Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dortim 20mg/ml + 5mg/ml Eye Drops Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre contains 20 mg of dorzolamide as dorzolamide hydrochloride and 5 mg of timolol as timolol maleate.

Excipients
Each ml contains 0.075 mg benzalkonium chloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.
Colourless, clear, viscous solution, free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product 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

The dose is one drop of Dortim in the (conjunctival sac of the) affected eye(s) two times daily.
If another topical ophthalmic agent is being used, Dortim and the other agent should be administered at least ten minutes apart.
Patients should be instructed to wash their hands before use and avoid allowing the tip of the dispensing container to come into contact with the eye or surrounding structures.
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.

Usage instructions
1. Before using the medication for the first time, be sure the tamper seal is unbroken.
2. To open the bottle, unscrew the cap.
3. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and eye.
4. Invert the bottle, and press lightly on the sides of the bottle until a single drop is dispensed into the eye as directed by your doctor. DO NOT TOUCH YOUR EYE OR EYELID WITH THE DROPPER TIP.
5. Repeat steps 3 & 4 with the other eye if instructed to do so by your doctor.
6. Replace the cap by turning until it is firmly touching the bottle.
7. The dispenser tip is designed to provide a pre-measured drop; therefore, do not enlarge the hole of the dispenser tip.

Paediatric use
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).

4.3 Contraindications

This medicinal product is contra-indicated 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
- sinus bradycardia, second- or third-degree atrioventricular block, overt cardiac failure, cardiogenic shock
- severe renal impairment (CrCl < 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
As with other topically-applied ophthalmic agents, the active substances may be absorbed systemically. The timolol component is a beta-blocker. Therefore, the same types of adverse reactions found with systemic administration of beta-blockers may occur with topical administration, including worsening of Prinzmetal's angina, worsening of severe peripheral and central circulatory disorders, and hypotension.
Because of the timolol maleate component, cardiac failure should be adequately controlled before beginning therapy with Dortim. In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.
Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and rarely death in association with cardiac failure, have been reported following administration of timolol maleate.

Hepatic impairment
Dortim 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, the active substances may be absorbed systemically. Dorzolamide contains a sulphonamido group, which also occurs in sulphonamides. Therefore the same types of adverse reactions found with systemic administration of sulphonamides may occur with topical administration. 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 Dortim. If such reactions occur, discontinuation of Dortim should be considered.
While taking β-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to accidental, diagnostic, or therapeutic repeated challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine 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.

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
Therapy with beta-blockers may mask certain symptoms of hypoglycaemia in patients with diabetes mellitus or hypoglycaemia.
Therapy with beta-blockers may mask certain symptoms of hyperthyroidism. Abrupt withdrawal of beta-blocker therapy may precipitate a worsening of symptoms.
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 Dortim, urolithiasis has been reported infrequently. Because Dortim 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 Dortim.

Other
The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Dortim 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. Topical dorzolamide should be used with caution in such patients.
Choroidal detachment concomitant with ocular hypotony have been reported after filtration procedures with administration of aqueous suppressant therapies.
As with the use of other antiglaucoma agents, 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
Dortim contains the preservative benzalkonium chloride, which may cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses.

Paediatric use
See section 5.1.

4.5 Interaction with other medicinal products and other forms of interaction

Specific interaction studies have not been performed with Dortim.

However, the potential exists for additive effects and production of hypotension and/or marked bradycardia when timolol maleate ophthalmic solution is administered together with oral calcium channel blockers, catecholamine-depleting or beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, narcotics, and monoamine oxidase (MAO) inhibitors.
Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, SSRIs) and timolol.

Although Dortim alone has little or no effect on pupil size, mydriasis resulting from concomitant use of ophthalmic timolol maleate and epinephrine (adrenaline) 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.

In clinical studies, Dortim 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).

4.6 Fertility, pregnancy and lactation

Use during pregnancy
Dortim 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
Well-controlled epidemiological studies with systemic beta-blockers showed no evidence of teratogenic effects, but some pharmacological effects such as bradycardia were observed in fetuses or neonates. If Dortim is administered until delivery, the neonate should be carefully monitored during the first days of life.

Use during lactation
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. Timolol does appear in human milk. If treatment with Dortim is required, then lactation 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 Dortim have been observed; adverse experiences have been limited to those that were reported previously with dorzolamide hydrochloride and/or timolol maleate.
During clinical studies, 1,035 patients were treated with Dortim. Approximately 2.4% of all patients discontinued therapy with Dortim 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 Dortim 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: (≥1/1000 to <1/100), and Rare: (≥1/10,000 to <1/1000)]

Nervous system disorders:

Dorzolamide hydrochloride eye drops, solution:	
Common:	headache*
Rare:	dizziness*, paresthesia*
Timolol maleate eye drops, solution:	
Common:	headache*
Uncommon:	dizziness*, depression*
Rare:	insomnia*, nightmares*, memory loss, paraesthesia*, increase in signs and symptoms of myasthenia gravis, decreased libido*, cerebrovascular accident*

Eye disorders:

Dortim:	
Very Common:	burning and stinging
Common:	conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing

Dorzolamide hydrochloride eye drops, 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 eye drops, solution:

Common:	signs and symptoms of ocular irritation 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)*

Ear and labyrinth disorders:

Timolol maleate eye drops, solution:

Rare:	tinnitus*

Cardiac and vascular disorders:

Timolol maleate eye drops, solution:

Uncommon:	bradycardia*, syncope*
Rare:	hypotension*, chest pain*, palpitation*, oedema*, arrhythmia*, congestive heart failure*, heart block*, cardiac arrest*, cerebral ischaemia, claudication, Raynaud's phenomenon*, cold hands and feet*

Respiratory, thoracic, and mediastinal disorders:

Dortim:

Common:	sinusitis
Rare:	shortness of breath, respiratory failure, rhinitis

Dorzolamide hydrochloride eye drops, solution:

Rare:	epistaxis*

Timolol maleate eye drops, solution:

Uncommon:	dyspnoea*
Rare:	bronchospasm (predominantly in patients with pre-existing bronchospastic disease)*, cough*

Gastro-intestinal disorders:

Dortim:

Very Common:	taste perversion

Dorzolamide hydrochloride eye drops, solution:

Common:	nausea*
Rare:	throat irritation, dry mouth*

Timolol maleate eye drops, solution:

Uncommon:	nausea*, dyspepsia*

Rare:	diarrhoea, dry mouth*

Skin and subcutaneous tissue disorders:

Dortim:	
Rare:	contact dermatitis
Dorzolamide hydrochloride eye drops, solution:	
Rare:	rash*
Timolol maleate eye drops, solution:	
Rare:	alopecia*, psoriasiform rash or exacerbation of psoriasis*

Renal and urinary disorders:

Dortim:	
Uncommon:	urolithiasis

Reproductive system and breast disorders:

Timolol maleate eye drops, solution:	
Rare:	Peyronie's disease*

General disorders and administration site disorders:

Dortim:	
Rare:	signs and symptoms of systemic allergic reactions, including angioedema, urticaria, pruritus, rash, anaphylaxis, rarely bronchospasm
Dorzolamide hydrochloride eye drops, solution:	
Common:	asthenia/fatigue*
Timolol maleate ophthalmic solution:	
Uncommon:	asthenia/fatigue*

*These adverse reactions were also observed with Dortim during post-marketing experience.

Laboratory findings
Dortim was not associated with clinically meaningful electrolyte disturbances in clinical studies.

4.9 Overdose

No data are available in humans in regard to overdose by accidental or deliberate ingestion of Dortim.
There have been reports of inadvertent overdoses with timolol maleate ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. The most common signs and symptoms to be expected with overdoses 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 overdose 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
Dortim 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 humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a non-selective beta-adrenergic receptor blocking agent. 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, Dortim 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. Dortim 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 Dortim 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 enrollment. In an analysis of the combined studies, the IOP-lowering effect of Dortim 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 Dortim 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 Dortim b.i.d. was demonstrated when measured at various time points throughout the day and this effect was maintained during long-term administration.

Paediatric use
A three 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 six and greater than or equal to two years of age whose IOP was not adequately controlled with monotherapy by dorzolamide or timolol received Dortim in an open label phase. Efficacy in those patients has not been established. In this small group of patients, twice daily administration of Dortim 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 CrCl 30-60 ml/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/ml and following afternoon dosing was 0.35 ng/ml.

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 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 Dortim.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxyethyl cellulose
Mannitol
Sodium citrate
Sodium hydroxide (to adjust pH)
Benzalkonium chloride
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
After first opening: 28 days maximum

6.4 Special precautions for storage

Store below 30°C.
Do not refrigerate or freeze.

6.5 Nature and contents of container

Dortim 20 mg/ml + 5 mg/ml Eye Drops Solution is filled into a 5 ml fill volume capacity white LDPE bottle equipped with a white LDPE dropper applicator and closed with a yellow HDPE tamper proof cap.

Pack sizes:
1 x 5 ml (a single 5 ml bottle)
2 x 5 ml (two 5 ml bottles)
3 x 5 ml (three 5 ml bottles)
6 x 5 ml (six 5 ml bottles)
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/79/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd July 2010

10 DATE OF REVISION OF THE TEXT