PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrJAMP-Timolol

Timolol Maleate Ophthalmic Solution

Sterile Solution, 0.5% w/v timolol (as timolol maleate), Ophthalmic

Manufacturer's Standard

Elevated Intraocular Pressure Therapy

JAMP Pharma Corporation
1310 rue Nobel
Boucherville, Québec
J4B 5H3, Canada

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RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed .

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

JAMP-Timolol (Timolol Maleate Ophthalmic Solution) is indicated for:

- the reduction of elevated intraocular pressure

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada, therefore, an indication for pediatric use has not been authorized.

1.2 Geriatrics

Geriatrics (>65 years of age): Evidence from experience in geriatric populations does not suggests significant differences in safety and effectiveness.

2 CONTRAINDICATIONS

Timolol maleate is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- 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-and third-degree atrioventricular block; overt cardiac failure; cardiogenic shock

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- If needed, concomitant therapy with other agent(s) for lowering intraocular pressure may be given with JAMP-Timolol. The use of two topical beta-adrenergic blocking agents is not recommended (see 7 WARNINGS AND PRECAUTIONS).
- Since in some patients the pressure-lowering response to JAMP-Timolol may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with JAMP-Timolol.

4.2 Recommended Dose and Dosage Adjustment

- Adults (≥18 years of age): The dosage is one drop of JAMP-Timolol in the affected eye(s) twice a day.

  If the intraocular pressure is maintained at satisfactory levels, many patients can be placed on once-a-day therapy. Because of naturally occurring diurnal variations in intraocular

pressure, satisfactory response is best determined by measuring the intraocular pressure at different times during the day.

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

How to Transfer Patients from Other Therapy

When a patient is transferred from another topical ophthalmic beta-adrenergic blocking agent, that agent should be discontinued after proper dosing on one day and treatment with JAMP-Timolol started on the following day with one drop of JAMP-Timolol in the affected eye(s) twice a day.

When a patient is transferred from a single antiglaucoma agent, other than a topical ophthalmic beta-adrenergic blocking agent, continue the agent already being used and add one drop of JAMP-Timolol in each affected eye twice a day. On the following day, discontinue the previously used antiglaucoma agent completely and continue with JAMP-Timolol.

When a patient is transferred from several concomitantly administered antiglaucoma agents, individualization is required. The physician may be able to discontinue some or all of the other antiglaucoma agents. Adjustments should involve one agent at a time.

Clinical trials have shown the addition of Timolol Maleate Ophthalmic Solution to be useful in patients who respond inadequately to the maximum tolerable antiglaucoma drug therapy.

- Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

4.5 Missed Dose

If a dose is missed, it should be applied as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the next dose should be taken as usual.

5 OVERDOSAGE

There have been reports of inadvertent overdosage with Timolol Maleate Ophthalmic Solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also 8 ADVERSE REACTIONS).

The following additional therapeutic measures should be considered:

Gastric lavage: If ingested. Studies have shown that timolol does not dialyze readily.

Symptomatic bradycardia: Use atropine sulfate intravenously in a dosage of 0.25 to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should

be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker may be considered.

***Hypotension**:* Use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or levarterenol. In refractory cases the use of glucagon hydrochloride has been reported to be useful.

***Bronchospasm**:* Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.

***Acute cardiac failure**:* Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed if necessary by glucagon hydrochloride which has been reported to be useful.

***Heart block (second- or third-degree)**:* Use isoproterenol hydrochloride or a transvenous cardiac pacemaker.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Ophthalmic	Solution / 0.5% w / v timolol	Benzalkonium chloride, monobasic and dibasic sodium phosphate, sodium hydroxide, water for injection Benzalkonium chloride 0.01% is added as preservative.

JAMP-Timolol is a clear, colourless, sterile, isotonic, buffered, aqueous solution. Each mL contains 5 mg of timolol (6.8 mg of timolol maleate).

JAMP-Timolol is supplied in a three-piece white, multidose low-density polyethylene (LDPE) bottle, a dropper with the same characteristics and a white high-density polyethylene (HDPE) screw-on cap with childproof system.

JAMP-Timolol equivalent to 5 mg (0.5% w/v) timolol per mL, is supplied in a 5 mL bottle.

7 WARNINGS AND PRECAUTIONS

General

As with other topically applied ophthalmic drugs, this drug may be absorbed systemically. The same types of cardiovascular, pulmonary and other adverse reactions reported with systemic beta-adrenergic blocking agents may occur with topical administration.

Carcinogenesis and Mutagenesis

See Carcinogenicity section in 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

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.

Cardiac failure should be adequately controlled before beginning therapy with JAMP-Timolol. Patients with a history of cardiovascular disease, including cardiac failure, should be watched for signs of deterioration of these diseases, and pulse rates should be checked.

Due to its negative effect on conduction time, beta blockers should only be given with caution to patients with first degree heart block.

Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and rarely death in association with cardiac failure, have been reported following administration of timolol maleate ophthalmic solutions.

Because of the potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patient with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with JAMP-Timolol, alternative therapy should be considered.

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

Driving and Operating Machinery

Temporary blurred vision or other visual disturbances may occur which can affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

Endocrine and Metabolism

Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus

JAMP-Timolol should be used with caution in patients subject to spontaneous hypoglycemia or in diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycemia.

Masking of Thyrotoxicosis

β-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of β-adrenergic blocking agents which might precipitate a thyroid storm.

Immune

Risk from Anaphylactic Reaction

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, either accidental, diagnostic, or therapeutic. These patients may be unresponsive to treatment of anaphylactic reactions with the usual doses of epinephrine since timolol may blunt the beta agonist effect of epinephrine. In such cases, alternatives to epinephrine should be considered.

Neurologic

Muscle Weakness

β-adrenergic blockade has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenic symptoms.

Ophthalmologic

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. Timolol maleate has little or no effect on the pupil. When JAMP-Timolol is used to reduce elevated intraocular pressure in angle - closure glaucoma they should be used with a miotic and not alone.

Choroidal Detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g., timolol, acetazolamide or combination) after filtration procedures. Management of eyes with chronic or recurrent choroidal detachment should include stopping all forms of aqueous suppressant therapy and treating endogenous inflammation vigorously.

As with the use of other antiglaucoma drugs, diminished responsiveness to Timolol Maleate Ophthalmic Solution after prolonged therapy has been reported in some patients. However, in clinical studies in which 164 patients have been followed for at least 3 years, no significant difference in mean intra ocular pressure has been observed after initial stabilization.

Contact Lenses

The preservative in JAMP-Timolol is benzalkonium chloride. This preservative is a quaternary ammonium compound that may be absorbed by soft contact lenses. Therefore, JAMP-Timolol should not be administered while wearing soft contact lenses. The contact lenses should be

removed before application of the drops and not be reinserted earlier than 15 minutes after use.

Peri-Operative Considerations

Major Surgery

The necessity or desirability of withdrawal of β-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures.

β-blocking ophthalmological preparations may block systemic β-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving JAMP-Timolol. Some patients receiving beta-adrenergic blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic blocking agents. If necessary during surgery, the effects of β-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.

Respiratory

In patients with mild/moderate chronic obstructive pulmonary disease (COPD), JAMP-Timolol should be used with caution, and only if the potential benefit outweighs the potential risk.

7.1 Special Populations

7.1.1 Pregnant Women

Timolol Maleate Ophthalmic Solution has not been studied in human pregnancy. The use of JAMP-Timolol requires that the anticipated benefit be weighed against possible hazards.

Teratogenic studies in the mouse and rabbit at dose levels of 2 to 50 mg/kg/day did not reveal evidence of teratogenicity but did suggest embryotoxicity at the highest dose.

Epidemiological studies have not revealed malformative effects, but show a risk of intrauterine growth retardation when beta-blockers are administered by the oral route.

In addition, signs and symptoms of betablockade (e.g., bradycardia, hypotension, respiratory distress and hypoglycemia) have been observed in the neonate when beta-blockers have been administered until delivery. JAMP-Timolol should not be used during pregnancy unless clearly necessary. If JAMP-Timolol is administered until delivery, the neonate should be carefully monitored during the first days of life.

7.1.2 Breast-feeding

Timolol is detectable in human milk. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (>65 years of age): Not applicable.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Like other topically applied ophthalmic drugs, Timolol Maleate Ophthalmic Solution is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta blocking agents. Listed adverse reactions include reactions seen within the class of ophthalmic beta- blockers. Adverse reactions reported in clinical experience with systemic timolol maleate may be considered potential side effects of ophthalmic timolol maleate.

The most frequent reported adverse reactions with Timolol eye drops are usually ocular (See Ophthalmologic).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The following adverse reactions have been reported with ocular administration of this or other timolol maleate formulations, either in clinical trials or since the drug has been marketed.

Body as a Whole

Headache, asthenia, fatigue.

Cardiovascular

Aggravation or precipitation of certain cardiovascular pulmonary and other disorders presumably related to effects of systemic beta blockade has been reported (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS). These include bradycardia, chest pain, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral

ischemia, palpitation, atrioventricular block, cardiac arrest, cardiac failure, congestive heart failure, edema, claudication, Raynaud's phenomenon, cold hands and feet and in insulin-dependent diabetics masked symptoms of hypoglycemia have been reported rarely.

Digestive

Dysgeusia, nausea, diarrhea, dyspepsia, dry mouth, abdominal pain, vomiting.

Ear and labyrinth disorders

Tinnitus.

Hypersensitivity

Signs and symptoms of allergic reactions including anaphylaxis, angioedema, pruritus, urticaria, localized and generalized rash.

Immunologic

Systemic lupus erythematosus.

Integumentary

Alopecia, psoriasiform rash or exacerbation of psoriasis.

Metabolism and Nutrition Disorders

Hypoglycemia.

Musculoskeletal

Myalgia.

Nervous System/Psychiatric

Depression, insomnia, nightmares, memory loss, increases in signs and symptoms of myasthenia gravis, dizziness, paresthesia.

Respiratory

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, cough.

Ophthalmologic

Signs and symptoms of ocular irritation: including burning and stinging, itching, tearing, redness, conjunctivitis, conjunctival injection, blepharitis, keratitis, blurred vision, decreased corneal sensitivity, and dry eyes. Visual disturbances: including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, corneal erosion ptosis, and choroidal detachment following filtration surgery (see 7 WARNINGS AND PRECAUTIONS).

Urogenital

Decreased libido, Peyronie's disease, sexual dysfunction.

Various adverse reactions with unclear causal relationship

The following adverse reactions have been reported but a causal relationship to therapy with Timolol Maleate Ophthalmic Solution has not been established: aphakic cystoid macular edema, nasal congestion, anorexia, CNS effects (e.g., behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances), hypertension, retroperitoneal fibrosis and pseudo pemphigoid.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

The concomitant use of two topical beta-adrenergic blocking agents is not recommended due to potential additive effects.

The concomitant use of oral calcium channel blocker or beta-adrenergic blocking agents, catecholamine-depleting drugs, antiarrhythmics, digitalis glycosides, parasympathomimetics, guanethidine, or CYP2D6 inhibitors may lead to potentiation of adverse systemic effects.

Due to exacerbation of the rebound hypertension, caution is recommended when clonidine is used concomitantly with JAMP-Timolol and when it is withdrawn.

Standard laboratory parameters may be affected rarely by the administration of JAMP-Timolol. No specific drug interaction studies have been performed with Timolol Maleate Ophthalmic Solution.

9.4 Drug-Drug Interactions

Beta-Adrenergic Blockers: Patients who are already receiving a beta blocker systemically and who are given JAMP-Timolol should be observed for a potential additive effect on the intraocular pressure or on the known systemic effects of beta blockers (hypotension and/or bradycardia). The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium Channel Blockers or Catecholamine-Depleting Drugs: The potential exists for additive effects and production of hypotension and/or marked bradycardia when JAMP-Timolol is administered together with an oral calcium channel blocker or beta-adrenergic blocking agents, catecholamine-depleting drugs such as reserpine, antiarrhythmics, digitalis glycosides, parasympathomimetics or guanethidine.

Clonidine: Oral β-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the β-adrenergic blocking agent should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by β-blocker therapy, the introduction of β-adrenergic blocking agents should be delayed for several days after clonidine administration has stopped.

Epinephrine: Although Timolol Maleate Ophthalmic Solution used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with timolol maleate ophthalmic solutions and epinephrine has been reported occasionally.

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

9.5 Drug-Food Interactions

No specific drug-food studies have been performed with Timolol Maleate Ophthalmic Solution.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Clinically important changes in standard laboratory parameters were rarely associated with the administration of systemic timolol maleate. Slight increases in blood urea nitrogen, serum potassium, serum uric acid and triglycerides and slight decreases in hemoglobin, hematocrit, and HDL-cholesterol occurred, but were not progressive or associated with clinical manifestations.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Timolol maleate is a general beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. Timolol maleate combines reversibly with a part of the cell membrane, the beta-adrenergic receptor, and thus inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the beta-adrenergic receptors by catecholamines having beta-adrenergic stimulating (agonist) activity, whether these originate from an endogenous or exogenous source. Reversal of this blockade can be accomplished by increasing the concentration of the agonist, which will restore the usual biologic response.

10.2 Pharmacodynamics

Timolol Maleate Ophthalmic Solution reduces elevated and normal intraocular pressure whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

Onset of action of timolol maleate is usually rapid, occurring approximately 20 minutes after topical application on the eye. Maximum reduction of intraocular pressure occurs in one to

two hours. Significant lowering of intraocular pressure has been maintained for as long as 24 hours with 0.5% Timolol Maleate Ophthalmic Solution twice a day. Repeated observations over a period of three years indicate that the intraocular pressure-lowering effect of Timolol Maleate Ophthalmic Solution is well maintained.

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. Unlike miotics, timolol maleate reduces intraocular pressure with little or no effect on accommodation or pupil size. Thus, changes in visual acuity due to increased accommodation are uncommon, and dim or blurred vision and night blindness produced by miotics are not evident. In addition, in patients with cataracts the inability to see around lenticular opacities when the pupil is constricted by miotics is avoided. When changing patients from miotics to JAMP-Timolol a refraction might be necessary when these effects of the miotic have passed.

10.3 Pharmacokinetics

Absorption: Timolol maleate (S(-) enantiomer) is significantly metabolized after oral and ophthalmic administration.

Distribution: Timolol is moderately (<60%) bound to plasma proteins.

Metabolism: Based on correlation with debrisoquine metabolism, timolol metabolism is mediated primarily by cytochrome P-450 2D6.

Elimination: The drug and the metabolites (hydroxyethylamino, hydroxyethylglycolamino derivatives and a third minor metabolite that results from the hydroxylation of a terminal methyl group on the tertiary butylamino moiety) are excreted primarily via the kidney.

In a study of plasma drug concentration in six subjects, the systemic exposure to timolol was determined following twice-daily topical administration of timolol maleate ophthalmic solution 0.5% for 8 days. The mean peak plasma concentration following morning dosing was 0.46 ng/mL and following afternoon dosing was 0.35 ng/mL.

By comparison to plasma concentrations (10 to 20 ng/mL) following oral 5 mg dose, it was estimated that timolol was approximately 50% bio-available systemically following intraocular administration.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°-25°C).

Protect from light.

Once opened, store at room temperature up to 25°C, out of direct light with in-use period of 1 month.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

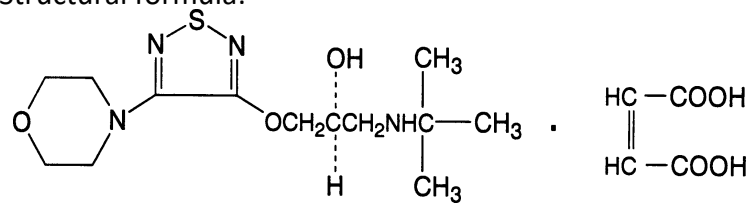
Drug Substance

Proper name: Timolol maleate

Chemical name: (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (*Z*)-2-butenedioate(1:1) (salt)

Molecular formula and molecular mass: $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$, 432.49 g/mol

Structural formula:



Physicochemical properties: Timolol maleate is a beta-adrenergic receptor blocking agent. It possesses an asymmetric carbon atom in its structure and is provided as (S)- isomer. It is a white odourless, powder which is soluble in water, methanol and alcohol.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Reduction of intraocular pressure

Timolol Maleate Ophthalmic Solution generally produced fewer and less severe side effects than either pilocarpine or epinephrine. Bradycardia was reported with Timolol Maleate Ophthalmic Solution (see WARNINGS AND PRECAUTIONS). At trough (12 hours post-dose), the mean reduction was 3.6 beats/minute. At two hours post- dose, the mean reduction in heart rate was 5 beats/minute.

Timolol Maleate Ophthalmic Solution has also been used in patients with glaucoma wearing conventional hard contact lenses. Timolol Maleate Ophthalmic Solution has not been studied in patients wearing lenses made with materials other than polymethylmethacrylate.

In clinical trials Timolol Maleate Ophthalmic Solution has been shown to reduce intraocular pressure in:

- Patients with chronic open-angle glaucoma
- Patients with ocular hypertension
- Aphakic patients having glaucoma, including those wearing contact lenses
- Patients with narrow angles and a history of spontaneous or iatrogenically-induced narrow-angle closure in the opposite eye in whom reduction of intraocular pressure is necessary (see 7 WARNINGS AND PRECAUTIONS).

15 MICROBIOLOGY

JAMP-Timolol contains the preservative benzalkonium chloride as an antimicrobial preservative.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Ocular Effects

No adverse ocular effects were observed in rabbits and dogs administered Timolol Maleate Ophthalmic Solution topically in studies lasting one and two years respectively.

Table 2 - Acute Toxicity (LD_{50})

Species and Age	Sex	Route of Administration	LD_{50} mg/kg
Mouse (A)	F	Oral	1190
	F	Intravenous	222
	F	Subcutaneous	1040
Rat (YA)	M	Oral	947
	F	Oral	900
	M	Oral (Fed)	1800
	M	Intraperitoneal	390
	F	Intraperitoneal	383
Rat (W)	M	Oral	1040
	F	Oral	969
	M/F	Intraperitoneal	409
Rat (I)	M/F	Oral	241
	M/F	Subcutaneous	143
Rabbit (A)	M/F	Oral	485
	M/F	Subcutaneous	34
(A)=Adult; (YA)=Young Adult; (W)=Weanling; (I)=Infant			

Signs of toxicity occurred immediately after intravenous administration and from 10 to 30 minutes following oral, intraperitoneal or subcutaneous administration. The signs observed included lacrimation, ataxia, tremors and bradypnea. Clonic convulsions usually preceded death.

Oral Interactions Studies

Oral acute interaction studies in mice in which timolol maleate was administered with probenecid, methyldopa, hydralazine, hydrochlorothiazide, or tolbutamide, showed that these drugs had no influence on the toxicity of timolol maleate. Timolol maleate had no effect on the hypoprothrombinemia induced by bishydroxycoumarin in the dog.

Subacute Toxicity

In rats treated with 100 to 400 mg/kg/day for seven weeks, excessive salivation seen 5 to 10 minutes after dosing had a dose related incidence in the first week of the study. At necropsy, organ weight studies revealed a significant increase in the kidneys, spleen and liver of some treated animals. Except for splenic congestion, there were no morphological changes to account for the increase in organ weights. Rats treated with 1 gram per day for eight weeks exhibited ptyalism, muscle tremors and transient pale extremities.

In dogs, doses of 200 mg/kg/day or higher, were lethal to some animals. Low grade tubular nephrosis and trace amounts of hyaline casts in the collecting and convoluted tubules occurred in one of two dogs administered 100 mg/kg/day and in both dogs receiving 400 mg/kg/day. Small foci of tubular degeneration and regeneration occurred in the nephrotic areas. Similar slight multi focal degeneration of the collecting tubules in the medulla of both kidneys was evident in one of four dogs in a 15-day intravenous toxicity study.

Chronic Toxicity

Rats

Timolol was administered orally to rats at dose levels of 5, 10 and 25 mg/kg/day for up to 67 weeks. No physical signs, ocular signs or deaths which could be attributed to the drug were evident.

Dogs

In a 54-week oral study timolol was administered at doses of 5, 10 and 25 mg/kg/day. Body weight and food consumption were normal and no physical signs attributable to treatment were evident. Slight focal hyperplasia of the transitional epithelium was seen in the renal pelvis of one dog receiving 25 mg/kg/day.

Carcinogenicity:

Lifetime studies with timolol have been completed in rats at oral doses of 25, 100 and 300 mg/kg/day and in mice at oral doses of 5, 50 and 500 mg/kg/day. In male and female rats and male mice at all dose levels, and in female mice at dose levels of 5 and 50 mg/kg/day, timolol demonstrated no carcinogenic effect. There was a slight increase in the incidence of mammary adenocarcinomas in female mice that received 500 mg/kg/day (about 500 times the maximum recommended human oral dose, on a mg/kg basis). Timolol caused dose-related elevations of serum prolactin in female mice at doses of 100 mg/kg/day or more, but only very slight transient elevations were found in male mice at doses of 500 mg/kg/day. Since numerous studies have demonstrated that drugs which cause elevations of serum prolactin are associated with mammary tumors in rodents, the mammary tumors in the female mice in

the highest dosage group of this study were considered to have resulted from an increased serum prolactin. In humans, no such association between serum prolactin and mammary carcinoma has been established.

Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

Reproductive and Developmental Toxicology:

Reproductive Studies

Teratogenic studies in the mouse and rabbit at dose levels of 2 to 50 mg/kg/day did not reveal evidence of teratogenicity but did suggest embryotoxicity at the highest dose. Oral administration of timolol maleate to rats at dose levels of 4 to 100 mg/kg/day did not adversely affect the fertility of male or female rats, their reproductive performance, or the development of their offspring.

17 SUPPORTING PRODUCT MONOGRAPHS

1. TIMOPTIC® (timolol maleate ophthalmic solution, 0.5% w/v), submission control 264123, Product Monograph, Elvium Life Sciences. (October 25, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrJAMP-Timolol

Timolol Maleate Ophthalmic Solution

Read this carefully before you start taking **JAMP-Timolol** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **JAMP-Timolol**.

What is JAMP-Timolol used for?

JAMP-Timolol lowers the pressure in the eye for conditions such as open-angle glaucoma and ocular hypertension.

How does JAMP-Timolol work?

The active ingredient, timolol maleate, is a beta-blocking drug. It helps lower the pressure in the eye.

What are the ingredients in JAMP-Timolol?

Medicinal ingredients: Timolol maleate

Non-medicinal ingredients: Benzalkonium chloride, monobasic and dibasic sodium phosphate, sodium hydroxide, water for injection

JAMP-Timolol comes in the following dosage forms:

Ophthalmic solution: 5 mg (0.5%) timolol (timolol maleate) per mL.

Do not use JAMP-Timolol if:

- You are allergic to any of its components (see **What are the ingredients in JAMP-Timolol section**).
- You have now or have had certain serious breathing problems such as asthma or chronic obstructive lung disease.
- You have certain heart diseases or conditions (such as slow or irregular heartbeats).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take JAMP-Timolol. Talk about any health conditions or problems you may have, including if you:

- Have any medical problems now or have had any in the past, especially asthma and other lung problems, heart problems or poor blood circulation.
- Have any allergies.
- Have now or have had in the past, thyroid problems.
- Have or have had in the past, diabetes or other blood sugar problems.
- Are planning major surgery, including eye surgery, as using JAMP-Timolol may change the effects of some medicines during anesthesia.
- Had past eye problems such as choroidal detachment.
- Had problems or develop problems with blood flow to the brain.
- Are pregnant or intend to become pregnant.
- Are breastfeeding or intend to breastfeed. Timolol has been detected in human breast milk.

Other warnings you should know about:

JAMP-Timolol is not recommended for children.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with JAMP-Timolol:

- Beta-blockers such as atenolol, epinephrine, quinidine.
- Calcium channel blockers or catecholamine depleting drugs such as reserpine.
- Clonidine.
- Epinephrine.

How to take JAMP-Timolol:

Read the following information carefully. If you need any explanations, or further information, ask your physician or pharmacist.

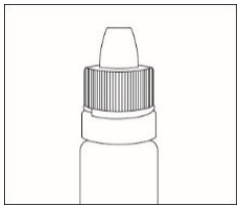
1. Do not start taking any other medicines unless you have discussed the matter with your physician or pharmacist.
2. If you develop any eye irritation or any new eye problems such as redness of the eye or swelling of the eyelids, contact your physician immediately.
3. If you are using JAMP-Timolol with another eye drop, the drops should be instilled at least 10 minutes apart.

4. Do not change the dosage of the drug without consulting your physician. If you must stop treatment, contact your physician immediately.
5. Do not allow the tip of the container to touch the eye or areas around the eye. It may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision. To avoid possible contamination of the container, keep the tip of the container away from contact with any surface.
6. Do not administer while wearing (soft) contact lenses. Remove lenses before application and reinsert no earlier than 15 minutes after use. JAMP-Timolol contains benzalkonium chloride as a preservative. This preservative may be absorbed by soft contact lenses.

Instructions for Use:

1. After receiving your prescription for JAMP-Timolol, carefully read the dosage instructions on the outer box.

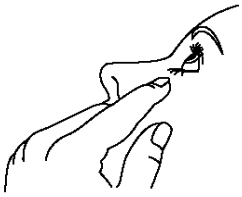
2. Before using the medication for the first time, be sure the Safety seal on the bottle is unbroken.



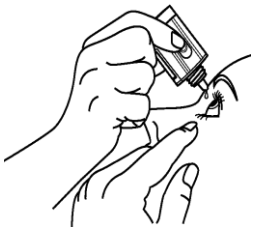
3. Twist the Safety seal to break the seal

4. After removing the cap from the product, turn the bottle upside down. Position the bottle over the affected eye.

5. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye.



6. Invert the bottle and press lightly with the thumb or index finger (as shown) until a single drop is dispensed into the eye as directed by doctor. Repeat as necessary.



7. Once dosage is completed, reapply cap. Store at room temperature up to 25°C, out of direct light.

If you have any adverse reactions, please contact your local pharmacist or your family physician.

Usual dose:

One drop in the affected eye(s) in the morning and in the evening. Your doctor may change your dose based on your condition.

Overdose:

If you put too many drops in your eye or swallow the contents of the bottle, you should contact your physician immediately.

If you think you, or a person you are caring for, have taken too much JAMP-Timolol, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is important to apply JAMP-Timolol as prescribed by your physician. If you miss a dose, apply it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to your regular dosing schedule. Do not double dose.

What are possible side effects from using JAMP-Timolol?

These are not all the possible side effects you may have when taking JAMP-Timolol. If you experience any side effects not listed here, tell your healthcare professional .

You may experience:

1. muscle pain
2. abdominal pain
3. nausea
4. vomiting
5. eye symptoms such as burning and stinging, dry eyes, redness of the eye, foreign body sensation or visual changes, such as double vision.

Other side effects may also occur rarely, and some of these may be serious. These may include shortness of breath.

JAMP-Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis.

There are side effects of JAMP-Timolol that may affect some patients' ability to drive and use machines.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Slow heartbeat			✓
RARE			
Heart effects such as irregular heartbeat, heart block, low blood pressure			✓
Allergic reactions with symptoms such as swelling of the mouth and throat, shortness of breath, hives, severe itching and rash			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature, 15-25°C.

Protect from light.

Once opened, store at room temperature up to 25°C, out of direct light with in-use period of 1 month.

Keep out of reach and sight of children.

If you want more information about JAMP-Timolol:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.jamppharma.com), or by calling 1-866-399- 9091.

This leaflet was prepared by JAMP Pharma Corporation

1310 rue Nobel
Boucherville, Québec
J4B 5H3, Canada

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