Public Assessment Report

Decentralised Procedure

Dorzolamide/Timolol 20 mg/ml + 5 mg/ml
Eye Drops, Solution

PL 13757/0010
PL 13757/0012

UK/H/2197/01/DC
UK/H/3250/01/DC

Dr. Gerhard Mann Chem.-pharm. Fabrik GmbH
Lay summary

On 9 May 2011 the MHRA granted Dr. Gerhard Mann Chem.-pharm. Fabrik GmbH Marketing Authorisations (licences) for the medicinal product Dorzolamide/Timolol 20 mg/ml + 5 mg/ml Eye Drops, Solution. This is a prescription-only medicine (POM).

Dorzolamide/Timolol Eye Drops contain the active ingredients dorzolamide and timolol. Dorzolamide belongs to a group of medicines known as carbonic anhydrase inhibitors and timolol belongs to a group of medicines known as beta-blockers. Both active ingredients reduce pressure in the eye in different ways. Dorzolamide/Timolol Eye Drops are used to lower raised pressure in the eye in the treatment of glaucoma, when beta-blocker eye drops alone are not enough.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of using Dorzolamide/Timolol 20 mg/ml + 5 mg/ml Eye Drops, Solution outweigh the risks; hence Marketing Authorisations have been granted.
# TABLE OF CONTENTS

Module 1: Information about Decentralised Procedures  
Page 4

Module 2: Summaries of Product Characteristics  
Page 5

Module 3: Product Information Leaflet  
Page 30

Module 4: Labelling  
Page 38

Module 5: Scientific Discussion  
Page 43

1 Introduction  
2 Quality aspects  
3 Preclinical aspects  
4 Clinical aspects  
5 Overall conclusions and benefit-risk assessment
## Module 1

### Information about Decentralised Procedure

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Dorzolamide / Timolol 20 mg/ml + 5 mg/ml Eye Drops, Solution</th>
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<td>Names of the active substances (INN)</td>
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<tr>
<td>Pharmacotherapeutic group (ATC code)</td>
<td>Glaucoma agents and miotics, beta-adrenoreceptor antagonists, timolol, combinations (ATC code: S01ED51)</td>
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<tr>
<td>Pharmaceutical form and strength</td>
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<td>Dr. Gerhard Mann Chem.-pharm. Fabrik GmbH</td>
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<td>Brunsbütteler Damm 165 – 173</td>
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<td>13581 Berlin -GERMANY</td>
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Module 2

Summary of Product Characteristics

1  NAME OF THE MEDICINAL PRODUCT
Dorzolamide / Timolol  20 mg/ml + 5 mg/ml Eye Drops, Solution
dorzolamide / timolol

2  QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml contains 22.26 mg dorzolamide hydrochloride, equivalent to 20 mg dorzolamide and 6.83 mg timolol maleate, equivalent to 5 mg timolol.
Excipients: Benzalkonium chloride 0.075 mg/ml.
For a full list of excipients, see section 6.1.

3  PHARMACEUTICAL FORM
Eye drops, solution
Dorzolamide/Timolol Eye Drops, Solution is a clear, colourless to light yellow, sterile eye drop solution.

4  CLINICAL PARTICULARS

4.1 Therapeutic indications
Indicated for the treatment of increased intraocular pressure (IOP) in patients with open-angle glaucoma or pseudo-exfoliative glaucoma, when monotherapy with a topical beta-blocker is not sufficient.

4.2 Posology and method of administration

Posology
Adults
Dosage is one drop into the conjunctival sac of each affected eye twice daily.

Method of administration
If another ophthalmic agent is being administered, Dorzolamide/Timolol Eye Drops, Solution and the other agent should be applied at an interval of at least 10 minutes.
Patients should be advised to wash their hands prior to administration and to avoid touching the eyes or surrounding area with the dropper tip.
Patients should also be advised that eye drops, if handled incorrectly, can become contaminated by ubiquitous bacteria, which may lead to eye infections. Serious ocular damage and subsequent loss of vision may result from using contaminated eye drops.
Patients should be informed how to handle the bottle correctly.

Instructions for use
1. Wash your hands and sit or stand comfortably.
2. Twist off the cap.
3. Tilt the head back.
4. Use your finger to gently pull down the lower eyelid of your affected eye.
5. Invert the bottle and place the tip of the bottle close to, but not touching your eye.
   **DO NOT TOUCH YOUR EYE OR EYELID WITH THE DROPPER TIP.**
6. Squeeze the bottle gently so that only one drop goes into your eye, then release the lower eyelid.
7. Close the eye and press a finger against the corner of the affected eye by the nose. Hold for 1 minute.
8. Repeat in your other eye if your doctor has told you to do this.
9. Put the cap back on the bottle.

**Paediatric population**
The efficacy of Dorzolamide / Timolol Eye Drops, Solution in children aged from birth to 18 years of age has not yet been established. Current available data regarding safety in paediatric patients aged between 2 and 6 years are described in section 5.1 but no recommendation on a posology can be made.

### 4.3 Contraindications
Dorzolamide/Timolol Eye Drops, Solution is contraindicated in patients with hypersensitivity to one or both active substances or to any of the excipients. reactive airway disease, including bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease sinus bradycardia, second- or third-degree AV block, symptomatic heart failure, cardiogenic shock severe renal dysfunction (creatinine clearance < 30 ml/min) or hyperchloraemic acidosis
The above statements refer to the respective active substances and are not only restricted to the combination.

### 4.4 Special warnings and precautions for use
*Cardiovascular reactions/respiratory reactions*
As with other topically administered ophthalmic agents, this medicinal product may be systemically absorbed. The timolol maleate component is a beta-blocker. Therefore, the same undesirable effects encountered in systemic treatment with beta-blockers may occur with topical administration, including worsening of Prinzmetal’s angina, worsening of severe peripheral/central circulatory disorders and hypotension. Due to the timolol maleate component, heart failure should be appropriately treated prior to commencing Dorzolamide/Timolol Eye Drops, Solution therapy. In patients with a history of severe cardiac disease, vigilance is required for signs of cardiac failure and the heart rate should be monitored.
Following administration of timolol maleate, there have been reports of respiratory and cardiac reactions, including fatalities in patients with asthma due to bronchospasm and rare fatalities in patients with heart failure.

**Hepatic dysfunction**
Dorzolamide/Timolol Eye Drops, Solution has not been tested in patients with hepatic dysfunction and should therefore be used with caution in such patients.

**Immunology and hypersensitivity**
As with other topically administered ophthalmic agents, this medicinal product may be systemically absorbed. Dorzolamide possesses a sulphonamide group that is also found in sulphonamides. Therefore, the same undesirable effects encountered in systemic sulphonamide treatment may occur with topical administration. If signs of serious reactions or hypersensitivity reactions occur, this preparation must be discontinued.

Local adverse ocular reactions, similar to those seen with dorzolamide hydrochloride eye drops, have been observed during Dorzolamide/Timolol Eye Drops, Solution treatment. If such reactions occur, discontinuation of Dorzolamide/Timolol Eye Drops, Solution therapy should be considered.

During administration of beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to various allergens may be more responsive than normal to repeated accidental, diagnostic or therapeutic exposure to such allergens. Such patients may be unresponsive to the usual adrenaline dose used in the treatment of anaphylactic reactions.

**Concomitant therapy**
Adjuvant administration of the following medications is not recommended:
- dorzolamide and oral carbonic anhydrase inhibitors
- topical beta-receptor blockers.

**Discontinuation of therapy**
As with systemic beta-blockers, if discontinuation of timolol maleate eye drops becomes necessary in patients with coronary heart disease, therapy should be tapered off gradually.

**Additional effects of beta-blockade**
Therapy with beta-blockers can mask certain symptoms of hypoglycaemia in patients with diabetes mellitus or hypoglycaemia.
Therapy with beta-blockers can mask certain symptoms of hyperthyroidism. Abrupt discontinuation of beta-blocker therapy may precipitate exacerbation of symptoms.
Therapy with beta-blockers can 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 imbalances, particularly in patients with a prior history of kidney stones. Although no disturbances in the acid-base balance have been observed with Dorzolamide/Timolol Eye Drops, Solution, there have been rare reports of urolithiasis. As Dorzolamide/Timolol Eye Drops, Solution contains a topical carbonic anhydrase inhibitor that is
systemically absorbed, there may be an increased risk of urolithiasis during Dorzolamide/Timolol Eye Drops, Solution administration in patients with a prior history of kidney stones.

**Others**
Treatment of patients with acute angle-closure glaucoma requires adjuvant therapeutic procedures, in addition to ocular hypotensive agents. Dorzolamide/Timolol Eye Drops, Solution has not been tested in patients with acute angle-closure glaucoma.

During use of dorzolamide, corneal oedema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery. Topical dorzolamide should be used with caution in such patients. After filtration surgery, choroidal detachment in conjunction with ocular hypotension has been reported with administration of medications that suppress aqueous humor production.

As with the use of other antiglaucoma agents, reduced response to timolol maleate eye drops has been reported in some patients after prolonged therapy. However, in clinical studies where 164 patients were monitored for at least 3 years, no significant changes in mean intraocular pressure were observed after initial stabilisation.

**Use of contact lenses**
Dorzolamide/Timolol Eye Drops, Solution contains benzalkonium chloride as a preservative, which may cause eye irritation. Contact lenses should be removed prior to use of the drops and should not be reinserted for at least 15 minutes post-administration. Benzalkonium chloride leads to discolouration of soft contact lenses.

**Effects when misused for doping purposes**
In doping tests, use of Dorzolamide/Timolol Eye Drops, Solution may lead to positive results.

**Paediatric population**
See section 5.1.

### 4.5 Interaction with other medicinal products and other forms of interaction
No specific interaction studies have been performed with Dorzolamide/Timolol Eye Drops, Solution. In clinical studies, Dorzolamide/Timolol Eye Drops, Solution was co-administered with the following systemic medications without any occurrence of interactions: ACE inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs including acetylsalicylic acid, and hormones (e.g. oestrogen, insulin, thyroxine). However, effects may be potentiated - and hypotension and/or marked bradycardia may be precipitated - when timolol maleate eye drops are administered together with oral calcium channel blockers, catecholamine-depleting agents or beta-receptor agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, narcotics and monoamine oxidase (MAO) inhibitors.
Potentiated systemic beta-blockade (e.g. reduced heart rate, cases of depression) has been reported during concomitant treatment with CYP2D6 inhibitors (e.g. quinidine, selective serotonin reuptake inhibitors [SSRIs]) and timolol.

The dorzolamide component of Dorzolamide/Timolol Eye Drops, Solution is a carbonic anhydrase inhibitor, which, although topically administered, is absorbed systemically. In clinical studies, no disturbances in the acid-base balance occurred during treatment with dorzolamide hydrochloride eye drops. However, such disturbances have been observed with administration of oral carbonic anhydrase inhibitors, leading to interactions in some cases (e.g. toxic effects during high-dose salicylate therapy). Therefore, the potential for such interactions should be considered in patients receiving Dorzolamide/Timolol Eye Drops, Solution.

Although Dorzolamide/Timolol Eye Drops, Solution alone has only little or no effect on pupil size, there have been uncommon reports of mydriasis with concomitant use of timolol maleate eye drops and adrenaline. Beta-blockers may potentiate the hypoglycaemic effect of antidiabetic agents. Upon discontinuation of clonidine, oral beta-blockers may aggravate any hypertension that may occur as a result of rebound effects.

4.6 Pregnancy and lactation

Pregnancy

Dorzolamide/Timolol Eye Drops, Solution should not be used during pregnancy.

Dorzolamide:
There are no adequate clinical data available on exposed pregnant women. In rabbits, dorzolamide resulted in teratogenic effects at maternotoxic doses (see section 5.3).

Timolol:
Controlled epidemiological studies showed no teratogenic effects with systemic use of beta-blockers, but a few pharmacological effects such as bradycardia were observed in fetuses or neonates. If Dorzolamide/Timolol Eye Drops, Solution has been used up until parturition, the neonate must be carefully monitored during the first few days of life.

Breastfeeding

Dorzolamide:
It is not known whether dorzolamide passes into breast milk. A reduction in body weight gain was observed in the offspring of lactating rats given dorzolamide.

Timolol:
Timolol is detectable in human breast milk.

If treatment with Dorzolamide/Timolol Eye Drops, Solution is required, breast-feeding is not recommended.
4.7 Effects on ability to drive and use machines
Dorzolamide/Timolol Eye Drops, Solution has moderate influence on the ability to drive and use machines. Possible adverse reactions, such as blurred vision, may impair the ability of some patients to drive and/or use machines.

4.8 Undesirable effects
In clinical studies no adverse experiences specific to a Dorzolamide/Timolol Eye Drops, Solution 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 a Dorzolamide/Timolol Eye Drops, Solution. Approximately 2.4% of all patients discontinued therapy with Dorzolamide/Timolol Eye Drops, Solution 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).

The following adverse reactions have been reported with Dorzolamide/Timolol Eye Drops, Solutions or one of its components either during clinical trials or during post-marketing experience:

Adverse events are categorized by frequency as follows:
- 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)
- Not known (cannot be estimated from the available data)

Musculoskeletal and connective tissue disorders:
- Timolol maleate eye drops:
  - Rare: systemic lupus erythematosus

Nervous system disorders:
- Dorzolamide hydrochloride eye drops:
  - Common: headache
  - Rare: dizziness, paraesthesia
- Timolol maleate eye drops:
  - Common: headache
  - Uncommon: dizziness, depression
  - Rare: insomnia, nightmares, memory loss, paraesthesia, increase in the objective and subjective symptoms of myasthenia gravis, reduced libido, cerebrovascular accident

Eye disorders:
- Dorzolamide/Timolol Eye Drops, Solution
  - Very common: burning and stinging
Common: conjunctival injection, blurred vision, corneal erosion, ocular itching, lacrimation
Dorzolamide hydrochloride eye drops:
Common: eyelid inflammation, eyelid irritation
Uncommon: iridocyclitis
Rare: irritation e.g. redness, pain, eyelid crusting, transient myopia (which resolved upon discontinuation of therapy), corneal oedema, ocular hypotension and choroidal detachment (after filtration surgery)
Timolol maleate eye drops:
Common: subjective and objective symptoms of ocular irritation including blepharitis, keratitis, reduced corneal sensitivity and dry eyes
Uncommon: visual disturbances including refractive changes (in some cases, due to discontinuation of miotic therapy)
Rare: ptosis, diplopia, choroidal detachment (following filtration surgery)

**Ear and labyrinth disorders:**
Timolol maleate eye drops:
Rare: tinnitus

**Cardiac and vascular disorders:**
Timolol maleate eye drops:
Uncommon: bradycardia, syncope
Rare: hypotension, chest pain, palpitations, oedema, arrhythmia, heart failure, heart block, cardiac arrest, cerebral ischaemia, claudication, Raynaud’s phenomenon, cold hands and feet

**Respiratory, thoracic, and mediastinal disorders:**
Dorzolamide/Timolol Eye Drops, Solution
Common: sinusitis
Rare: shortness of breath, respiratory failure, rhinitis
Dorzolamide hydrochloride eye drops:
Rare: epistaxis
Timolol maleate eye drops:
Uncommon: dyspnoea
Rare: bronchospasm (mainly in patients with pre-existing bronchospastic disease), cough*

**Gastrointestinal disorders:**
Dorzolamide/Timolol Eye Drops, Solution
Very common: taste perversion
Dorzolamide hydrochloride eye drops
Common: nausea,
Rare: throat irritation, dry mouth
Timolol maleate eye drops:
Uncommon: nausea, dyspepsia
Rare: diarrhoea, dry mouth

**Skin and subcutaneous tissue disorders:**
Dorzolamide/Timolol Eye Drops, Solution
Rare: contact dermatitis
Dorzolamide hydrochloride eye drops
*Rare:* exanthem

Timolol maleate eye drops:
*Rare:* alopecia, psoriasiform exanthem or worsening of psoriasis

**Renal and urinary disorders:**
Dorzolamide/Timolol Eye Drops, Solution
*Uncommon:* urolithiasis.

**Reproductive system and breast disorders:**
Timolol maleate eye drops:
*Rare:* Peyronie’s disease

**General disorders and administration site disorders:**
Dorzolamide/Timolol Eye Drops, Solution
*Rare:* subjective and objective symptoms of systemic allergic reactions, including angioedema, urticaria, pruritus, exanthem, anaphylaxis, bronchospasm

Dorzolamide hydrochloride eye drops:
*Common:* asthenia/fatigue
Timolol maleate eye drops:
*Uncommon:* asthenia/fatigue

### 4.9 Overdose
For humans, no data are available with regard to overdosage following inadvertent or deliberate ingestion of Dorzolamide/Timolol Eye Drops, Solution.

**Symptoms**
There are reports of inadvertent overdosage with timolol maleate eye drops, which have led to systemic effects similar to those seen with systemic beta-receptor blockers, such as dizziness, headache, shortness of breath, bradycardia, bronchospasm and cardiac arrest. The most common objective and subjective symptoms to be expected from overdosage with dorzolamide hydrochloride are electrolyte shifts, development of acidosis and possibly effects on the CNS.

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

**Treatment**
Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol is not rapidly dialysable.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: glaucoma agents and miotics, beta-adrenoreceptor antagonists, timolol, combinations, ATC code: S01ED51

Mechanism of action
Dorzolamide/Timolol Eye Drops, Solution comprises two components: dorzolamide hydrochloride and timolol maleate. Each of these two components lowers increased intraocular pressure by reducing aqueous humor production 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 production, presumably by slowing down the formation of bicarbonate ions, with a 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 intraocular 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 humor 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 (IOP) reduction, compared to either component administered alone.
Following topical administration, Dorzolamide/Timolol Eye Drops, Solution reduces 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. Dorzolamide/Timolol Eye Drops, Solution reduces intra-ocular pressure without the common side effects of miotics such as night-blindness, accommodative spasm and pupillary constriction.

Pharmacodynamic effects
Clinical effects:
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 3 month 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 6 and greater than or equal to 2 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 Eye Drops, Solution 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 orally administered carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows the drug to exert its effects directly in the eye at a significantly lower dose and hence with less systemic exposure. In clinical studies, this resulted in a reduction in intraocular pressure without acid-base imbalances or the electrolyte shifts characteristic of orally administered carbonic anhydrase inhibitors. Following topical administration, dorzolamide reaches the systemic circulation. To assess possible systemic carbonic anhydrase inhibition after topical administration, drug and metabolite concentrations in red blood cells and plasma were measured, as well as carbonic anhydrase inhibition in red blood cells. During maintenance therapy, dorzolamide accumulates in red blood cells as a result of selective binding to carbonic anhydrase II (CA-II), whilst extremely low concentrations of the free drug remain in plasma.

Although the parent drug forms a single N-desethyl metabolite that inhibits carbonic anhydrase II (CA-II) less potently than the parent drug, it also inhibits another less active isoenzyme (CA-I). The metabolite also accumulates in red blood cells, where it binds mainly to CA-I. Dorzolamide displays moderate plasma protein binding (approximately 33%) and is mainly eliminated unchanged in the urine; the metabolite is also excreted in the urine. Once administration has ended, dorzolamide is washed out of red blood cells in a non-linear manner, initially resulting in a rapid decline in concentration, followed by a slower elimination phase with a half-life of approximately four months.

Following oral administration of dorzolamide to simulate maximum systemic exposure after long-term use of the topical ophthalmic form, steady state was reached within 13 weeks. At steady state, neither the free drug nor metabolites were detectable in plasma; carbonic anhydrase inhibition in red blood cells was less than that deemed necessary for a pharmacological effect on renal function or respiration. Similar pharmacokinetic results were observed following topical maintenance therapy with dorzolamide hydrochloride. However, whilst some elderly patients with renal dysfunction (estimated creatinine clearance 30-60 ml/minute) showed higher metabolite concentrations in red blood cells, the findings revealed no significant differences with regard to carbonic anhydrase inhibition and no clinically significant systemic adverse effects.
**Timolol maleate**

Aqueous humor level: In rabbits maximum aqueous humor levels of 461 ng/100 mg were measured 60 minutes after administering 1 drop of timolol 1.0%. In humans the aqueous humor levels of timolol during the 1st and 2nd hours after administering 2 drops of timolol 0.5 % were 150 ng/100 mg. After 7 hours had elapsed, the level fell to 10 ng/100 mg.

Ocular tissue level:

After applying one drop of a 0.25 % solution of 14C-marked timolol, the different ocular tissues of the rabbit eye reached maximum radioactivities after 15 to 60 minutes. The cornea, nictitating membrane and iris/ciliary body yielded radioactivities corresponding to 1 to 10 ng timolol/100 mg tissue.

Systemic resorption:

Studies have shown that after local application to the eye timolol is systemically resorbed. In one study timolol was detected in the urine of all examined healthy subjects and patients. (Timolol hydrogen maleate and its metabolites are primarily excreted by the kidneys.)

Blood level:

Blood levels of timolol in humans after local application to the eye at the recommended clinical dose frequently cannot be detected (smaller than 2 ng/ml), neither after a single dose nor after a treatment period of two weeks. The maximum measured plasma levels were 9.6 ng/ml at a dose of 2 x 2 drops/day. The maximum plasma levels were achieved after 30 – 90 minutes.

It was shown in several cases that the application of timolol-containing eye drops in neonates and toddlers at the recommended dose led to significantly higher plasma concentrations of timolol than in adults. The plasma level in a three-week old neonate after administering 2 x daily 1 drop 0.25% timolol-containing eye drops was 34 ng/ml.

5.3 **Preclinical safety data**

The ocular and systemic safety profile of the individual active substances is sufficiently well-known. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

**Dorzolamide**

With use in rabbits of maternotoxic doses associated with metabolic acidosis, vertebral body malformations were observed.

**Timolol**

Preclinical effects were observed after exposure to timolol, if the administered amount was sufficiently above the maximum therapeutic dose for humans. The relevance for humans is considered to be minimal. 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 Eye Drops, Solution.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Benzalkonium chloride
Hydroxyethylcellulose
Mannitol
Sodium citrate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Shelf life: 24 months
Shelf life after first opening: 28 days

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

Keep the bottle in the outer carton to protect from light.

6.5 Nature and contents of container
Low density polyethylene (LDPE) bottle with LDPE dropper tip and polypropylene (PP) cap containing 5 ml solution.

Dorzolamide/Timolol Eye Drops, Solution is available in the following pack sizes:
Pack of 1 bottle of 5 ml
Pack of 3 bottles of 5 ml each
Pack of 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
Dr. Gerhard Mann Chem.-pharm. Fabrik GmbH
Brunsbütteler Damm 165 – 173
13581 Berlin – GERMANY

8 MARKETING AUTHORISATION NUMBER(S)
PL 13757/0010
2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml contains 22.26 mg dorzolamide hydrochloride, equivalent to 20 mg dorzolamide and 6.83 mg timolol maleate, equivalent to 5 mg timolol.
Excipients: Benzalkonium chloride 0.075 mg/ml.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Eye drops, solution
Dorzolamide/Timolol Eye Drops, Solution is a clear, colourless to light yellow, sterile eye drop solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Indicated for the treatment of increased intraocular pressure (IOP) in patients with open-angle glaucoma or pseudo-exfoliative glaucoma, when monotherapy with a topical beta-blocker is not sufficient.

4.2 Posology and method of administration
Posology
Adults
Dosage is one drop into the conjunctival sac of each affected eye twice daily.

Method of administration
If another ophthalmic agent is being administered, Dorzolamide/Timolol Eye Drops, Solution and the other agent should be applied at an interval of at least 10 minutes.
Patients should be advised to wash their hands prior to administration and to avoid touching the eyes or surrounding area with the dropper tip.
Patients should also be advised that eye drops, if handled incorrectly, can become contaminated by ubiquitous bacteria, which may lead to eye
infections. Serious ocular damage and subsequent loss of vision may result from using contaminated eye drops.

Patients should be informed how to handle the bottle correctly.

**Instructions for use**

1. Wash your hands and sit or stand comfortably.
2. Twist off the cap.
3. Tilt the head back.
4. Use your finger to gently pull down the lower eyelid of your affected eye.
5. Invert the bottle and place the tip of the bottle close to, but not touching your eye.
   
   **DO NOT TOUCH YOUR EYE OR EYELID WITH THE DROPPER TIP.**
6. Squeeze the bottle gently so that only one drop goes into your eye, then release the lower eyelid.
7. Close the eye and press a finger against the corner of the affected eye by the nose. Hold for 1 minute.
8. Repeat in your other eye if your doctor has told you to do this.
9. Put the cap back on the bottle.

**Paediatric population**

The efficacy of Dorzolamide / Timolol Eye Drops, Solution in children aged from birth to 18 years of age has not yet been established.

Current available data regarding safety in paediatric patients aged between 2 and 6 years are described in section 5.1 but no recommendation on a posology can be made.

**4.3 Contraindications**

Dorzolamide/Timolol Eye Drops, Solution is contraindicated in patients with hypersensitivity to one or both active substances or to any of the excipients.

reactive airway disease, including bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease

sinus bradycardia, second- or third-degree AV block, symptomatic heart failure, cardiogenic shock

severe renal dysfunction (creatinine clearance < 30 ml/min) or hyperchloraemic acidosis

The above statements refer to the respective active substances and are not only restricted to the combination.

**4.4 Special warnings and precautions for use**

**Cardiovascular reactions/respiratory reactions**

As with other topically administered ophthalmic agents, this medicinal product may be systemically absorbed. The timolol maleate component is a beta-blocker. Therefore, the same undesirable effects encountered in systemic
treatment with beta-blockers may occur with topical administration, including worsening of Prinzmetal’s angina, worsening of severe peripheral/central circulatory disorders and hypotension. Due to the timolol maleate component, heart failure should be appropriately treated prior to commencing Dorzolamide/Timolol Eye Drops, Solution therapy. In patients with a history of severe cardiac disease, vigilance is required for signs of cardiac failure and the heart rate should be monitored. Following administration of timolol maleate, there have been reports of respiratory and cardiac reactions, including fatalities in patients with asthma due to bronchospasm and rare fatalities in patients with heart failure.

**Hepatic dysfunction**

Dorzolamide/Timolol Eye Drops, Solution has not been tested in patients with hepatic dysfunction and should therefore be used with caution in such patients.

**Immunology and hypersensitivity**

As with other topically administered ophthalmic agents, this medicinal product may be systemically absorbed. Dorzolamide possesses a sulphonamide group that is also found in sulphonamides. Therefore, the same undesirable effects encountered in systemic sulphonamide treatment may occur with topical administration. If signs of serious reactions or hypersensitivity reactions occur, this preparation must be discontinued. Local adverse ocular reactions, similar to those seen with dorzolamide hydrochloride eye drops, have been observed during Dorzolamide/Timolol Eye Drops, Solution treatment. If such reactions occur, discontinuation of Dorzolamide/Timolol Eye Drops, Solution therapy should be considered. During administration of beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to various allergens may be more responsive than normal to repeated accidental, diagnostic or therapeutic exposure to such allergens. Such patients may be unresponsive to the usual adrenaline dose used in the treatment of anaphylactic reactions.

**Concomitant therapy**

Adjuvant administration of the following medications is not recommended:

- dorzolamide and oral carbonic anhydrase inhibitors
- topical beta-receptor blockers.

**Discontinuation of therapy**

As with systemic beta-blockers, if discontinuation of timolol maleate eye drops becomes necessary in patients with coronary heart disease, therapy should be tapered off gradually.

**Additional effects of beta-blockade**

Therapy with beta-blockers can mask certain symptoms of hypoglycaemia in patients with diabetes mellitus or hypoglycaemia. Therapy with beta-blockers can mask certain symptoms of hyperthyroidism. Abrupt discontinuation of beta-blocker therapy may precipitate exacerbation of symptoms. Therapy with beta-blockers can 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 imbalances, particularly in patients with a prior history of kidney stones. Although no disturbances in the acid-base balance have been observed with Dorzolamide/Timolol Eye Drops, Solution, there have been rare reports of urolithiasis. As Dorzolamide/Timolol Eye Drops, Solution contains a topical carbonic anhydrase inhibitor that is systemically absorbed, there may be an increased risk of urolithiasis during Dorzolamide/Timolol Eye Drops, Solution administration in patients with a prior history of kidney stones.

**Others**

Treatment of patients with acute angle-closure glaucoma requires adjuvant therapeutic procedures, in addition to ocular hypotensive agents. Dorzolamide/Timolol Eye Drops, Solution has not been tested in patients with acute angle-closure glaucoma.

During use of dorzolamide, corneal oedema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery. Topical dorzolamide should be used with caution in such patients.

After filtration surgery, choroidal detachment in conjunction with ocular hypotension has been reported with administration of medications that suppress aqueous humor production.

As with the use of other antiglaucoma agents, reduced response to timolol maleate eye drops has been reported in some patients after prolonged therapy. However, in clinical studies where 164 patients were monitored for at least 3 years, no significant changes in mean intraocular pressure were observed after initial stabilisation.

**Use of contact lenses**

Dorzolamide/Timolol Eye Drops, Solution contains benzalkonium chloride as a preservative, which may cause eye irritation. Contact lenses should be removed prior to use of the drops and should not be reinserted for at least 15 minutes post-administration. Benzalkonium chloride leads to discolouration of soft contact lenses.

**Effects when misused for doping purposes**

In doping tests, use of Dorzolamide/Timolol Eye Drops, Solution may lead to positive results.

**Paediatric population**

See section 5.1.

### 4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with Dorzolamide/Timolol Eye Drops, Solution.

In clinical studies, Dorzolamide/Timolol Eye Drops, Solution was co-administered with the following systemic medications without any occurrence of interactions: ACE inhibitors, calcium channel blockers, diuretics, non-
steroidal anti-inflammatory drugs including acetylsalicylic acid, and hormones (e.g. oestrogen, insulin, thyroxine).

However, effects may be potentiated - and hypotension and/or marked bradycardia may be precipitated - when timolol maleate eye drops are administered together with oral calcium channel blockers, catecholamine-depleting agents or beta-receptor agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, narcotics and monoamine oxidase (MAO) inhibitors.

Potentiated systemic beta-blockade (e.g. reduced heart rate, cases of depression) has been reported during concomitant treatment with CYP2D6 inhibitors (e.g. quinidine, selective serotonin reuptake inhibitors [SSRIs]) and timolol.

The dorzolamide component of Dorzolamide/Timolol Eye Drops, Solution is a carbonic anhydrase inhibitor, which, although topically administered, is absorbed systemically. In clinical studies, no disturbances in the acid-base balance occurred during treatment with dorzolamide hydrochloride eye drops. However, such disturbances have been observed with administration of oral carbonic anhydrase inhibitors, leading to interactions in some cases (e.g. toxic effects during high-dose salicylate therapy). Therefore, the potential for such interactions should be considered in patients receiving Dorzolamide/Timolol Eye Drops, Solution.

Although Dorzolamide/Timolol Eye Drops, Solution alone has only little or no effect on pupil size, there have been uncommon reports of mydriasis with concomitant use of timolol maleate eye drops and adrenaline.

Beta-blockers may potentiate the hypoglycaemic effect of antidiabetic agents. Upon discontinuation of clonidine, oral beta-blockers may aggravate any hypotension that may occur as a result of rebound effects.

4.6 Pregnancy and lactation

Pregnancy

Dorzolamide/Timolol Eye Drops, Solution should not be used during pregnancy.

Dorzolamide:
There are no adequate clinical data available on exposed pregnant women. In rabbits, dorzolamide resulted in teratogenic effects at maternotoxic doses (see section 5.3).

Timolol:
Controlled epidemiological studies showed no teratogenic effects with systemic use of beta-blockers, but a few pharmacological effects such as bradycardia were observed in fetuses or neonates. If Dorzolamide/Timolol Eye Drops, Solution has been used up until parturition, the neonate must be carefully monitored during the first few days of life.

Breastfeeding

Dorzolamide:

...
It is not known whether dorzolamide passes into breast milk. A reduction in body weight gain was observed in the offspring of lactating rats given dorzolamide.

Timolol:
Timolol is detectable in human breast milk.
If treatment with Dorzolamide/Timolol Eye Drops, Solution is required, breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines
Dorzolamide/Timolol Eye Drops, Solution has moderate influence on the ability to drive and use machines. Possible adverse reactions, such as blurred vision, may impair the ability of some patients to drive and/or use machines.

4.8 Undesirable effects
In clinical studies no adverse experiences specific to a Dorzolamide/Timolol Eye Drops, Solution 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 a Dorzolamide/Timolol Eye Drops, Solution. Approximately 2.4% of all patients discontinued therapy with Dorzolamide/Timolol Eye Drops, Solution 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).

The following adverse reactions have been reported with Dorzolamide/Timolol Eye Drops, Solutions or one of its components either during clinical trials or during post-marketing experience:

Adverse events are categorized by frequency as follows:
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)
Not known (cannot be estimated from the available data)

Musculoskeletal and connective tissue disorders:
Timolol maleate eye drops:
Rare: systemic lupus erythematosus

Nervous system disorders:
Dorzolamide hydrochloride eye drops:
Common: headache
Rare: dizziness, paraesthesia
Timolol maleate eye drops:
Common: headache
Uncommon: dizziness, depression
Rare: insomnia, nightmares, memory loss, paraesthesia, increase in the objective and subjective symptoms of myasthenia gravis, reduced libido, cerebrovascular accident

**Eye disorders:**
Dorzolamide/Timolol Eye Drops, Solution
Very common: burning and stinging
Common: conjunctival injection, blurred vision, corneal erosion, ocular itching, lacrimation
Dorzolamide hydrochloride eye drops:
Common: eyelid inflammation, eyelid irritation
Uncommon: iridocyclitis
Rare: irritation e.g. redness, pain, eyelid crusting, transient myopia (which resolved upon discontinuation of therapy), corneal oedema, ocular hypotension and choroidal detachment (after filtration surgery)
Timolol maleate eye drops:
Common: subjective and objective symptoms of ocular irritation including blepharitis, keratitis, reduced corneal sensitivity and dry eyes
Uncommon: visual disturbances including refractive changes (in some cases, due to discontinuation of miotic therapy)
Rare: ptosis, diplopia, choroidal detachment (following filtration surgery)

**Ear and labyrinth disorders:**
Timolol maleate eye drops:
Rare: tinnitus

**Cardiac and vascular disorders:**
Timolol maleate eye drops:
Uncommon: bradycardia, syncope
Rare: hypotension, chest pain, palpitations, oedema, arrhythmia, heart failure, heart block, cardiac arrest, cerebral ischaemia, claudication, Raynaud’s phenomenon, cold hands and feet

**Respiratory, thoracic, and mediastinal disorders:**
Dorzolamide/Timolol Eye Drops, Solution
Common: sinusitis
Rare: shortness of breath, respiratory failure, rhinitis
Dorzolamide hydrochloride eye drops:
Rare: epistaxis
Timolol maleate eye drops:
Uncommon: dyspnoea
Rare: bronchospasm (mainly in patients with pre-existing bronchospastic disease), cough*

**Gastrointestinal disorders:**
Dorzolamide/Timolol Eye Drops, Solution
Very common: taste perversion
Dorzolamide hydrochloride eye drops
Common: nausea,
Rare: throat irritation, dry mouth
Timolol maleate eye drops:
Uncommon: nausea, dyspepsia
Rare: diarrhoea, dry mouth

Skin and subcutaneous tissue disorders:
Dorzolamide/Timolol Eye Drops, Solution
Rare: contact dermatitis
Dorzolamide hydrochloride eye drops
Rare: exanthem

Timolol maleate eye drops:
Rare: alopecia, psoriasiform exanthem or worsening of psoriasis

Renal and urinary disorders:
Dorzolamide/Timolol Eye Drops, Solution
Uncommon: urolithiasis.

Reproductive system and breast disorders:
Timolol maleate eye drops:
Rare: Peyronie’s disease

General disorders and administration site disorders:
Dorzolamide/Timolol Eye Drops, Solution
Rare: subjective and objective symptoms of systemic allergic reactions, including angioedema, urticaria, pruritus, exanthem, anaphylaxis, bronchospasm

Dorzolamide hydrochloride eye drops:
Common: asthenia/fatigue
Timolol maleate eye drops:
Uncommon: asthenia/fatigue

4.9 Overdose
For humans, no data are available with regard to overdosage following inadvertent or deliberate ingestion of Dorzolamide/Timolol Eye Drops, Solution.

Symptoms
There are reports of inadvertent overdosage with timolol maleate eye drops, which have led to systemic effects similar to those seen with systemic beta-receptor blockers, such as dizziness, headache, shortness of breath, bradycardia, bronchospasm and cardiac arrest. The most common objective and subjective symptoms to be expected from overdosage with dorzolamide hydrochloride are electrolyte shifts, development of acidosis and possibly effects on the CNS.

Only limited information is available with regard to human overdosage following accidental or deliberate ingestion of dorzolamide hydrochloride. Following oral ingestion, somnolence has been reported; following topical application, nausea, dizziness, headache, fatigue, abnormal dreams and dysphagia have been reported.
Treatment
Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol is not rapidly dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: glaucoma agents and miotics, beta-adrenoreceptor antagonists, timolol, combinations, ATC code: S01ED51

Mechanism of action
Dorzolamide/Timolol Eye Drops, Solution comprises two components: dorzolamide hydrochloride and timolol maleate. Each of these two components lowers increased intraocular pressure by reducing aqueous humor production 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 production, presumably by slowing down the formation of bicarbonate ions, with a 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 intraocular 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 humor 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 (IOP) reduction, compared to either component administered alone. Following topical administration, Dorzolamide/Timolol Eye Drops, Solution reduces 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. Dorzolamide/Timolol Eye Drops, Solution reduces intra-ocular pressure without the common side effects of miotics such as night-blindness, accommodative spasm and pupillary constriction.

Pharmacodynamic effects
Clinical effects:
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 3 month 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 6 and greater than or equal to 2 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 Eye Drops, Solution 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 orally administered carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows the drug to exert its effects directly in the eye at a significantly lower dose and hence with less systemic exposure. In clinical studies, this resulted in a reduction in intraocular pressure without acid-base imbalances or the electrolyte shifts characteristic of orally administered carbonic anhydrase inhibitors. Following topical administration, dorzolamide reaches the systemic circulation. To assess possible systemic carbonic anhydrase inhibition after topical administration, drug and metabolite concentrations in red blood cells and plasma were measured, as well as carbonic anhydrase inhibition in red blood cells. During maintenance therapy, dorzolamide accumulates in red blood cells as a result of selective binding to carbonic anhydrase II (CA-II), whilst extremely low concentrations of the free drug remain in plasma. Although the parent drug forms a single N-desethyl metabolite that inhibits carbonic anhydrase II (CA-II) less potently than the parent drug, it also inhibits another less active isoenzyme (CA-I). The metabolite also accumulates in red blood cells, where it binds mainly to CA-I. Dorzolamide displays moderate plasma protein binding (approximately 33%) and is mainly eliminated unchanged in the urine; the metabolite is also excreted in the urine. Once administration has ended, dorzolamide is washed out of red blood cells in a non-linear manner, initially resulting in a rapid decline in concentration, followed by a slower elimination phase with a half-life of approximately four months. Following oral administration of dorzolamide to simulate maximum systemic exposure after long-term use of the topical ophthalmic form, steady state was reached within 13 weeks. At steady state, neither the free drug nor metabolites were detectable in plasma; carbonic anhydrase inhibition in red blood cells was less than that deemed necessary for a pharmacological effect on renal function.
or respiration. Similar pharmacokinetic results were observed following topical maintenance therapy with dorzolamide hydrochloride. However, whilst some elderly patients with renal dysfunction (estimated creatinine clearance 30-60 ml/minute) showed higher metabolite concentrations in red blood cells, the findings revealed no significant differences with regard to carbonic anhydrase inhibition and no clinically significant systemic adverse effects.

**Timolol maleate**
Aqueous humor level: In rabbits maximum aqueous humor levels of 461 ng/100 mg were measured 60 minutes after administering 1 drop of timolol 1.0%. In humans the aqueous humor levels of timolol during the 1st and 2nd hours after administering 2 drops of timolol 0.5% were 150 ng/100 mg. After 7 hours had elapsed, the level fell to 10 ng/100 mg.

Ocular tissue level:
After applying one drop of a 0.25% solution of 14C-marked timolol, the different ocular tissues of the rabbit eye reached maximum radioactivities after 15 to 60 minutes. The cornea, nictitating membrane and iris/ciliary body yielded radioactivities corresponding to 1 to 10 ng timolol/100 mg tissue. Systemic resorption:
Studies have shown that after local application to the eye timolol is systemically resorbed. In one study timolol was detected in the urine of all examined healthy subjects and patients. (Timolol hydrogen maleate and its metabolites are primarily excreted by the kidneys.)

Blood level:
Blood levels of timolol in humans after local application to the eye at the recommended clinical dose frequently cannot be detected (smaller than 2 ng/ml), neither after a single dose nor after a treatment period of two weeks. The maximum measured plasma levels were 9.6 ng/ml at a dose of 2 x 2 drops/day. The maximum plasma levels were achieved after 30 – 90 minutes.

It was shown in several cases that the application of timolol-containing eye drops in neonates and toddlers at the recommended dose led to significantly higher plasma concentrations of timolol than in adults. The plasma level in a three-week old neonate after administering 2 x daily 1 drop 0.25% timolol-containing eye drops was 34 ng/ml.

5.3 Preclinical safety data
The ocular and systemic safety profile of the individual active substances is sufficiently well-known.
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

*Dorzolamide*
With use in rabbits of maternotoxic doses associated with metabolic acidosis, vertebral body malformations were observed.

*Timolol*
Preclinical effects were observed after exposure to timolol, if the administered amount was sufficiently above the maximum therapeutic dose for humans. The relevance for humans is considered to be minimal.
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 Eye Drops, Solution.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Benzalkonium chloride
Hydroxyethylcellulose
Mannitol
Sodium citrate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Shelf life: 24 months
Shelf life after first opening: 28 days

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

Keep the bottle in the outer carton to protect from light.

6.5 Nature and contents of container
Low density polyethylene (LDPE) bottle with LDPE dropper tip and polypropylene (PP) cap containing 5 ml solution.

Dorzolamide/Timolol Eye Drops, Solution is available in the following pack sizes:
Pack of 1 bottle of 5 ml
Pack of 3 bottles of 5 ml each
Pack of 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
Dr. Gerhard Mann Chem.-pharm. Fabrik GmbH
Brunsbütteler Damm 165 – 173
13581 Berlin -GERMANY

8 MARKETING AUTHORISATION NUMBER(S)
PL 13757/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09/05/2011

10 DATE OF REVISION OF THE TEXT
09/05/2011
Module 3

Product Information Leaflet

The following text is the approved Product Information Leaflet (PIL) text. No PIL mock-ups have been provided. In accordance with medicines legislation, the product will not be marketed in the UK until approval of the PIL mock-ups has been obtained.
In this leaflet:

1. What Dorzolamide/Timolol Eye Drops, Solution is and what it is used for
2. Before you use Dorzolamide/Timolol Eye Drops, Solution
3. How to use Dorzolamide/Timolol Eye Drops, Solution
4. Possible side effects
5. How to store Dorzolamide/Timolol Eye Drops, Solution
6. Further information

1. WHAT DORZOLAMIDE/TIMOLOL EYE DROPS, SOLUTION IS AND WHAT IT IS USED FOR

Dorzolamide/Timolol Eye drops, solution contains two active substances: dorzolamide and timolol.

- Dorzolamide belongs to a group of medicines known as "carbonic anhydrase inhibitors".
- Timolol belongs to a group of medicines known as "beta-blockers". Both active substances reduce pressure within the eye in different ways.

Dorzolamide/Timolol Eye drops, solution is prescribed to lower raised pressure within the eye in the treatment of glaucoma, when beta-blocker eye drops alone are not adequate.

2. BEFORE YOU USE DORZOLAMIDE/TIMOLOL EYE DROPS, SOLUTION

Do not use Dorzolamide/Timolol Eye Drops, Solution

- if you are allergic (hypersensitive) to dorzolamide, timolol or any of the other ingredients of Dorzolamide/Timolol
- if you have, or have ever had, a respiratory disorder such as asthma, or if you have chronic obstructive airway disease (i.e. abnormal constriction of the airways)
- if you suffer from certain heart conditions, including certain heart rhythm disorders with an unusually slow heart rate or severe heart failure
- if you suffer from severe kidney problems
- if you suffer from a condition where the blood turns acidic, due to high chloride levels (hyperchloraemic acidosis).

If you are not sure whether you should use Dorzolamide/Timolol Eye drops, solution, ask your doctor or pharmacist.

Take special care with Dorzolamide/Timolol Eye Drops, Solution
Tell your doctor about any health problems that you currently have or have had in the past – particularly:

- asthma or any other lung disease
- heart conditions
- poor circulation or blood circulation problems
- low blood pressure
- diabetes or low blood sugar (hypoglycaemia)
- thyroid disorders
- muscle weakness or myasthenia gravis (a skeletal muscle disorder)
- liver problems
- any allergies or allergic reaction
- kidney stones

Contact your doctor immediately if you have any eye problems, such as:

- eye irritation
- any other eye problems, such as eye redness or swollen eyelids

Tell your doctor if:

- you develop an eye infection
- you receive an eye injury
- you are undergoing eye surgery
- you have any new or worsening symptoms.

Use of Dorzolamide/Timolol Eye drops, solution in the eye can affect the whole body.

If you wear soft contact lenses, consult your doctor before using Dorzolamide/Timolol Eye drops, solution. See also 'Important information about some of the ingredients of Dorzolamide/Timolol Eye drops, solution' at the end of section 2.

Use in children
There is limited experience with Dorzolamide/Timolol Eye drops, solution in infants and children.

Use in elderly patients
The effect of Dorzolamide/Timolol Eye drops, solution is similar among elderly and younger patients.

Effects when misused for doping purposes
In doping tests, use of Dorzolamide/Timolol Eye drops, solution may lead to positive results.

Using other medicines
Tell your doctor or pharmacist if you are taking/using or have recently taken/used any other medicines, including other eye drops or medicines obtained without a prescription.

This is particularly important if you are taking/using any of the following:

- medicines to lower your blood pressure or to treat a heart condition (such as calcium channel blockers, beta-blockers or digoxin)
- medicines to treat disturbed or irregular heartbeat such as calcium channel blockers, beta-blockers or digoxin
- other eye drops that contain beta-blockers to lower pressure within the eye
- other carbonic anhydrase inhibitors (such as acetazolamide) to lower pressure within the eye
- medicines called monoamine oxidase inhibitors (MAO inhibitors) to treat depression or another disease
- parasympathomimetic medicines, which may be prescribed to help you pass urine. Some parasympathomimetics medicines are also sometimes used to restore normal bowel movements
- narcotics such as morphine, used to treat moderate to severe pain
- large doses of aspirin
- medicines for the treatment of diabetes
- antidepressants.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking/using any medicine.

Use during pregnancy
You should not use Dorzolamide/Timolol Eye drops, solution during pregnancy.
Tell your doctor if you are pregnant or planning to become pregnant.

Use during breast-feeding
If treatment with Dorzolamide/Timolol Eye drops, solution is needed, breast-feeding is not recommended.
Tell your doctor if you are breast-feeding or intending to breast-feed.

Driving and using machines
During Dorzolamide/Timolol Eye drops, solution treatment, possible side effects such as blurred vision may affect your ability to drive and/or use machines. Do not drive and do not operate any tools or machinery until you feel better or your vision has cleared.

Important information about some of the ingredients of Dorzolamide/Timolol Eye Drops, Solution
Dorzolamide/Timolol Eye drops, solution contains benzalkonium chloride as a preservative, which may cause eye irritation.

If you wear contact lenses, they should be removed prior to use of the drops and should not be reinserted for at least 15 minutes post-administration, as benzalkonium chloride lead to discolouration of soft contact lenses.

3. HOW TO USE DORZOLAMIDE/TIMOLOL EYE DROPS, SOLUTION
Always use Dorzolamide/Timolol Eye drops, solution exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will decide on the proper dose and length of treatment.

The usual dose is:
One drop into each affected eye, in the morning and evening

If you are using Dorzolamide/Timolol Eye Drops, Solution together with other eye drops, the drops should be administered at least 10 minutes apart.

Do not change the prescribed dose of this medicine without asking your doctor first.
Do not touch your eyes - or the area around the eyes - with the dropper tip of the container. The eye drops may otherwise become contaminated with bacteria, which could lead to an eye infection, resulting in serious eye damage and even loss of vision. To avoid contamination of the container, wash your hands before using this medicine and prevent the tip of the container from coming into contact with any surfaces. If you think that your medicine is contaminated or if you develop an eye infection, contact your doctor immediately regarding further use of this bottle.

Instructions for use
1. Wash your hands and sit or stand comfortably.
2. Twist off the cap.
3. Tilt the head back.
4. Use your finger to gently pull down the lower eyelid of your affected eye.
5. Invert the bottle and place the tip of the bottle close to, but not touching your eye. DO NOT TOUCH YOUR EYE OR EYELID WITH THE DROPPER TIP.
6. Squeeze the bottle gently so that only one drop goes into your eye, then release the lower eyelid.
7. Close the eye and press a finger against the corner of the affected eye by the nose. Hold for 1 minute.
8. Repeat in your other eye if your doctor has told you to do this.
9. Put the cap back on the bottle.

If you use more Dorzolamide/Timolol Eye Drops, Solution than you should
If you have put too many drops into your eye or have swallowed some of the container contents, you may - among other effects - start feeling dizzy, experience breathing difficulties or sense your heart rate slowing down. If you feel any of the above effects you should seek medical attention immediately.

If you forget to use Dorzolamide/Timolol Eye Drops, Solution
It is important that you use Dorzolamide/Timolol Eye drops, solution as directed by your doctor. If you forget a dose, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and resume your regular dosing schedule. Do not use a double dose to make up for a forgotten dose.

If you stop using Dorzolamide/Timolol Eye Drops, Solution
If you would like to stop treatment with this medicine, talk to your doctor first.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Dorzolamide/Timolol Eye Drops, Solution can cause side effects, although not everybody gets them. If they do occur, you might need medical care.

Important side effects to look out for – and what to do if you are affected:
If you develop allergic reactions including
- hives (nettle rash)
- skin rash
• eye redness and itching
• swelling of the face
• lips
• tongue and/or throat, which may cause difficulties in breathing or swallowing
stop using this medicine and seek immediate medical advice.

The following side effects have been reported with Dorzolamide/Timolol Eye drops, solution or either of its active substances.

Other possible side effects:

Very common (affect more than 1 in 10 people)
• burning and stinging of the eyes
• impaired taste

Common (affect less than 1 in 10 people)
• headache
• redness in and around the eyes, itchy and streaming eyes, effects on the eye surface, swelling and/or irritation in and around the eyes, a feeling as if something is in the eye (corneal impairment), decreased sensitivity of the cornea (to foreign objects in the eye and pain), painful eyes, dry eyes, blurred vision
• sinus inflammation (sinusitis)
• nausea and tiredness

Uncommon (affect less than 1 in 100 people)
• dizziness, depression
• inflammation of the iris, blurred vision (in some cases due to withdrawal of miotic treatment/treatment or constriction of the pupil(s))
• slowed heart rate, fainting
• indigestion
• kidney stones (often marked by a sudden onset of excruciating, cramping pain in their low back and/or side, groin, or abdomen)

Rare (affect less than 1 in 1,000 people)
• trouble sleeping (insomnia), nightmares, memory loss, muscle weakness/worsening of myasthenia gravis (serious muscle weakness), reduced sex drive, stroke
• Temporary short-sightedness which is reversible once treatment has finished, choroidal detachment (after filtration surgery), drooping eyelids, double vision, eyelid crusting, swelling of the cornea (together with symptoms of visual disturbances), low pressure within the eye
• ringing in the ears
• low blood pressure, irregular heartbeat, chest pain, pounding of the heart (palpitations), heart attack, reduced blood circulation through the brain, swelling and feelings of coldness in the hands/feet and poor circulation in the arms and legs, leg cramps and/or pain on walking (claudication), tingling or numbness of the hands or feet
• shortness of breath, impaired lung function, blocked/runny nose, nosebleeds, airway constriction (bronchospasm, mainly in patients with pre-existing bronchospastic disease), cough
• throat irritation, dry mouth, diarrhoea
• allergic skin reaction (contact dermatitis), hair loss, psoriasis or worsening of psoriasis
• Peyronie’s disease (which can lead to curvature of the penis)
• weakness/tiredness, allergic reactions such as skin rash, hives (nettle rash), itchy skin, in
rare cases possible swelling of lips, eyes and mouth wheezing

- Systemic lupus erythematosus (an immune system disorder which can cause inflammation of the internal organs)

5. HOW TO STORE DORZOLAMIDE/TIMOLOL EYE DROPS, SOLUTION

Keep out of the reach and sight of children.

Do not use Dorzolamide/Timolol Eye drops, solution after the expiry date stated on the container (after “EXP”). The expiry date refers to the last day of that month.

You can use Dorzolamide/Timolol Eye drops, solution for up to 28 days after opening the bottle.

This medicinal product does not require any special temperature storage conditions. Keep the bottle in the outer carton in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Dorzolamide/Timolol Eye Drops, Solution contains

- The active substances are dorzolamide and timolol.
- Each ml contains 20 mg dorzolamide (as 22.26 mg dorzolamide hydrochloride) and 5 mg timolol (as 6.83 mg timolol maleate).
- The other ingredients are hydroxyethylcellulose, mannitol, sodium citrate, sodium hydroxide, water for injection, and benzalkonium chloride.

What Dorzolamide/Timolol Eye Drops, Solution looks like and contents of the pack

Dorzolamide/Timolol Eye drops, solution is a clear, colourless to light yellow, sterile eye drop solution.

Pack sizes

Dorzolamide/Timolol Eye Drops, Solution is available in the following pack sizes:

- Pack of 1 bottle of 5 ml
- Pack of 3 bottles of 5 ml each
- Pack of 6 bottles of 5 ml each

Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Dr. Gerhard Mann Chem.-pharm. Fabrik GmbH
Brnsbütteler Damm 165 – 173
13581 Berlin -GERMANY

Manufacturer:
Dr. Gerhard Mann Chem.-pharm. Fabrik GmbH
Brnsbütteler Damm 165 – 173
13581 Berlin -GERMANY
This medicinal product is authorised in the Member States of the EEA under the following names:

Austria, Belgium, Germany, Greece, Hungary, Italy, Lithuania, Luxembourg, The Netherlands, Poland:
ARUTIDOR

Czech Republic, Slovak Republic, Latvia:
BATIDOR

Estonia, Spain, Portugal, Romania:
DORZOLAMIDE / TIMOLOL DR. GERHARD MANN

France:
DORZOLAMIDE / TIMOLOL DR. GERHARD MANN. CHEM.-PHARM. FABRIK GMBH

United Kingdom:
Dorzolamide / Timolol 20 mg/ml + 5 mg/ml Eye drops, solution

This leaflet was last approved in: May 2011
Module 4

Labelling

The following text is the approved label text. No label mock-ups have been provided. In accordance with medicines legislation, the product will not be marketed in the UK until approval of the label mock-ups has been obtained.
PL 13757/0010:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Dorzolamide/Timolol 20 mg/ml + 5 mg/ml Eye drops, solution
dorzolamide / timolol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 22.26 mg dorzolamide hydrochloride and 6.83 mg timolol maleate, equivalent to 20 mg dorzolamide and 5 mg of timolol per ml.

3. LIST OF EXCIPIENTS

Also contains: Benzalkonium chloride, hydroxyethylcellulose, mannitol, sodium citrate, sodium hydroxide and water for injections.

Preservative added: Benzalkonium chloride (0.075 mg/ml)
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

1 bottle of 5 ml
3 bottle of 5 ml each
6 bottles of 5 ml each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Ocular use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS
This medicinal product does not require any special temperature storage conditions.
Keep the bottle in the outer carton in order to protect from light.

After first opening the bottle: use within four weeks.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dr. Gerhard Mann Chem.-pharm Fabrik GmbH
Brunsübtteler Damm 165-173
13581 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 13757/0010

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Prescription only medicine.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dorzolamide / Timolol Eye Drops, Solution

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Dorzolamide/Timolol 20 mg/ml + 5 mg/ml Eye drops, solution
dorzolamide / timolol

2. METHOD OF ADMINISTRATION

Ocular use

3. EXPIRY DATE

EXP
After first opening of the bottle: 28 days.

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER
PL 13757/0012:

   PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Dorzolamide/Timolol 20 mg/ml + 5 mg/ml Eye drops, solution
dorzolamide / timolol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

   1 ml contains 22.26 mg dorzolamide hydrochloride and 6.83 mg timolol maleate, equivalent to 20 mg dorzolamide and 5 mg of timolol per ml.

3. LIST OF EXCIPIENTS

   Also contains: Benzalkonium chloride, hydroxyethylcellulose, mannitol, sodium citrate, sodium hydroxide and water for injections.

   Preservative added: Benzalkonium chloride (0.075 mg/ml)

   See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

   1 bottle of 5 ml
   3 bottle of 5 ml each
   6 bottles of 5 ml each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

   Ocular use
   Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

   Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

   EXP

9. SPECIAL STORAGE CONDITIONS
This medicinal product does not require any special temperature storage conditions. Keep the bottle in the outer carton in order to protect from light.

After first opening the bottle: use within four weeks.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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Prescription only medicine.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Dorzolamide / Timolol Eye Drops, Solution

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Dorzolamide/Timolol 20 mg/ml + 5 mg/ml Eye drops, solution
dorzolamide / timolol

2. METHOD OF ADMINISTRATION

Ocular use

3. EXPIRY DATE

EXP
After first opening of the bottle: 28 days.

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER
Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy the Reference Member State (RMS) considers that the applications for Dorzolamide/Timolol 20 mg/ml + 5 mg/ml Eye Drops, Solution in the treatment of increased intraocular pressure (IOP) in patients with open-angle glaucoma or pseudo-exfoliative glaucoma, when monotherapy with a topical beta-blocker is not sufficient, could be approved.

EXECUTIVE SUMMARY

Problem statement
These are abridged applications for a locally acting product. This type of application is regarded as a hybrid application; therefore, these Decentralised applications were submitted under Article 10.3 of Directive 2001/83/EC, as amended. The reference product is Cosopt 20 mg/ml + 5 mg/ml, eye drops, solution, marketed by Merck Sharp & Dohme B.V in Denmark since 6 March 1998. The reference product has, therefore, been authorised in the EEA for at least 10 years and the legal basis of these applications is acceptable.

With the UK as the RMS in this Decentralised Procedure (DCP), Dr. Gerhard Mann Chem.-pharm. Fabrik GmbH is applying for Marketing Authorisations for Dorzolamide/Timolol 20 mg/ml + 5 mg/ml Eye Drops, Solution in Austria, Belgium, the Czech Republic, Germany, Estonia, Greece, Spain, France, Hungary, Italy, Lithuania, Luxembourg, Latvia, the Netherlands, Poland, Portugal, Romania and the Slovak Republic.

About the product
Dorzolamide/Timolol 20 mg/ml + 5 mg/ml Eye Drops, Solution is a combination product containing the carbonic anhydrase inhibitor dorzolamide and the beta-blocker timolol. The product is used to treat IOP in patients with open-angle glaucoma or pseudoexfoliation (PEX) glaucoma, when monotherapy with a topical beta-blocker is not sufficient. The term glaucoma encompasses a group of diseases that are characterized by elevated IOP, excavation of the optic nerve head and visual field loss. Primary open-angle glaucoma (POAG) is the most common form of glaucoma. It is caused by chronic obstruction of the outflow of aqueous humor within the trabecular meshwork.

General comments on the submitted dossier
The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall summaries of the dossier regarding the quality, preclinical and clinical parts have been submitted.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles
GMP
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GLP
No new preclinical studies were submitted in support of these applications, and none are needed for an application of this type.

A non-clinical literature review has been submitted. It is not known whether the studies cited were conducted in compliance with GLP regulations. However, it is assumed that the studies conducted by the Marketing Authorisation Holder of the innovator product were in compliance with the standards prevailing at the time.

GCP
No new clinical studies were submitted in support of these applications, and none are needed for an application of this type.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substances

(1) Dorzolamide hydrochloride

**rINN:** Dorzolamide hydrochloride

**Chemical name:** (4S,6S)-4-(Ethylamino)-6-methyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-2-sulphonamide 7,7-dioxide hydrochloride

4H-Thieno[2,3-b]thiopyran-2-sulfonamide, 4-(ethylamino)-5,6-dihydro-6-methyl-7,7-dioxide, monohydrochloride, (4S-trans)

(4S,6S)-4-(Ethylamino)-5, 6-dihydro-6-methyl-4H-thieno [2,3-b] thiopyran-2-sulfonamide 7,7-dioxide, monohydrochloride

**CAS number:** 130693-82-2
Structural formula:

![Structural formula of Dorzolamide]

**Molecular formula:** $C_{10}H_{17}ClN_2O_4S_3$

**Molecular weight:** 360.91

**General properties:** White or almost white crystalline powder, soluble in water (pH, 1% = 3.87), slightly soluble in methanol, very slightly soluble in anhydrous ethanol, optically active with two chiral centers at positions C-4 and C-6, exhibits polymorphism.

Dorzolamide hydrochloride is a well-known active substance described in the Ph Eur. All aspects of the manufacture and control of dorzolamide hydrochloride are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of dorzolamide hydrochloride for inclusion in this medicinal product.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the proposed packaging.

(2) Timolol maleate

**rINN:** Timolol maleate

**Chemical name:** (2R)-1-[(1,1-dimethylethyl)amino]-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol (Z)-butenedioate

**CAS number:** 26921-17-5

**Structural formula:**

![Structural formula of Timolol]

**Molecular formula:** $C_{13}H_{24}N_4O_3S,C_4H_4O_4$

**Molecular weight:** 432.5

**General properties:** A white or almost white, crystalline powder or colourless crystals, soluble in water and in ethanol (96 per cent). It melts at about 199 °C, with decomposition

Timolol maleate is a well-known active substance described in the Ph Eur. All aspects of the manufacture and control of timolol maleate are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of timolol maleate for inclusion in this medicinal product.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the proposed packaging.
**Drug Product**
The drug product is a clear, colourless to light yellow, sterile eye drop solution containing 20 mg/ml dorzolamide hydrochloride and 5 mg/ml timolol maleate. The eye drops also contain the excipients benzalkonium chloride, hydroxyethylcellulose, mannitol, sodium citrate, sodium hydroxide (for pH adjustment) and water for injections.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients. Suitable declarations issued by suppliers of the excipients confirming compliance with the requirements of the relevant guideline and Directives with regard to TSE are provided.

**Pharmaceutical development**
The objective of the development programme was to develop a formulation similar to the innovator product and to achieve pharmaceutical equivalence in terms of physicochemical properties and dosage form performance. A satisfactory account of the pharmaceutical development has been provided.

**Product manufacture**
A satisfactory account of the manufacturing process has been provided. In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted.

**Finished product specification**
The finished product specification is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-closure system**
The finished product is stored in low density polyethylene (LDPE) bottles with an LDPE dropper tip and polypropylene (PP) cap. Each bottle contains 5 ml solution and the eye drops are available in pack sizes of one, three or six bottles, although not all pack sizes may be marketed.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months for this product when the storage precaution ‘Keep the bottle in the outer carton to protect from light’ is applied.

**Product literature**
The SmPCs, PIL and labels are pharmaceutically acceptable.
A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Expert report**
The quality expert report has been written by an appropriately qualified person and is a suitable summary of the quality dossier.

**Quality conclusion**
There are no objections to the approval of Dorzolamide/Timolol Eye Drops from a quality point of view.

**Preclinical aspects**

**Preclinical overview**
The pharmacodynamic, pharmacokinetic and toxicological properties of dorzolamide hydrochloride and timolol maleate are well known. As dorzolamide hydrochloride and timolol maleate are widely used, well known active substances, no further studies are required, and the applicant has not provided any. An overview based on a literature review is, thus, appropriate.

The preclinical overview has been written by suitably qualified experts. The overview cites sixty references up to 2009 and is dated the 3 April, 2009; it is an adequate review of the preclinical pharmacology, pharmacokinetics and toxicology of dorzolamide hydrochloride and timolol maleate.

Since both the active substances and all the excipients comply with compendial standards, there are no issues with respect to the impurities or other related substances.

**Environmental risk assessment**
A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this product onto the market is unlikely to result in an increase in the combined sales of all products, containing dorzolamide hydrochloride and timolol maleate, which in turn is unlikely to increase exposure of the environment to dorzolamide hydrochloride and timolol maleate.

**Product literature**
The product literature is acceptable from a preclinical point of view.

**Preclinical conclusion**
There are no objections to the approval of Dorzolamide/Timolol Eye Drops from a preclinical point of view.
Clinical aspects

Biowaiver
Similarity to the innovator product, Cosopt 20 mg/ml + 5 mg/ml, eye drops, solution, is claimed on the basis of identical qualitative and quantitative composition, as well as physicochemical equivalence. The indications and posology of the proposed product are in line with the reference product. Granting of a biowaver is acceptable.

Pharmacodynamics
The pharmacodynamic characteristics of dorzolamide and timolol have been well-studied in the past. There would be no particular concerns for this medicinal product. No new data have been submitted and none are required.

Clinical efficacy and safety
No new data are presented and none are required. A comprehensive review of the published literature has been provided by the applicant, citing the well established clinical pharmacology, efficacy and safety of dorzolamide and timolol.

Pharmacovigilance system
The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk management plan (RMP)
No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for this application.

Expert report
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, summary of the clinical part of the dossier.

Product literature
All product literature (SmPCs, PIL and labelling) is medically satisfactory.

Clinical conclusion
There are no objections to the approval of Dorzolamide/Timolol Eye Drops from a clinical point of view.

BENEFIT RISK ASSESSMENT
These applications contain an adequate review of published clinical data and a biowaver can be considered acceptable based on the information supplied. Approval is recommended from the clinical point of view.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Dorzolamide/Timolol Eye Drops are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of these type.

EFFICACY
The use of dorzolamide and timolol in the treatment of glaucoma, when beta-blocker eye drops alone are not enough, is well established. New efficacy data is, therefore, not needed.

SAFETY
No new or unexpected safety concerns arise from these applications.

The SmPCs and PIL are satisfactory and consistent with those of the reference product. Satisfactory labelling has also been submitted.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with dorzolamide and timolol is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk ratio is, therefore, considered to be acceptable. Marketing Authorisations should be granted.