For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

(Bimatoprost 0.03%w/v with Timolol Maleate 0.5%w/v Ophthalmic Solution)

SENZOPT™ - T

Eye Drops

For the use of Registered Medical Practitioner only

COMPOSITION:

Bimatoprost …..... 0.03%w/v
Timolol Maleate USP equivalent to Timolol ..... 0.5% w/v
Benzalkonium chloride solution USP …..... 0.02%v/v
(As preservative)
Water for injection USP …..... q.s

Clinical Pharmacology

Senzopt-T combines bimatoprost, a synthetic prostamide and timolol, a beta adrenergic blocking agent, both of which have complementary mechanisms of actions in the reduction of elevated intraocular pressure (IOP).

Mechanism of Action

Senzopt-T combines two active ingredients namely bimatoprost and Timolol maleate, both having complementary mechanism in decreasing elevated intraocular pressure (IOP). The combine effect results in additional IOP reduction compared to either compound administrated alone. Senzopt-T has a rapid onset of action.

Bimatoprost is a potent synthetic prostamide, structurally related to prostaglandin F2 (PGF2) that does not act through any known prostaglandin receptors. It selectively mimics the effects of newly discovered biosynthesized substances called prostamides. The mechanism of action by which bimatoprost reduces intraocular pressure in man is by increasing aqueous humor outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol is a beta and beta2 non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane stabilizing) activity. It lowers IOP by reducing aqueous humor 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.

Pharmacokinetics

In a crossover study comparing the monotheraphy treatments to fixed dose combination (FDC) of bimatoprost and timolol in healthy subjects, systemic absorption of the individual components was minimal and not affected by co-administration in a single administration.

In two 12 month studies where systemic absorption was measured, no accumulation was observed with either of the individual components

Bimatoprost penetrates the human cornea and sclera well invitro. After ocular administration, the systemic exposure of bimatoprost is very low with no accumulation overtime. After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025ng/ml) within 1.5 hours after dosing. Mean Cmax and AUC0-24hr values were similar on days 7 and 14 at approximately 0.08ng/ml and 0.09ng.hr/ml, respectively indicating that the steady drug concentration was reached during the first week of ocular dosing. It is moderately distributed in to body tissues and the systemic volume of distribution in humans at steady state was 0.671/kg. In human blood resides mainly in the plasma.

The plasma protein binding of the bimatoprost is approximately 88%. Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N deethylation, glucuronidation to form a diverse variety of metabolites. It is eliminated primarily by renal excretion; up to 67%of an intravenous dose administered to healthy volunteers was excreted in the urine while 25% of the dose was excreted via the feces. The elimination half life determined after intravenous administration, was approximately 45 minutes, the total blood clearance was 1.5

1/hr/kg. in the elderly (subjects 65 years or older) the mean AUC0-24hrs value of 0.0634 ng.hr/mlbimatoprost after twice daily dosing were significantly higher than 0.0218 ng.hr/ml in young healthy adults. However, systemic exposure for both elderly and young subjects remained very low from ocular dosing. There was no accumulation of bimatoprost in the blood over time and the safety profile was similar in elderly and young patients

Timolol, after ocular administration in form of 0.5% eye drops solution in humans undergoing cataract surgery has peak concentration 898 ng/ml in the aqueous humor at one hour post dose. Part of the dose is absorbed systemically where it is extensively metabolized in the liver. The half-life of timolol in plasma is about 4 to 6 hours. It is partially metabolized by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bounded to plasma.

Indications

Senzopt-T is indicated for reduction of intraocular pressure (IOP) in patients with open-angle glaucoma who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

Contra-indications:

- Hypersensitivity to the active substances or to any of the excipients
- Reactive airway disease including bronchital asthma or a history of bronchial asthma
- Severe chronic obstructive pulmonary disease.
- Sinus bradycardia
- Second or third degree atrioventricular block
- Overt cardiac failure
- Cardiogenic shock

Warnings and precautions

FOR EXTERNAL USE ONLY NOT FOR INJECTION

Senzopt-T may be absorbed systemically like other topically applied ophthalmic agents. No enhancement of the systemic absorption of the individual active substances has been observed.

The cardiovascular and pulmonary adverse reactions as seen with systemic beta-blockers may occur with the FDC due to the presence of timolol. Cardiac failure should be adequately controlled before beginning this therapy Patients with a history of severe cardiac disease should be watched for the signs of cardiac failure and have their pulse rates checked. Cardiac and respiratory reactions including death due to bronchospasm in patients with asthma and rarely death in association with cardiac failures have been reported following administration of timolol maleate.

Beta-blockers may also mask the signs of hyperthyroidism 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 hypoglycemia or to diabetic patients (especially those with labile diabetics) as beta-blockers may mask the signs and symptoms of acute hypoglycemia.

While taking beta-blockers, patients with a 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

In patients with a history of mild liver disease or abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin at baseline, bimatoprost has no adverse reactions on liver function over 24 months. There are no known adverse reactions of ocular timolol on liver function.

Before treatment is initialized, patients should be informed of the possibility of eyelash growth; darkening of the eyelid skin and increased iris pigmentation since these have been observed during treatment with combination of bimatoprost and timolol. Some of these changes may be permanent and may lead to differences in appearance between the eyes if only one eye is treated. After discontinuation of the FDC of bimatoprost and timolol, pigmentation of iris may be permanent. After 12 months treatment with FDC of bimatoprost and timolol, the incidence of iris pigmentation was 0.2%.

Cystoid macular edema has not been reported with Senzopt-T, however it has been uncommonly reported with bimatoprost. Therefore it should be used with

caution in patients with known risk factors for macular edema (e.g aphakic patients, pseudophakic patients with a torn posterior lens capsule)

The preservative in Senzopt-T, benzalkonium chloride, may also cause eye irritation. Contact lenses must be removed prior in application with atleast a 15 minute wait before reinsertion. Benzalkonium chloride is known to discolor soft contact lenses. Contact with soft contact lenses must be avoided. Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Therefore monitoring is required with frequent or prolonged use of Senzopt-T in dry eye patients or where the cornea is compromised.

The FDC of bimatoprost and timolol has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle closure glaucoma, congenital glaucoma or narrow angle glaucoma

Senzopt-T has negligible influence on the ability to drive and use machines. As with any ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery..

Pregnancy and lactation

No adequate data on use of the FDC of bimatoprost and timolol in pregnant women is available

However beta-blockers when administered by oral route have shown a risk for intrauterine growth retardation. Epidemiological studies have not revealed malformative effects but 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 until delivery, if the FDC of bimatoprost is administered until delivery neonate should be carefully monitored during the first days of life. Consequently, Senzopt-T should not be used during pregnancy unless clearly necessary.

Timolol is excreted in breast milk. It is not known if bimatoprost is excreted in human breast milk so Senzopt-T should not be used by breast feeding woman.

Drug Interactions

No interation studies with the concentration have been performed but there is a potential for additive effects resulting in hypotension, and/or marked bradycardia when eye drops containing timolol are administered concomitantly with oral calcium channel blockers, guanethidine, or beta-blocking agents, anti-arrhythmics, digitalis, glycosides or parasympthomimetics.

Beta-blockers may increase the hypoglycemic effect of antidiabetic agents and can even mask the signs and symptoms of hypoglycemia.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

Side effects

The most commonly reported adverse effects with the combination of bimatoprost and timolol during clinical trial are conjunctival hyperemia, growth of eyelashes, superficial punctate keratitis, corneal erosion, burning sensation, eye pruritus, stinging sensation in the eye, foreign body sensation, eye dryness, eye erythema, eye pain, photophobia, eye discharge, visual disturbance, eyelid pruritus and blepharal pigmentation. The other side effects of bimatoprost and timolol are headache, iritis, eye irritation, conjunctival edema, blepharitis, epiphora, eyelid edema, eyelid pain, worsened visual acuity, asthenopia, trichiasis, rhinitis and hirsutism. While other additional adverse effects that have been seen with one of the components and may potentially occur with FDC of bimatoprost and timolol are infection (primarily colds and upper respiratory symptoms), dizziness, allergic conjunctivitis, cataract, eyelash darkening, increased iris pigmentation, blepharospasm, cystoid macular oedema, eyelid retraction, retinal hemorrhage, uveitis, hypertension, asthenia, peripheral edema, liver functions test (LFT)abnormal, Insomnia, nightmares libido memory loss, increase in signs and symptoms of myasthenia gravis, paresthesia, cerebral ischemia, decreased corneal sensitivity, diplopia, ptosis, Choroidal detachment (following filtration surgery, refractive changes due to withdrawal of miotic therapy in some cases) keratitis, tinnitus, heart block, cardiac arrest, arrhythmia, syncope, bradycardia, cardiac failure, congestive heart failure, hypotension, cerebrovascular accident, claudication, Raynaud's phenomenon, cold hands and feet, palpitation, bronchospasm (predominantly in patients with pre-existing

bronchospastic disease) dyspnea, cough, nausea, diarrhea, dyspepsia, dry mouth, alopecia, psoriasiform rash or exacerbation of psoriasis, systemic lupus erythematosis, Peyronie's disease, edema, chest pain, fatigue.

Overdosage

Due to ocular administration, overdose is likely to occur. No case of overdose has been reported till date.

However if the FDC of bimatoprost and timolol ophthalmic solution is accidently ingested, the following , the following information may be useful, in two week oral rat and mouse studies, doses of bimatoprost up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m2 is at atleast 70 times higher than the accidental dose of one bottle of Senzopt-T in a 10 kg child.

The symptoms of systemic timolol overdose are bradycardia, hypotension, bronchospasm, headache, dizziness, shortness of breath, and cardiac arrest. A study of patients showed that timolol did not dialyse readily.

If overdose occurs treatment should be symptomatic and supportive.

Dosage and administration

The recommended dose in adults (including the elderly)is one drop of Senzopt-T in the affected eye(s) once daily, administered in the morning. If one drop is missed, treatment should continue with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily, if more than one topical ophthalmic product is to be used, the different products should be instilled atleast 5 minutes apart.

The dropper tip or the other dispensing tip should be touched to any surface since this may contaminate the solution.

Pediatric Use: The FDC of bimatoprost and timolol has been only studied in adults and therefore its use is not recommended in the children and adolescents.

Hepatic impairment: Since the effect of FDC of bimatoprost and timolol has not been studied in patients with hepatic impairment, caution should be used in treating such patients.

Renal Impairment: Caution should be used in treating the patients with renal impairment as there are no adequate studies of FDC of bimatoprost and timolol in this group of patients.

Incompatibility None known

Storage and Handling:

Store between 15°C - 30°C.

Shell life 24 months from the date of manufacture.

KEEP OUT OF REACH OF CHILDREN
NOT FOR INJECTION
FOR EXTERNAL USE ONLY

Presentation:

A clear colourless solution filled in 5mL Sterile Gamma-irradiated white opaque LDPE bottle sealed with Sterile Gamma-irradiated natural transparent LDPE open nozzle and Sterile Gamma-irradiated white HDPE tamp safe cap in printed carton along with leaflet.

Directions for use :

Turn the tamper proof cap anti-clockwise to break the seal.

Remove the cap, dispense drops with gentle pressure.

Replace the cap immediately after every use.

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ETBPI-02

Month of publication of pack insert: June 2023