PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF MEDICINE

OPTITRIN 20 mg/ml + 5 mg/ml (Ophthalmic Solution)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 20 mg dorzolamide (as dorzolamide hydrochloride) and 5 mg timolol (as timolol maleate).

Excipient with known effect:

Each ml of solution contains 0,075 mg benzalkonium chloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ophthalmic solution.

Sterile, clear, slightly viscous, colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

OPTITRIN is indicated for the treatment of elevated intra-ocular pressure (IOP) in patients with ocular hypertension, open-angle glaucoma, pseudoexfoliative glaucoma or other secondary open-angle glaucomas when concomitant therapy is appropriate.

4.2 Posology and method of administration

Posology

Adults

The dose is one drop of OPTITRIN in the affected eye(s) two times daily.

When substituting OPTITRIN for another ophthalmic antiglaucoma agent(s), discontinue the other agent(s) after proper dosing on one day, and start OPTITRIN on the next day.

If another topical ophthalmic agent is being used, OPTITRIN and the other agent should be administered at least ten minutes apart.

Paediatrics

Safety and efficacy in paediatric patients below the age of 2 years have not been established. Although OPTITRIN has been used in children 2 to 6 years of age, however data on safety and efficacy are insufficient to recommend a safe and effective dose.

Method of administration

For ophthalmic use only.

Step 1: The tamper-proof seal on the bottle neck must be unbroken before the product is being used for the first time. A gap between the bottle and the cap is normal for an unopened bottle.

Step 2: The cap of the bottle should be taken off.

Step 3: The patient's head must be tilted back and the lower eyelid must be pulled gently down to form a small pocket between the eyelid and the eye.

Step 4: The bottle should be inverted and squeezed until a single drop is dispensed into the eye. The eye or eyelid must not be touched with the dropper tip.

Step 5: Steps 3 & 4 should be repeated with the other eye if it is necessary.

Step 6: The cap must be put back on and the bottle must be closed straight after it has been used.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic adverse reactions and an increase in local activity.

4.3 Contraindications

OPTITRIN is contraindicated in:

- Hypersensitivity to dorzolamide, timolol or to any of the excipients listed in section 6.1;
- Reactive airway disease, including bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease;
- Sinus bradycardia, sick sinus syndrome, sino-artrial block, second- or third-degree atrioventricular block not controlled with pacemaker, overt cardiac failure and cardiogenic shock;
- Severe renal impairment (CrCl < 30 ml/min) or hyperchloraemic acidosis;
- OPTITRIN contains the preservative benzalkonium chloride, which may be deposited in soft contact lenses. Therefore, OPTITRIN should not be administered while wearing these lenses. The lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use (see section 4.4);
- The safety of OPTITRIN in pregnant and lactating woman has not been established (see section 4.6).

4.4 Special warnings and precautions for use

Benzalkonium chloride

As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations cannot be excluded. Regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease.

Cardio-respiratory reactions

OPTITRIN 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 adverse drug reactions (ADRs) after topical ophthalmic administration is lower than for systemic administration. Because of the timolol maleate component, cardiac failure should be adequately controlled before beginning therapy with OPTITRIN.

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. OPTITRIN should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD).

Immunology and hypersensitivity

OPTITRIN is absorbed systemically. The dorzolamide component is a sulfonamide. Therefore, the same types of adverse reactions found with systemic administration of sulphonamides may occur with OPTITRIN. If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation. In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of dorzolamide hydrochloride ophthalmic solution. Some of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of therapy. Similar reactions have been reported with OPTITRIN. If such reactions are observed, discontinuation of treatment with OPTITRIN should be considered. While taking beta-blockers, including timolol, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to accidental, diagnostic, or therapeutic repeated challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine (adrenaline) used to treat anaphylactic reactions.

Renal and hepatic impairment

OPTITRIN is contraindicated in patients with severe renal impairment (CrCl less than 30 ml/min) (see section 4.3). Because dorzolamide hydrochloride and its metabolite are

excreted predominantly by the kidney, OPTITRIN is not recommended in such patients. OPTITRIN has not been studied in patients with hepatic impairment

Concomitant therapy

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving oral and topical carbonic anhydrase inhibitors concomitantly. The concomitant administration of OPTITRIN and oral carbonic anhydrase inhibitors has not been studied and is not recommended. Patients who are already receiving a beta-adrenergic blocking agent systemically and who are given OPTITRIN should be observed for a potential additive effect either on the intra-ocular pressure or on the known systemic effects of beta-blockade. The use of two topical beta-adrenergic blocking agents is not recommended.

Withdrawal therapy

As with systemic beta-blockers, if discontinuation of ophthalmic timolol is needed in patients with coronary heart disease, therapy should be withdrawn gradually.

Additional effects of Beta-Blockade

Hypoglycaemia and 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. Abrupt withdrawal of beta-blocker therapy may precipitate a worsening of symptoms.

Corneal diseases

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

Surgical anaesthesia

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. Therapy with beta-blockers may aggravate symptoms of myasthenia gravis.

Additional effects of carbonic anhydrase inhibition

Therapy with oral carbonic anhydrase inhibitors has been associated with urolithiasis as a result of acid-base disturbances, especially in patients with a prior history of renal calculi. Although no acid-base disturbances have been observed with this medicine, urolithiasis has been reported infrequently. Because OPTITRIN contains a topical carbonic anhydrase inhibitor that is absorbed systemically, patients with a prior history of renal calculi may be at increased risk of urolithiasis while using OPTITRIN.

Use in the Elderly

Of the total number of patients in clinical studies of OPTITRIN, 49 % were 65 years of age and over, while 13 % were 75 years of age and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Other

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive medicines. OPTITRIN has not been studied in patients with acute angle-closure glaucoma. Choroidal detachment has been reported

with administration of aqueous suppressant therapy (e.g., timolol, acetazolamide, dorzolamide) after filtration procedures. There is an increased potential for developing corneal oedema in patients with low endothelial cell counts. Precautions should be used when prescribing OPTITRIN to this group of patients.

Contact lens use

OPTITRIN contains the preservative, benzalkonium chloride, which may be deposited in soft contact lenses. Therefore, OPTITRIN should not be administered while wearing these lenses. The lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

Specific interaction studies have not been performed with OPTITRIN.

In clinical studies, OPTITRIN was used concomitantly with the following systemic medications without evidence of adverse interactions: ACE-inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin, and hormones (e.g., oestrogen, insulin, thyroxine).

The potential exists for additive effects and production of hypotension and/or marked bradycardia when timolol maleate ophthalmic solution is administered together with oral calcium channel blockers, catecholamine-depleting medicines or beta-adrenergic blocking agents.

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

The dorzolamide component of OPTITRIN is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. In clinical studies, dorzolamide hydrochloride ophthalmic solution was not associated with acid-base disturbances. However, these disturbances have been reported with oral carbonic anhydrase inhibitors and have in some instances, resulted in interactions (e.g., toxicity associated with high-dose salicylate therapy). Therefore, the potential for such interactions should be considered in patients receiving OPTITRIN.

Although OPTITRIN alone has little or no effect on pupil size, mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally. Beta-blockers may increase the hypoglycaemic effect of antidiabetic medicines.

Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of OPTITRIN in pregnant and lactating woman has not been established (see section 4.3). OPTITRIN should not be used during pregnancy.

Breastfeeding

Lactation is not recommended if treatment with [PROUCT NAME] is required.

Fertility

There is no data available on fertility with OPTITRIN.

4.7 Effects on ability to drive and use machines

Possible side effects such as blurred vision may affect some patients' ability to drive and/or operate machinery. Caution is advised until the effects of OPTITRIN in patients on treatment are known (see section 4.8).

4.8 Undesirable effects

a. Tabulated summary of adverse reactions

OPTITRIN

System Organ Class	Frequency	Undesirable effect
Eye disorders	*Frequent*	Burning and stinging, conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing
Gastrointestinal disorders	*Frequent*	Taste perversion (dysgeusia)
Skin and subcutaneous tissue disorders	*Less frequent*	Contact dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis
Renal and urinary disorders	*Less frequent*	Urolithiasis
Investigations	*Frequency unknown*	No clinically meaningful electrolyte disturbances

Immune system disorders	*Less frequent*	signs and symptoms of systemic allergic reactions, including angioedema, urticaria, pruritus, rash, anaphylaxis
Respiratory, thoracic, and mediastinal disorders	*Frequent*	Sinusitis
	Less frequent	Shortness of breath, respiratory failure, rhinitis, rarely bronchospasm

Dorzolamide Hydrochloride

System Organ Class	Frequency	Undesirable effect
Immune system disorders	*Less frequent*	Systemic allergic reactions including angioedema, urticaria, bronchospasm and pruritus
Nervous system disorders	*Frequent*	Headache
	Less frequent	Dizziness, paraesthesia
Eye disorders	*Frequent*	Eyelid inflammation, eyelid irritation, superficial punctuate keratitis
	Less frequent	Iridocyclitis, eyelid crusting, transient myopia (which resolved upon discontinuation of therapy), choroidal detachment (following filtration surgery), signs and symptoms of local reactions including palpebral reaction, corneal oedema, ocular hypotony, foreign body sensation in the eye

Respiratory, thoracic and mediastinal disorders	*Less frequent*	Epistaxis, dyspnoea
Gastrointestinal disorders	*Frequent*	Nausea
	Less frequent	Dry mouth, throat irritation
Skin and subcutaneous tissue disorders	*Less frequent*	Rash
General disorders and administration site conditions	*Frequent*	Asthenia, fatigue
Cardiac disorders	*Less frequent*	Palpitations

Timolol Maleate

System Organ Class	**Frequency**	**Undesirable effect**
Nervous system disorders	*Frequent*	Headache
	Less frequent	Dizziness, syncope, depression, insomnia, nightmares, memory loss, paraesthesia, increase in signs and symptoms of myasthenia gravis, decreased libido, cerebrovascular accident, cerebral ischaemia
Eye disorders	*Frequent*	Signs and symptoms of ocular irritation including blepharitis, keratitis, decreased corneal sensitivity, dry eyes, conjunctivitis
	Less frequent	Visual disturbances including refractive changes (due to withdrawal of miotic

		therapy in some cases), ptosis, diplopia, choroidal detachment (following filtration surgery), itching, tearing, redness, blurred vision, corneal erosion
Ear and labyrinth disorders	*Less frequent*	Tinnitus
Cardiac disorders	*Less frequent*	Bradycardia, hypotension, chest pain, palpitation, oedema, dysrhythmia, congestive heart failure, heart block, cardiac arrest
Vascular disorders	*Less frequent*	Hypotension, claudication, Raynaud's phenomenon, cold hands and feet
Respiratory, thoracic, and mediastinal disorders	*Less frequent*	Dyspnoea, bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, cough
Gastrointestinal disorders	*Less frequent*	Nausea, dyspepsia, diarrhoea, dry mouth, dysgeusia, abdominal pain, vomiting
Skin and subcutaneous tissue disorders	*Less frequent*	Alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash
Reproductive system and breast disorders	*Less frequent*	Peyronie's disease, decreased libido, sexual dysfunction
General disorders and administration site conditions	*Less frequent*	Asthenia, fatigue

Immune system disorders	*Less frequent*	Signs and symptoms of allergic reactions including angioedema, urticaria, localised and generalised rash, anaphylaxis, pruritus
Metabolism and nutrition disorders	*Less frequent*	Hypoglycaemia
Psychiatric disorders	*Less frequent*	Depression, insomnia, nightmares, memory loss, hallucination
Musculoskeletal and connective tissue disorders	*Less frequent*	Systemic lupus erythematosus, myalgia

b. Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No data is available with regard to human overdosage by accidental or deliberate ingestion of [PROUCT NAME]. There have been reports of inadvertent overdosage with timolol maleate ophthalmic solution 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. The most common signs and symptoms to be expected with overdosage of dorzolamide are electrolyte imbalance, development of an acidotic state, and possibly central nervous system effects (see section 4.8). Treatment

should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol does not dialyse readily.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.15.4 Ophthalmic Preparations, Other.

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, Beta blocking agents, Timolol, combinations

ATC Code: S01ED51

[PROUCT NAME] is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intra-ocular pressure by reducing aqueous humor secretion but does so by a different mechanism of action.

Dorzolamide hydrochloride is an inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport.

Timolol maleate is a nonselective beta-adrenergic receptor blocking agent and reduces intra-ocular pressure. The combined effect of these two agents results in additional intra-ocular pressure reduction compared to either component administered alone.

5.2 Pharmacokinetic properties

Dorzolamide Hydrochloride

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, agent and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of selective binding to CA-II while low concentrations of free medicine in plasma are maintained. The parent agent forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent agent but also inhibits a less active isoenzyme (CA-I). The metabolite also accumulates in RBCs where it binds primarily to CA-I. Dorzolamide binds moderately to plasma proteins (approximately 33 %). Dorzolamide is primarily excreted unchanged in the urine; the metabolite is also excreted in urine. After dosing ends, dorzolamide washes out of RBCs nonlinearly, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half-life of about four months.

Timolol Maleate

In a study of plasma drug concentration in six subjects, the systemic exposure to timolol was determined following twice daily topical administration of timolol maleate ophthalmic solution 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 Use

An ophthalmic solution containing 2 % dorzolamide hydrochloride and 0,5 % timolol has been used in children 2 to 6 years of age whose intraocular pressure could not be controlled on monotherapy with a 2 % dorzolamide hydrochloride solution. However, safety and efficacy data with this solution are insufficient to recommend a safe and effective dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)

Sodium citrate

Hydroxyethyl cellulose

Sodium hydroxide (for pH adjustment)

Benzalkonium chloride solution 50 %

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 24 months

After first opening: 28 days

6.4 Special precautions for storage

Store at or below 25 ºC.

Keep the container in the outer carton in order to protect from light.

Do not use more than 28 days after opening.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

White opaque medium density polyethylene bottle ophthalmic dispenser with a sealed LDPE dropper tip and a HDPE screw cap with tamper proof seal in a cardboard box.

Pack sizes: 1, 3 or 6 bottles of 5 ml each.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDERS OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

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