For patients insufficiently controlled with Beta blocker

**Duobrim-T**

(Brimonidine Tartrate 0.2% w/v + Timolol Maleate 0.5% w/v) Eye Drops

- Complimentary mechanism of action for better IOP reduction
  - 33 % reduction in IOP post single instillation
- Equally effective and better tolerated than the concomitant therapy
- Offers better patient compliance with twice daily dosing

Reference:
2. Craven ER, Poster presented at AAO October 20 – 23; 2002, Orlando, Florida
   and Motoloka MA et al AGS poster presentation; March 2006
DUOBRI-M®

(Brimonidine Tartrate and Timolol Maleate Eye drops)

Composition
Brimonidine tartrate…………………………..0.2% w/v
Timolol maleate IP equivalent to Timolol……0.5% w/v
Benzalkonium chloride General Formula…………0.02% w/v (as preservative)
Isotonic aqueous vehicle…………………..q.s

Pharmacological Action: Eye drop consists of two active substances: Brimonidine tartrate and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone. Eye drop has a rapid onset of action.

Brimonidine tartrate is an alpha-2 adrenergic receptor agonist that in 1000-fold more selective for the alpha-2 adrenergic receptor than the alpha-1 adrenergic receptor. This selectivity results in no mydriasis and the absence of peripheral alpha-1 receptors; the resulting bradycardia and decreased cardiac contractility are the consequences associated with human retinal ganglion cell axons. It is thought that brimonidine tartrate lowers IOP by enhancing uveoscleral outflow and reducing aqueous humour formation.

Timolol is a p1 and b2 non-selective adrenergic receptor-blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilizing) activity. Timolol lowers IOP by reducing aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.

The IOP-lowering effect of this fixed dose combination has been shown to be maintained in double-masked studies of up to 12 months.

Pharmacokinetics: Plasma brimonidine and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to timolol – timolol fixed combination treatment in healthy volunteers. Brimonidine was well absorbed and remained detectable in the plasma for at least 24 hours post-dose. Following oral administration to man, timolol is well absorbed and rapidly eliminated. The major part of the dose (around 74% of the dose) was excreted as metabolites in the kidney within five days; no unchanged drug was detected in urine. In vitro studies, using animal and human liver, indicate that the metabolism is mediated largely by aldehyde oxidase and cytochrome P450. Hence, the systemic elimination seems to be primarily hepatic metabolism.

Brimonidine binds extensively and reversibly to melanin in ocular tissues without any untoward effects. Accumulation does not occur in the absence of melanin.

Brimonidine is not metabolized to a great extent in humans. After instillation of brimonidine tartrate 0.2% eye drop solution in humans, plasma brimonidine concentrations are low. Brimonidine is not extensively metabolized in the human eye and plasma concentrations are therefore not expected to accumulate. The life of timolol in plasma is about 7 hours. Timolol is partially metabolized by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bound to plasma.

Indications: Brimonidine-timolol fixed combination is indicated for reduction of intraocular pressure (IOP) in patients with chronic open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers.

Warnings: For topical use only and not for injection or oral use.

Precautions: Like other topically applied ophthalmic agents, brimonidine-timolol fixed combination may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed.

Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta-blockers may occur.

Due to the alpha-2-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta-blockers may occur.

Caution should be exercised in treating patients with severe or unstable and uncontrolled cardiovascular disease. Cardiac failure should be adequately controlled before beginning therapy. Patients with a history of severe cardiac disease should be warned to seek signs of cardiac failure and have their pulse rates checked. Congestive heart failure, including death due to bronchopulmonary in patients with asthma, and, rarely, death in association with cardiac failure have been reported following administration of timolol maleate. Beta-blockers may also mask the signs of hypothyroidism and cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension.

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with tachyphylic diabetes) as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Brimonidine-timolol fixed combination should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud ’s phenomenon, orthostatic hypotension, or thromboangiitis obliterans. While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions. As with systemic beta-blockers, if discontinuation of treatment is needed in patients with coronary heart disease, therapy should be withdrawn gradually to avoid rhythm disorders, myocardial infarct or sudden death. The preservative in Eye drop, benzalkonium chloride, may cause eye irritation. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolor soft contact lenses.

Information for Patients: Avoid contaminating the applicator tip with material from the eye, fingers or other source.

Drug-Drug Interactions: Clinical drug interactions studies have not been conducted with brimonidine timolol fixed combination the theoretical possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered. There is potential for additive effects resulting in hypotension, and/or marked bradycardia when eye drops with timolol are administered concomitantly with oral calcium channel blockers, guanethidine, or beta-blocking agents, anti-arrhythmics, digitalis glycosides or parasympathomimetics. After the application of brimonidine-timolol fixed combination with systemic antiarrhythmics. Beta-blockers may increase the hydropenic effect of antiadrenergic drugs. Beta-blockers can mask the signs and symptoms of hypoglycemia. The hypotensive reaction may result in a further decrease of arterial blood pressure. Beta-blockers should be used with caution in patients with reactive airway disease including bronchial asthma and severe chronic obstructive pulmonary disease. Sinus bradycardia, second or third degree atrioventricular block, aortic failure, cardiac shock.

Beta-blockers are contraindicated in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with tachyphylic diabetes) as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

The theoretical possibility of an additive IOP lowering effect with prostaglandins, carbonic anhydrase inhibitors and pilocarpine should be considered.

Pregnancy: Pregnancy Category C Since there are no adequate and well-controlled studies in pregnant women, brimonidine – timolol fixed combination should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactating women: Timolol is excreted in human milk. It is not known if brimonidine is excreted in human milk but is excreted in the milk of the lactating rat. Therefore, brimonidine - timolol fixed combination should not be used by women breast-feeding infants.

Pediatric: Brimonidine - timolol fixed combination should not be administered to neonates. The safety and effectiveness of timolol fixed combination in children and adolescents have not been established and therefore, its use is not recommended in children or adolescents.

Geriatric: No overall differences in safety and effectiveness have been observed between elderly and younger patients.

Adverse Reactions: The undesirable effects with components of this combination are as follows:


Timolol: Eye disorder: decreased corneal sensitivity, diplopia, ptosis, choriocapillaris detachment (following filtration surgery), refractive changes (due to withdrawal of miotic therapy in some cases)

Psychiatric disorders: insomnia, nightmares, decreased appetite, general nervous system disorders: memory loss, increase in signs and symptoms of myasthenia gravis, paranoia,Court, and cerebral ischemia.


Overdose: No data are available with regard to overdose with brimonidine-timolol fixed combination.

Brimonidine itself has been shown to have the same potential for the medical treatment of ocular hypertension, symptoms of brimonidine overdose such as hypotension, bradycardia, hypothermia and apnoea have been reported in a few neonates receiving timolol. Oral overdoses of other alpha-2 agonists have been reported to cause symptoms such as hypotension, astasia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression and seizure.

Timolol: Symptoms of systemic timolol overdose are: bradycardia, hypotension, bronchospasm, headache, dizziness and cardiac arrest. A study of patients showed that timolol did not dialyze readily. If overdose occurs treatment should be symptomatic and supportive.

Storage Instructions: STORE BELOW 25OC. PROTECT FROM LIGHT. KEEP OUT OF REACH OF CHILDREN. FOR EXTERNAL USE ONLY.

Presentation: Duobrim-T is a sterile solution supplied in an opaque plastic bottle with a cap containing 5ml of solution.