USER INFORMATION
TIMOLAIN
TIMOLOL MALEATE OPHTHALMIC SOLUTION USP
(TIMOLOL 0.5%)

Product Description:
Timolol Maleate Ophthalmic Solution is a sterile, aqueous solution of Timolol Maleate. The solution is a clear and colourless to light yellow solution. Each mL solution contains Timolol 5mg corresponding to 6.8mg of Timolol Maleate and Benzalkonium Chloride 0.01% w/v as preservative.

Pharmacodynamics:
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. Unlike miotics, TIMOLAIN 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 TIMOLAIN; a refraction might be necessary when the effects of the miotic have passed. *Paediatric Population:* There is only very limited data available on the use of Timolol in the paediatric population.

Pharmacokinetics:
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. *Paediatric Population:* As already confirmed by adult data, 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.

Indication:
TIMOLAIN Ophthalmic Solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open angle glaucoma.

Recommended Dosage:
Adults and children over 12 years: recommended therapy is one drop of TIMOLAIN in the affected eye(s) twice a day.
Elderly: Dosage need not be modified for the elderly as there has been wide experience with the use of TIMOLAIN in elderly patients.
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.
Intraocular pressure should be reassessed approximately four weeks after starting treatment because response to TIMOLAIN may take a few weeks to stabilise. Provided that intraocular pressure is maintained at satisfactory levels, many patients can then be placed on once daily therapy.
If necessary, concomitant treatment with miotics, epinephrine and/or carbonic anhydrase inhibitors can be instituted. In order to prevent the active substance(s) from being washed out when additional ophthalmic medication is used, an interval of at least 10 minutes between each application is recommended. The use of two topical beta-adrenergic agents is not recommended.
Transfer from other topical beta-blocking agents: Discontinue use after a full day of therapy and start treatment with TIMOLAIN the next day, with one drop in each affected eye twice daily.
Transfer from a single antiglaucoma agent other than a topical beta-blocking agent: Continue the agent and add one drop of TIMOLAIN in each affected eye twice daily. On the following day, discontinue the previous agent completely, and continue with TIMOLAIN.
Patients should be instructed to remove soft contact lenses before using timolol.
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 decision is made on a surgical approach and in case of failed surgery while awaiting further options.
Posology: 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 strongly observed after the first dose for one to two hours in the office and closely monitored for ocular and systemic side effects until surgery is performed. With regard to paediatric use, the 0.1% active agent concentration might already be sufficient.
Method of administration: To limit potential adverse effects only one drop should be instilled per dosing time. Systemic absorption of topically administered beta-blockers can be reduced by nasolacrimal occlusion and by keeping the eyes closed as long as possible after instillation of drops.
Duration of treatment: For a transient treatment in the paediatric population.

Route of Administration: FOR TOPICAL OPHTHALMIC USE ONLY

Contraindications:
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 and third degree atrioventricular block not controlled with pace-maker, overt cardiac failure, cardiogenic shock. Hypersensitivity to the active substance or to any of the excipients.

Warning and Precautions:
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 TIMOLAIN. 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. TIMOLAIN 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 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. TIMOLAIN has been generally well tolerated in glaucoma patients wearing conventional hard contact lenses. TIMOLAIN has not been studied in patients wearing lenses made with material other than polymethylmethacrylate (PMMA), which is used to make hard contact lenses. TIMOLAIN contains benzalkonium chloride as a preservative which may be deposited in soft contact lenses; therefore TIMOLAIN 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. In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. TIMOLAIN has little or no effect on the pupil. When TIMOLAIN is used to reduce elevated intra-ocular pressure in angle-closure glaucoma it should be used with a miotic and not alone. Patients should 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 multidose container. 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.
Paediatric Population: Timolol solutions should generally be used cautiously in young glaucoma patients. It is important to notify the parents of potential side effects so they can immediately discontinue the drug therapy. Signs to look for are, for example, coughing and wheezing. Because of the possibility of apnoea and Cheyne-Stokes breathing, the drug should be used with extreme caution in neonates, infants and younger children. A portable apnoea monitor may also be helpful for neonates on Timolol.

Caution:
For topical ophthalmic use only. Not for injection into the eye.
Discard 28 days after first opening. Do not use if leakage is detected. Do not touch bottle tip to any surface, as this may contaminate the solution.

Interactions with Other Medications:
No specific drug interaction studies have been performed with timolol maleate. 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 TIMOLAIN 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.

Statement on Usage during Pregnancy and Lactation:
Pregnancy:
There are no adequate data for the use of timolol maleate in pregnant women. TIMOLAIN should not be used during pregnancy unless clearly necessary.

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

Adverse Effects/Undesirable Effects:
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 this or other timolol maleate formulations, either in clinical trials or since the drug has been marketed. 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 TIMOLAIN.

Eye disorders
Ocular: 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. Visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis and choroidal detachment following filtration surgery.

Ear and labyrinth disorders
Ocular: tinnitus.

Cardiac disorders
Ocular: bradycardia, chest pain, arrhythmia, heart block, congestive heart failure, palpitations, cardiac arrest, atrioventricular block, cardiac failure, oedema;
Systemic: AV block (second- or third-degree), sino-atrial block, pulmonary oedema, worsening of arterial insufficiency, worsening of angina pectoris, vasodilation.

Vascular disorders
Ocular: claudication, hypotension, Raynaud's phenomenon, cold hands and feet.

Respiratory, thoracic and mediastinal disorders
Ocular: bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnoea, cough.
Systemic: rales.

General disorders and administration site conditions
Ocular: asthenia, fatigue.
Systemic: extremity pain, decreased exercise tolerance.

Skin and subcutaneous tissue disorders
Ocular: alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash.
Systemic: sweating, exfoliative dermatitis.

Immune system disorders
Ocular: systemic lupus erythematosus, pruritus.
Systemic: signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash, anaphylactic reaction.

Psychiatric disorders
Ocular: depression, insomnia, nightmares, memory loss.
Systemic: diminished concentration, increased dreaming.

Nervous system disorders
Ocular: syncope, cerebrovascular accident, cerebral ischemia, headache, dizziness, increase in signs and symptoms of myasthenia gravis, paraesthesia.
Systemic: vertigo, local weakness

Gastrointestinal disorders
Ocular: nausea, diarrhoea, dyspepsia, dry mouth dysgeusia, abdominal pain vomiting.

Reproductive system and breast disorders
Ocular: decreased libido, Peyronie's disease, sexual dysfunction such as impotence.
Systemic: micturition difficulties.

Metabolism and nutrition disorders
Ocular: hypoglycaemia.
Systemic: hyperglycaemia.

Musculoskeletal and connective tissue disorders
Ocular: myalgia;
Systemic: arthralgia.

Blood and lymphatic system disorders
Systemic: non-thrombocytopenic purpura.

Overdose and Treatment:
No specific data are available. Overdosage is unlikely to occur as one 5ml bottle of Timolol Maleate Ophthalmic Solution (Timolol 0.5%) contains 25 mg of Timolol compared with the usual adult oral dose of 20-60 mg per day. However, in the rare event that overdosage occurs the most common signs and symptoms to be expected following overdosage with a beta-adrenergic receptor blocking agent are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure. If overdosage occurs, the following measures should be considered:
Gastric lavage, if ingested. Studies have shown that timolol does not dialyse readily.

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.
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.
Bronchospasm	:Isoprenaline hydrochloride should be used. Additional therapy with aminophylline may be considered.
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.
Heart block (second or third degree)	:Isoprenaline hydrochloride or a pacemaker should be used.

Storage conditions before and after opening: Do not store above 30°C. Protect from light.

Shelf life:
2 years from manufacturing date in the proposed storage condition. Discard 28 days after first opening. Do not use after expiry.

Dosage forms and packaging available:
5 mL X 20 LDPE Plastic Bottle per box.

Manufacturer/Product Registration Holder:

AIN MEDICARE SDN.BHD.
Lot 4933, 4934 & PT2464, Jalan 6/44, Kaw. Perindustrian Pengkalan Chepa 2, 16100 Kota Bharu, Kelantan, MALAYSIA.

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