Package leaflet: Information for the user

COMBIGAN 2 mg/ml + 5 mg/ml eye drops, solution
Brimonidine tartrate and timolol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What COMBIGAN is and what it is used for

COMBIGAN is an eye drop that is used to control glaucoma. It contains two different medicines (brimonidine and timolol) that both reduce high pressure in the eye. Brimonidine belongs to a group of medicines called alpha-2 adrenergic receptor agonists. Timolol belongs to a group of medicines called beta-blockers. COMBIGAN is prescribed to reduce high pressure in the eye when beta-blocker eye drops used alone are not enough.

Your eye contains a clear, watery liquid that feeds the inside of the eye. Liquid is constantly being drained out of the eye and new liquid is made to replace this. If the liquid cannot drain out quickly enough, the pressure inside the eye builds up and could eventually damage your sight. COMBIGAN works by reducing the production of liquid and increasing the amount of liquid that is drained. This reduces the pressure inside the eye whilst still continuing to feed the eye.

2. What you need to know before you use COMBIGAN Do

not use COMBIGAN:
- if you are **allergic** (hypersensitive) to **brimonidine tartrate, timolol, beta-blockers** or any of the **other ingredients** of this medicine (listed in section 6). Symptoms of an allergic reaction may include swelling of the face, lips and throat, wheeziness, feeling faint, shortness of breath, itching or redness around the eye.
- if you have now or have had in the past respiratory problems such as **asthma, severe chronic obstructive bronchitis** (severe lung disease which may cause wheeziness, difficulty in breathing and/or long-standing cough).
- if you have heart problems such as **low heart rate, heart failure, heart beat disorders** (unless controlled by a pacemaker).

- if you are taking **monoamine oxidase (MAO) inhibitors** or certain other **antidepressant drugs**.

If you think any of these points apply to you, do not use COMBIGAN until you have talked again to your doctor.

Warnings and precautions
Talk to your doctor before using COMBIGAN
- if you have now or have had in the past
  - coronary heart disease (symptoms can include chest pain or tightness, breathlessness or choking), heart failure, low blood pressure
  - disturbances of heart rate such as slow heart beat
  - breathing problems, asthma or chronic obstructive pulmonary disease
  - poor blood circulation disease (such as Raynaud's disease or Raynaud's syndrome)
  - diabetes as timolol may mask signs and symptoms of low blood sugar levels
  - over activity of the thyroid gland as timolol may mask signs and symptoms
  - kidney or liver problems
  - tumour of the adrenal gland
  - eye surgery to lower the pressure in your eye
- if you suffer or have suffered from any allergy (e.g. hayfever, eczema) or a severe allergic reaction be aware that the usual dose of adrenaline used to control a severe reaction may need to be increased.
- Tell the doctor before you have an operation that you are using COMBIGAN, as the timolol may change effects of some medicines during anaesthesia.

Children and adolescents
COMBIGAN should not be used in children less than 2 years old and should not usually be used in children aged 2 to 17.

Other medicines and COMBIGAN

COMBIGAN can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma. Tell your doctor or pharmacist if you are taking, have recently taken or might take other medicines, including medicines for any condition, even if unrelated to your eye condition, including medicines obtained without a prescription. There are a number of medicines which may interfere with COMBIGAN, so it is particularly important to tell your doctor if you are taking:

- pain killers
- medicines to help you sleep or for anxiety
- medicines to treat high blood pressure (hypertension)
- medicines for heart conditions (for example an abnormal heartbeat) such as beta blockers, digoxin or quinidine (used to treat heart conditions and some types of malaria)
- medicines to treat diabetes or high blood sugar
- medicines for depression such as fluoxetine and paroxetine
- another eye drop used to lower high pressure in the eye (glaucoma)
- medicines to treat severe allergic reactions
- medicines that affect some of the hormones in your body, like adrenaline and dopamine
- medicines that affect the muscles in your blood vessels
- medicines to treat heartburn or stomach ulcers

If the dose of any of your current medicines is changed or if you are regularly consuming alcohol you should tell your doctor.
If you are due to have an anaesthetic, you should tell the doctor or dentist that you are taking COMBIGAN.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Do not use COMBIGAN if you are pregnant unless your doctor considers it necessary.

Do not use COMBIGAN if you are breast-feeding. Timolol may get into your milk. Ask your doctor for advice before taking any medicine during breast-feeding.

Driving and using machines
COMBIGAN may cause drowsiness, tiredness or blurred vision in some patients. Do not drive or use any tools or machines until the symptoms have cleared. If you experience any problems, talk to your doctor.

COMBIGAN contains benzalkonium chloride

This medicine contains 0.25 mg benzalkonium chloride in each 5 ml of solution which is equivalent to 0.05 mg/ml.

- Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. You should remove contact lenses before using this medicine and put them back 15 minutes afterwards.
- Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye). If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor

COMBIGAN contains phosphates:

This medicine contains 52.9 mg phosphates in each 5 ml of solution which is equivalent to 10.58 mg/ml.

If you suffer from severe damage to the clear layer at the front of the eye (the cornea), phosphates may cause in very rare cases cloudy patches on the cornea due to calcium build-up during treatment.

3. How to use COMBIGAN

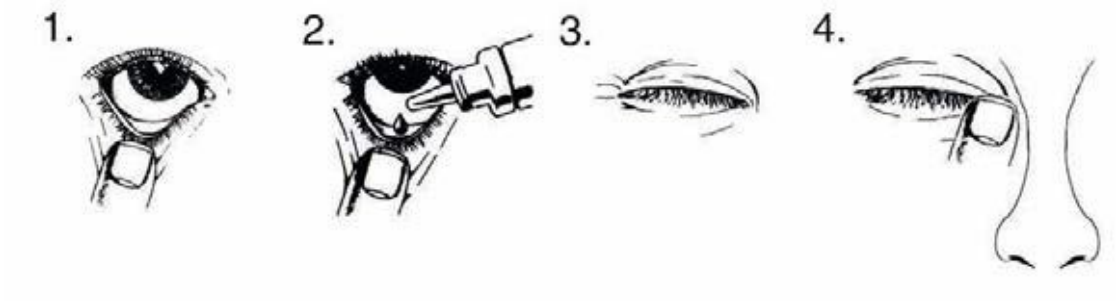
Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. COMBIGAN must not be used in infants below 2 years of age. COMBIGAN should not usually be used in children and adolescents (from 2 to 17 years).

The recommended dose is one drop of COMBIGAN, twice a day about 12 hours apart. Do not change the dose or stop taking it without speaking to your doctor.

If you have other eye drops as well as COMBIGAN, **leave at least 5 minutes** between using COMBIGAN and the other eye drops.

Instructions for use
You must not use the bottle if the tamper-proof seal on the bottle neck is broken before you first begin to use it.

Wash your hands before opening the bottle. Tilt your head back and look at the ceiling.



1. Gently pull down the lower eyelid until there is a small pocket.
2. Turn the bottle upside down and squeeze it to release one drop into each eye that needs treatment.
3. Let go of the lower lid, and close your eye.
4. Keep the eye closed and press your finger against the corner of your eye (the side where your eye meets your nose) for two minutes. This helps stop COMBIGAN getting into the rest of the body.

If a drop misses your eye, try again.

To avoid contamination, do not let the tip of the bottle touch your eye or anything else. Put the screw-cap back on to close the bottle, straight after you have used it.

If you use more COMBIGAN than you should
Adults
If you use more COMBIGAN than you should, it is unlikely to cause you any harm. Put your next drop in at the usual time. If you are worried, talk to your doctor or pharmacist.

Babies and Children
Several cases of overdose have been reported in babies and children receiving brimonidine (one of the ingredients of COMBIGAN) as part of medical treatment for glaucoma. Signs include sleepiness, floppiness, low body temperature, paleness and breathing difficulties. Should this happen, contact your doctor immediately.

Adults and Children
If COMBIGAN has been accidentally swallowed then you should contact your doctor immediately.

If you forget to use COMBIGAN
If you forget to use COMBIGAN, use a single drop in each eye that needs treatment as soon as you remember, and then go back to your regular routine. Do not take a double dose to make up for a forgotten dose.

If you stop using COMBIGAN
COMBIGAN should be used every day to work properly.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If

you experience any of the following side effects, please contact your doctor immediately:
- Heart failure (eg. chest pain) or irregular heart rate
- Increased or decreased heart rate or low blood pressure

Affecting the eye

Very common (May affect more than 1 in 10 people) :

- Eye redness or burning.

Common (May affect up to 1 in 10 people):

- Stinging or pain in the eye
- Allergic reaction in the eye or on the skin around the eye
- Small breaks in the surface of the eye (with or without inflammation)
- Swelling, redness or inflammation of the eyelid
- Irritation, or a feeling of something in the eye
- Itching of the eye and eyelid
- Follicles or white spots on the see through layer which covers the surface of the eye
- Vision disturbance
- Tearing
- Eye dryness
- Sticky eyes

Uncommon (May affect up to 1 in 100 people):

- Difficulty in seeing clearly
- Swelling or inflammation of the see-through layer which covers the surface of the eye
- Tired eyes
- Sensitivity to light
- Eyelid pain
- Whitening of the see-through layer which covers the surface of the eyes
- Swelling or areas of inflammation under the surface of the eye
- Floaters in front of the eyes

Not known (Frequency cannot be estimated from the available data):

- Blurred vision

Affecting the body:

Common (May affect up to 1 in 10 people):

- High blood pressure
- Depression
- Sleepiness
- Headache
- Dry mouth
- General weakness

Uncommon (May affect up to 1 in 100 people):

- Heart failure
- Irregular heart rate
- Light-headedness
- Fainting
- Dry nose

- Taste disturbance
- Nausea
- Diarrhoea

Not known (Frequency cannot be estimated from the available data):

- Increased or decreased heart rate
- Low blood pressure
- Face redness

Some of these effects may be due to an allergy to any of the ingredients. Additional side effects have been seen with brimonidine or timolol and therefore may potentially occur with COMBIGAN.

The following additional side effects have been seen with brimonidine:

- Inflammation within eye, small pupils, difficulty sleeping cold-like symptoms shortness of breath, symptoms involving the stomach and digestion, general allergic reactions, skin reactions including redness, face swelling itching rash and widening of blood vessels.

Like other medicines applied into eyes, COMBIGAN (brimonidine/timolol) is absorbed into the blood. Absorption of timolol, a beta blocker component of COMGIBAN, may cause similar side effects as seen with intravenous" and /or "oral" beta-blocking agents. Incidence of side effects after topical ophthalmic administration is lower than when medicines are for example, taken by mouth or injected. Listed side effects include reactions seen within the class of beta-blockers when used for treating eye conditions:

- Generalised allergic reactions, including swelling beneath the skin (that can occur in areas such as the face and limbs, and can obstruct the airway which may cause difficulty swallowing or breathing), hives (or itchy rash), localised and generalised rash, itchiness, severe sudden life threatening allergic reaction

- Low-blood glucose levels

- Difficulty in sleeping (insomnia), nightmares, memory loss, hallucination

- Stroke, reduced blood supply to the brain, increased signs and symptoms of myasthenia gravis (muscle disorder), unusual sensations (like pins and needles).

- Inflammation in the cornea, detachment of the layer below the retina that contains blood vessels following filtration surgery which may cause visual disturbances, decreased corneal sensitivity, corneal erosion (damage to the front layer of the eyeball), drooping of the upper eyelid (making the eye half closed), double vision

- Chest pain, oedema (fluid build up), changes in the rhythm or speed of the heartbeat, a type of heart rhythm disorder, heart attack, heart failure

- Raynaud's phenomenon, cold hands and feet

- Constriction of the airways in the lung (predominantly in patients with pre-existing disease) difficulty breathing, cough

- Indigestion , abdominal pain, vomiting

- Hair loss, skin rash with white silvery coloured appearance (psoriasiform rash) or worsening of psoriasis, skin rash

- Muscle pain not caused by exercise

- Sexual dysfunction, decreased libido

- Muscle weakness/tiredness

Other side effects reported with eye drops containing phosphates:
Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged cornea.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store COMBIGAN

Keep this medicine out of the sight and reach of children. Keep

the bottle in the outer carton to protect it from light. You should

only use one bottle at a time.

Do not use this medicine after the expiry date which is stated on the label of the bottle and the carton after EXP:. The expiry date refers to the last day of that month.

You must throw away the bottle four weeks after you first opened it, even if there are still some drops left. This will help to prevent infections. To help you remember, write down the date that you opened it in the space on the carton.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What COMBIGAN contains

- The active substances are brimonidine tartrate and timolol.
- One millilitre of solution contains 2 milligrams of brimonidine tartrate and timolol maleate equivalent to 5 milligrams of timolol.
- The other ingredients are benzalkonium chloride (a preservative), sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate and purified water. Small amounts of hydrochloric acid or sodium hydroxide may be added to bring the solution to the correct pH (a measure of the acidity or alkalinity of the solution).

What COMBIGAN looks like and contents of the pack

COMBIGAN is a clear, greenish-yellow eye drop solution in a plastic bottle with a screw- cap. Each bottle is about half full and contains 5 ml of solution. Packs are available containing either 1 or 3 bottles. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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