Patient Leaflet in Accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Combigan®

Eye drops, solution

Active ingredients and their concentrations:
Brimonidine tartrate 0.2% w/v and timolol (as maleate) 0.5% w/v

Inactive ingredients and allergens in the medicine: See section 2 under 'Important information about some of this medicine's ingredients', and section 6 'Additional information'.

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

1. WHAT IS THIS MEDICINE INTENDED FOR?

Combigan is used for lowering high intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Therapeutic group: The medicine contains two active ingredients - brimonidine, which belongs to a group of medicines called alpha-adrenergic receptor agonists. Timolol, which belongs to a group of medicines called beta-blockers.

Both of these active ingredients reduce pressure in the eye.

2. BEFORE USING THE MEDICINE

Do not use this medicine if:

- you are sensitive (allergic) to the active ingredients or to any of the additional ingredients in this medicine (detailed in section 6 'Additional information').
- you are suffering or suffered in the past from breathing problems, including bronchial asthma, chronic obstructive pulmonary disease.
- you suffer from overt cardiac failure, sinus bradycardia, second- or third-degree atrioventricular block, cardiogenic shock.
- in neonates and infants under the age of 2 years.

Special warnings regarding the use of this medicine

- **Before treatment with Combigan, tell the doctor if you suffer now, or have suffered in the past from:**
  - inadequate blood flow to the brain or heart
  - diabetes (especially uncontrolled diabetes) or spontaneous hypoglycaemia (low blood sugar levels).
  - any allergy or severe allergic reaction
  - depression
  - Raynaud's phenomenon
  - orthostatic hypotension (low blood pressure when switching to a standing position)
  - thromboangitis obliterans (inflammation of the blood vessels in the hands and feet)
  - hyperthyroidism

- myasthenia gravis or myasthenic symptoms (chronic fatigue and muscle weakness)

- Allergic (hypersensitivity) reactions in the eye have been reported with brimonidine tartrate 0.2% solutions, with some being reported to be associated with an increase in intraocular pressure.
- Inform your doctor in case of eye inflammation, eye injury, eye surgery or any new reaction, including aggravation of existing phenomena.
- Combigan contains timolol, and although it is instilled into the eye, it may get into the rest of the body, and side effects similar to those experienced with systemic beta-blockers may occur.
- Further infection could be caused by contaminated eye drops. To prevent this, do not allow the tip of the bottle to come into contact with any surface, including the eye. Close the bottle immediately after use.
- If you are about to undergo any surgical operation, inform your doctor that you are using this medicine.

If you are taking, or if you have recently taken other medicines, including non-prescription medicines and dietary supplements, tell the doctor or pharmacist.
Especially if you are taking:
- medicines to treat high blood pressure
- digitalis (for heart conditions)
- other beta-blocking medicines, either topically or systemically
- calcium channel blockers
- medicines which affect the amount of catecholamines in the body, e.g. reserpine
- opiate pain killers
- medicines to help you sleep or for anxiety, e.g., barbiturates
- quinidine (for heart conditions), medicines for depression and anxiety from the SSRIs (selective serotonin re-uptake inhibitors) group
- tricyclic antidepressants
- monoamine oxidase (MAO) inhibitors

If you are due to have an anaesthetic, you should tell the doctor or dentist that you are taking Combigan.

Using the medicine and alcohol consumption
You should inform the doctor if you are drinking alcohol.

Pregnancy and breastfeeding
Consult with a doctor before using this medicine.
Combigan should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Timolol has been found to be present in human breast milk following topical administration to the eye. Because of the potential for serious side effects in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the medicine, taking into account the importance of the medicine to the mother.

Driving and using machines
Use of this medicine may impair alertness and cause blurred vision; and therefore, caution should be exercised when engaging in activities such as driving a car, operating dangerous machinery and in any other activity that requires alertness and sharp vision.

Important information about some of this medicine's ingredients
This medicine contains benzalkonium chloride
This medicine contains benzalkonium chloride, which may be deposited in soft contact

lenses. Do not use this medicine while wearing these lenses. The lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.

3. HOW TO USE THE MEDICINE?

Always use the medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure about the dosage or the treatment regimen of this medicine. The dosage and treatment will be determined by the doctor only.
The recommended dosage is usually: One drop of Combigan in the affected eye(s) twice daily, approximately 12 hours apart.
Do not exceed the recommended dose.
Do not swallow!
This preparation is intended for use in the eyes only.
If more than one eye drop preparation is to be used, wait at least 5 minutes between the preparations. Do not use this medicine if the safety seal on the bottleneck is torn, before the first use of the medicine.

Directions for using the preparation:

1. In order to avoid contamination, do not allow the tip of the bottle to come into contact with any surface (including the eye itself). Keep the bottle tightly closed.
2. The bottle of drops may not be full. This is meant to allow better control over the drip rate.
3. How to use the drops: First, wash your hands. Tilt your head back. Using your index finger, pull your lower lid downward to create a 'pocket'. Drip the medicine into the 'pocket' that is formed. Close your eyes gently. Do not blink. Leave your eyes closed for 1-2 minutes.
4. Immediately after applying the drops into the eye, put pressure on the inner corner of the eye using your middle finger. Continue applying pressure for 1-2 minutes after applying the drops to the eye. This action helps to avoid the absorption of the medicine into the body and thus helps prevent side effects.
5. After using the medicine, wash your hands thoroughly in order to wash off remnants of the medicine.
6. In order to avoid transmitting the infection, the same container of medicine should not be used by more than one person.

Always replace the cap after use.

If you have accidentally taken a higher dose
If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately contact a doctor or proceed to a hospital emergency room and bring the medicine package with you.

With the exception of hypotension, very limited information is available on accidental ingestion of brimonidine. However, reported side effects experienced after accidental overdose of timolol eye drops include:

- Dizziness
- Headache
- Shortness of breath
- Slow heart rate
- Bronchospasm
- Cardiac arrest

Symptoms of brimonidine overdose have been reported in neonates, infants and children receiving brimonidine eye drop solutions as part of medical treatment for congenital glaucoma or by accidental swallowing. Should this happen, contact your doctor immediately.

If you forget to take the medicine
If you forgot to use this medicine at the scheduled time, do not take a double dose. Take the next dose at the usual time and consult the doctor.
Adhere to the treatment as recommended by the doctor.
Even if your health improves, do not stop taking the medicine without consulting the doctor.

Do not take medicines in the dark! Check the label and dose each time you take medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Combigan may cause side effects in some users. Do not be alarmed by the list of side effects. You may not experience any of them.

In clinical trials of 12 months duration with Combigan, the most frequent reactions associated with its use occurring in approximately 5% to 15% of the patients included:

- red enlarged blood vessels in the eye
- burning sensation in the eye
- stinging sensation
- itchy eye
- allergic reaction in the eye
- inflammation of the eyelid

The following side effects were reported in 1% to 5% of patients:

- watery eyes
- redness in the inner surface of the eye and eyelid
- eye pain
- eye dryness
- visual disturbances
- foreign body sensation in the eye
- eye discharge
- swollen eyelid
- itchy eyelid
- eye irritation
- small abrasions on the surface of the eye
- headache
- feeling weak
- depression
- high blood pressure
- dry mouth
- feeling drowsy

Additional side effects: the following additional side effects have been reported with the individual components, brimonidine and timolol, and may potentially occur with Combigan:
Brimonidine:

- dryness of the nose
- dizziness
- fatigue
- insomnia
- cold-like symptoms
- low blood pressure
- cough

- rash
- allergic reaction
- bronchitis
- cataract
- inflammation within the eye
- bleeding within the eye
- whitening of the clear layer covering the eye surface
- eye swelling
- inflammation of the surface of the eye
- indigestion
- shortness of breath
- flu-like symptoms
- eye allergies and redness of the inner surface of the eye and eyelid
- digestive disorder
- high levels of cholesterol in the blood
- infections (mainly colds and upper respiratory infections)
- stye
- eyelid infection
- crusting of eyelids
- sore throat
- sensitivity to light
- itchy, runny or blocked nose
- sinus infection
- blurred vision
- vision disturbances
- flashes or eye floaters
- tearing
- muscular pain

Timolol:

- chest pain
- arrhythmia
- slow heartbeat
- cardiac arrest
- heart failure
- insufficient blood flow to the brain
- stroke
- pain, discomfort or tiredness in the legs
- cold hands and feet
- fluid retention
- heart block
- palpitations
- Raynaud’s phenomenon
- fainting
- worsening of angina
- loss of appetite
- diarrhoea
- nausea
- systemic lupus erythematosus
- increase in signs and symptoms of myasthenia gravis (muscle weakness)
- difficulty sleeping
- nightmares
- prickling or burning sensation in the feet, legs, arms or hands

- confusion
- hallucinations
- anxiety
- disorientation
- nervousness
- memory loss
- alopecia
- psoriasiform rash or worsening of psoriasis
- allergic reactions including anaphylactic reactions, swelling of the skin, hives and generalised or localised rash
- bronchospasm (mainly in patients with pre-existing bronchospastic disease)
- shortness of breath
- blocked nose
- respiratory failure
- upper respiratory tract infections
- masked symptoms of low blood sugar levels (hypoglycaemia) in patients with diabetes
- double vision
- complications after surgery to reduce pressure in the eye
- swelling of the retina within the eye leading to worsening vision
- decreased sensitivity within the eye
- scarring of the eye surface
- drooping eyelid
- worsening of the vision
- ringing in the ears
- decreased libido
- impotence
- Peyronie's disease (scarring of the penis which may cause curvature of the penis)
- blockage of the tubes that carry urine from the kidney to the bladder

The following side effects have been identified during post-marketing use of brimonidine tartrate eye drops solution, timolol eye drops solution, or both in combination:
- redness and inflammation of the eyelids, cheeks or forehead
- allergies
- inflammation of the iris (coloured part of the eye)
- eye dryness
- pupillary constriction
- nausea
- skin reactions including redness and rash
- fast heartbeat
- In infants receiving brimonidine tartrate solutions the following side effects have been reported: pauses in breathing, slow heartbeat, coma, low body temperature, decreased muscle tone, abnormal drowsiness, pale skin and slow breathing rate.

The following additional side effects have been observed with oral timolol maleate or other oral beta- blockers and may be considered potential side effects of eye drops containing timolol:
- rash
- fever with sore throat
- temporary spasm of the vocal cords causing difficulty in breathing
- decreased exercise tolerance
- pain in the extremities
- weight loss

- blood vessels widening caused by relaxation of the muscles in the blood vessel walls
- reduced blood flow through the arteries
- stomach ache
- enlarged liver
- damage to the intestine caused by inadequate blood supply
- vomiting
- low white blood cell count
- a purplish discolouration of the skin
- blood sugar levels which are too high or too low
- increased skin pigmentation
- itchy skin
- skin irritation
- sweating
- painful joints
- spatial and temporal disorientation
- reduced concentration
- frequent or intense mood changes
- local weakness
- depression
- confusion
- vertigo
- airway obstruction
- a crackling sound when breathing
- difficulty in passing urine

If you experience any side effect, if any side effect gets worse or if you experience a side effect not mentioned in this leaflet, consult your doctor.

Reporting side effects

You can report side effects to the Ministry of Health by clicking on the link "Reporting side effects due to medical treatment" that is found on the homepage of the Ministry of Health website (www.health.gov.il) and using the online form for reporting side effects, or by using the link: https://sideeffects.health.gov.il

5. HOW TO STORE THE MEDICINE?

Prevent poisoning! To prevent poisoning, keep this and all other medicines in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by the doctor.

Do not use the medicine after the expiry date (exp. date) which is stated on the carton/label. The expiry date refers to the last day of that month.

Storage conditions:

Store below 25°C. Protect from light.

Use within 28 days after first opening and no later than the expiry date of the medicine.

Do not use the solution if you notice that it becomes discoloured or cloudy.

6. ADDITIONAL INFORMATION

In addition to the active ingredients, the medicine also contains:

sodium phosphate dibasic, heptahydrate; sodium phosphate monobasic, monohydrate; benzalkonium chloride, hydrochloric acid and/or sodium hydroxide and purified water.

What the medicine looks like and the contents of the package:

Combigan is a clear, greenish-yellow to light greenish-yellow coloured solution. The solution is supplied sterile in a white plastic bottle with a white tip and a blue plastic cap, in the following sizes: 5 ml or 10 ml. Not all pack sizes may be marketed.

Registration holder's name and address: AbbVie Biopharmaceuticals Ltd., 4 Haharash St., Hod Hasharon, Israel.

Manufacturer's name and address: Allergan Inc. USA, 2525 Dupont Drive, Irvine, California, USA.

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Registration number of the medicine in the National Drug Registry of the Ministry of Health: 137-56-31401-00