1. NAME OF THE MEDICINAL PRODUCT

Product name: Finarid Eye Drops
Generic name: Dorzolamide and Timolol Maleate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Dorzolamide Hydrochloride Ph. Eur..... 22.26 mg
equivalent to Dorzolamide.....20 mg
Timolol Maleate Ph. Eur..... 6.8 mg
Equivalent to Timolol..... 5.0 mg
Benzalkonium Chloride Ph. Eur.....0.075 mg
(As preservative)
Aqueous Buffered Vehicle..... q.s

{For a full list of excipients, see section 6.1}

3. PHARMACEUTICAL FORM

Eye Drops

Physical description of product: A clear, colourless, slightly viscous solution, free from visible particles.

4. Clinical particulars

4.1 Therapeutic indications

The preparation is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP determined after multiple measurements over time).

4.2 Posology and method of administration

Posology

The dose is one drop in the (conjunctival sac of the) affected eye(s) two times daily .If another topical ophthalmic agerit is being used, Dorzolamide 2.0 mg/ml and Timolol 5 mg/ml and the other agent should be administered at least ten minutes apart. The dosage of this eye drop should not exceed twice daily.
If one dose is missed, treatment should continue with the next dose as normal. The duration of the treatment should be as recommended by the doctor.
Patients should be instructed to wash their hands before use and 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:

- First wash your hands.
- Avoid touching the eye (or any other surface) with the tip of the bottle.
- If you wear soft contact lenses, they should be removed before using the eye drops and wait at least 15 minutes before reinserting.
- These drops are supplied in a plastic bottle with an insert cap assembly, with a tamper proof dust cover. When using the bottle for the first time, snap of the dust cover by turning it cloclcwise to break the seal.
- Unscrew the inner cap.
- Tilt your head back and look at the ceiling.

- Pull the lower eyelid gently downwards.
- Hold the bottle upside down above the eye and gently squeeze the bottle to release a drop into your eye.
- Keep the affected eye closed and presses your fingertip against the inside corner Of the closed eye, and hold for I minute.
- Repeat for the other eye if necessary.
- Recap the bottle after every use, tighten the inner cap on the nozzle. 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

Method of administration

The dose is one drop of the preparation in the affected eye(s) twice daily.
If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

4.3 Contraindications

Dorzolamide and Timolol Maleate Eye Drops 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 hyperchloraemic 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'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 Dorzolamide 20 mg/ml and Timolol 5 mg/ml.
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

Dorzolamide 20 mg/ml and Timolol 5 mg/ml 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, this medicinal product may be absorbed systemically. Dorzolamide contains a sulfonamido group, which also occurs in sulphonamides. Therefore, the same types of adverse reactions found with systemic administration of sulphonamides 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 Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution. If such reactions occur, discontinuation of Dorzolamide 20 mg/ml and Timolol 5 mg/ml 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 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 Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops, urolithiasis has been reported infrequently. Because it contains 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 this eye drops.

Other

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution 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 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 signiftcant difference in mean intraocular pressure has been observed after initial stabilisation.

Information about the preservative

Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution contains the preservative benzalkonium chloride. Benzalkonium Chloride may cause eye irritation. Use of benzalkonium chloride with soft contact lenses should be avoided.
Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolour 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 20 mg/ml and Timolol 5 mg/ml.

In clinical studies, Dorzolamide 20 mg/ml and Timolol 5 mg/ml was usedconcomitant1y 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).

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 Dorzolamide 20 mg/ml and Timolol 5 mg/ml 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.

4.6 Pregnancy and Lactation

Pregnancy:

Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution should not be used during pregnancy.

Dorzolamide:
No adequate clinical data in exposed pregnancies are available. In rabbits, dorzolamide produced teratogenic effect at matemotoxic 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 Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution 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 does appear in human milk. If treatment with Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution 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 Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution have been observed; adverse reactions have been limited to those that were reported previously with dorzolamide hydrochloride and/or timolol maleate. During clinical studies, 1035 patients were treated with Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution. Approximately 2.4% of all patients discontinued therapy 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 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution 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) and not known (cannot be estimated from the available data).

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, paraesthesia. 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:

Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution:
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:

Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution Common: sinusitis.
Rare: shortness of breath, respiratory failure, rhinitis. Rare: epistaxis.

Timolol maleate eye drops, solution:

Uncommon: dyspnoea.
Rare: bronchospasm (predominantly in patients with pre-existing bronchospastic disease), cough.
Gastro-intestinal disorders:

Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution 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:

Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution
Rare: contact dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis. Dorzolainide hydrochloride eye d'rops, "solution:
Rare: rash.

Timolol maleate eye drops, solution:
Rare: alopecia, psoriasiform rash or exacerbation of psoriasis. Renal and urinary disorders:

Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution Uncommon: urolithiasis.
Reproductive system and breast disorders:

Timolol maleate eye drops, solution:
Rare: Peyronie's disease.
General disorders and administration site conditions:

Dorzolamide 20 mg/ml. and Timolol 5 mg/ml Eye Drops Solution
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. Laboratory findings

Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution was riot associated with clinically meaningful electrolyte disturbances in clinical studies.
<Pediatric population>

4.9 Overdose

No data are available in humans in regard to overdose by accidental or deliberate ingestion of Dorzolamide 20 mg/ml and Timolol5 mg/ml Eye Drops Solution.

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 dialyse readily.

5. PHARMACOLOGICAL PROPERTIES

a. Pharmacodynamics properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, Beta blocking agents, Timolol, combinations, ATC code: S01ED51.
Mechanism of Action:
Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution 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 non-selective beta-adrenergic receptor blocking agent. The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that the predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.
The combined effect of these two agents results in additional intraocular pressure (IOP) reduction compared to either component administered alone. Following topical administration, Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution 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. It also reduces intra-ocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.
Pharmacodynamic effects Clinical effects:
Clinical studies of up to 15 months duration were conducted to compare the IOP lowering effect of Dorzolamide 20 ml and Timolol 5 mg/ml Eye Drops Solution b.i.d. (dosed morning and bedtime) to individually- and concomitantly-administered 0.5% timolol and 2.0% dorzolamide in patients with glaucoma or ocular hypertension for whom concomitant therapy was considered appropriate in the trials. This included both untreated patients and patients inadequately controlled with timolol monotherapy. The majority of patients were treated with topical beta-blocker monotherapy prior to study enrollment. In an analysis of the combined studies, the IOP lowering effect of Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution b.i.d. was greater than that of monotherapy with either 2% dorzolamide
t.i.d. or 0.5% timolol b.i.d. The lOP-lowering effect of Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution b.i.d. was equivalent to that of concomitant therapy with dorzolamide b.i.d. and timolol b.i.d. The IOP-lowering effect of Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution b.i.d. was demonstrated when measured at various tirrie points throughout the day and this effect was maintained during long-term administration. Paediatric population
A 3 month controlled study, with the primary objective of documenting the safety of2% 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 lOP was not adequately controlled with monotherapy by dorzolamide or timolol received
Dorzolamide 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution in an open label phase. Efficacy in those patients has not been established.
In this small group of patients, twice daily administration was generally well tolerated with 19 patients completing the treatment period and 11 patients discontinuing for surgery, a change in medication, or other reasons.

b. 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 imd therefore with less systemic exposure. In clinical trials, this resulted in a reduction in lOP 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-ll 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.

c. Preclinical safety data

The ocular and systemic safety profile of the individual components is well established. Dorzolarnide In rabbits given maternotoxic doses of dorzolarnide 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 dorzolarnide 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 20 mg/ml and Timolol 5 mg/ml Eye Drops Solution.

6. PHARMACEUTICAL PARTICULARS

a. List of excipients

Sr.No.	Ingredient	Grade
1.	Hydroxyethyl cellulose	Ph. Eur.
2.	Mannitol	Ph. Eur.
3.	Sodium Citrate	
4.	Benzalkonium Chloride	Ph. Eur.

5.	Sodium Hydroxide	Ph. Eur.
6.	Water for Injections	Ph. Eur.

b. Incompatibilities

Not applicable.

c. Shelf life

Unopened vial: 24 months
Opened vial: 28 days

d. Special precautions for storage

Do not store above 25ºC. Store bottle in the outer carton, in order to protect from light.

e. Nature and contents of container <and special equipment for use, administration or implantation

5 ml solution filled in 5 ml LDPE bottle with insert-cap assembly comprising of dark blue coloured HDPE screw cap over a LDPE nozzle with tamper-evident LDPE dustcover sealing the bottle cap

f. Special precautions for disposal <and other handling>

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Biogenerics Nigeria Limited
No. 13. Hughes Avenue, Alagomeji, Yaba, Lagos, Nigeria.
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Email: drabiogenerics@gmail.com,

8. DRUG PRODUCT MANUFACTURER

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Email: fdc@fdcindia.com

9. NAFDAC REGISTRATION NUMBER(S)

B4-8691