

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Eysano 2.5 mg/ml eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of Eysano 2.5 mg/ml solution contains 3.417 mg of timolol maleate (equivalent to 2.5 mg of timolol).

Excipient with known effect

Each ml of Eysano 2.5 mg/ml solution contains 12.72 mg phosphates.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.

Clear, colourless eye drops.

pH: 6.5-7.5

Osmolality: 270-330 mOsm/Kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Eysano eye drops, solution is a beta-adrenoreceptor blocking agent used topically in the reduction of elevated intra-ocular pressure in various conditions.

Eysano is indicated in adult patients with ocular hypertension; adult patients with chronic open-angle glaucoma including aphakic patients; some adult patients with secondary glaucoma.

4.2 Posology and method of administration

Adults

Posology

Recommended therapy is one drop of 2.5 mg/ml solution in the affected eye, once or twice (morning and evening) a day.

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

If clinical response is not adequate, dose may be changed to one drop of 5 mg/ml solution in each affected eye, once or twice (morning and evening) a day. If needed, Eysano may be used with other agent(s) for lowering intra-ocular pressure. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.4).

Intra-ocular pressure should be reassessed approximately four weeks after starting treatment because response to Eysano may take a few weeks to stabilise.

Provided that the intra-ocular pressure is maintained at satisfactory levels, many patients can then be placed on once-a-day therapy of Eysano.

Transfer from other agents

When another topical beta-blocking agent is being used, discontinue its use after a full day of therapy and start treatment with Eysano the next day with one drop of 2.5 mg/ml Eysano in each affected eye once or twice (morning and evening) a day. The dose may be increased to one drop of 5 mg/ml solution in each affected eye once or twice (morning and evening) a day if the response is not adequate.

When transferring a patient from a single anti-glaucoma agent other than a topical beta-blocking agent, continue the agent and add one drop of 2.5 mg/ml Eysano in each affected eye once or twice (morning and evening) a day. On the following day, discontinue the previous agent completely and continue with Eysano. If a higher dose of Eysano is required, substitute to one drop of 5 mg/ml solution in each affected eye once or twice (morning and evening) a day.

Eysano eye drops, solution is a sterile solution that does not contain a preservative.

Patients should be instructed to wash their hands before use and avoid allowing the tip of the container to come into contact with the eye or surrounding structures as this could cause injury to the eye.

Patients should also be instructed that ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Paediatric population

Due to limited data, timolol could only be recommended for use in primary congenital and primary juvenile glaucoma for a transitional period while a decision is made on a surgical approach and in case of failed surgery while awaiting further options.

Posology

Clinicians should strongly evaluate the risks and benefits when considering medical therapy with timolol in paediatric patients. A detailed medical history and examination to determine the presence of systemic abnormalities should precede the use of timolol.

No specific dose recommendation can be given as there is only limited clinical data (see also section 5.1).

However, if benefit outweighs the risk, it is recommended to use the lowest active agent concentration available once daily. If intra-ocular pressure (IOP) could not be sufficiently controlled, a careful up titration to a maximum of two drops of 5 mg/ml timolol eye drops solution daily per affected eye has to be considered. If applied twice daily, an interval of 12 hours should be preferred.

Furthermore, the patients, especially neonates, should be closely observed after the first dose for one to two hours in the office and closely monitored for ocular and systemic adverse reactions until surgery is performed.

Method of administration

To limit potential adverse reactions only one drop should be instilled per dosing time.

Systemic absorption of topically administered β -blockers can be reduced by nasolacrimal occlusion and by keeping the eyes closed as long as possible (e.g. for 3 - 5 minutes) after instillation of drops. See also sections 4.4 and 5.2.

Duration of treatment

For a transient treatment in the paediatric population.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

As with all products containing beta-receptor blocking agents, Eysano 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 atrioventricular (AV) block, not controlled with pace-maker
- Overt cardiac failure, cardiogenic shock

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic agents, timolol is absorbed systemically. Due to beta-adrenergic component, timolol, 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 section 4.2.

Other beta-blocking agents

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to 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).

In patients with closed-angle glaucoma, Eysano should be used in combination with miotics, as the immediate purpose of the treatment is to reopen the chamber angle which requires a constriction of the pupil. Timolol has little or no effect on the pupil.

Choroidal detachment

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

Anaphylactic reactions

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 and may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

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.

Eysano 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 may also mask the signs of hyperthyroidism.

Corneal diseases

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

Surgical anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

Eysano should also be used with great care in connection with the following diseases and conditions:

- Myasthenia: Beta-adrenergic blocking may potentiate muscle weakness corresponding to certain myasthenia symptoms (e.g. diplopia, ptosis, general weakening).
- Untreated pheochromocytoma.
- Metabolic acidosis.
- Large surgical procedures: It is recommended to gradually decrease the use of adrenergic beta-blocking medicinal products prior to the procedure in order to avoid the reflex stimuli of the beta-blockers on the heart and thus lessen the risk of hypotension and cardiac arrest during the anaesthesia.
- Intermittent claudication.
- Severely reduced kidney function. With dialysis patients, pronounced drop in blood pressure has been observed.

Patients with a history of contact hypersensitivity to silver should not use this product as dispensed drops may contain traces of silver.

Timolol has not been studied in patients using contact lenses.

Eysano should not be used while using soft contact lenses. The lenses should only be inserted 15 minutes after the drip.

Paediatric population

Timolol solutions should generally be used cautiously in young glaucoma patients (see also section 5.2).

It is important to notify the parents of potential adverse reactions so they can immediately discontinue the medicinal therapy (see section 4.8). Signs to look for are, for example, coughing and wheezing.

Because of the possibility of apnoea and Cheyne-Stokes breathing, the medicinal product should be used with extreme caution in neonates, infants and toddlers. A portable apnoea monitor may also be helpful for neonates on timolol.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies with other medicinal products have been performed with timolol maleate.

Cases of mydriasis have been reported with simultaneous use of ophthalmological beta-blockers and adrenalin. Even though timolol administered by itself has little or no effect on the size of the pupil, close ophthalmological monitoring is advised.

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.

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.

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

Timolol potentiates the effect of other medicinal products with effect on the bulbous tension.

Beta-blockers may increase the hypoglycaemic effect of insulin and oral anti-diabetic medicinal products and mask signs and symptoms of hypoglycaemia (see section 4.4).

If more than one ophthalmic medicinal product is used, at least 5 minutes have to pass between using the different eye drops.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Fertility

Non-clinical data do not show any effects of timolol on male or female fertility.

4.7 Effects on ability to drive and use machines

Eysano has minor influence on the ability to drive and use machines. 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

Summary of the safety profile

Like other topically applied ophthalmic medicinal products, timolol 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. The mentioned adverse reactions include reactions set within the group of ophthalmological beta-blockers.

The most common adverse reactions are burning or biting sensations after instillation, which occurs in approx. 13% of the patients.

Tabulated summary of adverse reactions

The following adverse reactions are classified according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) or not known (cannot be estimated from the available data).

Immune system disorders	
Rare	Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash
Psychiatric disorders	
Uncommon	Depression
Rare	Insomnia, nightmares, decreased libido

Not known	Hallucination
Nervous system disorders	
Common	Headache, dizziness
Uncommon	Syncope
Rare	Memory loss, increase in signs and symptoms of myasthenia gravis, paresthesia, cerebrovascular accident, cerebral ischemia
Eye disorders	
Common	Signs and symptoms of ocular irritation (e.g. burning, stinging, itching), conjunctival hyperemia, feeling of a foreign object in the eye, secretion, conjunctivitis, blepharitis, keratitis, decreased corneal sensitivity and dry eyes, blurred vision.
Uncommon	Visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases)
Rare	Diplopia, ptosis and choroidal detachment following filtration surgery (see section 4.4)
Ear and labyrinth disorders	
Rare	Tinnitus
Cardiac disorders	
Uncommon	Bradycardia
Rare	Arrhythmia, heart block, congestive heart failure, palpitations, cardiac arrest
Vascular disorders	
Rare	Hypotension, claudication, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea

Rare	Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, cough
Gastrointestinal disorders	
Uncommon	Nausea, dyspepsia
Rare	Diarrhoea, dry mouth
Skin and subcutaneous tissue disorders	
Rare	Alopecia, psoriasiform rash or exacerbation of psoriasis
Musculoskeletal and connective tissue disorders	
Rare	Systemic lupus erythematosus
Reproductive system and breast disorders	
Rare	Peyronie's disease
General disorders and administration site conditions	
Uncommon	Asthenia, fatigue
Rare	Oedema, cold hands and feet, chest pain

Additional adverse reactions have been seen with ophthalmic beta-blockers and may potentially occur with Eysano.

Immune system disorders	Systemic allergic reactions including pruritus
Metabolism and nutrition disorders	Hypoglycaemia
Eye disorders	Tearing, redness, corneal erosion
Cardiac disorders	Heart failure
Gastrointestinal disorders	Dysgeusia, abdominal pain, vomiting
Skin and subcutaneous tissue disorders	Skin rash
Musculoskeletal and connective tissue disorders	Myalgia
Reproductive system and breast	Sexual dysfunction

disorders	
------------------	--

Cases of corneal calcification have been reported very rarely in association with the use of phosphate-containing eye drops in some patients with significantly damaged corneas.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store).

4.9 Overdose

Symptoms of overdose are similar to those seen with systemic beta adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, cardiac arrest, acute cardiovascular insufficiency and hypotension (see section 4.8).

If overdose 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 may be considered.
3. Hypotension: a sympathomimetic pressor agent such as dopamine, dobutamine or noradrenaline should be used. In refractory cases, the use of glucagon has been reported to be 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 reported useful.
6. Heart block (second- or third-degree): isoprenaline hydrochloride or a pacemaker should be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antiglaucoma preparations and miotics, beta-blocking agents, ATC code: S01ED01

Mechanism of action

Eysano (timolol-maleate) is a non-selective beta-receptor blocker without beta-stimulating effect or significant membrane stabilizing local anaesthetic effect.

Pharmacodynamic effects

The pressure-reducing effect of timolol-maleate is more likely due to reduced influx of chamber fluid than an increased outflow, however, it is still unclear whether the pressure effect is a pure beta-blocking effect. The medicinal product does not influence blood pressure and heart rate.

Clinical efficacy and safety

Clinical studies show that timolol eye drops lower the intra-ocular pressure in glaucomatous eyes. No or insignificant changes in pupil size or visual acuity have been observed.

Paediatric population

There is only very limited data available on the use of timolol (2.5 mg/ml, 5 mg/ml twice daily one drop) in the paediatric population. In one small, double-masked, randomized, published clinical study conducted for a treatment period of up to 12 weeks on 105 children (n=71 on timolol) aged 12 days – 5 years the data have shown to some extent evidence, that timolol in the indication primary congenital and primary juvenile glaucoma is effective in short-term treatment.

5.2 Pharmacokinetic properties

Absorption

The onset of reduction in intra-ocular pressure can be detected within one-half hour after a single dose. The maximum effect occurs in one or two hours; significant lowering of IOP can be maintained for as long as 24 hours with a single dose.

In some cases, a decreased therapeutic effect has been observed in long-term treatment.

Paediatric population

As already confirmed by adult data, 80% of each eye drop passes through the nasolacrimal system where it may be rapidly absorbed into the systemic circulation via the nasal mucosa, conjunctiva, nasolacrimal duct, oropharynx and gut or the skin from tear overflow.

Due to the fact that the blood volume in children is smaller than that in adults a higher circulation concentration has to be taken into account. In addition, neonates have immature metabolic enzyme pathways and it may result in an increase in elimination half-life and potentiating adverse events.

Limited data show that plasma timolol levels in children after 2.5 mg/ml greatly exceed those in adults after 5 mg/ml, especially in infants and are presumed to increase the risk of adverse reactions such as bronchospasm and bradycardia.

5.3 Preclinical safety data

No adverse ocular reactions were observed in rabbits and dogs administered timolol topically in studies lasting one and twelve months.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dodecahydrate

Sodium dihydrogen phosphate dihydrate

Sodium hydroxide (For pH adjustment)

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

After first opening, the product may be stored for a maximum of 28 days. No special storage conditions are required.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

White opaque 11 ml LDPE bottle and white Novelia nozzle (HDPE and silicone) with a white HDPE cap.

Pack sizes: 1 or 2 bottles of 5 ml solution in a card box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aspire Pharma Ltd
Unit 4, Rotherbrook Court,
Bedford Road,
Petersfield,
Hampshire,
GU32 3QG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 35533/0105

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/06/2016

10 DATE OF REVISION OF THE TEXT

09/01/2020