**NYOGEL®**
(timolol as maleate)

**NAME OF THE MEDICINE**

Active ingredient: timolol maleate
Chemical name: (S)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl]-2-propanol maleate
Molecular formula: C$_{13}$H$_{24}$N$_{4}$O$_{3}$S.C$_{4}$H$_{4}$O$_{4}$
CAS number: 26921-17-5
Molecular weight: 432.49
Structural formula:

![Structural formula of timolol maleate]

**DESCRIPTION**

Nyogel contains timolol 1 mg/g (as timolol maleate 1.37 mg/g).
Excipients: benzalkonium chloride, carbomer 934P (974 P grade), lysine monohydrate, polyvinyl alcohol, sodium acetate, sorbitol and water for injections.

**PHARMACOLOGY**

**Pharmacodynamics**

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

Unlike miotics, timolol 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 ophthalmic solution occurs approximately 20 minutes after eye drop administration. The maximum effect is achieved within about 1 to 2 hours from administration and
significant lowering of intraocular pressure can be maintained for periods as long as 24 hours.

**Pharmacokinetics**

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

Pharmacokinetic data from studies in 24 healthy volunteers have shown that the mean value of the maximum plasma concentration is 0.18 ng/mL when timolol eye gel 1mg/g is given once daily to both eyes for 2 weeks, compared to 1.72 ng/mL after twice daily dosage of timolol eye drops 5 mg/mL, also given to both eyes for 2 weeks. This 90% reduction is due to the 10 times lower daily timolol maleate dose. In this same study, timolol eye gel 0.1% had a significantly smaller effect on the peak heart rate in an exercise test as compared to timolol 0.5% solution.

**CLINICAL TRIALS**

A total of 1200 subjects was treated with Nyogel in clinical trials and analysed for efficacy. Results from pivotal studies in patients with primary open angle glaucoma or ocular hypertension are summarised in Table 1. These studies were powered to detect a difference of ±1.5 mmHg in intraocular pressure between treatments. Patients were followed up for different durations ranging from 3 weeks up to more than 12 months. All Nyogel treated patients received one drop in both eyes once daily.

**Table 1: Intraocular Pressure (mean of worse eye mmHg ± standard deviation)**

<table>
<thead>
<tr>
<th>Treatment (n*)</th>
<th>Baseline</th>
<th>Pressure Reduction</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>(measured before application or 24 hours after the last dose)</td>
</tr>
<tr>
<td><strong>Study 1</strong> (Single-blind parallel group, 3 weeks, comparator administered once daily) Brewitt et al.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nyogel (84) TIM OS* 0.5% (85)</td>
<td>23.09 ± 3.92</td>
<td>5.60 ± 3.05</td>
</tr>
<tr>
<td></td>
<td>23.61 ± 3.31</td>
<td>6.12 ± 3.32</td>
</tr>
<tr>
<td><strong>Study 2</strong> (Single-blind parallel group, 4 weeks, comparator administered twice daily) Schnarr et al.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nyogel (68) TIM OS* 0.25% (63)</td>
<td>24.44 ± 1.35</td>
<td>5.28 ± 2.60</td>
</tr>
<tr>
<td></td>
<td>25.00 ± 1.50</td>
<td>6.13 ± 2.55</td>
</tr>
</tbody>
</table>
Study 3 (Double-blind, parallel group, 12 weeks, comparator administered twice daily)
Rouland et al.

| Nyogel (110) TIM OS* 0.5% (100) | 24.55 ± 2.22 | 24.49 ± 2.32 | 6.04 ± 3.27 | 6.99 ± 2.87 |

* n = number of patients in the intention-to-treat population.
+ TIM OS = timolol ophthalmic solution

These studies demonstrate that the ocular hypotensive effect of Nyogel is equivalent to conventional aqueous formulations of timolol maleate. Long term data are available from 3 trials in a total of 116 patients covering periods up to 103 weeks (110 of these patients were followed for periods up to 52 weeks). The IOP lowering effect of long term Nyogel was similar to that observed in the trials presented in Table 1 above. There are no comparative data beyond 6 months.

INDICATIONS

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

- ocular hypertension
- chronic open-angle glaucoma.

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 phaeochromocytoma
- hypotension
- corneal diseases
- hypersensitivity to timolol or to any of the excipients and/or other beta-blocking agent
- severe allergic rhinitis and bronchial hyperreactivity.
Nyogel is also contraindicated in case of association with amiodarone (see Interactions with Other Medicines).

**PRECAUTIONS**

Like other topically applied ophthalmic drugs, Nyogel is absorbed into the systemic circulation. This may cause similar undesirable side 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 prolonged hypotension have been observed in some patients using beta-blockers. The anaesthetist should be informed when the patient is receiving Nyogel. Since some degree of systemic absorption cannot be excluded, a gradual withdrawal of Nyogel is recommended prior to scheduled surgery. As with systemic beta-blockers, if discontinuation of ophthalmic Nyogel is needed in patients with coronary heart disease, therapy should be withdrawn gradually. 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 Interactions with Other Medicines).

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 treatment 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 Interactions with Other Medicines).

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 adrenaline 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 Interactions with Other Medicines).

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.

Carcinogenicity / Mutagenicity / Impairment of Fertility

No evidence of carcinogenicity was observed with timolol maleate at oral doses up to 100 mg/kg/day in rats and up to 50 mg/kg/day in mice. However, there was a statistically significant increase in the incidence of adrenal phaeochromocytomas in male rats administered 300 mg/kg/day. In female mice, statistically significant increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinomas were found at 500 mg/kg/day. The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg, but not at doses of 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin.
Timolol was not mutagenic in assays for gene mutations (Ames test) or chromosomal damage (mouse micronucleus and cytogenic assays). Timolol was also negative in an *in vitro* neoplastic cell transformation assay.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility after oral doses of up to 100 mg/kg/day.

**Use in Pregnancy (Category C)**

The use of Nyogel during pregnancy has not been studied. Owing to their pharmacological effects, β-adrenergic blocking agents may reduce placental perfusion, which may result in foetal death or premature delivery. In addition, undesirable effects, especially hypoglycaemia and bradycardia, may occur in the foetus or neonate. There is also an increased risk of cardiac and pulmonary complications in a neonate that has been exposed to a β-blocking agent. Nyogel should therefore not be used during pregnancy unless the expected therapeutic benefit clearly outweighs the potential risk to the foetus.

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

Timolol maleate was not teratogenic in mice, rats and rabbits. Embryofoetal development studies with timolol maleate in mice and rabbits showed no evidence of embryofoetal toxicity at oral doses up to 50 mg/kg/day. At higher doses, increases in resorptions and foetal variations (14 ribs and hypoplastic sternebrae) were noted in mice (1000 mg/kg/day) and increased resorption in rabbits (≥ 90 mg/kg/day). In rats, delayed ossification was seen at oral doses ≥ 50 mg/kg/day, and decreased number of caudal vertebral bodies and arches, and an increase in hypoplastic sternebrae were noted at 500 mg/kg/day.

**Use in Lactation**

The active substance timolol, 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.

**Paediatric Use**

Safety and effectiveness in children have not been established by adequate and well-controlled studies.

**Interactions with Other Medicines**

Although Nyogel has little effect on the size of the pupil, mydriasis has occasionally been reported when timolol has been used with mydriatic agents such as adrenaline.
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 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. Dihydropyrimine 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-blockers 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 anaesthetist should be informed when the patient is using Nyogel (see Precautions).

**Digitalis glycosides**: The concomitant use of digitalis glycosides and 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 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 increase the timolol concentration in the plasma.

Concomitant use of Nyogel is not recommended with:
Lignocaine i.v.; iodine contrast products.

**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**

**Adverse Events Reported in Clinical Trials**
Table 2 lists adverse events reported in at least 1% of patients receiving Nyogel regardless of perceived causal relationship to trial medication. The incidence of non-ocular adverse events was below 1% in all cases.

Table 2: Adverse Events Reported in at Least 1% of Patients Receiving Nyogel

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>Nyogel (n=1202)</th>
<th>Timolol Ophthalmic Solution (n=318)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Special Senses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred/abnormal vision</td>
<td>25.0</td>
<td>6.9</td>
</tr>
<tr>
<td>Burning/stinging sensation</td>
<td>11.6</td>
<td>23.6</td>
</tr>
<tr>
<td>Conjunctival hyperaemia</td>
<td>8.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>5.3</td>
<td>-</td>
</tr>
<tr>
<td>Keratitis +/- conjunctivitis</td>
<td>1.1</td>
<td>3.5</td>
</tr>
</tbody>
</table>

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

**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’s phenomenon and claudication.

**Respiratory, Thoracic and Mediastinal Disorders:**
Bronchospasm (predominantly in patients with pre-existing-bronchospastic disease), respiratory failure, dyspnoea and cough.

**General Disorders and Administration:**
Fatigue, asthenia.

**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.

**Psychiatric Disorders:**
Depression, insomnia, nightmares, memory loss.

**Nervous System Disorders**
Syncope, cerebrovascular disorder, cerebral ischaemia, increase in signs and symptoms of myasthenia gravis, dizziness, paraesthesiae, headache.

**Gastrointestinal Disorders:**
Nausea, diarrhoea, vomiting, dyspepsia, dry mouth.

**Immune System Disorders:**
Systemic lupus erythematosus, signs and symptoms of allergic reactions including angioedema.

**Metabolism and Nutrition Disorders:**
Hypoglycaemia.
Reproductive System and Breast Disorders:
Sexual dysfunction, syndrome of Peyronie.

Reactions with Unknown Causal Relationship:
The following undesirable reactions have occurred with the use of systemically administered timolol: 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.

DOSAGE AND 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.

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 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. If Nyogel is used concomitantly with other eye medications, there
must be an interval of at least 5 minutes between the two medications, and Nyogel should be the last one to be administered. No controlled clinical studies are available on concomitant use of Nyogel and other antiglaucoma medications.

When using nasolacrimal occlusion or closing the eyelids for 3 minutes, the systemic absorption may be reduced. This may result in a decrease in systemic side effects and an increase in local activity.

**Instructions for Use and Handling**

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.

After opening, Nyogel should be stored upside down in the carton. Nyogel should not be used for more than 4 weeks and any remaining contents should be discarded.

**OVERDOSAGE**

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.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

**PRESENTATION AND STORAGE CONDITIONS**

Eye gel; 5 g bottle.

**Storage:** Store below 25°C. Protect from light. Do not freeze.

**NAME AND ADDRESS OF SPONSOR**

Novartis Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
North Ryde NSW 2113

**Poisons Schedule:** Schedule 4.

Approved by the Therapeutic Goods Administration: 1 July 2004
Date of most recent amendment 4 October 2011.
* = Registered trademark