics, and oxygen should be instituted immediately. In refractory cases, the use of intravenous aminophylline is suggested. This may be followed, if necessary, by glucagon, which has been reported useful.
6. Heart block (second- or third-degree): isoprenaline hydrochloride or a pacemaker should be used.

5. Pharmacological Particulars:
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-glaucoma preparations and miotics, beta-blocking agents, selective
ATC code: S01ED01

Mechanism of action

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic activity. Timolol maleate combines reversibly with the beta-adrenergic receptor, and this inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the 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 biological response.

Clinical efficacy and safety

Unlike miotics, Timolol reduces IOP with little or no effect on accommodation or pupil size. In patients with cataracts, the inability to see around lenticular opacities when the pupil is constricted is avoided. When changing patients from miotics to Timolol a refraction might be necessary when the effects of the miotic have passed.
Diminished response after prolonged therapy with Timolol has been reported in some patients.

5.2 Pharmacokinetic properties

The onset of reduction in intra-ocular pressure can be detected within one-half hour after a single dose. The maximum effect occurs in one or two hours; significant lowering of IOP can be maintained for as long as 24 hours with a single dose.

5.3 Pre-clinical Safety:

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

No adverse ocular effects were observed in rabbits and dogs administered Timolol topically in studies lasting one and two years, respectively. The oral LD50 of the drug is 1,190 and 900 mg/kg in female mice and female rats, respectively.

Carcinogenesis, mutagenesis, impairment of fertility

In a two-year oral study of timolol maleate in rats there was a statistically significant (p0.05) increase in the incidence of adrenal phaeochromocytomas in male rats administered 300 mg/kg/day (300 times the maximum recommended human oral dose). Similar differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximum recommended human oral dose.

In a lifetime oral study in mice, there were statistically significant (p0.05) increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinoma in female mice at 500 mg/kg/day (500 times the maximum recommended human dose), but not at 5 or 50 mg/kg/day. In a subsequent study in female mice, in which post-mortem examinations were limited to uterus and lungs, a statistically significant increase in the incidence of pulmonary tumours was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinoma was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumours has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when evaluated in vivo (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 100 mcg/ml). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant (p0.05) elevations

of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose-response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

6. Pharmaceutical Particulars:

6.1 List of Excipients:

Boric acid	BP
Borax	BP
Di Sodium EDTA	BP
Benzalkonium chloride Solution	BP
Sodium Metabisulphite	BP
Sodium Hydroxide	BP
Water for Injetion	BP

6.2 Incompatibilities: Nil

6.3 Shelf Life: Unopened: 24 months

After the container is opened for the first time: 28 days

6.4 Special Precautions for storage:

Store below 30°C. Protect from light.

6.5 Nature and contents of container:

Timolol Maleate Ophthalmic Solution is filled in 5 ml sterile white plastic vials with cap and packed in a carton and pack insert.

6.6 Special precautions for disposal and other handling:

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, 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.

Any unused medicinal product should be disposed of in accordance with local requirements.

1. You must not use the bottle if the tamper-proof seal on the bottle neck is broken before you first use it.
2. To open the bottle unscrew the cap by turning it until the tamper-proof seal breaks.
3. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye.
4. Invert the bottle and press gently until a single drop as instructed by your doctor is dispensed into your eye. DO NOT TOUCH YOUR EYE OR EYELID WITH THE TIP OF THE CONTAINER.
5. Repeat steps 3 and 4 with the other eye if instructed to do so by your doctor.
6. Reclose the bottle by turning the cap firmly immediately after use and return the bottle to the original outer carton.
7. The dispenser tip is designed to provide a pre-measured drop; therefore, do not enlarge the hole of the dispenser tip.

7. Marketing Authorization Holder: HANUCHEM LABORATORIES

8. Marketing Authorization Number: ---

9. Date of first Authorization /renewal of the authorization: ---

10. Date of revision of text: February 2018

1.3.2 Labelling (outer & inner labels)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. PROPRIETARY NAME

NCI Timolol Eye Drops

2. INTERNATIONAL NON-PROPRIETARY NAME

Timolol Maleate Ophthalmic Solution

3. STATEMENT OF THE ACTIVE SUBSTANCE(S)

Timolol Maleate USP

4. LIST OF THE EXCIPIENTS

Boric acid BP

Borax BP

Di Sodium EDTA BP

Benzalkonium chloride Solution BP

Sodium Metabisulphite BP

Sodium Hydroxide BP

Water for Injection BP

5. PHARMACEUTICAL FORM AND CONTENT

Each ml Contains:

Timolol Maleate USP

Eq. to Timolol …….. 0.5%w/v

Benzalkonium Chloride Solution BP……0.02 % v/v

(As preservative)

Sterile aqueous base …… q.s

6. METHOD AND ROUTE(S) OF ADMINISTRATION

ocular

7. SPECIAL WARNING

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

8. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable

9. STERILE

10. BATCH NUMBER

_____

11. MANUFACTURING DATE

MFG: (MM/YYYY)

12. EXPIRY DATE

EXP: (MM/YYYY)

Shelf life: 2 Years (24months from the date of manufacture)

13. SPECIAL STORAGE CONDITIONS

Store at or below 30°C. Protect from light.

14. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS

Not Applicable

15. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

NCI Pharm Chem Ind. Ltd.

29 Igbehinadun Street,

Oshodi.Lagos, Nigeria

16. PHYSICAL ADDRESS OF THE SITE RESPONSIBLE FOR RELEASE OF THE FINISHED PRODUCT

Hanuchem Laboratories

Plot No.13, Sector-5, Industrial Area,

Parwanoo, Dist-Solan (HP), India.

17. GENERAL CLASSIFICATION FOR SUPPLY

Prescription only medicines

18. INSTRUCTIONS ON USE

Read the Patient Information Leaflet before use.

19. THE PROPRIETARY NAME, STRENGTH AND EXPIRY DATE IN BRAILLE

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20. REGISTRATION NUMBER ISSUED BY NDA
