

## I.O.P PLUS

## Eye Drops

### Composition

Dorzolamide (As Hydrochloride)	2%
Timolol maleate	0.5%

### Action

I.O.P plus is comprised of two components: Dorzolamide hydrochloride and Timolol maleate. Each of these two components decreases elevated intraocular pressure, whether or not associated with glaucoma, by reducing aqueous humor secretion. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous field loss and optic nerve damage

Dorzolamide hydrochloride is an inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a beta 2 (non-selective) adrenergic receptor-blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. The combined effect of these two agents administered as I.O.P plus b.i.d. results in additional intraocular pressure reduction compared to either component administered alone, but the reduction is not as much as when Dorzolamide t.i.d. and Timolol b.i.d. are administered concomitantly

### Indications

I.O.P plus is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers

### Contraindications

I.O.P plus is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease; (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure; (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

### Warnings

#### Systemic Exposure

I.O.P plus contains Dorzolamide, a sulfonamide, and Timolol maleate, a beta-adrenergic blocking agent; and although administered topically, is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides and/or systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe 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 systemic or ophthalmic administration of Timolol maleate.

Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

#### Cardiac Failure

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

*In Patients without a History of Cardiac Failure* continued depression of the myocardium with beta-blocking agents over a period could, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, I.O.P plus should be discontinued.

### **Obstructive Pulmonary Disease**

Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which I.O.P plus is contraindicated should, in general, not receive beta-blocking agents, including I.O.P plus.

### **Major Surgery**

The necessity or desirability of withdrawal of beta-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. Some patients receiving beta-adrenergic receptor 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 receptor blocking agents. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

### **Diabetes Mellitus**

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

### **Thyrotoxicosis**

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

### **Adverse Reactions**

The most frequently reported adverse events were taste perversion (bitter, sour, or unusual taste) or ocular burning and/or stinging in up to 30% of patients. Conjunctival hyperemia blurred vision, superficial punctate keratitis or eye itching were reported between 5-15% of patients.

The following adverse events were reported in 1-5% of patients: abdominal pain, back pain, blepharitis, bronchitis, cloudy vision, conjunctival discharge, conjunctival edema, conjunctival follicles, conjunctival injection, conjunctivitis, corneal erosion, corneal staining, cortical lens opacity, cough, dizziness, dryness of eyes, dyspepsia, eye debris, eye discharge, eye pain, eye tearing, eyelid edema, eyelid erythema, eyelid exudate/scales, eyelid pain or discomfort, foreign body sensation, glaucomatous cupping, headache, hypertension, influenza, lens nucleus coloration, lens opacity, nausea, nuclear lens opacity, pharyngitis, post-subcapsular cataract, sinusitis, upper respiratory infection, urinary tract infection, visual field defect, vitreous detachment.

The following adverse events have occurred either at low incidence (<1%) during clinical trials or have been reported during the use of I.O.P plus in clinical practice. They have been chosen for inclusion based on factors such as seriousness, frequency of reporting, possible causal connection to I.O.P plus, or a combination of these factors: bradycardia, cardiac failure, cerebral vascular accident, chest pain, depression, diarrhea, dry mouth, dyspnea, hypotension, iridocyclitis, myocardial infarction, nasal congestion, paresthesia, photophobia, respiratory failure, skin rashes, urolithiasis, and vomiting.

### **Precautions**

#### **General**

Dorzolamide has not been studied in patients with severe renal impairment (CrCl < 30 ml/min). Because the kidney excretes Dorzolamide and its metabolite predominantly, I.O.P plus is not recommended in such patients.

Dorzolamide has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of I.O.P plus. Many of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of drug therapy. If such reactions are observed, I.O.P plus should be discontinued and the patient evaluated before considering restarting the drug.

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. I.O.P plus has not been studied in patients with acute angle-closure glaucoma.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g., Timolol). Beta-adrenergic blockade has been reported to potentiate 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 myasthenia gravis or myasthenic symptoms.

### **Information for Patients**

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product.

I.O.P plus contains dorzolamide (which is a sulfonamide) and although administered topically is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration. Patients should be advised that if serious or unusual reactions or signs of hypersensitivity occur, they should discontinue the use of the product

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should discontinue use and seek their physician's advice. Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, could 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.

Patients also should be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart. Patients should be advised that I.O.P plus contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of I.O.P plus.

### **Pregnancy**

#### *Category C*

There are no adequate and well-controlled studies in pregnant women. I.O.P plus should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**

It is unknown whether Dorzolamide is excreted in human milk. Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from I.O.P plus 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.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

No overall differences in safety or effectiveness have been observed between elderly and younger patients

**Drug Interactions***Carbonic anhydrase inhibitors*

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and I.O.P plus. The concomitant administration of I.O.P plus and oral carbonic anhydrase inhibitors is not recommended.

*Beta-adrenergic blocking agents*

Patients who are receiving a beta-adrenergic blocking agent orally and I.O.P plus should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

*Calcium antagonists*

Caution should be used in the co-administration of beta-adrenergic blocking agents, such as I.O.P plus, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, Co-administration should be avoided.

*Catecholamine-depleting drugs*

Close observation of the patient is 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 result in vertigo, syncope, or postural hypotension.

*Digitalis and calcium antagonists*

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

*Quinidine*

Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with quinidine and Timolol, possibly because quinidine inhibits the metabolism of Timolol via the P-450 enzyme, CYP2D6.

*Clonidine*

Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic Timolol maleate

**Dosage and Administration**

The dose is one drop of I.O.P plus in the affected eye(s) two times daily.

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

**Presentation**

Bottle of 5 ml