SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

IOTIM 0.5% w/v Eye Drops (Timolol Maleate Ophthalmic Solution USP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Timolol …….....5.0 mg
(As Timolol Maleate)
Benzalkonium Chloride ……...0.1mg
(As preservative)
Water for Injection ……q.s.

3. PHARMACEUTICAL FORM

Ophthalmic Solution.

Description
A clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

IOTIM Eye Drops are used topically in adults for reduction of elevated intra-ocular pressure (IOP) in patients with ocular hypertension, chronic open-angle glaucoma, and primary open-angle glaucoma.

4.2 Posology and Method of Administration

For topical ocular instillation.
Adults:
One drop in the affected eye(s) twice a day.
If needed, timolol may be used with other agent(s) for lowering intra-ocular pressure. The use of two topical beta-adrenergic blocking agents is not recommended.
Intra-ocular pressure should be reassessed approximately 4 weeks after starting treatment because response to timolol may take a few weeks to stabilise.
If IOP 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 IOP, satisfactory response to the once-a-day dose is best determined by measuring the IOP at different times during the day.
Or, as directed by the physician.

Paediatric Population
Due to limited data, timolol could only be recommended for use in primary congenital and primary juvenile glaucoma for a transitional period while a decision is made on a surgical approach and in case of failed surgery while awaiting further options.
Clinicians should strongly evaluate the risks and benefits when considering medical therapy with timolol in paediatric patients. A detailed paediatric history and examination to determine the presence of systemic abnormalities should precede the use of timolol.
No specific dosage recommendation can be given as there is only limited clinical data.

However, if benefit outweighs the risk, it is recommended to use the lowest active agent concentration available once daily. If IOP could not be sufficiently controlled, a careful up titration to a maximum of two drops daily per affected eye has to be considered. If applied twice daily, an interval of 12 hours should be preferred.
Furthermore the patients, especially neonates, should be closely observed after the first dose for one to two hours in the office and closely monitored for ocular and systemic side effects.
Or, as directed by the physician.

Method of Administration

- Not for injection.
- For external use only.
- If irritation persists or increases, discontinue the use and consult the physician.
- Tighten the cap on the nozzle.
- The spike in the cap will pierce the tip of the vial.
- Dispense drops with gentle pressure.
- Replace the cap after every use.
- Keep the container tightly closed when not in use.
- 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.
- If more than one topical ophthalmic medicinal product is being used, the medicinal products should be administered at least 10 minutes apart.
- This product is sterile when packaged; to prevent contamination, care should be taken to avoid touching the container tip to the eye or to any other surface. 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.
- Use the solution within one month after opening the vial/container.

4.3 Contraindications

IOTIM Eye Drops are contraindicated in the following:

- Patients with known hypersensitivity to timolol maleate or to benzalkonium chloride 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 (COPD).
- 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 ophthalmic 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.

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. 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.
Cardiac failure should be adequately controlled before beginning therapy with timolol. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates monitored.

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 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.

Thyrotoxicosis
Beta-adrenergic blocking agents 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.

Corneal diseases
Ophthalmic beta-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.
There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoreceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy involving beta-blockade should be gradual.

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

Surgical anaesthesia
Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g., of epinephrine (adrenaline). The anaesthesiologist should be informed when the patient is receiving timolol.

Contact lenses
Timolol has been generally well tolerated in glaucoma patients wearing conventional hard contact lenses. Timolol has not been studied in patients wearing lenses made with material other than polymethylmethacrylate (PMMA), which is used to make hard contact lenses.

Angle-closure glaucoma
In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. Timolol has little or no effect on the pupil. When timolol is used to reduce elevated IOP in angle-closure glaucoma it should be used with a miotic and not alone.

Bacterial keratitis
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.

Anaphylactic reactions
While taking beta-blockers, patients with a 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, may be unresponsive to the usual dose of epinephrine (adrenaline) used to treat anaphylactic reactions.

Benzalkonium chloride (preservative)
IOTIM Eye Drops contains benzalkonium chloride as a preservative which may be deposited in soft contact lenses; therefore IOTIM Eye Drops should not be used while wearing these lenses. The lenses should be removed before application of the drops and not reinserted earlier than 15 minutes after use. Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction
No specific drug interaction studies have been performed with timolol maleate eye drops.
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, rauwolfia alkaloids, parasympathomimetics, guanethidine.
Although timolol alone has little or no effect on pupil size, mydriasis resulting from concomitant use of ophthalmic beta-blockers and epinephrine (adrenaline) has been reported occasionally.
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.
Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

Close observation of the patient is recommended when a beta-blocker 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 produce vertigo, syncope, or postural hypotension.
Oral calcium-channel antagonists may be used in combination with beta-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function.
The potential exists for hypotension, AV conduction disturbances and left ventricular failure to occur in patients receiving a beta-blocking agent when an oral calcium-channel blocker is added to the treatment regimen. The nature of any cardiovascular adverse effects tends to depend on the type of calcium-channel blocker used. Dihydropyridine derivatives, such as nifedipine, may lead to hypotension, whereas verapamil or diltiazem have a greater propensity to lead to AV conduction disturbances or left ventricular failure when used with a beta-blocker.
Intravenous calcium channel blockers should be used with caution in patients receiving beta-adrenergic blocking agents.
The concomitant use of beta-adrenergic blocking agents and digitalis with either diltiazem or verapamil may have additive effects in prolonging AV conduction time.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
There are no adequate data for the use of timolol maleate in pregnant women. IOTIM Eye Drops 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 is administered until delivery, the neonate should be carefully monitored during the first days of life.

Breast Feeding
Timolol is detectable in human milk. A decision for breastfeeding mothers, either to stop taking timolol or stop nursing, should be based on the importance of the drug to the mother.

Fertility
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. No human data is available.

4.7 Effects on 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 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 Effect
Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. The following adverse reactions have been reported with ocular administration of timolol maleate

formulations in clinical trials and during post-marketing experience. Additional side effects have been reported in clinical experiences with systemic timolol maleate, and may be considered potential effects of ophthalmic timolol maleate. Also listed are adverse reactions seen within the class of ophthalmic beta-blockers and may potentially occur with timolol.

System Organ Classification	Ocular	Systemic
Eye disorders	Signs and symptoms of ocular irritation, (e.g., burning, stinging, itching, tearing, redness), conjunctivitis, blepharitis, keratitis, dry eyes, decreased corneal sensitivity, blurred vision, corneal erosion. Eye discomfort, eye disorder, eye inflammation, vision disorders, visual disturbances, including refractive changes, diplopia, ptosis and choroidal detachment following filtration surgery. Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.	
Ear and labyrinth disorders	tinnitus.	
Cardiac disorders	bradycardia, chest pain, arrhythmia, heart block, congestive heart failure, palpitations, cardiac arrest, cardiac failure, oedema.	Atrioventricular block (second- or third-degree), sino-atrial block, pulmonary oedema, worsening of arterial insufficiency, worsening of angina pectoris, vasodilation
Vascular disorders	claudication, hypotension, Raynaud's phenomenon, cold hands and feet	
Respiratory, thoracic and mediastinal disorders	bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnoea, cough.	rales.
General disorders and administration site conditions	asthenia, fatigue.	extremity pain, decreased exercise tolerance.
Skin and subcutaneous tissue disorders	alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash.	sweating, exfoliative dermatitis
Immune system disorders	systemic lupus erythematosus, pruritus.	Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and

		generalised rash, anaphylactic reaction.
Psychiatric disorders	depression, insomnia, nightmares, memory loss, hallucination.	diminished concentration, increased dreaming.
Nervous system disorders	syncope, cerebrovascular accident, cerebral ischemia, headache, dizziness, increase in signs and symptoms of myasthenia gravis, paraesthesia.	vertigo, local weakness.
Gastrointestinal disorders	nausea, diarrhoea, dyspepsia, dry mouth, dysgeusia, abdominal pain, vomiting	
Reproductive system and breast disorders	decreased libido, Peyronie's disease, sexual dysfunction such as impotence;	micturition difficulties.
Metabolism and nutrition disorders	hypoglycaemia	hyperglycaemia.
Musculoskeletal and connective tissue disorders	myalgia.	arthralgia.
Blood and lymphatic system disorders		non-thrombocytopenic purpura.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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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, hypotension, bronchospasm, acute cardiac insufficiency 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 (i.v.), 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 PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic Group: Ophthalmologicals, antiglaucoma preparations and miotics, betablocking agents;
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.

Pharmacodynamic Effects

Timolol, when applied topically on the eye, has the action of reducing elevated as well as normal intraocular pressure (IOP), whether or not accompanied by glaucoma. Elevated IOP is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of IOP, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.
The onset of reduction in IOP can be detected within 30 minutes after a single dose. The maximum effect occurs in 1 or 2 hours; significant lowering of IOP can be maintained for as long as 24 hours with a single dose.

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.

<u>Paediatric Population</u>

There is only very limited data available on the use of timolol (0.25%, 0.5% twice daily one drop) in the paediatric population. In one small, double masked, randomized, published clinical study conducted for a treatment period up to 12 weeks on 105 children (n=71 on timolol) aged 12 days – 5 years the data have shown to some extent evidence, that timolol in the indication primary congenital and primary juvenile glaucoma is effective in short term treatment.

5.2 Pharmacokinetic Properties

Following topical ocular administration of timolol to humans, low concentrations of drug are found in plasma. After bilateral administration of a 0.5% timolol maleate solution to healthy volunteers, maximum plasma concentrations were generally below 5 ng/ml. In a study of plasma drug concentration in 6 subjects, the systemic exposure to timolol was determined following twice daily administration of timolol 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/ml and following afternoon dosing was 0.35 ng/ml.

Paediatric Population

Adult data indicate that around 80% of each eye drop passes through the nasolacrimal system where it may be rapidly absorbed into the systemic circulation via the nasal mucosa, conjunctiva, nasolacrimal duct, oropharynx and gut, or the skin from tear overflow.

Due to the fact that the blood volume in children is smaller than that in adults a higher circulation concentration has to be taken into account. In addition, neonates have immature metabolic enzyme pathways and it may result in an increase in elimination half-life and potentiating adverse events.

Limited data show that plasma timolol levels in children after 0.25% greatly exceed those in adults after 0.5%, especially in infants and are presumed to increase the risk of side effects such as bronchospasm and bradycardia.

5.3 Preclinical Safety Data

No adverse ocular effects were observed in rabbits and dogs administered timolol topically in studies lasting one and two years, respectively. The oral LD_{50} 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 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 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 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
Disodium Hydrogen Phosphate Dodecahydrate, Sodium Dihydrogen Phosphate Dihydrate, Disodium Edetate, Sodium Chloride, Benzalkonium Chloride, Polyvinyl alcohol, Sodium Hydroxide, Water for Injection

6.2 Incompatibilities
None known.

6.3 Shelf-life
24 months

6.4 Special Precautions for Storage
Store at a temperature not exceeding 30°C. Protect from light.

6.5 Nature and Contents of Container
5 ml labeled LDPE vial with HIPS spike cap packed in carton with pack insert.

6.6 Special Precautions for Disposal and Other Handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
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8. MARKETING AUTHORISATION NUMBER(S)
Certificate No. 06027/07557/REN/2020

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION
10. June 01, 2021

11. DATE OF REVISION OF THE TEXT
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