Patient package insert according to Pharmacists' Regulations (Preparations) – 1986.

This medicine can be sold with a doctor's prescription only

Dorzatol-Avenir Eye Drops Solution

Active ingredients:
Dorzolamide (as hydrochloride) 20 mg/ml
Timolol (as maleate) 5 mg/ml

Inactive ingredients and allergens in the preparation see section 6.
See also important information regarding some of the ingredients in section 2.

Read this entire leaflet carefully before you start using this medicine.
This leaflet contains concise information about the medicine, If you have any further questions, refer to your doctor or pharmacist. This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if you think that their medical condition is similar.

1. What is the medicine intended for?

The medicine is used for reduction of high intraocular pressure and for treatment of glaucoma.

Therapeutic group:
Dorzolamide belongs to a group called carbonic anhydrase inhibitors.
Timolol belongs to a group called beta blockers.
These medicines reduce intraocular pressure in different ways.

2. Before using the medicine

Do not use the medicine if:

- You are hypersensitive (allergic) to the active ingredients: dorzolamide hydrochloride, timolol maleate or to any of the other ingredients of the medicine (detailed in section 6).
- You are suffering now or have suffered in the past from impaired function of the respiratory system such as; asthma, severe chronic obstructive bronchitis (a severe lung disease that may cause wheezing, breathing difficulties and/or ongoing cough).
- You suffer from slow heartbeat, heart failure, or irregular heartbeat.
- You suffer from severe kidney disease or impaired kidney function or you have a history of kidney stones.
- You suffer from excess acidity of the blood due to accumulation of chloride in the blood (hyperchloremic acidosis).

Special warnings regarding the use of this medicine
Before treatment with Dorzatol-Avenir **tell the doctor if:**

- You suffer or have suffered in the past from any medical eye problem.
- You suffer from coronary heart disease (may be manifested by chest pain or tightness, shortness of breath or chocking), heart failure or low blood pressure.
- You suffer from impaired function of the respiratory system, such as mild to moderate chronic obstructive pulmonary disease.
- Circulatory system disorders (such as Raynaud's disease or Raynaud's syndrome).

- You suffer from diabetes, as timolol may mask the signs and symptoms of low blood sugar levels.
- You suffer or have suffered in the past from any liver function problem.
- You suffer ~~or have suffered in the past~~ from over-activity of the thyroid gland, as timolol may mask signs and symptoms.
- Tell the doctor that you are using Dorzatol-Avenir before undergoing surgery, as timolol may alter the effect of certain medicines used during anesthesia.

Special warnings during use of the medicine:

- Report to your doctor if you suffer from allergies or allergic reactions including hives, swelling of the face, lips, tongue and/or throat that may cause breathing or swallowing difficulties.
- Report to your doctor if you suffer from muscle weakness or have been diagnosed as having myasthenia gravis, manifested, among other things, by severe muscle weakness.
- If you develop eye irritation or any new eyes problem such as: redness of the eyes or swelling of the eyelids, report to your doctor immediately.
- If you suspect that the medicine is causing an allergic reaction or hypersensitivity (such as: skin rash, severe skin reaction, or redness and irritation of the eye) stop the treatment and report to your doctor immediately.
- Report to your doctor if you develop an eye infection, have injured your eye, are about to undergo eye surgery, develop new symptoms in the eye or worsening of symptoms in the eye.
- Instilling the medicine in the eye may affect the entire body.
- If you wear soft contact lenses you should consult your doctor before starting to use the medicine. See also "Essential information regarding several ingredients of this medicine".

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including non-prescription drugs and nutrition supplements

Dorzatol-Avenir may affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma. Tell your doctor if you are using or intend to use medicines to lower blood pressure, heart medicines or medicines for the treatment of diabetes. Tell your doctor or pharmacist if you are using, have recently used or may use any other medicines. This is especially important if you taking:

- Medicines for the treatment of high blood pressure or treatment of heart disease and heartbeat disorders (such as: calcium channel blockers, beta blockers or digoxin).
- Other eye drops that contain beta blockers.
- Other medicines that contain carbonic anhydrase inhibitors such as: acetazolamide.
- Medicines that contain monoamine oxidase inhibitors (MAOIs) prescribed for the treatment of depression.
- Para-sympathomimetic medicines that are prescribed to help pass urine. These medicines are also prescribed sometimes when it is required to restore normal bowel movement.
- Narcotics such as: morphine prescribed for relief of moderate to severe pain.
- Medicines for the treatment of diabetes.
- Antidepressants such as: fluoxetine and paroxetine.
- Medicines that contain sulfa.
- Medicines that contain quinidine (prescribed for treatment of certain heart diseases and certain types of malaria).

- Medicines that reduce catecholamine levels (for example, reserpine).
- Clonidine
- Epinephrine for injection.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding consult your doctor before taking the medicine.

Use during pregnancy
Do not use the medicine during pregnancy unless your doctor has determined the use is necessary.

Use while breastfeeding
Do not use the medicine while breastfeeding without consulting your doctor. Timolol may pass to your milk. If you are breastfeeding, consult your doctor before taking the medicine.

Driving and use of machinery
No studies have been conducted regarding effects on the ability to drive or operating machinery. There are side effects associated with Dorzatol-Avenir, such as blurred vision, that may affect your ability to drive and/or operate machinery. Do not drive or operate machinery until you feel well or your vision is clear.

Essential information regarding several ingredients of this medicine
Dorzatol-Avenir contains 0.15 ml/mg benzalkonium chloride as a preservative. If you wear soft contact lenses consult your doctor before use since benzalkonium chloride may change the color of the lenses. See also section 3 below.

Use in children
There is limited experience with use of Dorzatol-Avenir in infants and children. This medicine is not intended for use in children and infants.

Use in elderly
In studies of Dorzatol-Avenir, the effects of this medicine were similar in elderly and younger patients.

Use in patients with liver impairment
Tell your doctor if you suffer or have suffered in the past from any problem in liver function.

3. How to use this medicine?
Always use according to the doctor's instructions.
Check with your doctor or pharmacist if you are not sure.

- **The dosage and treatment regimen will be determined by the doctor only.**
- **The Usual recommended dosage is:** One drop in the morning and one drop in the evening. Your doctor will tell you if you should treat only one eye or both eyes.
- **Do not exceed the recommended dose.**

- If you are using other eye drops in addition to Dorzatol-Avenir, use the drops at least 10 minute apart.

- It is very important to use the medicine exactly as your doctor instructed. If you stop using the medicine, contact your doctor immediately.
- Dorzatol-Avenir contains a preservative called benzalkonium chloride. This preservative may be absorbed by soft contact lenses and change their color. Contact lenses should be removed before using Dorzatol-Avenir. The contact lenses can be reinserted 15 minutes after instilling the eye drops.
- Do not allow the tip of the bottle to touch the eye or areas around the eye. The bottle may be contaminated with bacteria. This may cause eye infections which can result in severe damage to the eye, even loss of vision. Wash your hands before using the medicine and keep the tip of the bottle away from contact with any surface to avoid contamination. If you are worried that the tip of the bottle has been contaminated and/or you developed an eye infection, consult the doctor immediately about continued use of this bottle.
- Use the medicine at set times as determined by your treating doctor.

- **Attention:**
  Do not swallow! This medicine is intended for external use only.

Instructions for use:
Wash your hands before instilling the drops.
1. To open the bottle unscrew the cap and remove it.
2. Tilt your head back and look towards the ceiling.
3. Gently pull your bottom eyelid downwards to form a kind of pocket between your eyelid and your eye.
4. Invert the bottle and press the bottle lightly until one drop is dispensed into your eye according to the doctor's instructions.
5. Close the eye and press your finger into the corner of the eye (by the nose) and hold for 2 minutes. This will help prevent the drop from draining via the tear duct to the rest of the body.
6. Repeat steps 3 and 4 if the doctor has instructed you to instill the drops in the other eye.
7. To avoid infection, make sure that the tip of the bottle does not come in contact with any surface including the finger and eye.
8. Replace the cap by turning and tightening it immediately after use.

If you have taken a higher dosage or if a child has accidently swallowed from the medicine, proceed immediately to a hospital emergency room and bring the package of the medicine with you. Symptoms of overdose may include: dizziness, breathing difficulties, feeling the heartrate has slowed. Refer immediately to your doctor.

If you forget to take the medicine at the set time, instill the dose as soon as you remember. However, if it is almost time for the next dose, skip the forgotten dose and return to your regular dosing schedule.

Do not instill a double dose to compensate for a forgotten dose.

If you stop taking the medicine: If you wish to stop taking the medicine, consult your doctor before you do so.

How can you assist in the success of the treatment?
1. To avoid contamination, make sure the nozzle of the bottle does not come in contact with any surface (including the eye itself). Keep the bottle sealed well.

2. The eye drop bottle may not be completely full; this is to enable better control of the instilling rate.
3. How to use the eye drops: see section **"instructions for use".**
4. After using the medicine, wash your hands well to clean them from medicine residue.
5. To avoid spreading an infection, do not use the same medicine container for more than one person.

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

If you have any further questions regarding the use of this medicine, consult your doctor or pharmacist.

4. Side effects

Like any medicine, the use of Dorzatol-Avenir may cause side effects in some of the users. Do not be alarmed while reading the list of side effects. You may not suffer from any of them, but if the side effects do not pass or are bothersome or they worsen, consult your doctor.

Stop treatment and refer immediately to a doctor or a hospital emergency room if the following side effects appear: allergic reaction that includes swelling of the facial area, the eyelids or the lips that may block the airways and cause swallowing or breathing difficulties, hives or an itchy rash, localized or generalised rash, itchiness, a severe, sudden life threatening allergic reaction.

The following side effects have been reported due to the use of the ingredients of the medicine during clinical trials or during post-marketing use:

Very common side effects (appear in 1 in 10 patients)- stinging or tingling in the eyes, distortion of the sense of taste.

Common side effects (appear in 1-10 patients in 100)- redness inside and around the eye, tearing or itching of the eyes, corneal abrasion (damage to the front layer of the eyeball), swelling and/or irritation inside the eye and around it, feeling of a foreign body in the eye, decreased sensitivity of the cornea (manifested by inability to feel the presence of a foreign body in the eye and not feeling pain), pain in the eye, dryness in the eye, blurred vision, headache, sinusitis (feeling of pressure or congested nose), nausea, weakness, fatigue and lethargy (severe fatigue).

Uncommon side effects (appear in 1-10 patients in 1,000)- dizziness, depression, inflammation of the iris, visual disturbances including refractive changes (in some cases as a result of stopping a miotic treatment that contracts the pupil), slowing of heartbeat, fainting, breathing difficulties (dyspnea), indigestion and kidney stones (characterized by a sudden sharp pain, cramping in the lower back, sides, groin or abdomen).

Rare side effects (appear in 1-10 patients in 10,000) – systemic lupus erythematosus (an autoimmune disease that may cause inflammation of internal organs), tingling or paresthesia in the hands or feet, insomnia, nightmares, memory loss, worsening of the signs and symptoms of myasthenia gravis (impaired muscle function), decreased sexual drive, stroke, temporary shortsightedness that may pass after stopping treatment, detachment of the layer below the retina, which contains blood vessels as a result of filtration surgery that may cause visual

disturbances, drooping of the eyelids (causes the eye to remain half closed), double vision, formation of a cream-like layer on the eyelids, swelling of the cornea (manifests as visual disturbances), low intraocular pressure, ringing in the ears, low blood pressure, changes in heartrate, heart failure (a disease manifested by shortness of breath and swelling of the legs due to fluid retention), edema, cerebral ischemia (reduced blood supply to the brain), chest pain, palpitations (rapid and irregular heartbeats), heart attack, Raynaud's phenomenon, swelling or coldness of the hands and feet, reduced circulation in your arms and legs, legs cramps and/or leg pain when walking (claudication), shortness of breath, feeling out of breath, runny or congested nose, nose bleed, constriction of the airways in the lungs causing breathing difficulties, cough, throat irritation, dry mouth, diarrhea, contact dermatitis, hair loss, a sliver colored rash on the skin (psoriasiform rash), Peyronie's disease (may cause a curvature of the penis), allergic reaction such as: rash, hives, itching, in rare cases there may be swelling in the lips, eyes and mouth, wheezing or severe skin reactions (Steve-Johnson syndrome, toxic epidermal necrolysis).

Like other medicines with topical ophthalmic administration, timolol is absorbed into the circulatory system. This may cause side effects similar to those caused by medicines that belong to the beta blocker group administered orally. The frequency of side effects after topical ophthalmic administration is lower than after oral administration or injection.
The additional side effects include reactions that occur when medicines from the beta blocker group are administered, when used for treatment of eye problems.

Side effects with unknown frequency – low blood sugar levels, heart failure, a type of heart rhythm disorder, abdominal pain, vomiting, muscle pain not caused by exercise, sexual dysfunction.

If a side effect occurs, or if one of the side effects worsens, or if you experience a side effect not mentioned in this leaflet, consult the doctor.

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" that can be found on the homepage of the Ministry of Health's website (www.health.gov.il), which refers to the online form reporting side effects,
or via the following link:
https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

5. How to store the medicine?

- Avoid poisoning! This medicine, and any other medicine, must be stored in a safe place out of the reach of children and/or infants to avoid poisoning that may be life threatening. See sections "Special warnings regarding the use of this medicine" and "If you have taken an overdose".
- Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) stated on the package and label. The expiry date refers to the last day of that month.
- After opening the package the medicine can be used for 28 days.
- Storage conditions:
  Store at a temperature of 25°C.
  Store in the original package to protect from light.

6. Additional information

- **In addition to the active ingredients, this medicine also contains:**
  Mannitol, Hydroxy ethyl cellulose, sodium citrate dihydrate, Benzalkonium chloride, Hydrochloric acid and/ or Sodium hydroxide, Water for injection.

- **What the medicine looks like and contents of the pack**
  Dorzatol-Avenir is a clear and colorless solution in a bottle that contains 5 ml with a dropper on the tip.

- **Registration holder and importer**
  BioAvenir Ltd., 1 David Hamelech St., Herzeliya Pituach 4666101

- **Manufacturer**
  Tubilux Pharma S.p.A , Pomezia, Italy

- This leaflet was checked and approved by the Ministry of Health in May 2016.

- **Drug registration numbers at the national medicines registry of the Ministry of Health:** 155-93-34413-00