NEW ZEALAND DATA SHEET – VIZO-PF DORZOLATIM (DORZOLAMIDE HYROCHLORIDE AND TIMOLOL MALEATE)

1. Vizo-PF Dorzolatim (Eye drop solution)

Dorzolamide (as hydrochloride) 20 mg/mL and timolol (as maleate) 5 mg/mL eye drop solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre of Vizo-PF Dorzolatim contains 20.00 mg (2.0% w/v) dorzolamide (22.26 mg of dorzolamide hydrochloride) and 5.00 mg (0.5% w/v) timolol (6.83 mg of timolol maleate) as the active ingredients.

For the full list of excipients, see **Section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Vizo-PF Dorzolatim eye drop solution is a clear, slightly viscous, colourless, aqueous, sterile ophthalmic solution practically free from visible particulates.

The solution is preservative free, isotonic and buffered and contains no antimicrobial agents.

Vizo-PF Dorzolatim eye drop solution has an osmolality of 251 – 289 mOsm/kg, viscosity of 70 – 160 cP and pH of 5.0 – 6.0.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Vizo-PF Dorzolatim is indicated in 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 Vizo-PF Dorzolatim in the affected eye(s) two times daily.

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

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

Paediatric population

Efficacy in paediatric patients has not been established. Safety in paediatric patients below the age of 2 years has not been established. (For information regarding safety in paediatric patients ≥ 2 and < 6 years of age, see **Section 4.4 Special warnings and precautions for use/Paediatric population**).

Method of administration

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

For individual patient use only.

4.3 CONTRAINDICATIONS

Vizo-PF Dorzolatim is contraindicated in patients with:

- reactive airway disease, bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease, or a history of bronchospasm
- uncontrolled heart failure (see **Section 4.4 Special warning and precautions for use, Systemic effects of beta-adrenergic blocking agents, Cardiac failure**) sinus bradycardia, sino-atrial block, 2nd or 3rd degree atrioventricular block, infranodal AV block, overt cardiac failure, severe bradycardia, cardiogenic shock
- hypersensitivity to any component of this product (see **Section 6.1 List of excipients**).

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

Because of the timolol maleate component, cardiac failure should be adequately controlled before beginning therapy with Vizo-PF Dorzolatim. 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.

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), Vizo-PF Dorzolatim 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.

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/timolol 2%/0.5% preservative-containing eye drops[1]. If such reactions are observed, discontinuation of treatment with Vizo-PF Dorzolatim should be considered.

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 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 hydrochloride and timolol maleate eye drop 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 Vizo-PF Dorzolatim 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 hydrochloride and timolol maleate eye drop 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 Vizo-PF Dorzolatim to this group of patients.

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.

There have been reports of bacterial keratitis associated with the use of multidose containers of topical ophthalmic products. These containers have been inadvertently contaminated by patients who, in most

[1] available in other brands

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.

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

Dorzolamide/timolol 2%/0.5% preservative-free eye drops have not been studied in people wearing contact lenses.

Systemic effects of beta-adrenergic blocking agents

Cardiac failure

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, Vizo-PF Dorzolatim should be discontinued.

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 adrenergic agonists such as isoproterenol, dopamine, dobutamine or levarterenol (see **Section 4.9 Overdose**).

Masking of hypoglycemic symptoms in patients with diabetes mellitus

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

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.

Muscle weakness

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.

General

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 VIZO-PF DORZOLATIM, alternative therapy should be considered.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, 2nd or 3rd degree atrioventricular block, or cardiac failure should be advised not to take this product (see **Section 4.3 Contraindications**).

Use in hepatic impairment

Dorzolamide hydrochloride and timolol maleate eye drop has not been studied in patients with hepatic impairment and therefore should be used with caution in such patients.

Use in renal impairment

Dorzolamide hydrochloride and timolol maleate eye drop 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, Vizo-PF Dorzolatim is not recommended in such patients.

Use in the elderly

Of the total number of patients in clinical studies of dorzolamide/timolol 2%/0.5% preservative-containing eye drops, 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 population

See **Section 5.1 Pharmacodynamic properties, Paediatric population**.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Specific medicine interaction studies have not been performed with dorzolamide hydrochloride and timolol maleate eye drop .

In clinical studies, dorzolamide/timolol 2%/0.5% preservative-containing eye drops were 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 Vizo-PF Dorzolatim 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 Vizo-PF Dorzolatim.

Although dorzolamide/timolol 2%/0.5% preservative free eye drops used alone has little or no effect on pupil size, mydriasis resulting from concomitant use of timolol maleate and adrenaline has been reported occasionally.

Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two medicines are co-administered, the beta-adrenergic blocking agent should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-adrenergic blocking agents should be delayed for several days after clonidine has stopped.

4.6 FERTILITY, PREGNANCY AND LACTATION

Fertility

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/day, 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.

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 1,000 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. Vizo-PF Dorzolatim should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breastfeeding

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 this medicine is excreted in human milk.

Timolol has been detected in human milk following oral and ophthalmic medicine administration. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Vizo-PF Dorzolatim a decision should be made whether to discontinue nursing or to discontinue the medicine, taking into account the importance of the medicine to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are side effects associated with Vizo-PF Dorzolatim that may affect some patients' ability to drive and/or operate machinery, such as blurred vision. See **Section 4.8 Adverse effects (Undesirable effects)**.

4.8 ADVERSE EFFECTS

In a clinical study, no adverse experiences specific to dorzolamide/timolol 2%/0.5% preservative-free eye drops have been observed; adverse reactions have been limited to those that were reported previously with dorzolamide/timolol 2%/0.5% preservative-containing eye drops, dorzolamide hydrochloride and/or timolol maleate.

During clinical studies, 1,035 patients were treated with dorzolamide/timolol 2%/0.5% preservative-containing eye drops. Approximately 2.4% of all patients discontinued therapy with dorzolamide/timolol 2%/0.5% preservative-containing eye drops 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.

Clinical 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

Post-marketing experience

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 side effects that have been seen with one of the components and may be potential side effects of Vizo-PF Dorzolatim are:

Dorzolamide hydrochloride
Headache; eyelid inflammation; eyelid irritation; eyelid crusting; asthenia/fatigue; iridocyclitis; rash; dizziness; paresthesia; 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; contact dermatitis, epistaxis, 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; psoriasisform 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; 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 (2^{nd} or 3^{rd} 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.

Laboratory findings

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at 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/timolol 2%/0.5% preservative-free eye drops.

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.

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 information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764766) (New Zealand).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

Vizo-PF Dorzolatim 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 nonselective 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 hydrochloride and timolol maleate eye drop 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 hydrochloride and timolol maleate eye drop reduces intraocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

Paediatric population

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 received dorzolamide and timolol ophthalmic solution. In those patients dorzolamide and timolol ophthalmic solution was generally well tolerated. Dorzolamide has not been studied in patients less than 36 weeks gestational age and less than 1 week of age. Patients with significant renal tubular immaturity should only receive dorzolamide after careful consideration of the risk benefit balance because of the possible risk of metabolic acidosis.

Clinical trials

Clinical studies of up to 15 months duration (double-masked phase of up to 3 months, followed by up to 12 months open-label treatment with dorzolamide/timolol 2%/0.5% preservative-containing eye drops) were conducted to compare the IOP-lowering effect of dorzolamide/timolol 2%/0.5% preservative-containing eye drops b.i.d. (dosed morning and bedtime) to individually- and concomitantly-administered 0.5% timolol and 2.0% dorzolamide in patients with glaucoma or ocular hypertension for whom concomitant therapy is appropriate. This includes both untreated patients and patients inadequately controlled with timolol monotherapy. The IOP-lowering effect of dorzolamide/timolol 2%/0.5% preservative-containing eye drops b.i.d. was greater than that of monotherapy with either 2% dorzolamide t.i.d. or 0.5% timolol b.i.d. The IOP-lowering effect of dorzolamide/timolol 2%/0.5% preservative-containing eye drops b.i.d. was equivalent to that of concomitant therapy with dorzolamide b.i.d. and timolol b.i.d. The IOP lowering effect of dorzolamide/timolol 2%/0.5% preservative-containing eye drops b.i.d. was approximately 1 mmHg less than that of concomitant therapy with 2% dorzolamide t.i.d. and 0.5% timolol b.i.d.

A. Comparison to concomitant therapy (Patients initiated on timolol therapy)

In a 3-month randomised, double-masked, parallel clinical study, patients receiving dorzolamide/timolol 2%/0.5% preservative-containing eye drops b.i.d. (n=151) were compared to patients receiving 0.5% timolol b.i.d. plus 2.0% dorzolamide b.i.d. concomitantly (n=148). At morning trough (hour 0) and morning peak (hour 2), patients receiving dorzolamide/timolol 2%/0.5% preservative-containing eye drops experienced IOP-lowering that was equivalent to that seen in the patients receiving the individual components concomitantly. (Equivalence was defined as a 90% confidence that the absolute difference between mean change in IOP for the 2 treatments was less than 1.5 mmHg). The following reductions in IOP were observed relative to the baseline value obtained after 2 weeks of 0.5% timolol b.i.d. monotherapy:

TABLE 1	Additional mean reduction in IOP from timolol baseline (mmHg)* [mean % reduction in IOP]	
	Day 90 (hour 0)	Day 90 (hour 2)
Dorzolamide/timolol 2%/0.5% preservative-containing eye drops b.i.d.	4.2 [16.3%]	5.4 [21.6%]
0.5% timolol b.i.d. + 2.0% dorzolamide b.i.d.	4.2 [16.3%]	5.4 [21.8%]

*Patients were required to have baseline IOP ≥ 22 mmHg for enrolment.

Four 3-month randomized, double-masked parallel clinical studies were conducted to compare dorzolamide/timolol 2%/0.5% preservative-containing eye drops b.i.d to 0.5% timolol b.i.d monotherapy and 2.0% dorzolamide t.i.d monotherapy. Two studies (n=685) were conducted in patients with baseline IOP ≤ 24 mmHg after a washout of all previous ocular hypotensive therapies. The other two studies (n=500) were conducted in patients with elevated IOP ≤ 22 mmHg inadequately controlled after 3 weeks of 0.5% timolol b.i.d monotherapy. Based upon post-hoc analyses of the combined washout studies data and the combined timolol run-in studies data, the estimated difference between the IOP-lowering effects of dorzolamide/timolol 2%/0.5% preservative-containing eye drops and dorzolamide was 1.9 – 2.4 mmHg (7.8 – 8.9%) at morning trough (hour 0) and 2.3 – 2.7 mmHg (9.9%) at morning peak (hour 2), while the estimated difference between the IOP-lowering effects of dorzolamide/timolol 2%/0.5% preservative-containing eye drops and timolol was 0.8 – 0.9 mmHg (2.9 – 3.5%) at morning trough (hour 0) and 1.8 – 2.3 mmHg (6.9 – 9.0%) at morning peak (hour 2). These differences are statistically significant in favour of the combination.

Long-term studies
Open-label extensions of two studies were conducted for up to 12 months. During this period, the IOP-lowering effect of dorzolamide/timolol 2%/0.5% preservative-containing eye drops b.i.d. was demonstrated throughout the day and this effect was maintained during the follow up period.

Preservative-free formulation study
In an active-treatment controlled, parallel, double masked study in 261 patients with elevated intraocular pressure > 22 mm Hg in one or both eyes, dorzolamide/timolol 2%/0.5% preservative-free eye drops has an IOP-lowering effect equivalent to that of dorzolamide/timolol 2%/0.5% preservative-containing eye drops over a period of 12 weeks. The safety profile of dorzolamide/timolol 2%/0.5% preservative-free eye drops was similar to dorzolamide/timolol 2%/0.5% preservative-containing eye drops.

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, medicine 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 medicine in plasma are maintained. The parent medicine forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent medicine 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 medicine delivered by topical ocular administration of dorzolamide 2% t.i.d. Steady state was reached within 13 weeks. At steady state, there was virtually no free medicine 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 side effects were directly attributable to this finding.

Timolol maleate
In a study of plasma medicine 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

Mannitol
Sodium citrate (may be added to adjust pH)
Hyetellose
Sodium hydroxide (may be added to adjust pH)
Water for injections

6.2. INCOMPATIBILITIES

Not applicable.

6.3. SHELF LIFE

Vizo-PF Dorzolatim has a shelf life of 36 months from the date of manufacture.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Unopened bottle: Store below 25 °C. Protect from heat.
Opened bottle: Store below 25 °C. Discard contents 4 weeks after opening the bottle. Protect from heat.

Vizo-PF Dorzolatim is a sterile solution that does not contain a preservative. To avoid contamination of the solution, keep the container tightly closed. Do not let the dropper tip touch any surface. Discard contents 4 weeks after opening the bottle. Contents are sterile if seal is intact.

6.5. NATURE AND CONTENTS OF CONTAINER

Vizo-PF Dorzolatim eye drops are supplied in a multidose container – white opaque LDPE bottle with white Novelia nozzle (HDPE and silicone) and blue tip and sealed with a white HDPE cap. Each 11 mL bottle is packed into a cardboard carton.

The bottle does not include an overfill.

Each bottle contains not less than 5 mL eye drop solution.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (S4)

8. SPONSOR

AFT Pharmaceuticals Ltd
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Takapuna
Auckland, 0622
NEW ZEALAND

Email: customer.service@aftpharm.com
Freephone: 0800 423 823

9. DATE OF FIRST APPROVAL

1-06-2023