1. NAME OF THE MEDICINAL PRODUCT

ONATIM EYE DROPS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Timolol Maleate BP

Eq. to Timolol 0.5%w/v

Benzalkonium Chloride BP 0.02%w/v

(As preservative)

Sterile aqueous base.....q.s.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye Drops
Clear, colourless to light yellow, sterile eye drops solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Timolol Eye Drops is indicated in the reduction of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

4.2 Posology and method of administration

Posology

Adults

The usual starting dose is one drop of 0.25% timolol maleate in the affected eye(s) twice a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5% solution in the affected eye(s) twice a day.
For a small proportion of patients one drop of 0.1 percent timolol maleate eye drops in the affected
eye(s) twice a day may be satisfactory. If the clinical response is not adequate with 0.1 percent solution, the dosage should be increased to one drop of 0.25 percent in the affected eye(s) twice a day.
If needed, concomitant therapy with other agent(s) for lowering intraocular pressure may be given with Timolol Maleate Eye Drops. The use of two topical beta-adrenergic blocking agents is not recommended. Since in some patients the intraocular pressure-lowering response to timolol may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with timolol.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.
If the dose is missed, then it should be used as soon as it is remembered. If it is almost time for the next dose, then the missed dose should be skipped. Double dose should not be used to make up for a forgotten dose. If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.
Dosages above one drop of 0.5 percent timolol twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with pilocarpine and other miotics, and/or epinephrine, and/or systemically administered carbonic anhydrase inhibitors, such as acetazolamide, can be instituted.
When a patient is transferred from another topical ophthalmic beta-adrenergic blocking agent, that agent should be discontinued after proper dosing on one day and treatment with timolol started on the following day with 1 drop of 0.25 percent timolol in the affected eye(s) twice a day. The dose may be increased to one drop of 0.5 percent timolol twice a day if the clinical response is not adequate.
When a patient is transferred from a single antiglaucoma agent, other than a topical ophthalmic

betaadrenergic blocking agent, continue the agent already being used and add 1 drop of 0.25 percent timolol in the affected eye(s) twice a day. On the following day, discontinue the previously used antiglaucoma agent completely and continue with timolol. If a higher dosage of timolol is required, substitute one drop of 0.5 percent solution in the affected eye(s) twice a day.

Pediatric Population
Paediatric Use:

Safety and effectiveness in pediatric patients have not been established.

Hepatic and renal impairment

The safety and efficacy of this medicine in patients with hepatic or renal impairment have not been established.

Method of administration

- For ocular use only.
- To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye.
- When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- 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, overt cardiac failure or cardiogenic shock.

4.4 Special warnings and precautions for use

General

Like other topically applied ophthalmic agents, timolol is absorbed systemically.

Due to the beta-adrenergic blocking component in Timolol maleate eye drops, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-blockers may occur.
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. (See 4.3 CONTRAINDICATIONS.)

Cardiac disorders

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. Cardiac failure should be adequately controlled before beginning therapy with Timolol Eye Drops.
Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and for adverse reactions.
Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.
Rarely death in association with cardiac failure have been reported following systemic or ophthalmic administration of timolol maleate.
In Patients Without a History of Cardiac Failure:

Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure.
At the first sign or symptom of cardiac failure timolol should be discontinued.

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.
Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency.If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with timolol, alternative therapy should be considered.

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.

Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which timolol is contraindicated, see CONTRAINDICATIONS), should, in general, not receive beta-blockers, including timolol.

Hypoglycemia/diabetes

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycemia or to patients with labile diabetes who are receiving insulin or oral hypoglycemic agents, as beta-blockers may mask the signs and symptoms of acute hypoglycemia.

Hyperthyroidism

Beta-blockers may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism.

Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

Muscle weakness

Beta-adrenergic blocking agents have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalized weakness).

Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

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 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 (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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 (epinephrine) 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 anesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline.

The anaesthesiologist should be informed when the patient is receiving timolol.

Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of betaadrenergic receptor blocking agents.
If necessary, during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists
Ocular
As with the use of other antiglaucoma drugs, diminished responsiveness to timolol after prolonged therapy has been reported in some patients.
When Timolol is used to reduced elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone. In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.
Patients should also be instructed those 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 an intercurrent ocular condition (e. g., trauma, ocular surgery or infection), they should immediately seek their physician's advice concerning the continued use of the present multiple dose container.
Contact lenses
Benzalkonium chloride may cause irritation and is known to discolor soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of Timolol and wait at least 15 minutes before reinsertion.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions are expected with Timolol due to potential drug interactions:

- 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.
- There is a potential for additive effects resulting in hypotension and/or marked bradycardia when an ophthalmic beta-blocker solution is administered concomitantly with oral calcium channel blockers, beta- adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics and catecholamine-depleting drugs.The use of two topical β-adrenergic blocking agents is not recommended.
- Beta-blockers can decrease the response to adrenaline used to treat anaphylactic reactions. Special caution should be exercised in patients with a history of atopy or anaphylaxis (see section 6 Warnings and precautions)
- Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

- **Calcium antagonists:** Caution should be used in the co-administration of beta-adrenergic blocking agents, such as timolol, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, or hypotension. In patients with impaired cardiac function, coadministration should be avoided.
- **Clonidine**: Oral β-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.
- **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.

4.6 Pregnancy and Lactation

Pregnancy

There are no adequate data regarding the ocular use of timolol in pregnant women. 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 betablockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycemia) have been observed in the neonate when beta-blockers have been administered to the mother until delivery.

Timolol should not be used during pregnancy unless clearly necessary. However, if Timolol Maleate is administered during pregnancy up to the time of delivery, the neonate should be carefully monitored during the first days of life.

Breast-feeding

Timolol is transferred into human breast milk following ocular topical administration. Oral beta blockers have the potential to cause serious adverse reactions in the breastfed infant. However, in the case of ocular administration at therapeutic doses, the amounts of timolol present in breast milk are not likely to produce clinical symptoms of beta-blockade in the infant.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Timolol and any potential adverse effects on the breast-fed child from Timolol. Because of the potential for serious adverse reactions from timolol 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.

Females and males of reproductive potential – Infertility

There are no data on the effects of Timolol Maleate on human fertility. Fertility studies in rats with timolol showed no effects at doses up to 1,700 times the MRDOHD, based on BSA.

4.7 Effects on ability to drive and use machines

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first.
Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

System Organ Classification	**Adverse Drug Reactions**
Psychiatric disorders	*Rare:* depression *Unknown*: confusion, hallucinations, anxiety, disorientation, nervousness
Nervous system disorders	*Uncommon:* headache *Rare:* cerebral ischaemia, dizziness, migraine *Unknown:* Increase in signs and symptoms of myasthenia gravis, somnolence
Eye disorders	*Common:* vision blurred, eye pain, eye irritation, ocular discomfort, ocular hyperaemia *Uncommon:* corneal erosion, punctate keratitis, keratitis, iritis, conjunctivitis, blepharitis, reduced visual acuity, photophobia, dry eye, lacrimation increased, eye discharge, eye pruritus, eyelid margin crusting, anterior chamber inflammation, eyelid oedema, conjunctival hyperaemia *Rare:* uveitis, diplopia, asthenopia, eczema of eyelids, erythema of eyelid, eyelid pruritus, conjunctival oedema, corneal pigmentation *Unknown*: foreign body sensation, ptosis; decreased corneal sensitivity; cystoid macular edema, pseudopemphigoid
Cardiac disorders	*Uncommon:* bradycardia *Rare:* myocardial infarction
Vascular disorders	*Uncommon:* hypotension *Rare:* blood pressure increased, oedema peripheral, peripheral coldness

Respiratory, thoracic and mediastinal disorders	*Uncommon:* asthma, bronchitis, dyspnoea *Rare:*chronic obstructive pulmonary disease, bronchospasm, cough, wheezing, nasal congestion *Unknown:* respiratory failure, upper respiratory *infections.*
Gastrointestinal disorders	*Uncommon:* dysgeusia *Rare:* dyspepsia, abdominal discomfort, dry mouth
Skin and subcutaneous tissue disorders	*Rare:* swelling face, erythema
General disorders and administration site conditions	*Uncommon:* fatigue *Rare:* asthenia, chest discomfort

Reporting of suspected adverse reactions
Healthcare professionals are requested to report any suspected adverse reactions via national Pharmacovigilance Electronic Reporting Systems to the respective national regulatory authorities.

4.9 Overdose

In case of accidental ingestion, symptoms of overdose from beta blockade may include dizziness, headache, shortness of breath, bradycardia, hypotension, cardiac failure, cardiac arrest and bronchospasm.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-glaucoma agent. ATC code: S01ED01

Timolol maleate is a non-selective beta-receptor blocker without beta-stimulating effect or significant membrane-stabilizing (local anesthetic) effect.
The IOP-lowering effect of timolol is probably due more to a reduced inflow of aqueous humor than to an increased outflow, but it is not yet clear whether the effect on pressure is a purely beta-blocking effect. Timolol can affect blood pressure and pulse rate. It is not known to cause any changes in local blood flow. Clinical studies show that timolol maleate reduces IOP in eyes with both normal and raised pressure. No changes, or only insignificant changes, have been observed in pupil size or visual acuity.
Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.
The onset of reduction in intraocular pressure following administration of timolol maleate can usually be detected approximately 20 minutes 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 0.25 percent or 0.5 percent timolol eye drops.

Repeated observations over a period of three years indicate that the intraocular pressure-lowering effect of timolol is well maintained.
The precise mechanism of the ocular hypotensive action of timolol is not clearly established at this time. Tonography and fluorophotometry studies in man suggest that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. 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.
Timolol Eye Drops, when applied topically on the eye, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma.
In clinical studies Timolol Eye Drops was generally effective in more patients and produced fewer and less severe side effects than either pilocarpine or epinephrine.

Timolol has also been used in patients with glaucoma wearing conventional (PMMA) hard contact lenses, and has generally been well tolerated. Timolol has not been studied in patients wearing lenses made with materials other than PMMA.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, maximum timolol plasma concentrations are achieved within 2 hours or less. Plasma concentrations decline with terminal half-life of 4 to 5 hours. In addition to local absorption of topically applied timolol into the cornea and aqueous humour, systemic absorption via the conjunctival veins and flow off through the nasal lacrimal duct also occurs.
In a clinical study in 16 volunteers dosed bilaterally with 0.5% timolol solution twice daily for 2 weeks (600 micrograms total dose per administration), peak steady-state plasma concentrations ranged from below the 1 ng/mL quantitation limit to 5 ng/mL.
Distribution
Following topical ocular administration of 1.5 mg radiolabelled timolol to rabbits, maximum aqueous humor concentrations of about 870 ng/mL were achieved within 30 minutes. Aqueous humor concentrations declined to about 6 ng/mL at 24 hours. Studies in pigmented rabbits showed that timolol had prolonged retention and slow elimination from iris and ciliary body, indicating significant binding to melanin.
Metabolism

In humans, timolol is metabolized by cleavage of the morpholine ring to form two primary metabolites. There is an acetyl ethanol secondary amine derivative which undergoes subsequent loss of the acetyl side chain to form an ethanolic primary amine analog. Hydroxylation of the terminal methyl group on the t-butyl moiety to form an alcohol is a

minor metabolic pathway in humans. Timolol is primarily metabolized in the liver by the CYP2D6 isozyme. No timolol metabolism occurs within the eye.

Excretion

Approximately 20% of the dose was excreted as unchanged drug in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium Chloride BP

Di Sodium Hydrogen Orthophosphate Decahydrate BP
Sodium Di Hydrogen Orthophosphate Dihydrate BP

Sodium Chloride BP

Di Sodium Edetate BP

Sodium Hydroxide Pellets

Water for Injection

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months from the date of Manufacturing (unopened). Discard after 1 month (30 days) after first opening.

6.4 Special precautions for storage

Do not store above 30°C. Protect from direct sunlight.

6.5 Nature and contents of container

5 ml LDPE dropper bottle with white cap and nozzle packed in a carton along with leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

Dawa Limited,
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P.O Box 16633-00620
Nairobi, Kenya

8. MARKETING AUTHORIZATION NUMBER

H2025/CTD11912/25922

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

2025 March 06

10. DATE OF REVISION OF THE TEXT

2025 March 06