Module I Administrative Information
Product Name: DORZOLAMIDE &TIMOLOL EYE DROPS

Summary Product Characteristics

1. Name of the medicinal product: DORZOLAMIDE &TIMOLOL EYE DROPS

2. Qualitative and Quantitative composition:

Batch size: 100 Litres

SR. No	Ingredients	Specification	Label Claim per ml	Qty/ml in (mg)	Over ages	Qty. / Vial in mg	Qty/ batch (kg)	Reason for inclusion
ACTIVE								
1.	Dorzolamide Hydrochloride	USP	2.0%w/v	22.50	--	112.50	2.250	Active
2.	Timolol Maleate	USP	0.5%w/v	7.00	--	35.00	0.700	Active
EXCIPIENTS								
3.	HPMC	BP	--	2.50	--	12.50	0.2500	Viscosity modifier
4.	Sodium Citrate	BP	--	1.00	--	5.00	0.100	Alkalizing agents
5.	Mannitol	BP	--	50.00	--	250.00	5.0	Isotonic agent
6.	Benzalkonium chloride Solution	BP	0.02% v/v	0.0002 ml	--	0.001 ml	20 ml	Preservative
7.	Water for Injetion	BP	--	q.s to 1 ml	--	q.s to 5 ml	q.s to 100 Liter	Vehicle

Where,
USP: United State Pharmacopiea; BP: British Pharmacopoeia; q.s: Quantity sufficient.

Note: Quantity of active ingredients to be taken by consideration of their Assay and water contents.

Calculation:

- 360.91 molecular weight of Dorzolamide Hydrochloride is equivalent to 324.443 molecular weight of Dorzolamide, Hence 22.50 mg of Dorzolamide hydrochloride is equivalent to 100 mg of Dorzolamide
- 432.50 molecular weight of Timolol maleate is equivalent to 316.42 molecular weight of Timolol. Hence 7.00 mg of Timolol maleate is equivalent to 25 mg of Timolol.

3. Pharmaceutical Form: Eye Drops (Ophthalmic Solution)

4. Clinical Particulars:

4.1 Therapeutic Indications
Dorzolamide/Timolol Eye Drops Solution is indicated in the treatment of elevated intra-ocular pressure (IOP) in patients with open-angle glaucoma or pseudo-exfoliative glaucoma when topical beta-blocker monotherapy is not sufficient.

4.2 Posology and method of administration:
Posology
The dose is one drop of Dorzolamide/Timolol Eye Drops Solution in the (conjunctival sac of the) affected eye(s) two times daily.
If another topical ophthalmic agent is being used, Dorzolamide/Timolol Eye Drops Solution and the other agent should be administered at least ten minutes apart.
Method of Administration
For ocular use only
When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.
Paediatric population
Efficacy in paediatric patients has not been established.
Safety in paediatric patients below the age of two years has not been established. (For information regarding safety in paediatric patients ≥ 2 and < 6 years of age.

4.3 Contraindications
Dorzolamide/Timolol Eye Drops Solution is contraindicated in patients with:
• Hypersensitivity to the active substances, or to sulphonamides or any of the excipients
• Reactive airway disease, including 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 controlled with pace-maker, 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
Like other topically applied ophthalmic agents timolol is absorbed systemically. Due to betaadrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption.
Cardiac disorders:
In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular

diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

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

Vascular disorders:

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

Respiratory disorders:

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. [Dorzolamide/Timolol] should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hepatic impairment

The fixed combination of dorzolamide and timolol has not been studied in patients with hepatic impairment and therefore should be used with caution in such patients.

Immunology and hypersensitivity

As with other topically-applied ophthalmic agents, this medicinal product may be absorbed systemically. The active substance dorzolamide contains a sulphonamide group. Therefore the same types of adverse reactions found with systemic administration of sulphonamides may occur with ocular use, 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 reactions, similar to those observed with dorzolamide hydrochloride eye drops, have been seen with the fixed combination of dorzolamide and timolol. If such reactions occur, discontinuation of Dorzolamide/Timolol Eye Drops Solution should be considered.

Anaphylactic reactions

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 repeated challenge with such allergens and unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Concomitant therapy

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

The use of dorzolamide and oral carbonic anhydrase inhibitors is not recommended.

Withdrawal of therapy

As with systemic beta-blockers, if discontinuation of ophthalmic timolol is needed in patients with coronary heart disease, therapy should be withdrawn gradually.

Additional effects of beta-blockade

Hypoglycaemia/diabetes

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Beta-blockers may also mask the signs of hyperthyroidism. Abrupt withdrawal of beta-blocker therapy may precipitate a worsening of symptoms.

Corneal diseases

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

Surgical anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

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

Additional effects of carbonic anhydrase inhibition

Therapy with oral carbonic anhydrase inhibitors has been associated with urolithiasis as a result of acid-base disturbances, especially in patients with a prior history of renal calculi. Although no acid-base disturbances have been observed with the fixed combination of dorzolamide and timolol, urolithiasis has been reported infrequently. Because Dorzolamide/Timolol Eye Drops Solution contains a topical carbonic anhydrase inhibitor that is absorbed systemically, patients with a prior history of renal calculi may be at increased risk of urolithiasis while using Dorzolamide/Timolol Eye Drops Solution.

Other

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. The fixed combination of dorzolamide and timolol has not been studied in patients with acute angle-closure glaucoma.

Corneal oedema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intra-ocular surgery while using dorzolamide. There is an increased potential for developing corneal oedema in patients with low endothelial cell counts. Precautions should be used when prescribing Dorzolamid/Timolol to these groups of patients.

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

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

Contact lens use

Dorzolamide/Timolol Eye Drops Solution contains the preservative benzalkonium chloride, which may cause eye irritation.

Contact lenses should be removed prior to application and at least 15 minutes should have passed before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses.

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

No specific interaction studies have been performed with the fixed combination of dorzolamide and timolol.

In clinical studies, the fixed combination of dorzolamide and timolol was used concomitantly with the following systemic medicinal products without evidence of adverse interactions: ACE-inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory active substances including acetylsalicylic acid, and hormones (e.g. oestrogen, insulin, thyroxine).

However, there is a potential for additive effects resulting in hypotension and/or marked bradycardia when timolol maleate ophthalmic solution is administered concomitantly with

oral calcium channel blockers, catecholamine-depleting medicines or beta-adrenergic blocking agents, anti-arrhythmics (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.
The active substance dorzolamide in [Dorzolamide/Timolol] is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. In clinical studies, dorzolamide hydrochloride ophthalmic solution was not associated with acid-base disturbances. However, these disturbances have been reported with oral carbonic anhydrase inhibitors and have in some instances, resulted in interactions (e.g., toxicity associated with high-dose salicylate therapy). Therefore, the potential for such interactions should be considered in patients receiving [Dorzolamide/Timolol].
Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally, although [Dorzolamide/Timolol] alone has little or no effect on pupil size.
Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents.
Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

4.6 Pregnancy and Lactation

Pregnancy
Dorzolamide/Timolol 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.
Timolol
There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy unless clearly necessary.
To reduce the systemic absorption.
Epidemiological studies have not revealed malformative effects but show a risk for intra uterine growth retardation when betablockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If [Dorzolamide/Timolol] is administered until delivery, the neonate should be carefully monitored during the first days of life.
Breast-feeding
It is not known whether dorzolamide is excreted in human milk. In lactating rats receiving dorzolamide, decreases in the body weight gain of offspring were observed.
Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption. If treatment with Dorzolamide/Timolol is required, then lactation is not recommended.

4.7 Effects on the 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 dizziness and visual disturbances may affect some patients' ability to drive and/or operate machinery.

4.8 Undesirable effects:

In clinical studies the observed adverse reactions for the fixed combination have been consistent with those that were reported previously with dorzolamide hydrochloride and/or timolol maleate.

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

Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic betablocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.

The following adverse reactions have been reported with the fixed combination of dorzolamide and timolol or one of its components either during clinical studies or during post-marketing experience:

Very common (≥ 1/10)
Common (≥ 1/100, < 1/10)
Uncommon (≥ 1/1,000, < 1/100)
Rare (≥ 1/10,000, < 1/1,000)
not known (cannot be estimated from the available data)

Immune system disorders:

Timolol maleate ophthalmic solution:
Unknown: systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylactic reaction.

Metabolism and nutrition disorders:

Timolol maleate ophthalmic solution:
Unknown: hypoglycaemia.

Nervous system and Psychiatric disorders:

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

Timolol maleate ophthalmic 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:

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

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

Timolol maleate ophthalmic solution:
Common: signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness) including blepharitis*, keratitis*, decreased corneal sensitivity, and dry eyes*
Uncommon: visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases)*
Rare: ptosis, diplopia, choroidal detachment (following filtration surgery) (see Section 4.4)*
Unknown: blurred vision, corneal erosion

Ear and labyrinth disorders:
Timolol maleate ophthalmic solution:
Rare: tinnitus*

Cardiac and Vascular disorders:
Timolol maleate ophthalmic 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*
Unknown: atrioventricular block and cardiac failure

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

Gastro-intestinal disorders:
Dorzolamide/Timolol ophthalmic solution:
Very Common: dysgeusia
Dorzolamide hydrochloride ophthalmic solution:
Common: nausea*
Rare: throat irritation, dry mouth*
Timolol maleate ophthalmic solution:
Uncommon: nausea*, dyspepsia*
Rare: diarrhoea, dry mouth*
Unknown: abdominal pain and vomiting

Skin and subcutaneous tissue disorders:
Dorzolamide/Timolol ophthalmic solution:
Rare: contact dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis
Dorzolamide hydrochloride ophthalmic solution:
Rare: rash*
Timolol maleate ophthalmic solution:
Rare: alopecia*, psoriasiform rash or exacerbation of psoriasis*
Unknown: skin rash

Musculoskeletal and connective tissue disorders:
Timolol maleate ophthalmic solution:
Rare: systemic lupus erythematosus

Unknown: myalgia
Renal and Urinary disorders:
Dorzolamide/Timolol ophthalmic solution:
Uncommon: urolithiasis
Reproductive system and breast disorders:
Timolol maleate ophthalmic solution:
Rare: Peyronie's disease*
Unknown: sexual dysfunction, decreased libido
General disorders and administration site disorders:
Dorzolamide/Timolol ophthalmic solution:
Rare: signs and symptoms of systemic allergic reactions, including angioedema, urticaria, pruritus, rash, anaphylaxis, rarely bronchospasm
Dorzolamide hydrochloride ophthalmic solution:
Common: asthenia/fatigue*
Timolol maleate ophthalmic solution:
Uncommon: asthenia/fatigue*
*These adverse reactions were also observed with Dorzolamide/Timolol ophthalmic solution during post-marketing experience.
Laboratory findings
Dorzolamide/Timolol eye drops solution was not associated with clinically meaningful electrolyte disturbances in clinical studies.
*These adverse reactions were also observed with the fixed combination of dorzolamide and timolol during post-marketing experience.
**Additional adverse reactions have been seen with ophthalmic beta-blockers and may potentially occur with the fixed combination of dorzolamide and timolol.

4.9 Overdose
No data are available in humans in regard to overdose by accidental or deliberate ingestion of the fixed combination of dorzolamide and timolol
Symptoms
There have been reports of inadvertent overdose 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 overdose 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 Particulars:
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, Beta-Blocking Agents, Timolol, Combinations.
ATC code: S01E D51

Mechanism of action
Dorzolamide/Timolol Eye Drops Solution 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 ocular use, Dorzolamide/Timolol Eye Drops Solution reduces elevated intra-ocular pressure, whether or not associated with glaucoma. Elevated intra-ocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. Dorzolamide/Timolol Eye Drops Solution reduces intra-ocular pressure without the common adverse reactions 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 the fixed combination of dorzolamide and timolol 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 the fixed combination of dorzolamide and timolol 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 the fixed combination of dorzolamide and timolol 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 the fixed combination of dorzolamide and timolol b.i.d. was demonstrated when measured at various time points throughout the day and this effect was maintained during long-term administration.

Paediatric population
A three 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 the fixed combination of dorzolamide and timolol in an open label phase. Efficacy in those patients has not been established. In this small group of patients, twice daily administration of the fixed combination of dorzolamide and timolol was generally well tolerated with 19 patients completing the treatment period and 11 patients discontinuing for surgery, a change in medication, or other reasons.

5.2 Pharmacokinetic properties
Dorzolamide hydrochloride
Unlike oral carbonic anhydrase inhibitors, ocular use 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 studies, 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 ocular use, 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 fraction of the 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 dorzolamide 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, ocular use of dorzolamide hydrochloride. However, some elderly patients with renal impairment (estimated CrCl 30-60 millilitre/min) had higher metabolite concentrations in RBCs, but no meaningful differences in carbonic anhydrase inhibition and no clinically significant systemic adverse reactions were directly attributable to this finding.
Timolol maleate
In a study of plasma concentration in six subjects, the systemic exposure to timolol was determined following twice daily ocular use of timolol maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/millilitre and following afternoon dosing was 0.35 ng/millilitre.

5.3 Pre-clinical Safety:
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 reactions 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:

HPMC	BP
Sodium Citrate	BP
Mannitol	BP
Benzalkonium chloride Solution	BP
Water for Injetion	BP

6.2 Incompatibilities: Nil

6.3 Shelf Life: Unopened: 24 months
After the container is opened for the first time: 28 days

6.4 Special Precautions for storage:
Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container:
Dorzolamide &Timolol Eye Drops is filled in 10 ml sterile plastic vials with cap and packed in a carton and pack insert.

6.6 Special precautions for disposal and other handling:
Patients should be instructed to avoid allowing the tip of the dispensing container to contact 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.
Patients should be informed of the correct handling of the Dorzolamide/Timolol Eye Drops Solution eye drops solution.
Instructions for use
Please follow these instructions carefully when using Dorzolamide/Timolol Eye Drops Solution eye drops solution. It is recommended that you wash your hands before putting in your eye drops.
1. You must not use the bottle if the tamper-proof seal on the bottle neck is broken before you first use it.

2. To open the bottle unscrew the cap by turning it until the tamper-proof seal breaks.
3. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye.
4. Invert the bottle and press gently until a single drop as instructed by your doctor is dispensed into your eye. DO NOT TOUCH YOUR EYE OR EYELID WITH THE TIP OF THE CONTAINER.
5. Repeat steps 3 and 4 with the other eye if instructed to do so by your doctor.
6. Reclose the bottle by turning the cap firmly immediately after use and return the bottle to the original outer carton.
7. The dispenser tip is designed to provide a pre-measured drop; therefore, do not enlarge the hole of the dispenser tip.

7. Marketing Authorization Holder:

NCI Pharm Chem Ind. Ltd.
29 Igbehinadun Street,
Oshodi.Lagos, Nigeria

8. Marketing Authorization Number: ---

9. Date of first Authorization /renewal of the authorization: ---

10. Date of revision of text: February 2018