001002

Worldwide Patient Product Information (WPPI)
Information For The Patient

About TIMOPTOL-XE®

Santen

Please read this leaflet carefully before you start to take your medicine, even if you have just refilled your prescription. Some of the information in the previous leaflet may have changed.
Remember that your doctor has prescribed this medicine only for you. Never give it to anyone else.

What is TIMOPTOL-XE?

TIMOPTOL-XE® (timolol maleate) is a sterile eyedrop containing timolol as the active ingredient. This eyedrop also contains a new delivery vehicle which is obtained from a natural substance. This vehicle allows the eye drop to form a clear transparent gel when it contacts the eye. This gel increases the contact time of timolol with the eye.

TIMOPTOL-XE is available in two strengths. Each mL of TIMOPTOL-XE 0.25% or TIMOPTOL-XE 0.5% contains 2.5 mg or 5 mg timolol as the active ingredient, respectively.

In addition, TIMOPTOL-XE contains the following inactive ingredients: Gellan gum, mannitol, tromethamine, and water for injection. Benzododecinium bromide is added as preservative.

Each vial of TIMOPTOL-XE 0.25% or TIMOPTOL-XE 0.5% contains 2.5 mL of solution. Not all presentations may be available locally.

TIMOPTOL-XE is an ophthalmic beta-blocking drug which lowers pressure in the eye.

Why has my doctor prescribed TIMOPTOL-XE?

TIMOPTOL-XE is prescribed to lower raised pressure in the eye and to treat glaucoma.

Elevated pressure in the eye may damage the optic nerve resulting in deterioration of vision and possible blindness. There generally are few symptoms that you can feel to tell you whether you have elevated pressure within your eye. Your doctor's examination is needed to determine this. If you have raised pressure in your eye, regular eye examinations and measurements of the pressure within your eyes will be necessary.

What should I know before or while using TIMOPTOL-XE?

Who should not use TIMOPTOL-XE?

Do not use TIMOPTOL-XE if you:

- have now or have had in the past certain serious breathing problems such as asthma
- have chronic obstructive lung disease
- have certain heart diseases (such as slow or irregular heartbeats)
- have known or suspected hypersensitivity (allergy) to any of its components

If you are not sure whether you should use TIMOPTOL-XE, contact your doctor or pharmacist.

What should I tell my doctor before or while using TIMOPTOL-XE?

Tell your doctor about any medical problems you have now or have had in the past:

- heart problems (such as coronary heart disease, heart failure or low blood pressure)
- heart rate disturbances (such as slow or irregular heartbeats)
- poor blood circulation problems (such as Raynaud's syndrome)
- lung or breathing problems (such as asthma or chronic obstructive lung disease)
- diabetes or other blood sugar problems
- thyroid disease

Tell your doctor before you have an operation that you are using TIMOPTOL-XE, as it may change the effects of some medicines during anesthesia.

Also tell your doctor if you have allergies to any medications.

If you suspect that TIMOPTOL-XE is causing an allergic reaction (for example, skin rash, or redness and itching of the eye), stop its use and contact your doctor immediately.

Tell your doctor if you develop an eye infection, receive an eye injury, have eye surgery, or develop a reaction including new or worsening symptoms.

If you wear soft contact lenses, you should consult your doctor before using TIMOPTOL-XE.

Use in children.

Safety and effectiveness in children have not been established.

Use in pregnancy.

Tell your doctor if you are pregnant or intend to become pregnant. Your doctor will decide if you should use TIMOPTOL-XE.

Use in breast-feeding.

Do not use TIMOPTOL-XE while breast-feeding. If you intend to breast-feed, consult your doctor.

Can I use TIMOPTOL-XE with other medicines?

Tell your doctor about all drugs, including other eyedrops, that you are using or plan to use, including those obtained without a prescription. This is particularly important if you are taking medicine to lower blood pressure or to treat heart disease, diabetes or depression.

Can I drive or operate machinery while using TIMOPTOL-XE?

Your vision may be temporarily blurred for 30 seconds to 5 minutes immediately after putting TIMOPTOL-XE in your eye. Make sure that your vision is clear before you drive a motor vehicle or operate machinery. There are additional side effects associated with this product that may affect your ability to drive or operate machinery (see **What undesirable effects may TIMOPTOL-XE have?**).

How should I use TIMOPTOL-XE?

The usual starting dose is one drop of TIMOPTOL-XE 0.25% in the affected eye(s) once a day. In some cases, your doctor may prescribe one drop of TIMOPTOL-XE 0.5% in the affected eye(s) once a day.

If your doctor recommends that you use TIMOPTOL-XE with another eyedrop, this other medicine should be administered at least 10 minutes before TIMOPTOL-XE.

Do not change the dosage recommended by your doctor. If you must stop treatment, consult your doctor immediately.

TIMOPTOL-XE

Invert the closed container and shake once before each use. It is not necessary to shake the container more than once.

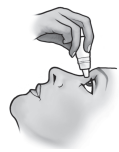
Do not allow the tip of the container to touch the eye or areas around the eye. It may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision. To avoid possible contamination of the container, keep the tip of the container away from contact with any surface. If you think your medication may be contaminated, or if you develop an eye infection, contact your doctor immediately concerning continued use of this container.

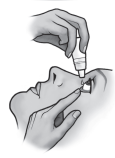
Instructions for Use:

Do not use the bottle if the plastic safety strip around the neck is missing or broken. When opening the bottle for the first time, tear off the plastic safety strip.

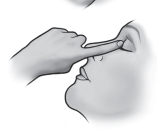
Every time you use TIMOPTOL-XE:

1. Wash your hands
2. Open the bottle. Take special care that the tip of the dropper bottle does not touch your eye, the skin around your eye or your fingers.
3. Tilt your head backwards and hold the bottle upside down over the eye.
4. Pull the lower eyelid downwards and look up. Gently squeeze the bottle and let one drop fall into the space between the lower eyelid and the eye.





5. Press a finger into the corner of your eye, by the nose, or close your eyelids for 2 minutes. This helps to stop the medicine from getting into the rest of the body.
6. Repeat steps 3 to 5 with the other eye if instructed to do so by your doctor.
7. Put the cap back on and close the bottle tightly.



What should I do in case of overdose?

If you put too many drops in your eye or swallow the contents of the bottle, among other effects, you may become light-headed, have difficulty breathing or feel that your heart rate has slowed. Contact your doctor immediately.

What should I do if I miss a dose?

Use TIMOPTOL-XE as prescribed by your doctor. If you miss a dose, use it as soon as possible. However, if it is almost time for the next dose, skip the missed dose, and go back to your regular dosing schedule.

What undesirable effects may TIMOPTOL-XE have?

Any medicine may have unintended or undesirable effects, so-called side effects. Although not all of these side effects may occur, if they do occur, you may need medical attention.

TIMOPTOL-XE usually does not cause problems. Occasionally, patients experience transient blurred vision. This generally lasts from 30 seconds to 5 minutes immediately after putting in the eye drop.

Less common possible side effects include eye symptoms such as burning and stinging, redness of the eye, dry eyes, discharge, the feeling of having something in your eye, and itching. In addition, the following side effects may occur: ringing in your ears, headache, tiredness, dizziness, depression, insomnia, nightmares, memory loss, tingling, nausea, diarrhea, upset stomach, dry mouth, chest pain, fainting, palpitations, an irregular heartbeat, a slowing of your heart rate, swelling or coldness of your hands and feet, shortness of breath, cough, hair loss, rash, itching, or other more severe allergic-type reactions, muscle pain, sexual dysfunction, and less desire to have sex.

Other side effects may also occur rarely, and some of these may be serious. Ask your doctor or pharmacist for more information about side effects. Both have a more complete list of side effects.

Please tell your doctor [or pharmacist] promptly about any of these or any other unusual symptom.

How can I learn more about TIMOPTOL-XE and increased eye pressure or glaucoma?

You may obtain further information from your physician or pharmacist, who have more detailed information about TIMOPTOL-XE and your eye condition.

How long can I keep my medicine?

Do not use this medicine after the date shown by the four digits following EX (or EXP) on the container. The first two digits indicate the month; the last two digits indicate the year.

How should I store TIMOPTOL-XE?

Store at or below 30°C. Protect from light. Avoid freezing.

Discard one month after first opening.

Other Information

To avoid possible contamination, keep the tip of the container away from contact with any surface.

Keep all medicines safely away from children.

Further information may be obtained from your doctor or pharmacist, who have the full prescribing information.

When was this package last revised?

This package leaflet was last revised in Apr-2021.

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PACKAGE INSERT
Ophthalmic Gellan Solution
TIMOPTOL-XE®
(timolol maleate)

Santen

TIMOPTOL-XE® (timolol maleate) is a formulation of TIMOPTOL (timolol maleate) containing a novel delivery vehicle. TIMOPTOL-XE reduces elevated and normal intraocular pressure whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

Clinical studies have shown that the intraocular pressure lowering effect of TIMOPTOL-XE administered once a day is equivalent to TIMOPTOL administered twice a day. The vehicle of TIMOPTOL-XE increases the contact time of the drug with the eye.

Gellan solution contains a highly purified anionic heteropolysaccharide derived from gellan gum. Aqueous solutions of gellan gum form a clear transparent gel at low polymer concentrations in the presence of cations. When TIMOPTOL-XE contacts the precorneal tear film, it becomes a gel.

Maximum reduction of intraocular pressure occurs in two to four hours with TIMOPTOL-XE. Significant lowering of intraocular pressure has been maintained for 24 hours with both 0.25% and 0.5% TIMOPTOL-XE.

TIMOPTOL-XE has a safety profile similar to that of TIMOPTOL, and both are generally well tolerated. Bradycardia was reported less frequently with TIMOPTOL-XE than with TIMOPTOL. In the three studies comparing TIMOPTOL-XE 0.5% once a day to TIMOPTOL 0.5% twice a day, TIMOPTOL-XE did not reduce mean heart rate as much as TIMOPTOL (see PRECAUTIONS). At trough (24 hours post-dose TIMOPTOL-XE, 12 hours post-dose TIMOPTOL), the mean reduction was 0.8 beats/minute for TIMOPTOL-XE and 3.6 beats/minute for TIMOPTOL; whereas at two hours post-dose, the mean reduction in heart rate was comparable (3.8 beats/minute for TIMOPTOL-XE and 5 beats/minute for TIMOPTOL). There was a higher incidence of transient blurred vision following instillation in patients administered TIMOPTOL-XE.

Timolol maleate is a nonselective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

Onset of action of timolol maleate is usually rapid, occurring approximately 20 minutes after topical application to the eye. The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established. 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.

In clinical studies timolol maleate was generally effective in more patients and produced fewer and less severe side effects than either pilocarpine or epinephrine.

Unlike miotics, timolol maleate reduces intraocular pressure with little or no effect on accommodation or pupil size. Thus, changes in visual acuity due to increased accommodation are uncommon, and the dim or blurred vision and night blindness produced by miotics are not evident. In addition, in patients with cataracts the inability to see around lenticular opacities when the pupil is constricted by miotics is avoided. When changing patients from miotics to TIMOPTOL-XE, refraction may be necessary after the effects of the miotic have passed.

As with other antiglaucoma drugs, diminished responsiveness to timolol maleate after prolonged therapy has been reported in some patients. However, in clinical studies of TIMOPTOL in which 164 patients were followed for at least 3 years, no significant difference in mean intraocular pressure was observed after initial stabilization. This indicates that the intraocular pressure-lowering effect of timolol maleate is well maintained.

INDICATIONS
TIMOPTOL-XE is indicated for the reduction of elevated intraocular pressure in patients with:

- ocular hypertension
- chronic open-angle glaucoma
- aphakia and glaucoma
- secondary glaucoma (some cases)
- narrow angles and a history of spontaneous or iatrogenically induced narrow-angle closure in the opposite eye in whom reduction of intraocular pressure is necessary (see PRECAUTIONS)

DOSAGE AND ADMINISTRATION
The usual starting dose is one drop of 0.25% TIMOPTOL-XE in the affected eye(s) once a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5% TIMOPTOL-XE in the affected eye(s) once a day. Invert the closed container and shake once before each use. It is not necessary to shake the container more than once.

If needed, concomitant therapy with other agent(s) for lowering intraocular pressure may be given with TIMOPTOL-XE. The use of two topical beta-adrenergic blocking agents is not recommended (See PRECAUTIONS). Other topically applied medications should be administered no less than 10 minutes before TIMOPTOL-XE.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in an increase in local activity.

HOW TO TRANSFER PATIENTS FROM OTHER THERAPY

When a patient is transferred from TIMOPTOL to TIMOPTOL-XE, TIMOPTOL should be discontinued after proper dosing on one day, and treatment with the same concentration of TIMOPTOL-XE started on the following day.

When a patient is transferred from another topical ophthalmic beta-adrenergic blocking agent, that agent should be discontinued after proper dosing on one day and treatment with TIMOPTOL-XE started on the following day with one drop of 0.25% TIMOPTOL-XE in the affected eye once a day. The dose may be increased to one drop of 0.5% TIMOPTOL-XE once a day if the clinical response is not adequate.

When a patient is transferred from a single antiglaucoma agent, other than a topical ophthalmic beta-adrenergic blocking agent, continue the agent and add one drop of 0.25% TIMOPTOL-XE to each affected eye once a day. On the following day, discontinue the previously used antiglaucoma agent and continue TIMOPTOL-XE. If a greater response is required, substitute one drop of 0.5% TIMOPTOL-XE for the 0.25% dosage.

CONTRAINDICATIONS
TIMOPTOL-XE is contraindicated in patients with:

- Reactive airway disease, bronchial asthma or with 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; overt cardiac failure; cardiogenic shock
- Hypersensitivity to any component of this product

PRECAUTIONS
As with other topically applied ophthalmic drugs, this drug may be absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration.

CARDIO-RESPIRATORY REACTIONS

Cardiac failure should be adequately controlled before beginning therapy with TIMOPTOL-XE. Patients with a history of cardiovascular disease, including cardiac failure, should be watched for signs of deterioration of these diseases, and pulse rates should be monitored.

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

Respiratory complications, including death due to bronchospasm in patients with asthma, and cardiac complications, including rarely death in association with cardiac failure, have been reported following administration of beta-adrenergic blocking agents. These are potential complications of therapy with TIMOPTOL-XE.

In patients with mild/moderate chronic obstructive pulmonary disease (COPD), TIMOPTOL-XE should be used with caution, and only if the potential benefit outweighs the potential risk.

VASCULAR DISORDERS

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

MASKING OF HYPOGLYCEMIC SYMPTOMS IN PATIENTS WITH DIABETES MELLITUS

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycemia.

MASKING OF THYROTOXICOSIS

Beta-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

SURGICAL ANESTHESIA

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

OTHER

Patients who are already receiving a beta-adrenergic blocking agent systemically and who are given TIMOPTOL-XE should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade (see circular for systemic timolol maleate products). The use of two topical beta-adrenergic blocking agents is not recommended.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. Timolol maleate has little or no effect on the pupil. Should TIMOPTOL-XE be used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

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

TIMOPTOL-XE has not been studied in patients wearing contact lenses. In a clinical study, the time required to eliminate 50% of the gellan solution from the eye was up to 30 minutes.

RISK FROM ANAPHYLACTIC REACTION

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 repeated challenge with such allergens, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

DRUG INTERACTIONS

Although timolol maleate used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with epinephrine has been reported occasionally. The potential for mydriasis exists from concomitant therapy with TIMOPTOL-XE and epinephrine.

The potential exists for additive effects and production of hypotension and/or marked bradycardia when TIMOPTOL-XE is administered together with a calcium-channel blocker, a catecholaminedepleting drug, antiarrhythmics, parasympathomimetics or another beta-adrenergic blocking agent (see **DRUG INTERACTIONS**).

Oral β-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

Concomitant use of omidenepag isopropyl and drugs containing timolol is cautioned.

USE IN PREGNANCY

TIMOPTOL-XE has not been studied in human pregnancy. The use of TIMOPTOL-XE requires that the anticipated benefit be weighed against possible hazards.

NURSING MOTHERS

Timolol is detectable in human milk. Because of the potential for serious adverse reactions from TIMOPTOL-XE in infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

USE IN CHILDREN

Timolol maleate ophthalmic solution has been shown to be efficacious and well-tolerated in children; however, the formulation of timolol maleate found in TIMOPTOL-XE has not been studied in the pediatric age group.

DRUG INTERACTIONS
Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

The potential exists for hypotension, atrioventricular (AV) conduction disturbances and left ventricular failure to occur in patients receiving a beta-blocking agent when an oral calcium-channel blocker is added to the treatment regimen. The nature of any cardiovascular adverse effect tends to depend on the type of calcium-channel blocker used. Dihydropyridine derivatives, such as nifedipine, may lead to hypotension, whereas verapamil or diltiazem have a greater propensity to lead to AV conduction disturbances or left ventricular failure when used with a beta-blocker.

The concomitant use of beta-adrenergic blocking agents and digitalis with either diltiazem or verapamil may have additive effects in prolonging AV conduction time.

Oral calcium-channel antagonists may be used in combination with beta-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function.

Intravenous calcium-channel blockers should be used with caution in patients receiving beta-adrenergic blocking agents.

Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine and SSRIs) and timolol.

SIDE EFFECTS
TIMOPTOL-XE is usually well tolerated. The most frequent drug-related complaint in the original clinical trials for TIMOPTOL-XE was transient blurred vision (6.0%), lasting from 30 seconds to 5 minutes, following instillation.

The following possibly, probably, or definitely drug-related adverse reactions occurred with a frequency of at least 1% inactive treatment controlled clinical trials:

Ocular

Burning and stinging, tearing, redness, conjunctival injection, discharge, foreign body sensation, itching.

The following additional adverse reactions have been reported with ocular administration of this or other timolol maleate formulations, either in clinical trials or since the drug has been marketed.

Special Senses

Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, decreased corneal sensitivity, and dry eyes. Visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis, choroidal detachment following filtration surgery (see PRECAUTIONS), tinnitus, blurred vision, corneal erosion.

Cardiovascular

Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischemia, congestive heart failure, palpitation, cardiac arrest, edema, claudication, Raynaud's phenomenon, cold hands and feet, chest pain, cardiac failure, aggravation of existing intermittent claudication.

Respiratory

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, cough, shortness of breath.

Body as a Whole

Headache, asthenia, fatigue, chest pain.

Integumentary

Alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash.

Hypersensitivity

Signs and symptoms of allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylactic reaction.

Nervous system/Psychiatric

Dizziness, depression, insomnia, nightmares, memory loss, syncope, cerebrovascular accident, cerebral ischemia, paresthesia, hallucination, nervousness.

Neuromuscular

Increase in signs and symptoms of myasthenia gravis.

Digestive

Nausea, diarrhea, dyspepsia, dry mouth, abdominal pain, dysgeusia, vomitting.

Urogenital

Decreased libido, Peyronie's disease, sexual dysfunction, impotence.

Immunologic

Systemic lupus erythematosus.

Musculoskeletal

Myalgia, arthropathy

Potential Side Effects

Side effects reported in clinical experience with systemic timolol maleate may be considered potential side effects of ophthalmic timolol maleate.

OVERDOSAGE
There have been reports of inadvertent overdosage with TIMOPTOL 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 (see also SIDE EFFECTS).

AVAILABILITY
TIMOPTOL-XE 0.5% is supplied in 2.5mL bottle.

The bottle is made up of a white translucent low-density polyethylene bottle, a transparent dropper tip and a white cap. Not all presentations may be available locally.

STORAGE

TIMOPTOL-XE is a sterile, colorless to nearly colorless, slightly opalescent, slightly viscous, aqueous ophthalmic solution.

Store at or below 30°C. Protect from light. Avoid freezing. Discard 1 month after first opening.

MANUFACTURED BY:

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