SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

XOLATIM 2% + 0.5% Eye Drops, Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances:
Each ml contains 22.26 mg dorzolamide hydrochloride equivalent to 20 mg dorzolamide and 6.83 mg timolol maleate equivalent to 5 mg timolol.

Excipient(s) with known effect:
Benzalkonium chloride.....0.075 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops.
Clear and colorless, slightly viscous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

XOLATIM is used for the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension, open-angle glaucoma, pseudoexfoliative glaucoma or other secondary open-angle glaucoma, where combination therapy is indicated.

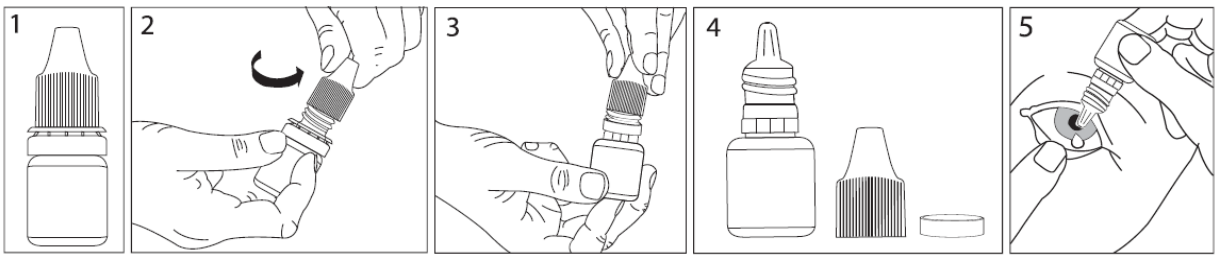
4.2 Posology and method of administration

Posology/frequency and duration of administration
Instill one drop of XOLATIM into affected eye(s) twice a day

If another topical ophthalmic agent is being used, XOLATIM and the other agent should be administered at least 10 minutes apart.

When substituting XOLATIM for another ophthalmic anti-glaucoma agent, discontinue the other agent after proper dosing on one day, and start XOLATIM on the next day

Method of administration
It is instilled into eye as below.



1. Open the cap of the bottle (see Figure 2).
2. Remove the ring under the cap (see Figure 3 and Figure 4).
3. Using your finger, gently pull the lower lid of the affected eye downwards.
4. Bring the tip of the dripper close to the eye, but do not touch it.
5. Squeeze the dropper gently and put ONLY one drop into the eye. Then release the lower eyelid.
6. Press the corner of the eye on the nose side with your finger. It should be kept like this for about a minute with the eyes closed.
7. If your doctor has told you to use medication for both eyes, repeat the same procedures for the other eye.
8. Close the cap of the bottle.

Systemic absorption is reduced when there is nasolacrimal occlusion or eyelid closure. This causes a decrease in systemic side effects and an increase in local activity.

The dropper is adjusted to drop just one drop at a time. Do not try to widen the dropper.

Patients should be instructed to wash their hands before use and avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ophthalmic solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Contact Lens Users
Lenses should be removed prior to instillation of the drop into the eye and should not be reinserted for at least 15 minutes after the drop has been instilled.

Additional information on special populations
Renal impairment
Dorzolamide has not been studied in patients with severe renal impairment (creatinine clearance <30 ml/min). Because dorzolamide and its metabolites are excreted predominantly by the kidney, XOLATIM is therefore contraindicated in such patients.

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

Pediatric population
There are no studies on efficacy in pediatric patients.
Safety in pediatric patients below the age of 2 years has not been established. (For information regarding safety in pediatric patients ≥2 and <6 years of age, see section 5.1).

Geriatric population
There are no studies with dorzolamide in geriatric patients.

4.3 Contraindications

XOLATIM is contraindicated in patients with:
- Reactive airway disease, bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease

- Sinus bradycardia, sick sinus syndrome sino-atrial block, second or third degree atrioventricular block not, overt cardiac failure, cardiogenic shock
- Severe renal impairment (creatinine clearance <30 ml/min) or hyperchloremic acidosis
- Hypersensitivity to any component of this product.

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

4.4 Special warning and precautions for use

As with other topically-applied ophthalmic agents, this medicine may be absorbed systemically. The timolol component is a beta-blocker. Therefore, the same types of adverse reactions found with systemic administration of beta-adrenergic blocking agents like worsening of Prinzmetal's angina, severe peripheral and central circulatory disorders and hypertension may occur with topical administration.

Cardiovascular/respiratory reactions
Because of the timolol maleate component, cardiac failure should be adequately controlled before beginning therapy with XOLATIM.

Patients with a history of cardiovascular disease, including cardiac failure should be watched for signs of deterioration of these diseases and pulse rates should be checked e.g. coronary heart disease, Prinzmetal's angina).

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

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

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

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

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

Masking of thyrotoxicosis
Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be evaluated for thyroid abrupt withdrawal of beta-adrenergic blocking agent use.

Surgical anesthesia
The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery

is controversial. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists. The anesthesiologist should be informed when the patient is receiving timolol maleate (see section 4.9).

Immunology and hypersensitivity
As with other topically applied ophthalmic agents, this drug may be absorbed systemically. The dorzolamide component is a sulphonamide. Therefore the same types of adverse reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) 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 dorzolamide/timolol maleate. If such reactions occur, discontinuation of XOLATIM should be considered.

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens either as coincidental or for diagnostic or therapeutic purposes. These patients may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

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

The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is used in combination with a systemic beta-blocking agent.

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.

Therapy with beta-blockers may aggravate symptoms of myasthenia gravis.

Additional effects of carbonic anhydrase inhibition
Therapy with oral carbonic anhydrase inhibitors has been associated with urolithiasis as a result of acid-base disturbances, especially in patients with a prior history of renal calculi. Although no acid-base disturbances have been observed with dorzolamide hydrochloride and timolol maleate combination, urolithiasis has been reported infrequently. Because XOLATIM 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 XOLATIM.

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

Corneal edema 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 has been reported with administration of aqueous suppressant therapy after filtration procedures.

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

Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Interactions with biological testing
Dorzolamide/timolol has not been found to be associated with clinically significant electrolyte disturbances.

Excipient warnings
Sodium: No warning required due to its route of administration (ocular).

Mannitol: No warning required due to its route of administration (ocular).

Benzalkonium chloride: May cause eye irritation. Avoid contact with soft contact lenses. Before applying, remove the contact lens and wait at least 15 minutes before inserting the lens. This excipient is known to cause discoloration of soft contact lenses.

4.5 Interaction with other medicinal products and other forms of interaction

Specific drug interaction studies have not been performed with dorzolamide/timolol.

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

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

XOLATIM alone has little or no effect on pupil size. Mydriasis has been reported occasionally with concomitant use of timolol maleate ophthalmic solution and epinephrine (adrenaline).

Beta-blockers may increase the hypoglycemic effect of antidiabetic agents.

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

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is C.

Women of child-bearing potential/Contraception
No clinical data on pregnancies are available for dorzolamide/timolol.

Pregnancy
XOLATIM should not be used during pregnancy.

Dorzolamide
No adequate clinical data on exposure to dorzolamide during pregnancy are available. In rabbits, dorzolamide produced teratogenic effects at maternotoxic doses (see Section 5.3).

Timolol
Well-controlled epidemiological studies conducted with systemic beta-blockers have not revealed any symptoms regarding teratogenic effects but show some pharmacological effects in fetus and newborns like bradycardia. If XOLATIM is administered until delivery, the neonate should be carefully monitored during the first days of life.

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 are excreted in breast milk.
If treatment with XOLATIM is required, then lactation is not recommended.

Reproductive ability / Fertility
Reproduction and fertility studies in rats with either timolol maleate or dorzolamide hydrochloride demonstrated no adverse effect on male or female fertility at doses up to approximately 100 times the systemic exposure following the maximum recommended human ophthalmic dose.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In clinical studies no adverse experiences specific to dorzolamide/timolol have been observed; adverse experiences have been limited to those that were reported previously with dorzolamide and/or timolol.

During clinical studies, 1,035 patients were treated with dorzolamide/timolol. Approximately 2.4% of all patients discontinued therapy with dorzolamide/timolol because of local ocular adverse reactions, approximately 1.2 % of all patients discontinued because of local adverse reactions suggestive of allergy or hypersensitivity (such as lid inflammation and conjunctivitis).

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

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data)

Immune system disorders:
Dorzolamide hydrochloride / Timolol maleate eye drops, solution; and timolol maleate eye drops, solution:
Rare: Signs and symptoms of systemic allergic reactions including angioedema, urticaria, pruritus, rash, anaphylaxis

Timolol maleate eye drops, solution:
Rare: Signs and symptoms of systemic allergic reactions including angioedema, urticaria, localized and generalized rash, anaphylaxis
Not known: Pruritus

Metabolism and nutrition disorders:
Timolol maleate eye drops, solution:
Not known: Hypoglycemia

Psychiatric disorders:
Timolol maleate eye drops, solution:
Uncommon: Depression*
Rare: Insomnia*, nightmares*, memory loss.

Nervous system disorders:
Dorzolamide hydrochloride eye drops, solution:
Common: Headache*
Rare Dizziness*, paresthesia*

Timolol maleate eye drops, solution:
Common: Headache*
Uncommon: Dizziness*, syncope*
Rare: Paresthesia*, increase in signs and symptoms of myasthenia gravis, decrease in libido*, cerebrovascular accident*, cerebral ischemia

Eye disorders:
Dorzolamide hydrochloride / Timolol maleate eye drops, solution:
Very common: Burning and stinging
Common: Conjunctival redness, 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 edema*, ocular hypotonia*, 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)* (see section 4.4)
Not known: Itching, tearing, eye redness, blurred vision, corneal erosion

Ear and labyrinth disorders:
Timolol maleate eye drops, solution:
Rare: Tinnitus*

Cardiac disorders:
Timolol maleate eye drops, solution:
Uncommon: Bradycardia* *
Rare: Chest pain*, palpitations*, edema*, arrhythmia*, congestive heart failure*, cardiac arrest*, heart block*
Not known: Atrioventricular block, cardiac failure

Vascular disorders:
Timolol maleate eye drops, solution:
Rare: Hypotension*, claudication, Raynaud's phenomenon*, cold hands and feet*

Respiratory, thoracic and mediastinal disorders:
Dorzolamide hydrochloride / Timolol maleate eye drops, solution:
Common: Sinusitis
Rare: Shortness of breath, respiratory failure, rhinitis, rarely bronchospasm

Dorzolamide hydrochloride eye drops, solution:
Rare: Epistaxis*

Timolol maleate eye drops, solution:
Uncommon: Dyspnea*
Rare: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, cough*

Gastrointestinal disorders:
Dorzolamide hydrochloride eye drops, solution:
Very common: Dysgeusia

Dorzolamide/Timolol eye drops, solution:
Common: Nausea*
Rare: Throat irritation, dry mouth*

Timolol maleate eye drops, solution:
Uncommon: Nausea*, dyspepsia*
Rare: Diarrhea, dry mouth*
Not known: Dysgeusia, abdominal pain, vomiting

Skin and subcutaneous tissue disorders:
Dorzolamide hydrochloride / Timolol maleate eye drops, solution:
Rare: Contact dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis
Dorzolamide hydrochloride eye drops, solution:

Rare: Redness*

Timolol maleate eye drops, solution:
Rare: Alopecia*, psoriasiform rash or exacerbation of psoriasis*
Not known: Skin rash

Musculoskeletal and connective tissue disorders:
Timolol maleate eye drops, solution:
Rare: Systemic lupus erythematosus
Not known: Myalgia

Renal and urinary disorders:
Dorzolamide hydrochloride / Timolol maleate eye drops, solution:
Uncommon: Urolithiasis

Reproductive system and breast disorders:
Timolol maleate eye drops, solution:
Rare: Peyronie's disease*, decreased libido
Not known: Sexual dysfunction

General disorders and administration site condition:
Dorzolamide hydrochloride / Timolol maleate eye drops, solution:
Rare: Signs and symptoms of systemic allergic reactions including angioedema, urticaria, rash, anaphylaxis, rarely bronchospasm

Dorzolamide hydrochloride eye drops, solution:
Common: Asthenia/fatigue*

Timolol maleate eye drops, solution:
Uncommon: Asthenia/fatigue*

*These adverse reactions were also observed with dorzolamide/timolol during post-marketing experience.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

No data are available in humans in regard to overdose by accidental or deliberate ingestion of XOLATIM.

Symptoms
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, acidosis, 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 dialyze readily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combination of a medicine that inhibits ophthalmic carbonic anhydrase and an ophthalmic beta-blocker medicine.
ATC code: S01ED51

Mechanism of action
XOLATIM 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 tomography 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, XOLATIM 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. XOLATIM reduces intra-ocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

Pharmacodynamics
Clinical effects:
Clinical studies of up to 15 months duration were conducted to compare the intraocular pressure-lowering effect of dorzolamide + timolol b.i.d. (dosed morning and bedtime) to individually- and concomitantly-administered 0.5 % timolol and 2% 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 intraocular pressure lowering effect of dorzolamide + timolol (formulation containing preservative) b.i.d. was greater than that of monotherapy with either 2% dorzolamide t.i.d. or 0.5% timolol b.i.d. The intraocular pressure-lowering effect of dorzolamide + timolol (formulation containing preservative) b.i.d. was equivalent to that of concomitant therapy

with dorzolamide b.i.d. and timolol b.i.d. The intraocular pressure lowering effect of dorzolamide + timolol (formulation containing preservative) b.i.d. was demonstrated when measured at various time points throughout the day and this effect was maintained during long-term administration.

Pediatric use
A 3 months controlled study, with the primary objective of documenting the safety of 2% dorzolamide hydrochloride ophthalmic solution in children under the age of 6 years has been conducted. In this study, 30 patients under 6 and greater than or equal to 2 years of age whose intraocular pressure was not adequately controlled with monotherapy by dorzolamide or timolol received dorzolamide+timolol in an open label phase. Efficacy in those patients has not been established. In this small group of patients, twice daily administration of dorzolamide+timolol was generally well tolerated with 19 patients completing the treatment period and 11 patients discontinuing for surgery, a change in medication, or other reasons.

5.2 Pharmacokinetic properties

Dorzolamide hydrochloride:
Absorption:
Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows for the drug 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 intraocular pressure without the acid-base disturbances or alterations in electrolytes characteristic of oral carbonic anhydrase inhibitors.

Distribution:
When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase (CA) inhibition following topical administration, active substance and metabolite concentrations in red blood cells and plasma and carbonic anhydrase inhibition in red blood cells 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.

Biotransformation:
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%).

Elimination:
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. For this purpose, active substance and metabolite concentrations in plasma and red blood cells and carbonic anhydrase levels in RBC were measured. At steady state, there was virtually no free active substance or metabolite in plasma; CA (carbonic anhydrase) inhibition in RBCs was less than that anticipated to be necessary for a pharmacological effect on renal function or respiration. Similar pharmacokinetic results were

observed after chronic, topical administration of dorzolamide hydrochloride. However, some elderly patients with renal impairment (estimated creatinine clearance 30-60 ml/min) had higher metabolite concentrations in red blood cells, but no meaningful differences in carbonic anhydrase inhibition and no clinically significant systemic side effects were directly attributable to this finding.

Timolol maleate:
Absorption:
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.

Distribution:
Timolol is bound only in small amount to plasma proteins; it passes into placenta and breast-milk. Plasma half-life is reported as 4 hours. No information is available regarding the levels distributed in systemic circulation.

Biotransformation:
Timolol is mainly metabolized in the liver.

Elimination:
Metabolites are eliminated via the urine with some unchanged timolol. Timolol cannot be removed by hemodialysis.

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 XOLATIM.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Sodium citrate dehydrate
Hydroxyethylcellulose
Mannitol
Sodium hydroxide
Water for injection

6.2 Incompatibilities

There is not any known incompatibility.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at room temperature below 25°C. Protect from light.
Once the bottle is opened, the medicine should be used within 28 days.

6.5 Nature and contents of container

As the primary packaging material for the product; an opaque, white, low-density polyethylene (LDPE) bottle containing 5 ml of eye drops, with LDPE dropper and yellow colored high-density polyethylene (HDPE) screw is used. It is presented as one bottle in a cardboard box with a package leaflet.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece/İSTANBUL - TURKEY

8. MARKETING AUTHORIZATION NUMBER

2015/101

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 06.02.2015
Date of renewal:

10. DATE OF REVISION OF THE TEXT

13.07.2021