Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nyogel 0.1% w/w eye gel.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g gel contains 1.37 mg timolol maleate, corresponding to 1 mg of timolol.

Excipients: benzalkonium chloride (0.05mg/g)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye gel.

Colourless, opalescent, odourless gel, free of visible particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Nyogel eye gel is used to reduce elevated intraocular pressure in the following conditions:
- Ocular hypertension
- Chronic open-angle glaucoma

4.2 Posology and method of administration

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

Elderly
The above dosage can be used for the elderly.

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

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 stabilize.

If necessary, Nyogel eye gel can be used concomitantly with miotics, epinephrine and/or carbonic anhydrase inhibitors. To prevent the active substance from being washed out from the eye, an interval of at least 5 minutes between application of different drugs is required, and Nyogel eye gel 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 eye gel 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 eye gel in each affected eye once a day. On the following day, discontinue the previous agent completely, and continue with Nyogel eye gel.

Method of administration
Nyogel eye gel is to be instilled into the conjunctival cul-de-sac. It can be used also for long-term therapy.

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 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4.3 Contraindications

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

- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree artrioventricular (AV) block not controlled with pace-maker
- Overt cardiac failure
- Cardiogenic shock
- Untreated phaeochromocytoma
- Hypersensitivity to timolol maleate or to any of the excipients
- Severe allergic rhinitis and bronchial hyperreactivity

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic agents, timolol maleate is absorbed systemically. Due to beta-adrenergic component, timolol maleate, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see 4.2.

Cardiac disorders:
In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.
Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

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

Respiratory disorders:
Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.
Timosan should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hypoglycaemia/diabetes
Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Beta-blockers should be used with caution in patients with metabolic acidosis.

Beta-blockers may also mask the signs 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.

Corneal diseases
Ophthalmic β-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Concomitant use of amisulpride with Nyogel eye gel 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).

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).

Although the concentration of timolol maleate in the plasma following application of Nyogel eye gel is lower than after administration of timolol eye drops, the product should generally not be used in combination with amiodarone, calcium antagonists, (bepridil, verapamil, diltiazem) or with beta blockers (see section 4.5).

Nyogel eye gel 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.

Other beta-blocking agents
The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol maleate is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.5).

Anaphylactic reactions
Whil taking beta-blockers, patients with a history of atopy, a history of severe anaphylactic reactions a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.
Nyogel eye gel 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.

Beta-blockers may increase the risk of rebound hypertension.

The concomitant administration of MAO inhibitors should be avoided.

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

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

Surgical anaesthesia
β-blocking ophthalmological preparations may block systemic β-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol maleate. A gradual withdrawal of Timosan eye gel over 1 to 2 weeks is recommended in high risk patients (including patients with coronary heart disease) prior to scheduled surgery. Sudden withdrawal of Timosan eye gel may lead to exacerbation of angina and development of hypertension and arrhythmias; Timosan eye gel 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).

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with timolol maleate.

1. Other eye drops

If concomitant treatment with other eye drops is used, their administration should be separated by at least a 5 minute interval and the eye gel should be administered last.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

2. Other drugs

Despite the lower systemic exposure after instillation of the once daily Nyogel 0.1% eye gel compared to the twice daily Nyogel 0.5% eye drops, timolol maleate is absorbed systemically and interactions observed with oral beta-blockers may occur.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

Amisulpride

Increased risk of ventricular arrhythmia, particularly torsades de points.

Amiodarone
Supression of compensatory sympathetic mechanisms may lead to conduction and myocardial contractility disorders.

Calcium antagonists
Bradyarrhythmias (excessive bradycardia, sinus arrest), sinoatrial or atrioventricular conduction disorders and cardiac failure via a synergistic effect.

The nature of any cardiovascular adverse effects tends to depend 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.

Oral beta-blockers
When Nyogel eye gel 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.

Catecholamine-depleting drugs (e.g. 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.

Digitalis glycosides
The concomitant use of digitalis glycosides and beta-blockers may slow down atrioventricular conduction.

Class I anti-arrhythmic drugs
Class I anti-arrhythmic drugs (e.g. disopyramide, propafenone, quinidine, lidocain i.v.,) and amiodarone may have a potentiating effect on atrial conduction and thus induce a negative inotropic effect.

CYP2D6 inhibitors (e.g. quinidine, SSRIs)

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

Parasympathomimetics
Increased risk of bradycardia.

Volatile halogenated anaesthetic agents
Reductions in compensatory cardiovascular mechanisms by beta blockers (beta-adrenergic inhibition may be counteracted during surgery by beta-stimulants). As a general rule do not discontinue beta-blocker therapy and in any event, avoid a sudden discontinuation. The anaesthetist should be advised of this treatment. (see section special warnings and precautions for use).

Potentiation of the systemic beta-blocking effects of eye drops and an increase in plasma levels of the beta-blocker have been reported when beta-blocker eye drops are combined with quinidine, probably due to inhibition of the beta-blocker metabolism by quinidine (described for timolol). In addition, cimetidine and hydralazine may increase the timolol maleate concentration in the plasma.

Mefloquine
Prolongation of the QT interval may occur.

Clonidine and other centrally acting antihypertensive agents (methyldopa, guanfacine, moxonidine, rilmenidine)
Close observation of the patient is recommended. To avoid rebound hypertension, abrupt withdrawal of the drugs should be avoided.

Insulin, oral hypoglycaemic agents
All beta blockers may mask certain symptoms of hypoglycaemia: palpitations and tachycardia.
Most of the non-cardioselective beta-blockers increase the frequency and severity of hypoglycaemia. Warn the patient and particularly at the beginning of treatment, self-monitoring of glucose by the patient should be increases.

Contrast media
Iodine contrast products.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data for the use of timolol maleate in pregnant women. Timolol maleate should not be used during pregnancy unless clearly necessary.
To reduce the systemic absorption, see 4.2.

Epidemiological studies have not revealed malformative effects but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If Timosan is administered until delivery, the neonate should be carefully monitored during the first days of life.

Breast-feeding
Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol maleate in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see 4.2.

4.7 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.

4.8 Undesirable effects

Like other topically applied ophthalmic drugs, timolol maleate is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents.
Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

Immune system disorders
Systemic lupus erythematosus, systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylactic reaction.

Metabolism and nutrition disorders
Hypoglycaemia.

Psychiatric disorders
Insomnia, depression, nightmares, memory loss.

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

Eye disorders
Signs and symptoms of ocular irritation (e.g. burning stinging, itching, tearing, redness), blepharitis, keratitis, blurred vision and choroidal detachment following filtration surgery (see 4.4 “Special warning and precautions for use”), decreased corneal sensitivity, dry eyes , corneal erosion, ptosis, diplopia and conjunctivitis.

Cardiac disorders
Bradycardia, chest pain, palpitations, oedema, arrhythmia, congestive heart failure, atrioventricular block, cardiac arrest cardiac failure, heart block .

Vascular disorders
Hypotension, Raynaud’s phenomenon, cold hands and feet, claudication.

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

Gastrointestinal disorders
Dysgeusia, nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting.

Skin and subcutaneous tissue reactions disorders
Alopecia,hypersensitivity reactions, local and generalised erythema psoriasiform-rash or exacerbation of psoriasis, skin rash.

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.

Musculoskeletal and connective tissue disorders
Arthropathy, myalgia.

Reproductive system and breast disorders
Sexual dysfunction (such as impotence), decreased libido), syndrome of Peyronie.

General disorders and administration
Asthenia, fatigue.

Biologically
Rare cases of antinuclear antibodies have been observed during treatment with timolol maleate, only exceptionally accompanied by clinical symptoms such as systemic lupus erythematosus syndrome. The antibodies have regressed on discontinuation of the treatment.

4.9 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 cardiovascular insufficiency.

If overdosage occurs, the following measures should be considered:

1. Administration of activated charcoal, if the preparation has been taken orally. Studies have shown that timolol maleate cannot be removed by haemodialysis.
2. Symptomatic bradycardia: Atropine sulphate, 0.25 to 2 mg intravenously, should be used to induce vagal blockade. If bradycardia persists, intravenous isoprenaline hydrochloride should be administered cautiously. In refractory cases, the use of a cardiac pacemaker should be considered.
3. Hypotension: A sympathomimetic agent such as dopamine, dobutamine or noradrenaline should be given. In refractory cases, the use of glucagon has been useful.
4. Bronchospasm: Isoprenaline hydrochloride should be given. Concomitant therapy with aminophylline may be considered.
5. Acute cardiac failure: Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases, the use of intravenous aminophylline is recommended.
   This may be followed, if necessary, by glucagon, which has been found useful.
6. Heart blocks: Isoprenaline hydrochloride or a pacemaker should be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 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.

5.2 Pharmacokinetic properties

Nyogel 1 mg/g 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 Nyogel 1 mg/g has been shown to be reduced by 90% as compared to timolol 5 mg/ml eye drops. This is due to the 10 times lower daily timolol maleate dose. Nyogel 1 mg/g eye gel had a significantly smaller effect on the peak heart rate in an exercise test as compared to timolol 5 mg/ml 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 eye gel is given once daily, which is approximately 10 times lower than achieved after twice daily dosage of timolol eye drops 5 mg/ml.

5.3 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 phaeochromocytomas in male rats, and mammary adenomas, pulmonary tumours and benign uterine polyps in mice, but only at high oral doses.
Repeated application of Nyogel eye gel did not produce any local or systemic intolerance in rabbits or dogs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Sorbitol
Polyvinyl alcohol
Carbomer 974 P
Sodium acetate trihydrate
Lysine monohydrate
Water for injections

6.2 Incompatibilities

For information on use of the product with contact lenses see under 4.4.

6.3 Shelf life

18 months. The shelf-life after first opening is 4 weeks.

6.4 Special precautions for storage

Keep the container in the outer carton in order to protect from light. 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 eye gel must be kept out of the reach and sight of children

6.5 Nature and contents of container

Plastic (LDPE) bottle and dropper tip, plastic(HDPE) screw cap
Pack sizes: 5 g and 3 x 5 g.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 13/100/1

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