1 Tradenames

CUSIMOLOL® 0.5% Solution

TIMOLOL® 0.25% Solution

TIMOLOL® 0.5% Solution

2 Description and composition

Pharmaceutical form(s)

Eye drops, solution.

Sterile, preserved, isotonic aqueous solution.

Active substance(s)

One mL of the 0.25% eye drop solution contains 3.4 mg timolol maleate corresponding to 2.5 mg timolol

One mL of the 0.5% eye drop solution contains 6.8 mg timolol maleate corresponding to 5 mg timolol

Excipients

Excipient with known effect: 1 mL of the 0.25% and 0.5% eye drop solution contains 0.1 mg benzalkonium chloride.

Other excipients: Sodium dihydrogen phosphate dihydrate (or sodium phosphate), disodium phosphate dodecahydrate,hydrochloric acid and/or sodium hydroxide (or sodium chloride), purified water.

Information might differ in some countries.

3 Indications

Timolol® is used to reduce intraocular pressure (IOP) in the following conditions:

- Ocular hypertension
- Chronic open-angle glaucoma (including aphakic patients)

4 Dosage regimen and administration

Dosage regimen

General target population

Adults

The recommended dose is one drop of Timolol 0.25% in the affected eye(s) twice a day. If clinical response to the 0.25% solution is not adequate, the dosage may be changed to one drop Timolol 0.5% in the affected eye(s) twice a day.

If IOP is maintained at satisfactory levels at the dosage described above, a switch to a once daily dosage may be considered; however, because of natural diurnal variations, IOP should be measured at different times of the day to establish whether the patient is responding satisfactorily to the treatment.

If the dose is missed, then it should be used as soon as it is remembered. If it is almost time for the next dose, then the missed dose should be skipped. Double dose should not be used to make up for a forgotten dose.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

Special populations

Renal and hepatic impairment

The safety and efficacy of this medicine in patients with hepatic or renal impairment have not been established.

Pediatric patients (below 18 years)

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

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

If the benefit outweighs the risk, it is recommended to use the lowest active agent concentration available once daily. If IOP could not be sufficiently controlled, a careful up titration to a maximum of 2 drops daily per affected eye has to be considered. If applied twice daily, an interval of 12 hours is preferred.

Patients, especially neonates, should be closely observed after the first dose for 1 to 2 hours in the office and closely monitored for ocular and systemic side effects until surgery is performed.

Method of administration

- For ocular use only.

- To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye.
- 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.
- Patients must be instructed to remove soft contact lenses prior to application of Timolol and wait 15 minutes after instillation of the dose before reinsertion.

5 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- 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 block, overt cardiac failure, or cardiogenic shock.

6 Warnings and precautions

General

Like other topically applied ophthalmic agents, timolol is absorbed systemically. Due to the beta-adrenergic blocking component in ophthalmic timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur.

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 for adverse reactions.

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.

Hypoglycemia/diabetes

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

Hyperthyroidism

Beta-blockers may mask the signs of hyperthyroidism.

Muscle weakness

Beta-adrenergic blocking agents have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalized weakness).

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 8 Interactions).

Anaphylactic reactions

While taking beta-blockers, patients with 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 unresponsive to the usual dose of adrenaline (epinephrine) used to treat anaphylactic reactions.

Choroidal detachment

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

Surgical anesthesia

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

Contact lenses

Benzalkonium chloride may cause irritation and is known to discolor soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of Timolol and wait at least 15 minutes before reinsertion.

7 Adverse drug reactions

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-1 Percentage of patients with adverse drug reactions in clinical trials

System organ classification	Adverse drug reaction	Frequency category
Psychiatric disorders	Depression	*Rare*
Nervous system disorders	Headache	*Uncommon*

System organ classification	Adverse drug reaction	Frequency category
	Cerebral ischaemia, dizziness, migraine	*Rare*
Eye disorders	Vision blurred, eye pain, eye irritation, ocular discomfort, ocular hyperaemia	*Common*
	Corneal erosion, punctate keratitis, keratitis, iritis, conjunctivitis, blepharitis, reduced visual acuity, photophobia, dry eye, lacrimation increased, eye discharge, eye pruritus, eyelid margin crusting, anterior chamber inflammation, eyelid oedema, conjunctival hyperaemia	*Uncommon*
	Uveitis, diplopia, asthenopia, eczema of eyelids, erythema of eyelid, eyelid pruritus, conjunctival oedema, corneal pigmentation	*Rare*
Cardiac disorders	Bradycardia	*Uncommon*
	Myocardial infarction	*Rare*
Vascular disorders	Hypotension	*Uncommon*
	Blood pressure increased, oedema peripheral, peripheral coldness	*Rare*
Respiratory, thoracic and mediastinal disorders	Asthma, bronchitis, dyspnoea	*Uncommon*
Gastrointestinal disorders	Dysgeusia	*Uncommon*
	Dyspepsia, abdominal discomfort, dry mouth	*Rare*
Skin and subcutaneous tissue disorders	Swelling face, erythema	*Rare*
	Fatigue	*Uncommon*
General disorders and administration site conditions	Asthenia, chest discomfort	*Rare*

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Timolol via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 7-2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

System organ classification	Adverse drug reaction
Immune system disorders	Angioedema, hypersensitivity
Metabolism and nutrition disorders	Hypoglycaemia
Psychiatric disorders	Hallucination [1], insomnia, amnesia, nightmares

System organ classification	Adverse drug reaction
Nervous system disorders	Cerebrovascular accident, syncope, paraesthesia
Eye disorders	Choroidal detachment (following filtration surgery), eyelid ptosis
Cardiac disorders	Cardiac arrest, atrioventricular block (complete, lower degree or aggravation), congestive cardiac failure (aggravation), arrhythmia, palpitations
Vascular disorders	Raynaud's phenomenon
Gastrointestinal disorders	Vomiting, diarrhoea, nausea
Skin and subcutaneous tissue disorders	Urticaria, psoriasis, rash, alopecia
Musculoskeletal and connective tissue disorders	Arthropathy
Reproductive system and breast disorder	Sexual dysfunction

8 Interactions

The following interactions are expected with Timolol due to potential drug interactions:

- 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 an ophthalmic beta-blocker solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics.
- Beta-blockers can decrease the response to adrenaline used to treat anaphylactic reactions. Special caution should be exercised in patients with a history of atopy or anaphylaxis (see section 6 Warnings and precautions)
- Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

There are no adequate data regarding the ocular use of timolol in pregnant women. Epidemiological studies have not revealed malformative effects but show a risk for intrauterine 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 hypoglycemia) have been observed in the neonate when beta-blockers have been administered to the mother until delivery.

Reproduction studies in mice, rats and rabbits with orally administered timolol showed no malformations at doses up to 290 times the maximum recommended ocular human dose (MROHD), based on body surface area (BSA) [2] (see Animal data).

Timolol should not be used during pregnancy unless clearly necessary. However, if Timolol is administered during pregnancy up to the time of delivery, the neonate should be carefully monitored during the first days of life.

Animal data

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (290 times the MROHD based on BSA) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, no adverse effects were noted on postnatal development of offspring. Dose of 1,000 mg/kg/day (5,790 times the MROHD based on BSA) was maternal toxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at 100 mg/kg/day or 2,310 times the MROHD based on BSA, and without apparent maternal toxicity [2].

9.2 Lactation

Risk summary

Timolol is transferred into human breast milk following ocular topical administration. Oral beta blockers have the potential to cause serious adverse reactions in the breast-fed infant. However, in the case of ocular administration at therapeutic doses, the amounts of timolol present in breast milk are not likely to produce clinical symptoms of beta-blockade in the infant.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Timolol and any potential adverse effects on the breast-fed child from Timolol.

9.3 Females and males of reproductive potential

Infertility

There are no data on the effects of Timolol on human fertility. Fertility studies in rats with timolol showed no effects at doses up to 1,700 times the MROHD, based on BSA [2].

10 Overdosage

In case of accidental ingestion, symptoms of overdose from beta blockade may include bradycardia, hypotension, cardiac failure and bronchospasm.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group:

Anti-glaucoma agent. ATC code: S01ED01

Mechanism of action (MOA)

Timolol (timolol maleate) is a non-selective beta-receptor blocker without beta-stimulating effect or significant membrane-stabilizing (local anesthetic) effect. The IOP-lowering effect of timolol is probably due more to a reduced production of aqueous humor than to an increased outflow, but it is not yet clear whether the effect on pressure is a purely beta-blocking effect. Timolol can affect blood pressure and pulse rate. It is not known to cause any changes in local blood flow.

Pharmacodynamics (PD)

Clinical studies show that timolol reduces IOP in eyes with both normal and raised pressure. No changes, or only insignificant changes, have been observed in pupil size or visual acuity.

There is only very limited data available on the use of timolol (0.25% , 0.5%, 1 drop twice daily) in the pediatric population for a treatment period of up to 12 weeks. One small, double blind, randomized, published clinical study conducted with 105 children (N = 75, timolol) aged 12 days to 5 years shows evidence, to some extent, that timolol used for the indication of primary congenital and primary juvenile glaucoma is effective in short-term treatment.

Pharmacokinetics (PK)

Absorption

Following oral administration, maximum timolol plasma concentrations are achieved within 2 hours or less. Plasma concentrations decline with terminal half-life of 4 to 5 hours. In addition to local absorption of topically applied timolol into the cornea and aqueous humour, systemic absorption via the conjunctival veins and flow off through the nasal lacrimal duct also occurs.

In a clinical study in 16 volunteers dosed bilaterally with 0.5% timolol solution twice daily for 2 weeks (600 micrograms total dose per administration), peak steady-state plasma concentrations ranged from below the 1 ng/mL quantitation limit to 5 ng/mL.

Distribution

Following topical ocular administration of 1.5 mg radiolabelled timolol to rabbits, maximum aqueous humor concentrations of about 870 ng/mL were achieved within 30 minutes. Aqueous humor concentrations declined to about 6 ng/mL at 24 hours. Studies in pigmented rabbits showed that timolol had prolonged retention and slow elimination from iris and ciliary body, indicating significant binding to melanin.

Biotransformation/metabolism

In humans, timolol is metabolized by cleavage of the morpholine ring to form two primary metabolites. These are an acetyl ethanol secondary amine derivative which undergoes subsequent loss of the acetyl side chain to form an ethanolic primary amine analog. Hydroxylation of the terminal methyl group on the t-butyl moiety to form an alcohol is a minor metabolic pathway in humans. Timolol is primarily metabolized in the liver by the CYP2D6 isozyme. No timolol metabolism occurs within the eye.

Elimination

Following oral administration of radiolabelled timolol to human volunteers, approximately 72% of the dose was excreted within 84 hours, with 66% excreted in urine and 6% in feces. Approximately 20% of the dose was excreted as unchanged drug in the urine.

12 Clinical studies

Timolol is a well established product.

13 Non-clinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity and repeated dose toxicity, genotoxicity, carcinogenicity, and in topical ocular irritation and toxicity studies. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. For information on reproductive studies, see section 9 Pregnancy, lactation, females and males of reproductive potential [2].

14 Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Keep container in the outer carton. Protect from light.

This medicinal product does not require any special storage conditions.

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

Information might differ in some countries.

Special precautions for disposal

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

15 References

Newly added references - CDS update v2.0 – 28-May-2020

1. 2.5 Clinical Overview Timolol- Azarga- DuoTrav - Rationale for changes to Core Data Sheet (CDS) / Product Information – Hallucination. Novartis. May-2020.
2. 2.4 Nonclinical Overview Timolol. Novartis. May-2020.

16 CDS history table

Version	Effective date	GLC/PSB approval date	SLC Tracking No.	Section keyword	Refs.	Author(s) GLM/GPRD/ GPRM
1.0	31-Jul-2014	07-2014	ALCON TDOC-0018306	CDS creation		Shankardas J. Day M.
2.0	28-May-2020	05-May-2020	2020-PSB/GLC-1101-s	CDS Update: Remove Driving Statement from W/P,Add ADR “hallucination”	1-2	Mukerjee A./ Brabant S.