Nyolol® eye gel

Composition
Active substance: Timolol, as timolol maleate
Excipients: Benzalkonium chloride as preservative, vehicle excipients

Pharmaceutical form and quantity of active substance per unit
5 g dropper bottle of eye gel containing 0.1% timolol (as 0.137% timolol maleate)

Indications / Potential uses
Elevated intraocular pressure, open-angle glaucoma, patients with aphakic glaucoma, some patients with secondary glauccoma.

Dosage and Administration
Adults
Instill 1 drop of Nyolol eye gel into the affected eye once daily. To avoid washing out the active substance with other eye drops, there must be an interval of at least 5 minutes between instillations. Eye drops should be applied before Nyolol eye gel. It is possible to switch to Nyolol eye gel from another glaucoma medication. As some time is required before the effect stabilizes, it is recommended that intraocular pressure be checked 3–4 weeks after the start of treatment. Intraocular presssure should also be measured regularly thereafter because the response to timolol may change.

To date there has been no experience with Nyolol eye gel in children.

Contraindications
Heart failure, arrhythmia, second or third degree AV block in particular, bradycardia, cardiogenic shock, bronchial asthma, chronic obstructive lung disease with a tendency to bronchospasm (or a history of this condition).
Hypersensitivity to timolol maleate, benzalkonium chloride or any other component of Nyolol eye gel.

Warnings and Precautions
Heart failure should be brought under adequate control before starting treatment with Nyolol eye gel. Patients with a history of severe heart disease should be monitored for possible signs of heart failure, with heart rates also being checked.
When Nyolol eye gel is used in patients already undergoing oral treatment with beta-blockers, these patients should be monittored both for a possible additive effect on intraocular pressure and for the known systemic effects of beta-blockade.
In patients with angle-closure glaucoma, efforts should first be made to reopen the iridocorneal angle, which requires use of a miotic to constrict the pupil. Nyolol eye gel itself has no effect on the pupil.
If Nyolol eye gel is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be administered together with a miotic.
As with other glaucoma medications, there have been reports of reduced response to timolol maleate in some patients after long-term treatment. On the other hand, in clinical studies involving 164 patients monitored for at least 3 years, mean intraocular pressure was not found to have increased significantly beyond what it had been at the time of initial successful stabilization. This shows that the reduction in intraocular pressure achieved with timolol maleate is maintained.
During treatment with beta-blockers, patients with a history of atopy or severe anaphylactic reactions to various allergens may overreact when re-exposed to these allergens by chance or in the course of diagnosis or therapy. The doses of adrenaline normally used to treat anaphylactic reactions may not be effective in these patients.
Although Nyolol eye gel has little or even no effect on pupil diameter, mydriasis has occasionally been observed in patients receiving concomitant treatment with Nyolol eye gel and adrenaline.
If Nyolol eye gel is concomitantly administered with oral calcium channel blockers, catecholamine-depleting agents or other beta-blockers, additive effects are possible and hypotension and/or marked bradycardia may occur (see **Interactions**).

Note for contact lens wearers
Contact lenses should be removed before use and should not be reinserted until at least 15 minutes have elapsed.

Interactions
Medicinal products that release catecholamines
Close monitoring is recommended in patients treated concurrently with beta-blockers and medicinal products that deplete catecholamine reserves, e.g. reserpine. This is because effects may be additive and lead to hypotension and/or marked bradycardia, thereby causing dizziness, syncope or orthostatic hypotension.

Calcium channel blockers
Orally administered calcium channel blockers may be of benefit in combination with beta-blockers if cardiac function is normal, but the combination should not be used if cardiac function is compromised.
Intravenously administered calcium channel blockers should be used with caution in patients being treated with beta-blockers. There is a potential risk of hypotension, AV conduction disturbances and left ventricular heart failure when patients treated with an oral beta-blocker are also given an oral calcium channel blocker. The nature of the adverse cardiovascular effects depends on the type of calcium channel blocker used. When combined with a beta-blocker, dihydropyridine derivatives such as nifedipine may lead to hypotension, while verapamil and diltiazem tend to cause AV conduction disturbances or left ventricular heart failure.

Digitalis
Concomitant use of beta-blockers and digitalis with either diltiazem or verapamil may lead to prolongation of AV conduction time.

Pregnancy and Lactation
Caution is required when using Nyolol eye gel during pregnancy.
There have been no controlled studies in pregnant women.
Timolol has been detected in breast milk. Timolol may cause severe adverse effects in breastfed infants and a decision must therefore be made as to whether to discontinue breastfeeding or withdraw the drug.

Effects on ability to drive and use machines
Vision may be blurred for a short time following application. This should be borne in mind when using machines or driving.

Adverse effects
Ocular effects reported in clinical studies were mild hyperaemia, sensation of a foreign object in the eye, uncommon to common cases (more than 1–3%) of stinging and burning immediately following application of the product, and blurred vision occasionally lasting more than 3 minutes.
Like other topically applied ophthalmic products, this medicinal product can be absorbed systemically. Topical application may therefore give rise to the same adverse effects as those that occur following systemic administration of beta-blockers.
There have been reports of respiratory and cardiac reactions – including fatal bronchospasm in asthmatic patients and, rarely, death in association with heart failure – following topical application of Nyolol eye gel to the eye.

Nervous system
Depression, dizziness, exacerbation of the signs and symptoms of myasthenia gravis.

Eyes
Irritation and sensation of foreign object in the eye, stinging, burning, conjunctivitis, keratitis, brief blurring of vision. If use follows cessation of miotic therapy, vision may be disturbed. Beta-blockers may cause "dry eye". Rare: Blepharitis, ptosis, diplopia, reduced corneal sensitivity.

Cardiovascular reactions
Syncope, bradycardia. Rare: Hypotension, palpitations, arrhythmia, congestive heart failure, heart block, cardiac arrest, cerebral ischaemia, stroke.

Respiratory tract
Dyspnoea. Rare: Bronchospasm (particularly in patients with pre-existing bronchospastic conditions), respiratory failure.

Skin
Rash, urticaria, alopecia.

Gastrointestinal effects
Nausea.

General symptoms
Headache, asthenia, fatigue, chest pain.

Overdose
No data are available with respect to overdosage in humans.
The most likely symptoms of overdose with a systemic beta-blocker are symptomatic bradycardia, hypotension, bronchosppasm and acute heart failure.
The following therapeutic measures should be considered:
1. Gastric lavage: Studies have shown that timolol is not easily removed by dialysis.
2. Symptomatic bradycardia: Administer 0.25 –2 mg atropine sulphate i.v. to induce vagal blockade. If bradycardia persists, cautiously administer isoprenaline i.v. In refractory cases, use of a cardiac pacemaker may be required.
3. Hypotension: Use sympathomimetic pressor therapy with a drug such as dopamine, dobutamine or noradrenaline. Glucaggon has proven useful in refractory cases.
4. Bronchospasm: Administer isoprenaline, possibly also with aminophylline.
5. Acute heart failure: Standard therapy with digitalis, diuretics and oxygen must be instituted immediately. In refractory cases, intravenous administration of aminophylline is recommended, followed by glucagon if necessary.
6. Heart Block (second or third degree): Use isoprenaline or a transvenous pacemaker.

Properties and Actions
ATC code: S01ED01
Nyolol eye gel is a non-selective beta-receptor blocker which lowers elevated intraocular pressure. Intraocular pressure is lowered because a smaller amount of aqueous humour is produced. Like other beta-blockers, Nyolol eye gel has a slight effect on the aqueous outflow system. It has not yet been established whether it has a significant effect on the vasculature of the anterior chamber. Timolol has only a slight local anaesthetic action, and no intrinsic sympathomimetic activity (ISA). It does not alter either the pupil or accommodation. Clinical investigations have shown the good efficacy of Nyolol in patients with open-angle glaucoma and elevated intraocular pressure. Nyolol is also effective in secondary glaucoma. In clinical studiies, Nyolol eye gel (1 drop once daily) was shown to have the same efficacy in reducing intraocular pressure as either 0.25% (1 drop twice daily) or 0.50% (1 drop once daily) ophthalmic solutions of timolol.

Pharmacokinetics
The maximum effect in the eye is achieved a few hours after instillation and is maintained for 24 hours. Timolol can be systemically absorbed by way of the conjunctiva, the nasal mucosa and the gastrointestinal tract, thereby reaching the circulatory system. Only rarely are serum levels detected within 90 minutes of the instillation, but minimal concentrations of timolol are always found in the urine.

Preclinical data
Chronic toxicity
In one- and two-year studies involving topical administration of timolol maleate in rabbits and dogs, there were no adverse effects on the eye. Even following long-term oral administration of high doses in dogs and rats, there were no special findings except for bradycardia and organ weight increases in the heart, kidney and liver.

Mutagenicity and carcinogenic potential
There has been no extensive study of mutagenicity. Results of in vitro tests carried out thus far have been negative. In a two-year study in rats involving oral administration of timolol maleate, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal phaeochromocytoma in male rats that had been given doses 300 times higher than the maximum recommended oral dose in humans (1 mg/kg/day). Such changes did not occur in rats given 25–100 times the maximum recommended oral dose in humans. In a lifetime study in mice involving oral administration of timolol, there was a statistically significant increase in the incidence both of benign and malignant pulmonary tumours and of benign uterine polyps in female mice given doses of 500 mg/kg/day. However, an increase of this kind was not seen with doses of 5 or 50 mg/kg/day.
There was also an increase in the incidence of mammary adenocarcinoma at doses of 500 mg/kg/day. This was associated with the serum prolactin levels found in female mice given 500 mg/kg/day, but not 5 or 50 mg/kg/day. An increase in the incidence of mammary adenocarcinoma in rodents was associated with various products that elevate serum prolactin levels. No clinically relevant changes in serum prolactin have been found in adult women given oral doses of up to 60 mg timolol maleate, the maximum recommended oral dose in humans. There was a statistically significant ($p \leq 0.05$) rise in the general incidence of neoplasms in female mice given doses of 500 mg/kg/day.

Reproductive toxicity
Reproductive toxicity studies and fertility studies in rats showed no harmful effects on male or female fertility at doses up to 150 times the maximum recommended oral dose in humans. Teratological studies with timolol in mice and rabbits given doses of up to 50 mg/kg/day (50 times the maximum recommended oral dose in humans) yielded no evidence of fetal malformation.
Although there was delayed ossification in rats at this dose, there were no further effects on the postnatal development of the offspring. Doses of 1000 mg/kg/day (1000 times the maximum recommended oral dose in humans) proved to be maternally toxic in mice, which lead to an increase in fetal resorption. This has also been found in rabbits given doses up to 100 times the maximum recommended oral dose in humans, but without any clear signs of maternal toxicity.

Other information
Shelf-life
When stored in the unopened package, Nyolol eye gel may be used until the expiry date (= EXP) printed on the pack.

Special precautions for storage
See folding box

Pack sizes
Country specific pack sizes

Manufacturer
See folding box

Information last revised
December 2004

Approval date (text)
2 May 2005

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament
– A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
– The doctor and the pharmacist are experts in medicine, its benefits and risks.
– Do not by yourself interrupt the period of treatment prescribed for you.
– Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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