

NEW ZEALAND DATA SHEET

NYOGEL[®]

TIMOLOL

1mg/g, eye gel

Qualitative and quantitative composition

One g of 0.1% Nyogel contains 1.37 mg timolol maleate, corresponding to 1 mg of timolol. For a full list of excipients, see section 6.1 List of excipients.

Pharmaceutical form

Eye gel.

Clinical particulars

Therapeutic indications

Nyogel is used to reduce intraocular pressure , in the following conditions:

- Ocular hypertension,
- Chronic open-angle glaucoma.

Dosage and method of administration

Adults and children over the age of 12 years: The recommended dosage is one drop of Nyogel in the affected eye(s) daily, preferably in the morning.

Children under the age of 12 years: Paediatric use is not recommended.

Elderly: The above dosage can be used for the elderly.

All age groups:

Intraocular pressure should be reassessed 2 to 4 weeks after starting treatment, because response to treatment may take a few weeks to stabilise.

If necessary, Nyogel can be used concomitantly with miotics, epinephrine, prostaglandin analogues , alpha-2-agonists and/or carbonic anhydrase inhibitors . To prevent the active substance from being washed out of the eye, an interval of at least 5 minutes between application of different drugs is required, and Nyogel should be the last one to be administered.

In case of transfer from other topical beta blocking agents: discontinue their use after a full day of therapy and start treatment with Nyogel the next day. Instill one drop in each affected eye once a day, preferably in the morning .

In case of transfer from a single antiglaucoma agent other than topical beta blocking agent: continue the agent and add one drop of Nyogel in each affected eye once a day. On the following day, discontinue the previous agent completely, and continue with Nyogel .

Method of administration

Nyogel is to be instilled into the conjunctival cul-de-sac. Glaucoma medication should be continued until otherwise instructed by the physician.

For a correct dosing during application, the eye-drop bottle must be held vertically during administration.

The dispenser remains sterile until the original closure is broken. Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures as this may contaminate the gel.

When using nasolacrimal occlusion or closing the eyelids for 5 minutes the systemic absorption may be reduced . This may result in a decrease in systemic side effects and an increase in local activity.

Contraindications

As with all products containing beta-receptor blocking agents, Nyogel is contraindicated in patients with:

- Bronchial asthma
- History of bronchial asthma , or severe obstructive pulmonary disease
- Sinus bradycardia
- Sick sinus syndrome (including sino-auricular block)
- Atrioventricular (AV) block
- Overt cardiac failure
- Cardiogenic shock
- Severe peripheral circulatory disturbance (Raynaud's disease) and peripheral disorders
- Prinzmetal's angina
- Untreated pheochromocytoma
- Hypotension
- Corneal diseases
- Hypersensitivity to timolol maleate or to any of the excipients and/or other beta-blocking agent
- Severe allergic rhinitis and bronchial hyperreactivity

Special warnings and precautions for use

Like other topically applied ophthalmic drugs, timolol maleate is absorbed into the systemic circulation . This may cause similar systemic effects as seen with oral beta-

blocking agents. Therefore it should be used with caution in patients with metabolic acidosis .

During anaesthesia severe bradycardia and hypotension have been observed in some patients using beta-blockers. The anaesthesiologist should be informed when the patient is receiving Nyogel. A gradual withdrawal of Nyogel over 1 to 2 weeks is recommended in high risk patients (including patients with coronary heart disease) prior to scheduled surgery. Sudden withdrawal of Nyogel may lead to exacerbation of angina and development of hypertension and arrhythmias; Nyogel should therefore be discontinued at least 24 to 48 hours prior to surgery (see section 4.5 Interaction with other medicinal products and other forms of interaction) .

Nyogel may cause worsening systolic heart failure or new heart failure in patients who depend on high sympathetic drive to maintain cardiac output. Cardiac failure should be adequately controlled before beginning therapy and patients with a history of severe cardiac disease should be monitored for early signs of possible cardiac failure .

Beta-blocking agents may mask certain symptoms of hyperthyroidism, e.g. tachycardia.

Patients suspected of developing thyrotoxicosis should be watched carefully to avoid abrupt withdrawal of beta-blocking agents, which might cause a thyroid storm .

Concomitant use of amisulpride with Nyogel may lead to increased risk of ventricular arrhythmia, particularly torsades de pointes. Therefore, caution is recommended in patients with pre-existing bradycardia (see section 4.5 Interaction with other medicinal products and other forms of interaction) .

Signs and symptoms of hypoglycaemia, especially tachycardia, palpitations and sweating may be masked. Diabetic patients should be advised to reinforce self-monitoring of their glycaemia at the beginning of treatment .

Risk of anaphylactic reactions: Patients with a history of atopy or serious anaphylactic reactions to different allergens may be more sensitive to repeated exposure to allergens . The exposure may be accidental, diagnostic or therapeutic. When Nyogel is used in such patients, the normal epinephrine dose used to treat anaphylactic reactions may be insufficient.

Respiratory and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death associated with cardiac failure have been reported .

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy .

Close monitoring of cardiac function and observation of the patient for bradycardia or heart block is advised when amiodarone and a beta adrenergic blocker are coadministered (see section 4.5 Interaction with other medicinal products and other forms of interaction) .

The concomitant administration of MAO inhibitors should be avoided.

Caution should be exercised if Nyogel is used with systemic beta-blockers.

Nyogel should not be used with another topical beta-blocker .

Nyogel has little or no effect on the pupil. When this eye gel is used to lower intraocular pressure in patients with angle-closure glaucoma, it should be given in combination with a miotic. In these patients, the immediate treatment objective is to open the angle by constriction of the pupil with a miotic agent.

Nyogel contains benzalkonium chloride as a preservative. Benzalkonium chloride may cause eye irritation and is known to discolour soft contact lenses. Therefore avoid contact with soft contact lenses. Remove contact lenses prior to drug application and wait at least 15 minutes before reinsertion.

As with any glaucoma treatment, regular examination of the intraocular pressure and cornea is recommended.

Interaction with other medicinal products and other forms of interaction

Although Nyogel has little effect on the size of the pupil, mydriasis has occasionally been reported when Nyogel has been used with mydriatic agents such as epinephrine .

When Nyogel is administered to patients receiving an oral beta-blocking agent, both the reduction in intraocular pressure and the effects of systemic beta-blockade may be intensified. The response of such patients should be closely observed.

As timolol maleate is absorbed systemically the following interactions (as those seen with systemic beta-blockers) may occur:

Coadministration of Nyogel with class I anti-arrhythmic drugs (e.g., disopyramide, quinidine, propafenone) and amiodarone may have a potentiating effect on atrial conduction and thus induce a negative inotropic effect .

The nature of any cardiovascular adverse effects varies depending on the type of calcium-channel blocker used. Dihydropyridine derivatives, such as nifedipine, may lead to hypotension, whereas verapamil or diltiazem tend to cause AV conduction disturbances or left ventricular failure when used with beta-blocker .

Clonidine: Beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine .

Concomitant use with anaesthetic drugs may attenuate compensatory tachycardia and increase the risk of hypotension. The anaesthesiologist should be informed when the patient is using Nyogel (see section 4.4 Special warnings and precautions for use) .

Digitalis glycosides: association with beta-blockers may slow down atrioventricular conduction time.

Catecholamine-depleting drugs (rauwolfia alkaloids such as reserpine): Close observation of the patient is also 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.

Parasympathomimetics: Increased risk of bradycardia .Amisulpride: Increased risk of ventricular arrhythmia, particularly torsades de pointes .

CYP2D6 inhibitors (e.g. quinidine, SSRIs): potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported .

Mefloquine: Prolongation of the QT interval may occur .

Insulin and oral antidiabetic drugs may further lower the glucose concentration in the blood, and beta-blockade may mask the signs of hypoglycaemia (tachycardia) .

Cimetidine and hydralazine: may induce increased plasma level of the timolol maleate .

Concomitant use of Nyogel is not recommended with:

Lidocain i.v. ; iodine contrast products .

Pregnancy and lactation

Pregnancy

The use of Nyogel during pregnancy has not been studied. Beta-blockers reduce placental perfusion, which may result in foetal death or premature delivery. In addition, undesirable effects, especially hypoglycaemia and bradycardia, may also occur in foetuses and neonates. There is an increased risk of cardiac and pulmonary complications in a neonate that has been exposed to a beta-blocking agent . Nyogel should therefore not be used during pregnancy unless there is a clear benefit.

In case of treatment until delivery, close monitoring of neonate (heart and glycemia for the first 3 or 5 days of life) is recommended .

Lactation

The active substance timolol maleate, is absorbed into the systemic circulation and excreted into the breast milk having the potential to cause serious undesirable effects in the infant of the nursing mother. Use of the preparation during breast-feeding is therefore not recommended.

Effects on ability to drive and use machines

No studies on the effect of this medicinal product on the ability to drive have been conducted. While driving vehicles or operating different machines, it should be taken into account that occasionally visual disturbances may occur including refractive changes, diplopia, ptosis, frequent episodes of mild and transient blurred vision and occasional episodes of dizziness or fatigue.

Adverse effects

Like other topically applied ophthalmic drugs, timolol maleate may be absorbed into the systemic circulation. This may cause similar undesirable effects as seen with oral beta-blocking agents.

Immune system disorders: Systemic lupus erythematosus, signs and symptoms of allergic reactions including angioedema .

Metabolism and nutrition disorders: Hypoglycaemia .

Psychiatric disorders : Depression, insomnia, nightmares, memory loss.

Nervous system disorders : Syncope, cerebrovascular disorder, cerebral ischaemia, increase in signs and symptoms of myasthenia gravis , dizziness, paraesthesia, headache .

Eye disorders: Symptoms of ocular irritation include conjunctivitis, blepharitis, keratitis, and decreased corneal sensitivity . Blurred vision of short duration may occur in 30 to 50% of patients. Other possible reactions are eye irritation (burning), eye pain (stinging) , visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, eyelid ptosis and choroidal detachment following filtration surgery . Dry eyes have been reported during beta-blocker therapy .

Cardiac disorders : Bradycardia , atrioventricular block (complete or lower degree) or worsening of an existing atrioventricular block, cardiac failure , arrhythmia, palpitation cardiac arrest and chest pain.

Vascular disorders: Hypotension , Raynaud phenomenon and claudication.

Respiratory, thoracic and mediastinal disorders : Bronchospasm (predominantly in patients with pre-existing bronchospastic disease) , respiratory failure, dyspnoea and cough.

Gastrointestinal disorders: Nausea , diarrhoea, vomiting , dyspepsia, dry mouth.

Skin and subcutaneous tissue disorders: Hypersensitivity reactions including local and generalised rash, erythema, urticaria, alopecia, psoriasiform-like lesions or exacerbation of psoriasis.

The incidence of the symptoms is low, and in most cases the symptoms have cleared after discontinuation of treatment. The use of the medication should be discontinued if any such reaction is not otherwise explicable. Benzalkonium chloride is known to cause allergy in sensitive patients.

Musculoskeletal and connective tissue disorders: Arthropathy .

Reproductive system and breast disorders: Sexual dysfunction , syndrome of Peyronie.

General disorders and administration: Fatigue , asthenia.

Reactions with unknown causal relationship: The following undesirable reactions have occurred with the use of systemically administered timolol maleate: aphakic cystoid macular oedema, nasal congestion, anorexia, dyspepsia, CNS effects (confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychiatric disturbances), hypertension and retroperitoneal fibrosis. The side effects seen with oral timolol maleate may occur with topical use of Nyogel.

Overdose

No data specific to this preparation are available. The most common side effects caused by beta-blocker overdosage are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, beta blocking agents.
ATC code: S01ED01.

Timolol maleate is a non-selective beta-blocker that does not have any significant cardiac stimulating or direct cardiac depressant or local anaesthetic (membrane stabilizing) activity. When applied topically in the eye, it reduces both elevated and normal intraocular pressure. Although not all mechanisms of action of timolol maleate are known yet, it is thought to primarily reduce the production of aqueous humour. It may also have a lesser effect on the outflow of aqueous humour.

Unlike miotics, timolol maleate reduces intraocular pressure with little effect on pupil size or visual acuity. Thus, impairment of vision or night blindness does not occur as with the use of miotics. In cataract patients, the impairment of vision, caused by lenticular opacities when the pupil is constricted, is avoided.

The onset of reduction in intraocular pressure following ocular administration of timolol maleate can usually be detected within 30 minutes after eye drop administration. The maximum effect is achieved within about 2 hours from administration and significant lowering of intraocular pressure can be maintained for periods as long as 24 hours.

Pharmacokinetic properties

Nyogel 0.1% is an eye-drop formulation in gel form, which due to the particular chemical characteristics, maximise the drug absorption in the eye and reduces its absorption into the systemic circulation.

The systemic absorption after topical administration of timolol maleate 0.1% has been shown to be reduced by 90% as compared to Timolol 0.5% eye drops. This is due to the 10 times lower daily timolol maleate dose. Nyogel 0.1% had a significantly smaller effect on the peak heart rate in an exercise test as compared to Timolol 0.5% solution.

Pharmacokinetic data from studies in healthy volunteers have shown that the mean value of the maximum plasma concentration is 0.18 ng/mL when Nyogel 1 mg/g is given once daily, which is approximately 10 times lower than achieved after twice daily dosage of Timolol eye drops 5 mg/mL.

Preclinical safety data

No adverse local effects were observed in rabbits or dogs receiving timolol maleate by ocular administration for 4 weeks.

Timolol maleate was not mutagenic and did not affect fertility in rats.

Carcinogenicity studies produced an increased incidence of pheochromocytomas in male rats, and mammary adenomas, pulmonary tumors and benign uterine polyps in mice, but only at high oral doses.

Repeated application of Nyogel did not produce any local or systemic intolerance in rabbits or dogs.

Carcinogenicity

In a two-year oral study in male rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas with the administration of 300 mg/kg/day of timolol maleate. With the administration of 500 mg/kg/day of timolol maleate in a lifetime oral study in mice, there was a statistically significant increase in the incidence of mammary adenocarcinoma, benign and malignant pulmonary tumors, and benign uterine polyps .

Mutagenicity

When evaluated *in vivo* in the micronucleus test and cytogenic assay in mice and *in vitro* in a neoplastic cell transformation assay, timolol maleate was devoid of mutagenic potential .

Reproduction and Fertility

At doses of up to 125 times the maximum human oral dose, no adverse effects on male or female fertility in rats were observed .

Pharmaceutical particulars

List of excipients

Benzalkonium chloride; Sorbitol; Polyvinyl alcohol; Carbomer 974 P; Sodium acetate x 3 H₂O; Lysine monohydrate; Water for injections.

Incompatibilities

For information on use of the product with contact lenses see under section Special warnings and precaution for use.

Shelf life

18 months.

The shelf-life after first opening is 4 weeks.

Special precautions for storage

Keep the container in the outer carton. Do not store above 25°C.

Store the dropper bottle upside down in the carton below 25°C after first opening.

Do not freeze.

Nyogel must be kept out of the reach and sight of children.

Nature and contents of container

The eye-drop bottle contains 5 g gel and it is made of low-density polyethylene (LDPE). The tip of the bottle is also of LDPE and the cap is of high-density polyethylene.

Instructions for use and handling

None.

Medicine classification

Prescription Medicine

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Date of preparation

28 September 2010