# DORTIMOPT

## 1. Product Name

DORTIMOPT 20 mg/ml + 5 mg/ml eye drops solution.

## 2. Qualitative and Quantitative Composition

Each ml of eye drops solution contains 20 mg of dorzolamide (22.26 mg dorzolamide hydrochloride) and 5 mg of timolol (6.83 mg of timolol maleate).

Excipient with known effect: benzalkonium chloride 0.075 mg/ml as a preservative.

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical Form

A clear, nearly colourless to colourless, slightly viscous solution.

## 4. Clinical Particulars

### *4.1 Therapeutic indications*

DORTIMOPT is indicated for the treatment of elevated intraocular pressure (IOP) in patients with:

- ocular hypertension
- open-angle glaucoma
- pseudoexfoliative glaucoma
- or other secondary open-angle glaucoma's

and who are:

- insufficiently responsive to topical beta blocker monotherapy
- currently receiving concomitant antiglaucoma therapies such as dorzolamide hydrochloride and timolol maleate.

### *4.2 Dose and method of administration*

**Dose**

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

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

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

***Paediatric population***

Safety and efficacy in paediatric patients below the age of 2 years have not been established. (For information regarding use in paediatric patients ≥ 2 years of age and < 6 years see section 4.4).

### Method of administration

The solution is applied as a drop to the affected eye(s).

## *4.3 Contraindications*

DORTIMOPT is contraindicated in patients with:

- reactive airway disease, bronchial asthma or a history of bronchial asthma, other obstructive lung disorders or a history of bronchospasm
- uncontrolled heart failure (see section 4.4)
- cardiogenic shock
- sick sinus syndrome
- second or third degree atrioventricular block and infranodal atrioventrical block
- severe bradycardia
- sino-atrial block
- hypersensitivity to one or both active substances, or to any of the excipients listed in section 6.1.

The above are based on the components and are not unique to the combination.

## *4.4 Special warnings and precautions for use*

The timolol component is a beta-blocker and although administered topically, is absorbed systemically. Therefore, the same types of adverse reactions found with systemic administration of beta-blockers may occur with topical administration.

### Cardio-respiratory 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.

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 DORTIMOPT should be discontinued.

Because of the timolol maleate component, cardiac failure should be adequately controlled before beginning therapy with DORTIMOPT. Patients with a history of cardiovascular disease, including cardiac failure should be watched for signs of deterioration of these diseases and pulse rates should be checked.

Due to its negative effect on conduction time, beta-blockers should be given with caution to patients with first degree heart block.

Because of potential effects of beta-adrenergic blocking agents relative to 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 DORTIMOPT, alternative therapy should be considered.

Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and rarely death in association with cardiac failure, have been reported following administration of timolol maleate ophthalmic solution.

In patients with mild/moderate chronic obstructive pulmonary disease (COPD), DORTIMOPT should be used with caution, and only if the potential benefit outweighs the potential risk.

## Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (e.g. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

## Masking of hypoglycemic symptoms in patients with diabetes mellitus

Beta-adrenergic blocking agents should be administered with caution in patients' subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycaemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycaemia.

## Masking of thyrotoxicosis

Beta-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g. tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

## Surgical anesthesia

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol (see section 4.9).

## Immunology and hypersensitivity

The dorzolamide component is a sulfonamide and although administered topically, is absorbed systemically. Therefore, the same types of adverse reactions found with systemic administration of sulfonamides may occur with topical administration, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. 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 medicine therapy. Similar reactions have been reported with dorzolamide and timolol ophthalmic solution. If such reactions are observed, discontinuation of treatment with DORTIMOPT should be considered.

While taking β-blockers, 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 adrenaline (epinephrine) used to treat anaphylactic reactions.

## 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 dorzolamide and timolol ophthalmic solution 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 DORTIMOPT should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta-blockade. The use of two topical beta-adrenergic blocking agents is not recommended.

## Other

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Dorzolamide and timolol ophthalmic solution 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 DORTIMOPT to this group of patients.

Beta-adrenergic blockade has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis, and generalised weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenic symptoms.

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 be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should be advised that if they develop an intercurrent ocular condition (e.g. trauma, ocular surgery or infection), or any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice concerning the continued use of the product.

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.

### Contact lens use

DORTIMOPT contains the preservative benzalkonium chloride, which may be deposited in soft contact lenses; therefore, DORTIMOPT 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.

### Use in hepatic impairment

Dorzolamide and timolol ophthalmic solution has not been studied in patients with hepatic impairment and therefore should be used with caution in such patients.

### Use in renal impairment

Dorzolamide and timolol ophthalmic solution has not been studied in patients with severe renal impairment (CrCl < 30 millilitre/min). Because dorzolamide hydrochloride and its metabolite are excreted predominantly by the kidney, DORTIMOPT is not recommended in such patients.

### Use in the elderly

Of the total number of patients in clinical studies of dorzolamide and timolol ophthalmic solution, 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.

### Paediatric use

The safety and usage of 2% dorzolamide hydrochloride ophthalmic solution has been tested in a clinical study of three months' duration in children under the age of 6 years. In this study, patients under 6 and greater than 2 years of age whose IOP was not controlled with monotherapy with dorzolamide or 0.5% timolol gel forming solution received dorzolamide and timolol ophthalmic solution. Nineteen of 66 patients randomised to dorzolamide monotherapy and 11 of 35 patients randomised to timolol monotherapy were transferred to dorzolamide and timolol ophthalmic solution. Of those 30 patients transferred to preserved dorzolamide and timolol ophthalmic solution, three patients had the following drug related adverse events: cough, burning / stinging eye and ocular injection.

### Effects on laboratory tests

Dorzolamide and timolol ophthalmic solution was not associated with clinically meaningful electrolyte disturbances in clinical studies.

## *4.5 Interaction with other medicines and other forms of interaction*

Specific medicine interaction studies have not been performed with dorzolamide and timolol ophthalmic solution.

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

However, the potential exists for additive effects and production of hypotension and/or marked bradycardia when timolol maleate ophthalmic solution is administered together with calcium channel blockers, catecholamine-depleting medicines, antiarrhythmics, parasympathomimetics 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, SSRIs) and timolol.

The dorzolamide component of DORTIMOPT 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 medicine interactions (e.g., toxicity associated with high-dose salicylate therapy). Therefore, the potential for such medicine interactions should be considered in patients receiving DORTIMOPT.

Although DORTIMOPT used alone has little or no effect on pupil size, mydriasis resulting from concomitant use of timolol maleate and adrenaline has been reported occasionally.

Beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. Caution should be exercised in patients using these medicines concomitantly. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

## *4.6 Fertility, pregnancy and lactation*

### Pregnancy

Category C.

Beta-adrenergic blocking agents may cause pharmacological effects such as bradycardia in the foetus and newborn infant.

Developmental toxicity studies with dorzolamide hydrochloride in rabbits at oral doses of ≥ 2.5 mg/kg/day (foetal red blood cell $C_{max}$ was approximately twice the maternal red blood cell $C_{max}$ after the recommended human ophthalmic dose) revealed malformations of the vertebral bodies. These malformations occurred at doses that caused metabolic acidosis with decreased body weight gain in dams and decreased foetal weights. No treatment-related malformations were seen at 1.0 mg/kg/day. There were no treatment-related foetal malformations in developmental toxicity studies with dorzolamide hydrochloride in rats at oral doses up to 10 mg/kg/day.

Developmental studies with timolol in mice, rats and rabbits at oral doses up to 50 mg/kg/day demonstrated no evidence of foetal malformations. Although delayed foetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of the offspring. Doses of 1000 mg/kg/day were maternotoxic in mice and resulted in an increased number

of foetal resorptions. Increased foetal resorptions were also seen in rabbits at oral doses of 100 mg/kg/day, in this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. DORTIMOPT should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

### Breast-feeding

Dorzolamide was excreted in the milk of lactating rats and decreases in the body weight gain of the offspring were seen during lactation after an oral dose of 7.5 mg/kg/day. A slight delay in postnatal development (incisor eruption, vaginal canalisation and eye openings), secondary to lower foetal body weight, was noted. It is not known whether dorzolamide is excreted in human milk.

Timolol has been detected in human milk following oral and ophthalmic administration of the medicine. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in the breast-feeding infant from DORTIMOPT, a decision should be made whether to discontinue breast-feeding or to discontinue the medicine, taking into account the importance of the medicine to the mother.

### Fertility

No data available in humans.

*Dorzolamide hydrochloride*

In reproduction studies of dorzolamide hydrochloride in rats, there were no adverse effects on the reproductive capacity of males or females at oral doses up to 15 and 7.5 mg/kg, respectively.

*Timolol maleate*

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses of up to 100 mg/kg/day.

## *4.7 Effects on ability to drive and use machines*

There are side effects associated with DORTIMOPT (such as blurred vision) that may affect some patients' ability to drive and/or operate machinery (see section 4.8).

## *4.8 Undesirable effects*

During clinical studies, 1035 patients were treated with dorzolamide and timolol ophthalmic solution. Approximately 2.4% of all patients discontinued therapy with dorzolamide and timolol ophthalmic solution because of local ocular adverse reactions. Approximately 1.2% of all patients discontinued because of local adverse reactions suggestive of allergy or hypersensitivity.

The most frequently reported medicine-related adverse effects were: ocular burning and stinging, taste perversion, corneal erosion, conjunctival injection, blurred vision, tearing and ocular itching. Urolithiasis was reported rarely.

Clinically adverse experiences in ≥ 1% of patients receiving combination therapy in phase III studies:

| | |
|---|---|
| **Body as a whole:** | abdominal pain |
| **Cardiovascular:** | hypertension |
| **Digestive:** | dyspepsia, nausea |
| **Musculoskeletal:** | back pain |
| **Nervous/psychiatric:** | dizziness, headache, paraesthesia |
| **Respiratory:** | bronchitis, cough, upper respiratory infection, influenza, pharyngitis, sinusitis |

| | |
|---|---|
| **Special senses:** | blepharitis, blurred vision, burning or stinging of the eye, conjunctivitis, visual field defect, eye discharge, eyelid oedema, corneal erosion, foreign body sensation, conjunctival injection, eye itching, lens opacity, eye pain, taste perversion, corneal staining, eye tearing |
| **Urogenital:** | urinary tract infection |

The following adverse reactions have been reported in post-marketing experience: dyspnoea, respiratory failure, contact dermatitis, bradycardia, heart block, choroidal detachment following filtration surgery, nausea, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Additional adverse effects that have been seen with one of the components and may be potential adverse effects of DORTIMOPT are:

### Dorzolamide hydrochloride

Headache; eyelid inflammation; nausea; eyelid irritation; eyelid crusting; asthenia/fatigue; iridocyclitis; rash; dizziness; paraesthesia, superficial punctate keratitis; transient myopia (which resolved upon discontinuation of therapy); signs and symptoms of local reactions including palpebral reactions and systemic allergic reactions including angioedema, bronchospasm, urticaria and pruritus; epistaxis, contact dermatitis, throat irritation, dry mouth. Choroidal detachment has been reported with administration of dorzolamide after filtration procedures.

### Timolol maleate (topical formulation)

Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, and decreased corneal sensitivity, dry eyes; visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, and ptosis; choroidal detachment following filtration surgery; tinnitus; bradycardia; arrhythmia; hypotension; syncope; heart block; cerebrovascular accident; cerebral ischaemia; congestive heart failure; palpitation; cardiac arrest; oedema, claudication, Raynaud's phenomenon, cold hands and feet; bronchospasm (predominantly in patients with pre-existing bronchospastic disease); cough; respiratory failure; dyspnoea; headache; asthenia; fatigue; chest pain; alopecia, psoriasiform rash or exacerbation of psoriasis; signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash; dizziness; depression, insomnia, nightmares, memory loss, hallucinations; increase in signs and symptoms of myasthenia gravis, paraesthesia; nausea, diarrhoea, dyspepsia, dry mouth, abdominal pain; decreased libido, Peyronie's disease, sexual dysfunction; systemic lupus erythematosus, myalgia.

### Timolol maleate (systemic formulation)

Extremity pain; decreased exercise tolerance; AV block (2nd or 3rd degree); sinoatrial block; pulmonary oedema; worsening of arterial insufficiency; worsening of angina pectoris; vasodilation; vomiting; diarrhoea, hyperglycaemia; hypoglycaemia; pruritis; sweating; exfoliative dermatitis; arthralgia; vertigo; local weakness; diminished concentration; increased dreaming; nonthrombocytopenic purpura; rales; impotence; micturition difficulties.

Clinically important changes in standard laboratory parameters were rarely associated with the administration of systemic timolol maleate. Slight increases in serum urea, serum potassium, serum uric acid and triglycerides; and slight decreases in haemoglobin, haematocrit and HDL-cholesterol occurred; but were not progressive or associated with clinical manifestations.

#### 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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

## *4.9 Overdose*

No data are available with regard to human overdosage by accidental or deliberate ingestion of dorzolamide and timolol ophthalmic solution.

There have been reports of inadvertent overdoses 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.

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.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

# 5. Pharmacological Properties

## *5.1 Pharmacodynamic properties*

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, Beta blocking agents, Timolol, combinations, ATC code: S01ED51

### Mechanism of action

DORTIMOPT is comprised of two components: dorzolamide hydrochloride and timolol maleate. It is the first combination of a topical carbonic anhydrase inhibitor and a topical beta-adrenergic receptor blocking agent. Each of these two components decreases elevated intraocular pressure by reducing aqueous humor secretion but does so by a different mechanism of action.

Dorzolamide hydrochloride is a potent 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 non-selective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that its predominant action may be related to reduced aqueous formation. However, in some studies, a slight increase in outflow facility was also observed. The combined effect of these two agents results in additional intraocular pressure reduction compared to either component administered alone.

Following topical administration, dorzolamide and timolol ophthalmic solution reduces elevated intraocular pressure, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage. Dorzolamide and timolol ophthalmic solution reduces intraocular pressure without the common adverse effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

## *5.2 Pharmacokinetic properties*

### Dorzolamide hydrochloride

Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows for the medicine to exert its effects directly in the eye at substantially lower doses and therefore with less systemic exposure. In clinical trials, this resulted in a reduction in IOP without the acid-base disturbances or alterations in electrolytes characteristic of oral carbonic anhydrase inhibitors.

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, drug 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 extremely low concentrations of free drug in plasma are maintained. The parent drug forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent drug 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 medicine concentration initially, followed by a slower elimination phase with a half-life of about four months.

To simulate maximum exposure after long term topical ocular administration, dorzolamide was given orally to eight healthy subjects for up to 20 weeks. The oral dose of 4 mg/day closely approximates the maximum amount of drug delivered by topical ocular administration of dorzolamide 2% three times daily. Steady state was reached within 13 weeks. At steady state, there was virtually no free drug or metabolite in plasma; CA inhibition in RBCs was less than that anticipated to be necessary for a pharmacological effect on renal function or respiration. Similar pharmacokinetic results were observed after chronic, topical administration of dorzolamide hydrochloride. However, some elderly patients with renal impairment (estimated CrCl 30-60 millilitre/min) had higher metabolite concentrations in RBCs, but no meaningful differences in carbonic anhydrase inhibition and no clinically significant systemic adverse effects were directly attributable to this finding.

### 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 less than the lower limit of quantification of the assay, 0.375 ng/mL.

## *5.3 Preclinical safety data*

### Genotoxicity

#### *Dorzolamide hydrochloride*

Dorzolamide showed no mutagenic potential in a series of standard assays for gene mutations, chromosomal damage and DNA damage.

#### *Timolol maleate*

*In vitro* and *in vivo* studies (Ames test, neoplastic cell transformation assay, cytogenetic assay and micronucleus test in mice) showed no genotoxicity of timolol.

### Carcinogenicity

#### *Dorzolamide hydrochloride*

In a two-year study of dorzolamide hydrochloride administered orally to male and female Sprague-Dawley rats, urinary bladder papillomas were seen in male rats in the highest dosage group of 20 mg/kg/day. No treatment-related tumours were seen in a 21-month study in male and female mice given oral doses up to 75 and 37.5 mg/kg/day, respectively.

The increased incidence of urinary bladder papillomas seen in the high-dose male rats appears to be a class-effect of carbonic anhydrase inhibitors in rats. Rats are particularly prone to developing papillomas in response to foreign bodies, compounds causing crystalluria and diverse sodium salts.

No changes in bladder urothelium were seen in dogs given oral dorzolamide hydrochloride for one year at 2 mg/kg/day or monkeys dosed topically to the eye at 0.4 mg/kg/day for one year.

#### *Timolol Maleate*

In a 2-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day. Similar differences were not observed in rats administered oral doses of 100 mg/kg/day.

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 adenocarcinomas in female mice at 500 mg/kg/day, but not at 50 mg/kg/day. In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumours was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg, but not at doses of 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumours has been established in humans. 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.

# 6. Pharmaceutical Particulars

## *6.1 List of excipients*

DORTIMOPT eye drops solution also contains

- sodium citrate
- hydroxyethyl cellulose
- sodium hydroxide
- mannitol
- benzalkonium chloride
- water for injection.

## *6.2 Incompatibilities*

Not applicable.

## *6.3 Shelf life*

3 years

DORTIMOPT should be used no longer than 28 days after first opening the container.

## *6.4 Special precautions for storage*

Store at or below 25°C.

For storage conditions after first opening the container, see section 6.3.

## *6.5 Nature and contents of container*

White opaque MDPE bottle with a sealed dropper tip, and a cap with a tamper proof seal.
Pack size of 5 ml of solution.

## *6.6 Special precautions for disposal*

No special requirements for disposal.

# 7. Medicines Schedule

Prescription Medicine

# 8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

# 9. Date of First Approval

20 October 2011

# 10. Date of Revision of the Text

22 March 2022

**Summary table of changes**

| Section | Summary of new information |
|---|---|
| - | Update to Viatris logo |
| 1 and 2 | Corrected dose form to “eye drops” to align with registered details. |
| 4.3 | Addition of a history of bronchial asthma. Expansion of abbreviated AV. |
| 4.4 | Reworded and relocation of text.<br>Included adrenaline as synonym for epinephrine.<br>Addition of ocular reactions, particularly conjunctivitis and lid reactions under “Other”.<br>Addition of Use in the elderly.<br>Paediatric use information relocated from section 5.1. |
| 4.5 | Addition of mydriasis resulting from concomitant use of timolol maleate and adrenaline.<br>Rewording of statement regarding caution in patients using beta-adrenergic blocking agents and clonidine concomitantly. |
| 4.6 | Addition of pregnancy category C. Additional animal toxicity information.<br>Additional information regarding dorzolamide and lactating rats.<br>Additional fertility information from animal studies. |
| 4.7 | Addition of adverse experiences from phase III studies.<br>Additional of potential effects identified from systemic formulation timolol maleate . |
| 5.2 | Additional information on subjects and dosing used for maximum exposure simulation. |
| 5.3 | Additional information on genotoxicity and carcinogenicity. |
| 8 | Sponsor details and telephone number updated to Viatris. |