BRIMODIN Eye Drops (Brimonidine tartrate 0.2%)

**Composition**

Each ml contains:
Brimonidine Tartrate ............... 2 mg
(equivalent to 1.32 mg as Brimonidine base)
Benzalkonium Chloride, NF (as preservative) ............ 0.005% w/v
Sterile aqueous vehicle .......... q.s.

**Dosage Form**

Ophthalmic solution

**Pharmacology**

**Pharmacodynamics**

**Mechanism of Action**

Brimonidine tartrate is an alpha-2 adrenergic receptor agonist that is 1,000-fold more selective for the alpha-2 adrenoceptor than the alpha-1 adrenoreceptor. This selectivity results in no mydriasis and the absence of vasoconstriction in microvessels associated with human retinal xenografts. Topical administration of brimonidine tartrate decreases intraocular pressure (IOP) in humans with minimal effect on cardiovascular or pulmonary parameters. Limited data are available for patients with bronchial asthma showing no adverse effects.

Brimonidine has a rapid onset of action, with peak ocular hypotensive effect occurring at 2 hours post-dosing. In two 1 year studies, Brimonidine tartrate 0.2% ophthalmic solution lowered IOP by mean values of approximately 4–6 mmHg. Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action of reducing the aqueous humor production and increasing uveoscleral outflow.

Clinical trials show that Brimonidine 0.2% is effective in combination with topical beta-blockers. Shorter term studies also suggest that Brimonidine 0.2% has a clinically relevant additive effect in combination with travoprost (6 weeks) and latanoprost (3 months).

**Pharmacokinetics**

**Absorption**

After ocular administration of a 0.2% solution, plasma concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 hours. The area under the plasma concentration-time curve over 12 hours at steady state (AUC\(_{0-12h}\)) was 0.31 ng·hr/ml, as compared to 0.23 ng·hr/ml after the first dose.

**Distribution**

The plasma protein binding of brimonidine tartrate after topical dosing in humans is approximately 29%. Brimonidine tartrate binds reversibly to melanin in ocular tissues, in vitro and in vivo. Following 2 weeks of ocular
instillation, the concentrations of brimonidine tartrate in the iris, ciliary body and choroid-retina were 3- to 17-fold higher than those after a single dose. Accumulation does not occur in the absence of melanin. The significance of melanin binding in humans is unclear. However, no significant ocular adverse reaction was found during biomicroscopic examination of eyes in patients treated with brimonidine tartrate, 0.2%, ophthalmic solution for up to one year.

**Metabolism**

In humans, brimonidine is extensively metabolized by the liver.

**Excretion**

Urinary excretion is the major route of elimination of brimonidine and its metabolites. Approximately 87% of an orally-administered radioactive dose of brimonidine was eliminated within 120 hours, with 74% found in the 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.

**Kinetics Profile**

No great deviation from dose proportionality for plasma $C_{\text{max}}$ and AUC was observed following a single topical dose of 0.08%, 0.2% and 0.5%.

**Characteristics in Patients**

The $C_{\text{max}}$, AUC, and apparent half-life of brimonidine are similar in the elderly (subjects 65 years or older) after a single dose compared with young adults, indicating that its systemic absorption and elimination are not affected by age. Based on data from a 3-month clinical study, which included elderly patients, systemic exposure to brimonidine was very low.

<table>
<thead>
<tr>
<th>Indications</th>
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<tbody>
<tr>
<td>Brimonidine tartrate 0.2% ophthalmic solution is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension.</td>
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<tr>
<td>As monotherapy in patients in whom topical beta-blocker therapy is contraindicated.</td>
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<tr>
<td>As adjunctive therapy to other intraocular pressure lowering medications when the target is not achieved with a single agent.</td>
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<td>The recommended dose is one drop of brimonidine tartrate, 0.2%, ophthalmic solution in the affected eye(s) three times daily, approximately 8 hours apart.</td>
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<tr>
<td>Brimonidine tartrate ophthalmic solution may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.</td>
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<tr>
<td>As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctal occlusion) for 1 minute. This should be performed immediately following the instillation of each drop.</td>
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<td>Brimonidine tartrate 0.2% ophthalmic solution is contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in neonates and infants (under the age of 2 years), patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants that affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).</td>
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</table>
**Warnings And Precautions**

**Potentiation of Vascular Insufficiency**

Brimonidine tartrate 0.2%, ophthalmic solution may potentiate syndromes associated with vascular insufficiency. Brimonidine tartrate 0.2%, ophthalmic solution should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud’s phenomenon, orthostatic hypotension or thromboangiitis obliterans.

**Severe Cardiovascular Disease**

Although brimonidine tartrate ophthalmic solution had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

**Somnolence in Children**

Children of 2 years of age and above, especially those in the 2 to 7 years age range and/or weighing ≤20 kg, should be treated with caution and closely monitored due to the high incidence and severity of somnolence.

**Ocular Allergic Reactions**

Some (12.7%) patients in clinical trials experienced an ocular allergic type reaction with brimonidine tartrate 0.2% ophthalmic solution. If allergic reactions are observed, treatment should be discontinued. Delayed ocular hypersensitivity reactions have been reported with brimonidine tartrate 0.2% ophthalmic solution, with some reported to be associated with an increase in IOP.

**Hepatic or Renal Impairment**

Brimonidine tartrate 0.2%, ophthalmic solution has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

**Contamination of Topical Ophthalmic Products after Use**

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

**Use with Contact Lenses**

The preservative in brimonidine tartrate ophthalmic solution benzalkonium chloride may cause eye irritation and may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling brimonidine tartrate ophthalmic solution to insert soft contact lenses.

**Drug Interactions**

*Anti-hypertensives/Cardiac Glycosides*

Because brimonidine tartrate ophthalmic solution may reduce blood pressure, caution in using drugs such as anti-hypertensives and/or cardiac glycosides with brimonidine tartrate ophthalmic solution is advised.

*CNS Depressants*

Although specific drug interaction studies have not been conducted with brimonidine, the possibility of an additive or potentiating effect with central nervous system (CNS) depressants (alcohol, barbiturates, opiates, sedatives or anaesthetics) should be considered.

*Tricyclic Anti-depressants*

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 tartrate ophthalmic solution in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

**Monoamine Oxidase Inhibitors**

Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

**Concomitant Systemic Agents**

Caution is advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of pharmaceutical form) which may interact with alpha-adrenergic agonists or interfere with their activity i.e. agonists or antagonists of the adrenergic receptor e.g. (isoprenaline, prazosin).

### Effects on Ability to Drive and Use Machines

Brimonidine may cause fatigue and/or drowsiness which may impair the ability to drive or operate machinery. Brimonidine tartrate 0.2% ophthalmic solution may cause blurred and/or abnormal vision, which may impair the ability to drive or to use machinery, especially at night or in reduced lighting. The patient should wait until these symptoms have cleared before driving or using machinery.

### Use in Renal and Hepatic Impairment

Brimonidine tartrate 0.2% ophthalmic solution, has not been studied in patients with hepatic or renal impairment. The effect of dialysis on brimonidine pharmacokinetics in patients with renal failure is not known. Caution should be used in treating such patients.

### Pregnancy

**Teratogenic Effects**

**Pregnancy Category B**

There are no adequate and well-controlled studies in pregnant women; however, in animal studies, brimonidine crossed the placenta and entered the fetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, brimonidine tartrate ophthalmic solution should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

### Lactation

It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. Because of the potential for serious adverse reactions from brimonidine tartrate ophthalmic solution in nursing infants, a decision should be made whether to discontinue lactation or to discontinue the drug, taking into account the importance of the drug to the mother.

### Paediatric Use

Brimonidine tartrate ophthalmic solution is contraindicated in children under the age of 2 years. During post-marketing surveillance, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate have not been studied in children below the age of 2 years.

In a well-controlled clinical study conducted in paediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with Brimonidine tartrate ophthalmic solution, 0.2% dosed three times daily were somnolence (50%-83% in patients ages 2 to 6 years) and decreased alertness. In paediatric patients 7 years of age or older (>20kg),
Somnolence appears to occur less frequently (25%). The most commonly observed adverse event was somnolence. Approximately 16% of patients on Brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

### Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

### Undesirable Effects

The following serious adverse reactions are described elsewhere in the labelling:
- Potentiation of Vascular Insufficiency
- Severe Cardiovascular Disease
- Contamination of Topical Ophthalmic Products after Use
- Neonates and Infants (under the age of 2 years)

#### Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse reactions occurring in approximately 10-30% of the subjects (in descending order): oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

Adverse reactions occurring in approximately 3-9% of the subjects (in descending order): corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid oedema, conjunctival oedema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

Adverse reactions reported <3% of the patients: lid crusting, conjunctival haemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

Symptoms of ocular allergic reactions occurred in 12.7% of subjects (causing withdrawal in 11.5% of subjects) in clinical trials, with the onset being between 3 and 9 months in the majority of patients.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The following terminologies have been used in order to classify the occurrence of undesirable effects: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (1/10,000 to <1/1,000); very rare (<1/10,000); and, not known (cannot be estimated from the available data).

#### Cardiac Disorders

Uncommon: Palpitations/arrhythmias (including bradycardia and tachycardia).

#### Nervous System Disorders

Very common: Headache, drowsiness.

Common: Dizziness, abnormal taste.

Very rare: Syncope.

#### Eye Disorders

Very common:

- Ocular irritation (hyperaemia, burning and stinging, pruritus, foreign body sensation, conjunctival follicles).
- Blurred vision.
Allergic blepharitis, allergic blepharoconjunctivitis, allergic conjunctivitis, ocular allergic reaction, and follicular conjunctivitis.

Common:
Local irritation (eyelid hyperaemia and oedema, blepharitis, conjunctival oedema and discharge, ocular pain and tearing).
Photophobia, corneal erosion and staining, ocular dryness, conjunctival blanching, abnormal vision, conjunctivitis.

Very rare:
Iritis, miosis.

**Respiratory, Thoracic and Mediastinal Disorders**
Common: Upper respiratory symptoms.
Uncommon: Nasal dryness.
Rare: Dyspnoea.

**Gastrointestinal Disorders**
Very common: Oral dryness.
Common: Gastrointestinal symptoms, abnormal taste

**Vascular Disorders**
Very rare: Hypertension, hypotension.

**General Disorders And Administration site conditions**
Very common: Fatigue.
Common: Asthenia.

**Immune System Disorders**
Uncommon: Systemic allergic reactions.

**Psychiatric Disorders**
Uncommon: Depression.
Very rare: Insomnia

**Post-marketing Experience**

The following reactions have been identified during post-marketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include:

- Bradycardia; conjunctivitis; hypersensitivity; hypotension; iritis; keratoconjunctivitis sicca; lacrimation increased; miosis; nausea; skin reactions (including erythema, eyelid pruritus, rash, and vasodilation); and tachycardia.
- Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence in infants receiving brimonidine tartrate ophthalmic solutions.

The following adverse reactions have been identified during post-marketing use of brimonidine tartrate 0.2% ophthalmic solution, in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made:

**Not known**

**Eye disorders**
- Iridocyclitis (anterior uveitis).
- Eyelid pruritus.

**Skin and Subcutaneous Tissue Disorders**
- Skin reactions, including erythema, face oedema, pruritus, rash and vasodilatation.

In cases where brimonidine tartrate has been used as part of the medical treatment of congenital glaucoma, symptoms of brimonidine tartrate overdose such as loss of consciousness, lethargy, somnolence, hypotension, hypotonia, bradycardia, hypothermia, cyanosis, pallor, respiratory depression and apnoea have been reported in neonates and infants receiving brimonidine tartrate.

In a 3-month, phase 3 study in children aged 2 to 7 years with glaucoma, inadequately controlled by beta-blockers, a high prevalence of somnolence (55%) was reported with brimonidine tartrate 0.2% ophthalmic solution, as adjunctive treatment. In 8% of the children, this was severe and led to discontinuation of treatment in 13%. The incidence of somnolence decreased with increasing age, being least in the 7-years-old age group (25%), but was more affected by weight, occurring more frequently in those children weighing ≤20 kg (63%), compared to those weighing >20 kg (25%).

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024. By reporting side-effects, you can help provide more information on the safety of this product.

### Overdosage

**Ophthalmic Overdose (Adults)**

In those cases received, the events reported have generally been those already listed as adverse reactions.

**Systemic Overdose Resulting from Accidental Ingestion (Adults)**

There is very limited information regarding accidental ingestion of brimonidine in adults. The only adverse event reported to date was hypotension. It was reported that the hypotensive episode was followed by rebound hypertension. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving brimonidine tartrate as part of medical treatment of congenital glaucoma or by accidental oral ingestion.

Treatment of oral overdose includes supportive and symptomatic therapy; patient’s airways should be maintained. Oral overdoses of other alpha-2-agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression and seizure.

**Paediatric Population**

Reports of serious adverse effects following inadvertent ingestion of brimonidine tartrate 0.2% ophthalmic solution by paediatric subjects have been reported. The subjects experienced symptoms of CNS depression, typically temporary coma or low level of consciousness, lethargy, somnolence, hypotonia, bradycardia, hypothermia, pallor, respiratory depression, apnoea, and required admission to intensive care with intubation, if indicated. All subjects were reported to have made a full recovery, usually within 6–24 hours.

### Incompatibility

Not applicable

### Shelf-Life

2 years
Storage And Handling Instructions

Store in a cool, dry place. Protect from light.

Packaging Information

**BRIMODIN Eye Drops:** Vial of 5 ml

Information For Patients

Handling the Container

Patients should be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eyes or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eyes and subsequent loss of vision may result from using contaminated solutions. Always replace the cap after using. If the solution changes colour or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

When to Seek Physician Advice

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.

Use with Contact Lenses

Advise patients that contact lenses should be removed prior to instillation of brimonidine tartrate ophthalmic solution and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs

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

Potential for Decreased Mental Alertness

As with other similar medications, brimonidine tartrate ophthalmic solution may cause fatigue and/or drowsiness in some patients. Caution patients who engage in hazardous activities of the potential for a decrease in mental alertness.

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