Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dorzolamide/Timolol Mylan 20mg/ml + 5mg/ml Eye drops, Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:

Each ml of eye drops solution contains 0.15 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution
Clear, slightly viscous, colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dorzolamide/Timolol Mylan 20mg/ml + 5mg/ml Eye drops, Solution is indicated in the treatment of elevated intra-ocular pressure (IOP) in patients with open-angle glaucoma or pseudo-exfoliative glaucoma when topical beta-blocker monotherapy is not sufficient.

4.2 Posology and method of administration

Posology

The dose is one drop of Dorzolamide/Timolol Mylan in the (conjunctival sac of the) affected eye(s) two times daily.

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

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

Paediatric population:
Efficacy in paediatric patients has not been established.

Safety in paediatric patients below the age of two years has not been established. (for information regarding safety in paediatric patients ≥ 2 and < 6 years of age, see section 5.1).

Method of administration

For ocular use.

Patients should be instructed to wash their hands before use and avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.
In order to secure correct dosage - the dropper tip should not be enlarged.

Patients should also be instructed that 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.

Patients should be informed of the correct handling of the ophthalmic Dorzolamide/Timolol Mylan.

Usage instructions:
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.
2. The cap of the bottle should be taken off.
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.
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.**
5. Steps 3 & 4 should be repeated with the other eye if it is necessary.
6. The cap must be put back on and the bottle must be closed straight after it has been used.

4.3 Contraindications

Dorzolamide/Timolol Mylan is contra-indicated in patients with:
• hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
• reactive airway disease, including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease
• sinus bradycardia, sick sinus syndrome sino-atrial block, second or third degree atrioventricular block not controlled with a pace-maker, overt cardiac failure, cardiogenic shock
• severe renal impairment (creatinine clearance < 30 ml/min) or hyperchloraemic acidosis

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

4.4 Special warnings and precautions for use

Cardiovascular/respiratory reactions
Like other topically applied ophthalmic agents, dorzolamide/timolol is absorbed systemically. Due to beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

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/disordes (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.

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

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

Immunology and hypersensitivity
As with other topically-applied ophthalmic agents, this drug may be absorbed systemically. The dorzolamide component is a sulphonamide. Therefore the same types of adverse reactions found with systemic administration of sulphonamides may occur with topical administration, including severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation.

Local ocular adverse effects, similar to those observed with dorzolamide hydrochloride eye drops, have been seen with dorzolamide/timolol. If such reactions occur, discontinuation of Dorzolamide/Timolol Mylan should be considered.

Anaphylactic reactions:
While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Concomitant therapy
The following concomitant medication is not recommended:
− dorzolamide and oral carbonic anhydrase inhibitors
− topical beta-adrenergic blocking agents.

Other beta-blocking agents:
The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.5)

Withdrawal of 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/diabetes:
Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes mellitus, 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 dorzolamide/timolol urolithiasis has been reported infrequently. Because Dorzolamide/Timolol Mylan 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 Dorzolamide/Timolol Mylan.

Other
The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Dorzolamide/timolol has not been studied in patients with acute angle-closure glaucoma.

Corneal oedema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intra-ocular surgery while using dorzolamide. There is an increased potential for developing corneal oedema in patients with low endothelial cell counts. Topical dorzolamide should be used with caution in such patients.

Choroidal detachment
Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

As with the use of other antiglaucoma drugs, diminished responsiveness to ophthalmic timolol maleate after prolonged therapy has been reported in some patients. However, in clinical studies in which 164 patients have been followed for at least three years, no significant difference in mean intra-ocular pressure has been observed after initial stabilisation.

Contact lens use
Dorzolamide/Timolol Mylan contains the preservative benzalkonium chloride, which may cause eye irritation. Benzalkonium chloride is known to discolour soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion.

Paediatric population
See section 5.1.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with dorzolamide/timolol.

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

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, catecholamine-depleting medicines or beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

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

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

Although dorzolamide/timolol 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 agents.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Dorzolamide/Timolol Mylan should not be used during pregnancy.

Dorzolamide
No adequate clinical data in exposed pregnancies are available. In rabbits, dorzolamide produced teratogenic effects at maternotoxic doses (see Section 5.3).

Timolol
There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy unless clearly necessary. To reduce systemic absorption, see section 4.2.

Epidemiological studies have not revealed malformative effects but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If Dorzolamide/Timolol Mylan is administered until delivery, the neonate should be carefully monitored during the first days of life.

Breast-feeding

It is not known whether dorzolamide is excreted in human milk. In lactating rats receiving dorzolamide, decreases in the body weight gain of offspring were observed. Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2.

If treatment with Dorzolamide/Timolol Mylan is required, then breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Possible side effects such as blurred vision may affect some patients' ability to drive and/or operate machinery.

4.8 Undesirable effects

In clinical studies no adverse experiences specific to dorzolamide/timolol have been observed; adverse experiences have been limited to those that were reported previously with dorzolamide hydrochloride and/or timolol maleate. In general, common adverse experiences were mild and did not cause discontinuation.
During clinical studies, 1,035 patients were treated with dorzolamide/timolol. Approximately 2.4% of all patients discontinued therapy with dorzolamide/timolol because of local ocular adverse reactions, approximately 1.2% of all patients discontinued because of local adverse reactions suggestive of allergy or hypersensitivity (such as lid inflammation and conjunctivitis).

Like other topically applied ophthalmic drugs, dorzolamide/timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers

The following adverse reactions have been reported with dorzolamide/timolol eye drops solution or one of its components either during clinical trials or during post-marketing experience:

[Very common (≥1/10), Common: (≥1/100 to <1/10), Uncommon (≥1/1.000 to <1/100), Rare (≥1/10.000 to <1/1.000), Very rare (<1/10.000) and Not known (cannot be estimated from the available data)].

Immune system disorders:

Dorzolamide/Timolol ophthalmic solution
Rare: signs and symptoms of systemic allergic reactions, including angioedema, urticaria, pruritus, rash, anaphylaxis

Timolol maleate ophthalmic solution:
Rare: signs and symptoms of systemic allergic reactions including angioedema, urticaria, localised and generalised rash, anaphylactic reaction
*Not known**:* pruritus

Metabolism and nutrition disorders:

Timolol maleate ophthalmic solution:
*Not known**:* hypoglycaemia

Psychiatric disorders:

Timolol maleate ophthalmic solution:
Uncommon: depression*
Rare: insomnia*, nightmares*, memory loss.

Nervous system disorders:

Dorzolamide hydrochloride ophthalmic solution
Common: headache*
Rare: dizziness*, paraesthesia*

Timolol maleate ophthalmic solution
Common: headache*
Uncommon: dizziness*, syncope*
Rare: paraesthesia*, increase in signs and symptoms of myasthenia gravis, cerebrovascular accident*, cerebal ischaemia

Eye disorders:

Dorzolamide/Timolol ophthalmic solution
Very common: burning and stinging
Common: conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing

Dorzolamide hydrochloride ophthalmic solution
Common: eyelid inflammation*, eyelid irritation*
Uncommon: iridocyclitis*
Rare: irritation including redness*, pain*, eyelid crusting*, transient myopia (which resolved upon discontinuation of therapy), corneal oedema*, ocular hypotony*, choroidal detachment (following filtration surgery)*

Timolol maleate ophthalmic solution
Common: signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness) including blepharitis*, keratitis*, decreased corneal sensitivity, and dry eyes*
Uncommon: visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases)*

Rare: ptosis, diplopia, choroidal detachment following filtration surgery (see section 4.4)*
*Not known***:* itching, tearing, redness, blurred vision, corneal erosion

Ear and labyrinth disorders:

Timolol maleate ophthalmic solution
Rare: tinnitus*

Cardiac disorders:

Timolol maleate ophthalmic solution
Uncommon: bradycardia*
Rare: chest pain*, palpitations*, oedema*, arrhythmia*, congestive heart failure*, cardiac arrest*, heart block
*Not known***:* atrioventricular block, ,cardiac failure.

Vascular disorders:

Timolol maleate ophthalmic solution:
Rare: hypotension*, claudication, Raynaud's phenomenon*, cold hands and feet*

Respiratory, thoracic, and mediastinal disorders:

Dorzolamide/Timolol ophthalmic solution
Common: sinusitis
Rare: shortness of breath, respiratory failure, rhinitis, rarely bronchospasm

Dorzolamide hydrochloride ophthalmic solution
Rare: epistaxis*

Timolol maleate ophthalmic solution
Uncommon: dyspnoea*
Rare: bronchospasm (predominantly in patients with pre-existing bronchospastic disease)*, respiratory failure, cough*

Gastrointestinal disorders:

Dorzolamide/Timolol ophthalmic solution
Very common: dysgeusia

Dorzolamide hydrochloride ophthalmic solution
Common: nausea*
Rare: throat irritation, dry mouth*

Timolol maleate ophthalmic solution
Uncommon: nausea*, dyspepsia*
Rare: diarrhoea, dry mouth*
*Not known***:* dysgeusia, abdominal pain, vomiting

Skin and subcutaneous tissue disorders:

Dorzolamide/Timolol ophthalmic solution
Rare: contact dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Dorzolamide hydrochloride ophthalmic solution
Rare: rash*

Timolol maleate ophthalmic solution
Rare: alopecia*, psoriasiform rash or exacerbation of psoriasis*
*Not known***:* skin rash

Musculoskeletal and connective tissue disorders:

Timolol maleate ophthalmic solution
Rare: systemic lupus erythematosus
*Not known***:* myalgia

Renal and urinary disorders:

Dorzolamide/Timolol ophthalmic solution
Uncommon: urolithiasis

Reproductive system and breast disorders:

Timolol maleate ophthalmic solution
Rare: peyronie's disease*, decreased libido
*Not known***:* sexual dysfunction

General disorders and administration site disorders:

Dorzolamide hydrochloride ophthalmic solution
Common: asthenia/fatigue*

Timolol maleate ophthalmic solution
Uncommon: asthenia/fatigue*
*These adverse reactions were also observed with dorzolamide/timolol ophthalmic solution during post-marketing experience.

**Additional adverse reactions have been seen with ophthalmic beta-blockers and may potentially occur with Dorzolamide/Timolol Mylan.

Laboratory findings
Dorzolamide/timolol eye drops solution was not associated with clinically meaningful electrolyte disturbances in clinical studies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

No data are available in humans in regard to overdosage by accidental or deliberate ingestion of dorzolamide/timolol.

Symptoms
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.

Only limited information is available with regard to human overdosage by accidental or deliberate ingestion of dorzolamide hydrochloride. With oral ingestion, somnolence has been reported. With topical application the following have been reported: nausea, dizziness, headache, fatigue, abnormal dreams, and dysphagia.

Treatment
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

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, beta-blocking agents, ATC code: S01E D51

Mechanism of action
Dorzolamide/Timolol 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 a potent inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humour 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. The precise mechanism of action of timolol maleate in lowering intra-ocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that the 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 intra-ocular pressure reduction compared to either component administered alone.

Following topical administration, dorzolamide/timolol reduces elevated intra-ocular pressure, whether or not associated with glaucoma. Elevated intra-ocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.
Dorzolamide/timolol reduces intra-ocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

Pharmacodynamic effects

Clinical effects

Adult patients
Clinical studies of up to 15 months duration were conducted to compare the IOP-lowering effect of Dorzolamide/Timolol eye drops solution 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 was considered appropriate in the trials. This included both untreated patients and patients inadequately controlled with timolol monotherapy. The majority of patients were treated with topical beta-blocker monotherapy prior to study enrolment. In an analysis of the combined studies, the IOP-lowering effect of Dorzolamide/Timolol eye drops solution 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 eye drops solution 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 eye drops solution b.i.d. was demonstrated when measured at various time points throughout the day and this effect was maintained during long-term administration.

Paediatric population
A three months controlled study, with the primary objective of documenting the safety of 2% dorzolamide hydrochloride ophthalmic solution in children under the age of 6 years has been conducted. In this study, 30 patients under six and greater than or equal to two years of age whose IOP was not adequately controlled with monotherapy by dorzolamide or timolol received Dorzolamide/Timolol eye drops solution in an open label phase.

Efficacy in those patients has not been established. In this small group of patients, twice daily administration of Dorzolamide/Timolol was generally well tolerated with 19 patients completing the treatment period and 11 patients discontinuing for surgery, a change in medication, or other reasons.

5.2 Pharmacokinetic properties

Dorzolamide hydrochloride:

Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows for the active substance 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, active substance and metabolite concentrations in red blood cells (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 active substance in plasma are maintained. The parent active substance forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent active substance 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 non-linearly, resulting in a rapid decline of active substance concentration initially, followed by a slower elimination phase with a half-life of about four months.

When dorzolamide was given orally to simulate the maximum systemic exposure after long term topical ocular administration, steady state was reached within 13 weeks. At steady state, there was virtually no free active substance 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 creatinine clearance 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 active substance 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/millilitre and following afternoon dosing was 0.35 ng/millilitre.

5.3 Preclinical safety data

The ocular and systemic safety profile of the individual components is well established.

Dorzolamide
In rabbits given maternotoxic doses of dorzolamide associated with metabolic acidosis, malformations of the vertebral bodies were observed.

Timolol
Animal studies have not shown a teratogenic effect.

Furthermore, no adverse ocular effects were seen in animals treated topically with dorzolamide hydrochloride and timolol maleate ophthalmic solution or with concomitantly-administered dorzolamide hydrochloride and timolol maleate. *In vitro* and *in vivo* studies with each of the components did not reveal a mutagenic potential. Therefore, no significant risk for human safety is expected with therapeutic doses of Dorzolamide/Timolol Mylan.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol Hydroxyethyl cellulose
Sodium citrate Sodium hydroxide
Benzalkonium chloride
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
After first opening: 28 days

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture.

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 size: 1, 3 or 6 bottles of 5 ml each

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd.
T/A Gerard Laboratories
35-36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0577/124/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th August 2011

10 DATE OF REVISION OF THE TEXT

October 2015