SUMMARY OF PRODUCTS CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Twinzol SDU 20 mg/ml + 5 mg/ml, Sterile ophthalmic solution in single dose unit

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 22.26 mg of dorzolamide hydrochloride corresponding to 20 mg dorzolamide and 6.83 mg of timolol maleate corresponding to 5 mg timolol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution, single dose container

Clear, colourless to nearly colourless, slightly viscous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated in the treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or pseudoexfoliative glaucoma when topical beta-blocker monotherapy is not sufficient.

4.2 Posology and method of administration

The dose is one drop of Twinzol SDU in the (conjunctival sac of the) affected eye(s) two times daily.

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

twinzol SDU is a sterile solution that does not contain a preservative. The solution from one individual single dose container is to be used immediately after opening for administration to the affected eye(s). Since sterility cannot be maintained after the individual single dose container is opened, any remaining contents must be discarded immediately after administration.

Patients should be instructed to avoid allowing the tip of the 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. Open the sachet which contains 15 individual single dose containers. There are three strips of 5 single dose containers each in the sachet.

2. First wash your hands then break off one single dose container from the strip and twist open the top.

3. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and eye.

4. Instill one drop in the affected eye(s) as directed by your physician. Each single dose container contains enough solution for both eyes.

5. After instillation, discard the used single dose container even if there is solution remaining.

6. Store the remaining single dose containers in the sachet; the remaining single dose containers must be used within 15 days after opening of the sachet.

Pediatric Use

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

4.3 Contraindications

Twinzol SDU is contraindicated in patients with:

• reactive airway disease, including bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease
• sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock
• severe renal impairment (CrCl < 30 ml/min) or hyperchloremic acidosis
• hypersensitivity to one or both active substances or to any of the excipients.

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, this medicinal product 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 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 Twinzol SDU. 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
Twinzol SDU has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

Immunology and Hypersensitivity
As with other topically-applied ophthalmic agents, Twinzol SDU may be absorbed systemically. Dorzolamide contains a sulfonamido group, which also occurs in sulfonamides. Therefore, the

same types of adverse reactions found with systemic administration of sulfonamides may occur with topical administration, including severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation.

Local ocular adverse effects, similar to those observed with dorzolamide hydrochloride eye drops, have been seen with Twinzol SDU. If such reactions occur, discontinuation of Twinzol SDU should be considered. While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to accidental, diagnostic, or therapeutic repeated challenge with such allergens. Such patients may be unresponsive to the usual doses of 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 hypoglycemia in patients with diabetes mellitus or hypoglycemia.

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 Twinzol (preserved formulation), urolithiasis has been reported infrequently. Because Twinzol SDU 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 Twinzol SDU.

Other

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Twinzol SDU has not been studied in patients with acute ngle-closure glaucoma.

Corneal oedema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intraocular 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 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 intraocular pressure has been observed after initial stabilization.

Contact Lens Use

Twinzol SDU has not been studied in patients wearing contact lenses.

Paediatric Use

See section 5.1.

4.5 Interaction with other medicinal products and other forms of interaction
Specific drug interaction studies have not been performed with Twinzol SDU.

In a clinical study, Twinzol SDU 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., estrogen, insulin, thyroxine).

However, the potential exists for additive effects and production of hypotension and/or marked bradycardia when timolol maleate ophthalmic solution is administered together with oral calcium channel blockers, catecholamine-depleting drugs 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 Twinzol (preserved formulation) 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 hypoglycemic effect of antidiabetic agents.

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

4.6 Pregnancy and lactation

Use During Pregnancy

Twinzol SDU should not be used during pregnancy.

Dorzolamide
No adequate clinical data in exposed pregnancies are available. In rabbits, dorzolamide produced teratogenic effect 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 foetuses or neonates. If Twinzol SDU 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 Twinzol SDU 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 a clinical study no adverse experiences specific to Twinzol SDU have been observed; adverse reactions have been limited to those that were reported previously with Twinzol (preserved formulation), dorzolamide hydrochloride and/or timolol maleate.

During clinical studies, 1035 patients were treated with Twinzol (preserved formulation).Approximately 2.4% of all patients discontinued therapy with Twinzol (preserved formulation) 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).

Twinzol SDU has been shown to have a similar safety profile to Twinzol (preservative containing formulation) in a repeat dose double-masked, comparative study.

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

[Very Common: (≥1/10), Common: (≥1/100, <1/10), Uncommon: (≥1/1000, <1/100), and Rare: (≥1/10,000, <1/1000)]

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

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, paresthesia*, increase in signs and symptoms of myasthenia gravis, decreased libido*, cerebrovascular accident*

Eye disorders:
Twinzol:
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*, edema*, arrhythmia*, congestive heart failure*, heart block*, cardiac arrest*, cerebral ischemia, claudication, Raynaud's phenomenon*, cold hands and feet*

Respiratory, thoracic, and mediastinal disorders:
Twinzol:
Common: sinusitis
Rare: shortness of breath, respiratory failure, rhinitis

Dorzolamide hydrochloride eye drops, solution:
Rare: epistaxis*

Timolol maleate eye drops, solution:
Uncommon: dyspnea*
Rare: bronchospasm (predominantly in patients with pre-existing bronchospastic disease)*, cough*

Gastrointestinal disorders:
Twinzol:
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: diarrhea, dry mouth*

Skin and subcutaneous tissue disorders:
Twinzol:
Rare: contact dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Dorzolamide hydrochloride eye drops, solution:

Rare: rash*

Timolol maleate eye drops, solution:
Rare: alopecia*, psoriasiform rash or exacerbation of psoriasis*

Renal and urinary disorders:
Twinzol:
Uncommon: urolithiasis

Reproductive system and breast disorders:
Timolol maleate eye drops, solution:
Rare: Peyronie's disease*

General disorders and administration site disorders:
Twinzol:
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 eye drops, solution:
Uncommon: asthenia/fatigue*

*These adverse reactions were also observed with Twinzol(preserved formulation) during post-marketing experience.

Laboratory Findings
Twinzol (preserved formulation) 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 Twinzol (preserved formulation) or Twinzol SDU.

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, 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 dialyze readily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action

Twinzol SDU is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intraocular pressure by reducing aqueous humor secretion, but does so by a different mechanism of action.

Dorzolamide hydrochloride is a potent inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a nonselective beta-adrenergic receptor blocking agent. 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 formation. However, in some studies a slight increase in outflow facility was also observed. The combined effect of these two agents results in additional intraocular pressure reduction (IOP) compared to either component administered alone.

Following topical administration, Twinzol SDU reduces elevated intraocular pressure, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.
Twinzol SDU reduces intraocular 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 Twinzol (preserved formulation) b.i.d. (dosed morning and bedtime) to individuallyand 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 Twinzol (preserved formulation) 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 Twinzol (preserved formulation) 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 Twinzol (preserved formulation) b.i.d. was demonstrated when measured at various time points throughout the day and this effect was maintained during long-term administration.

In an active-treatment-controlled, parallel, double-masked study in 261 patients with elevated intraocular pressure ≥22 mmHg in one or both eyes, Twinzol SDU had an IOP-lowering effect equivalent to that of Twinzol(preserved formulation). The safety profile of Twinzol SDU was similar to Twinzol (preserved formulation).

Paediatric use

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 Twinzol (preserved formulation) in an open label

phase. Efficacy in those patients has not been established. In this small group of patients, twice daily administration of Twinzol(preserved formulation) 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 nonlinearly, 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 0.46ng/ml and following afternoon dosing was 0.35ng/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 Twinzol SDU.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Hydroxypropyl methyl cellulose(E5)
Mannitol
Citric acid anhydrous
Sodium citrate dihydrate
Hydrochloric acid/ sodium hydroxide.
Water for injections.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.
Discard the opened single dose container immediately after first use.

6.4 Special precautions for storage
Do not store above 30°C.
Do not freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container
Twinzol SDU is available in 0.2 ml low density polyethylene single dose containers in an aluminum sachet containing 15 single -dose containers.

Pack sizes:
30 x 0.2 ml (2 sachets with 15 single dose containers)
60 x 0.2 ml (4 sachets with 15 single dose containers)
120 x 0.2 ml (8 sachets with 15 single dose containers)
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER

Orchidia pharmaceutical industries

8. Marketing authorisation number(s)
32747/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
12/07/2018 12/07/2021

10. DATE OF REVISION OF THE TEXT
15/1/2019