SUMMARY PRODUCT CHARACTERISTICS (SPC)

TIMOLOL EYE DROPS (Ivytimol 0.5% eye drops)

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1. NAME OF MEDICINAL PRODUCT:

TIMOLOL EYE DROPS (Ivytimol eye drops)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative composition:

Tmolol (as timolol maleate) BP

Quantitative composition:

Timolol (as timolol maleate) 0.5%$^{w}/_{v}$. (5 mg/ml)

For full list of Excipients, see section 6.1

3. PHARMACEUTICAL FORM OF THE DRUG PRODUCT

EYE DROP

4. CLINICAL PARTICULARS

4.1 INDICATIONS

Timolol maleate eye drops are a beta-adrenergic receptor antagonist used topically for the reduction of elevated intra-ocular pressure in various conditions including patients with ocular hypertension; patients with chronic open-angle glaucoma including patients with aphakia; and some patients with Secondary glaucoma.

4.2 Posology and method of administration:

One drop to be instilled into the affected eye twice daily or as directed by your doctor.

Use in the elderly:

There has been wide experience with the use of Timolol maleate in elderly patients.

The dosage recommendations above reflect the clinical data derived from this experience.

4.3 Contraindications:

Hypersensitivity to the active substance (substances), 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 pre cautions for use:
Like other topically applied ophthalmic agents Timolol Maleate is absorbed systemically. Due to beta-adrenergic component, Timolol Maleate, 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. To reduce the systemic absorption, 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.

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.
Hypoglycemia/diabetes
Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycemia. 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 Maleate 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 Maleate.
If Timolol maleate ophthalmic solution is used to reduce elevated intra-ocular pressure in angle closure glaucoma they should be used with a miotic and not alone.
There have been reports of skin rashes and/or dry eyes associated with the use of Beta-adrenergic receptor 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.
Timolol Eye Drops contain Benzalkonium chloride as a preservative, which may be deposited in soft contact lenses. Therefore, Timolol eye drops should not be used while wearing soft contact lenses. The lenses should be removed before application of the drops and not reinserted earlier than 15 minutes after use.
Timolol Eye Drops have generally been well tolerated in glaucoma patients wearing Conventional hard contact lenses. Timolol maleate ophthalmic solution has not been Studied in patients wearing lenses made of material other than polymethyl methacrylate (PMMA) which is used to make hard contact lenses.
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.

4.5 Interactions with other medicinal products and other forms of interactions
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, parasympathomimetics, guanethidine.
Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (Epinephrine) 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 β-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. Timolol may potentially add to the effects of oral calcium antagonists,

rauwolfia alkaloids or beta-blockers, to induce hypotension and/or marked bradycardia.
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 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 entry blocker is added to the treatment regimen. The nature of any cardiovascular adverse effect tends to depend on the type of calcium 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. The concomitant use of beta-adrenergic blocking agents and digitalis with either diltiazem or verapamil may have additive effects in prolonging AV conduction time. Those treated with Insulin may find its hypoglycaemic activity enhanced. Intravenous calcium channel blockers should be used with caution in patients receiving beta-adrenergic blocking agents.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data for the use of Timolol Maleate in pregnant women. Timolol Maleate should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption. 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 Maleate 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. However the decision for breast-feeding mothers either to stop taking Timolol eye drops or stop Nursing should be based on the importance of the drug to the mother. To reduce the systemic absorption.

4.7 Effects on ability to drive and use machines

Instillation of Timolol Eye Drops may cause dizziness and transient blurring of vision. Patients should be warned not to drive or operate moving machinery until any dizziness or blurring of vision has totally regressed.

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 beta blocking 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 beta-blockers.

Timolol Eye Drops is usually well tolerated. 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:

Blood and lymphatic system disorders

Non-thrombocytopenic purpura.

Immune system disorders:

Systemic allergic reactions including angioedema, urticaria, localized and Generalized rash, systemic lupus erythematosus, pruritus, anaphylactic reaction.

Metabolism and nutrition disorders:

Hypoglycaemia and hyperglycaemia.

Psychiatric disorders:

Insomnia, depression, nightmares, memory loss, increased dreaming.

Nervous system disorders:

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

Eye disorders**:**

Signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, and redness), blepharitis, conjunctivitis, keratitis, blurred vision and choroidal detachment following filtration surgery (see 4.4 Special warnings and special precautions for use). Visual disturbances, including refractive Changes (due to withdrawal of miotic therapy in some cases). Decreased corneal sensitivity, dry eyes, corneal erosion ptosis, and diplopia**.**

Cardiac disorders:

B Bradycardia, chest pain, palpitations, edema, arrhythmia, congestive heart failure, claudication, sino-atrial block, pulmonary oedema, worsening of arterial insufficiency, worsening of angina pectoris, vasodilation, **Atrioventricular block, cardiac arrest, cardiac failure.**

Vascular disorders:

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

Respiratory, thoracic, and mediastinal disorders:

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnoea, cough, respiratory failure, rales,

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, sweating, exfoliative dermatitis.
Musculoskeletal and connective tissue disorders:
Myalgia, arthralgia
Ear and labyrinthine disorders:
Tinnitus
Reproductive system and breast disorders:
Sexual dysfunction, decreased libido, Peyronie's disease, impotence, micturition difficulties.
General disorders and administration site conditions:
Asthenia/fatigue, extremity pain, decreased exercise tolerance.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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, 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 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.
Paediatric Population:
There is only very limited data available on the use of Timolol (0.25%, 0.5% twice daily one drop) in the paediatric population for a treatment period up to 12 weeks. One small, double blinded, randomized, published clinical study conducted on 105 children (n=71 on Timolol) aged 12 days – 5 years show 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

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.

5.3 Preclinical safety data

No adverse ocular effects were observed in rabbits and dogs administered Timolol maleate eye drops 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 (p 0.05) 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 (p 0.05) increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinoma in female mice at 500mg/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 500mg/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 100mcg/ml). In Ames

tests the highest concentrations of Timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant (p 0.05) 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

Name of ingredient	**Reference**	**Amount per ml**	**Function/Reason For inclusion.**
Disodium edetate	BP	1.5mg	Chelating agent
Sodium chloride	BP	3.1mg	Tonicity adjusting agent
Benzalkonium chloride	BP	0.1mg	Preservative
Sodium phosphate dibasic	BP	10mg	Buffering agent
Sodium phosphate monobasic	BP	3.2mg	Buffering agent
Water for injection	BP	Quantity Sufficient to volume	Solvent

6.2 Incompatibilities
None known.

6.3 Shelf life
Unopened shelf-life is 24 months.
Opened shelf-life 28 days.
But the patient is advised to discard any remaining drops after the prescribed course of treatment.

6.4 Special precautions for storage
Store in a cool place (below 25° C) away from light. Keep out of reach of children

6.5 Nature and contents of container
5ml low density polyethylene bottles with a polypropylene spiked cap.

6.6 Special precautions for disposal

No special requirement

7 MARKETING AUTHORISATION HOLDER

(Company) Name: **IVEE AQUA EPZ LTD.**

Address: **P.O BOX 47536, GPO 00100**
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8 MARKETING AUTHORISATION NUMBER

Registration number: **NAFDAC REG NO. 04 – 3367**

9 DATE OF FIRST REGISTRATION/ RENEWAL OF REGISTRATION

10 DATE OF REVISION OF TEXT

November 2020-11-25

11 DOSIMETRY (IF APPLICABLE) Not Applicable

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUICALS (IF APPLICABLE) Not applicable