

## **Brimonidine AFT**

*Brimonidine tartrate 0.2%w/v Ophthalmic solution*

### **Presentation**

BRIMONIDINE-AFT is a clear, greenish-yellow sterile ophthalmic solution containing brimonidine tartrate 0.2% (2mg/mL)

### **Uses**

#### **Actions**

Brimonidine is an alpha-2 adrenergic agonist that is 1000-fold more selective for the alpha-2 adrenoceptor than the alpha-1 adrenoceptor. Affinity at human alpha-1 and alpha-2 adrenoceptors are ~2000 nM and ~2 nM, respectively. This selectivity results in no mydriasis and the absence of vasoconstriction in microvessels associated with human retinal xenografts.

Topical administration of BRIMONIDINE-AFT eye drops decreases intraocular pressure (IOP) in humans. When used as directed, BRIMONIDINE-AFT eye drops have the action of reducing elevated IOP with minimal effect on cardiovascular parameters.

BRIMONIDINE eye drops have a rapid onset of action, with the peak ocular hypotensive effect occurring at two hours post-dosing. The duration of effect is 12 hours or greater.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action. BRIMONIDINE-AFT eye drops lower IOP by reducing aqueous humor production and enhancing uveoscleral outflow.

#### **Pharmacokinetics**

After ocular administration of a 0.2% solution of bromonidine tartrate eye drops twice daily in humans for 10 days, plasma concentrations were low (mean  $C_{max}$  0.06 ng/mL). Plasma concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours.

In humans, systemic metabolism of brimonidine is extensive; brimonidine does not accumulate. It is metabolised primarily by the liver. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally-administered radioactive dose was eliminated within 120 hours, with 74% found in the urine.

#### **Indications**

BRIMONIDINE-AFT eye drops are effective for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

### **Dosage and Administration**

The recommended dose is one drop of BRIMONIDINE-AFT eye drops in the affected eye(s) twice daily, approximately 12 hours apart.

If more than one topical ophthalmic medicine is to be used, other eye drops should not be used within five to ten minutes of using BRIMONIDINE-AFT eye drops.

In order to minimise systemic absorption of BRIMONIDINE-AFT eye drops, apply pressure to the tear duct immediately following administration.

#### **Paediatric Use**

Safety and effectiveness in paediatric patients have not been established. Symptoms of bradycardia, hypotension, hypothermia, hypotonia and apnea have been reported (rarely) in neonates receiving brimonidine.

## **Contraindications**

- Patients with hypersensitivity to brimonidine tartrate or any component of this medication
- Patients receiving monoamine oxidase (MAO) inhibitor therapy.

## **Warnings and Precautions**

Although brimonidine tartrate eye drops had minimal effect on blood pressure and heart rate of patients in clinical studies, caution should be observed in treating patients with severe, uncontrolled cardiovascular disease.

BRIMONIDINE-AFT eye drops have not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

BRIMONIDINE-AFT eye drops should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

Patients wearing soft contact lenses should be instructed to remove lenses before administering BRIMONIDINE-AFT eye drops and wait at least 15 minutes after using BRIMONIDINE-AFT eye drops to re-insert lenses.

### ***Carcinogenesis, mutagenesis and impairment of fertility***

No compound-related carcinogenic effects were observed in 21 month and 2 year studies in mice and rats given oral doses of 2.5 mg/kg/day (as the free base) and 1.0 mg/kg/day respectively ((77 and 118 times, respectively, the human plasma drug concentration following the recommended ophthalmic dose).

Brimonidine tartrate eye drops were not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames tests, host-mediated assay, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, cytogenic studies in mice and dominant lethal assay.

### ***Use during Pregnancy and Lactation***

Category B1

Reproduction studies have been performed in rats at oral doses more than 100 times (0.66 mg base/kg) the plasma drug concentration in humans receiving multiple ophthalmic doses and have revealed no evidence of impaired fertility or harm to the foetus due to BRIMONIDINE eye drops. Additionally, teratogenicity studies showed no adverse effects in rats or rabbits when oral doses were administered at approximately 333 and 24 times respectively, the human drug plasma concentrations resulting from multiple ophthalmic doses. There are no studies of BRIMONIDINE eye drops in pregnant women, however in animal studies, brimonidine crossed the placenta and entered into the foetal circulation to a related extent. BRIMONIDINE-AFT eye drops should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

It is not known whether brimonidine is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. 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.

### ***Effects on ability to drive and use machines***

As with other alpha-agonists, BRIMONIDINE-AFT eye drops can potentially cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities requiring mental alertness, including driving, should be cautioned of the potential for a decrease in mental alertness.

## **Adverse Effects**

In clinical studies, most adverse events were usually transient and not commonly of a severity requiring discontinuation of treatment.

The most frequently reported adverse events were:

- Ocular:  
Ocular hyperemia, burning and stinging, blurring and foreign body sensation.

- **Systemic:**

Oral dryness, headache, fatigue/drowsiness.

Events occurring in 1-10% of subjects included:

- **Ocular:**

Ocular pruritis (itching), corneal staining/erosion, photophobia, ocular allergic reaction, ocular dryness, conjunctival follicles, tearing, ocular ache/pain, eyelid erythema, conjunctival blanching, conjunctival edema, eyelid edema, ocular irritation, abnormal vision, blepharitis, conjunctival discharge.

- **Systemic:**

Upper respiratory symptoms, dizziness, gastrointestinal symptoms, asthenia, abnormal taste, and nasal dryness.

Events occurring infrequently (less than 1%) in subjects included:

- **Ocular:**

Conjunctival papillae.

- **Systemic:**

Systemic allergic reaction, depression and palpitations.

## **Interactions**

Although specific drug interaction studies have not been conducted with BRIMONIDINE-AFT eye drops, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

Because BRIMONIDINE-AFT eye drops may reduce blood pressure, caution using drugs such as antihypertensives and/or cardiac glycosides is advised.

Caution is advised when initiating or changing the dose of a concomitant systemic agent which may interact with alpha-adrenergic agonists or interfere with their activity (ie. sympathomimetic agents, agonists or antagonists of the adrenergic receptor).

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with BRIMONIDINE-AFT eye drops can lead to an interference in IOP lowering effect. No data on the level of circulating catecholamines after BRIMONIDINE-AFT eye drops are instilled are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

## **Overdosage**

No information is available on overdosage in humans. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

In the event of a topical overdosage, flush eye with a topical ocular irrigant.

## **Pharmaceutical Precautions**

To avoid contamination of the solution, keep container tightly closed. Do not touch dropper tip to any surface. Contents are sterile if seal is intact.

Shelf life: 3 years when stored below 25°C

Discard contents 4 weeks after opening the bottle.

## **Medicines Classification**

Prescription Medicine

## **Package Quantities**

BRIMONIDINE-AFT 0.2% eye drops are supplied in white LDPE dropper bottles (5 mL).

**Further Information**

Each mL of BRIMONIDINE eye drops contains 2.0 mg brimonidine tartrate, equivalent to 1.32 mg as brimonidine free base.

**List of excipients**

PRESERVATIVE: benzalkonium chloride

INACTIVES: polyvinyl alcohol, sodium chloride, sodium citrate, citric acid, and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

**Clinical trial results**

Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. BRIMONIDINE-AFT eye drops have the action of lowering IOP with minimal effect on cardiovascular and pulmonary parameters.

The long term efficacy of Brimonidine tartrate eye drops was demonstrated in two multicentre studies for one year and 6 months duration in subjects with glaucoma or ocular hypertension. The IOP lowering effect of Brimonidine tartrate eye drops ranged from an overall mean reduction of 4.1mm Hg at trough to a peak effect of 6.4mm Hg. These results represent approximately 16%-26% mean reduction from baseline measurements. IOP decreases were maintained for up to one year; no tachyphylaxis was observed. Eight percent of subjects were discontinued from the studies due to inadequately controlled IOP.

Analyses of the proportion of subjects who exhibited decreases of  $\geq 3$ mm Hg at two consecutive visits within the first month of treatment were performed. This subgroup represented 66% of subjects. In these subjects, the overall mean reduction of IOP with Brimonidine tartrate eye drops ranged from 5.3mm Hg at trough to a peak effect of 7.2mm Hg. These results represent approximately 20%-30% mean reduction from baseline measurements. At the end of one year, greater than 50% of subjects had IOP reductions of  $\geq 5$ mm Hg.

**Name and Address**

AFT Pharmaceuticals Ltd  
26 Anzac Street (Level 1)  
Takapuna  
Auckland  
Email:customer.service@aftpharm.com

**Date of Preparation**

13 December 2005