

# Arrow-Brimonidine

*brimonidine tartrate*

0.2% w/v Ophthalmic Solution

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## Presentation

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A clear, greenish yellow solution in a 5 mL dropper bottle. Each mL contains 2.0 mg brimonidine tartrate equivalent to 1.32 mg as brimonidine free base.

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## Uses

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### **Actions**

Brimonidine is an alpha-2 adrenergic receptor agonist that is 1000-fold more selective for the alpha-2 adrenoreceptor 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 and pulmonary parameters.

Limited data are available for patients with bronchial asthma showing no adverse effects.

ARROW - BRIMONIDINE has a rapid onset of action, with the peak ocular hypotensive effect seen at two hours post-dosing. In two 1 year studies, brimonidine tartrate 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. It is thought that brimonidine tartrate may lower IOP by reducing aqueous humour formation and enhancing uveoscleral outflow.

Clinical studies show that brimonidine eye drops are effective in combination with topical beta-blockers. Shorter term studies also suggest that brimonidine eye drops have a clinically relevant additive effect in combination with travoprost (6 weeks) and latanoprost (3 months.)

### **Pharmacokinetics**

After ocular administration of a 0.2% solution twice daily for 10 days, plasma concentrations were low (mean  $C_{max}$  0.06 ng/mL). There was a slight accumulation in the blood after multiple (2 times daily for 10 days) instillations. 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. The mean apparent half-life in the systemic circulation was approximately 3 hours in humans after topical dosing.

The plasma protein binding of brimonidine after topical dosing in humans is approximately 29%.

Brimonidine binds reversibly to melanin in ocular tissues, in vitro and in vivo. Following 2 weeks of ocular instillation, the concentrations of brimonidine in 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 eye drops for up to one year, nor was significant ocular toxicity found during a one year ocular safety study in monkeys given approximately 4 times the recommended dose.

Following oral administration to man, brimonidine is well absorbed and rapidly eliminated. The major part of the dose (around 75%) is excreted as metabolites in urine within 5 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.

No great deviation from dose proportionality for plasma C<sub>max</sub> and AUC has been observed following a single topical dose of 0.08%, 0.2% and 0.5%.

The C<sub>max</sub>, 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.

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## Indications

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

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## Dosage and Administration

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

If more than one topical ophthalmic medicine is to be used, the different eye drops should be instilled 5 to 15 minutes apart.

As with any eye drops, to reduce possible systemic absorption of ARROW - BRIMONIDINE, it is recommended that the lachrymal sac be compressed at the medial canthus (punctal occlusion) for one minute. This should be performed immediately following the instillation of each drop.

No dosage adjustment is required in elderly patients.

### ***Use in renal and hepatic impairment***

Brimonidine tartrate eye drops have not been studied in patients with renal or hepatic impairment.

### ***Paediatric Use***

No clinical studies have been performed in adolescents (12 to 17 years).

Brimonidine tartrate eye drops are not recommended for use in children below 12 years and are contraindicated in neonates and infants (less than 2 years of age) (see Contraindications, Warnings and Precautions and Overdosage sections). It is known that severe adverse reactions can occur in neonates. The safety and efficacy of brimonidine tartrate eye drops has not been established in children.

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## **Contraindications**

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Contraindicated in patients with known hypersensitivity to brimonidine tartrate or to any of the excipients in ARROW – BRIMONIDINE.

Contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenergic transmission (eg. tricyclic antidepressants and mianserin).

Contraindicated in neonates and infants less than 2 years of age (see Dosage and Administration – Paediatric Use).

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## **Warnings and Precautions**

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Children of 2 years of age and above, especially those in the 2 to 7 age range and/or weighing less than 20 kg, should be treated with caution and closely monitored due to the high incidence of somnolence (see Adverse Effects).

Caution should be observed in treating patients with severe or unstable and uncontrolled cardiovascular disease.

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

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

ARROW – BRIMONIDINE contains benzalkonium as a preservative, which may cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Known to discolour soft contact lenses.

Some patients (12.7%) in clinical trials experienced ocular allergic type reaction with brimonidine eye drops (see Adverse Effects). If allergic reactions are observed, treatment with ARROW – BRIMONIDINE should be discontinued.

### ***Pregnancy and Lactation***

The safety of use during human pregnancy has not been established. In animal studies, brimonidine tartrate did not cause any teratogenic effects. In rabbits, brimonidine tartrate at plasma levels higher than are achieved during therapy in humans, has been shown to cause increased preimplantation loss and postnatal growth reduction. ARROW - BRIMONIDINE should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the foetus.

It is not known whether brimonidine is excreted in human milk. The compound is excreted in the milk of the lactating rat. ARROW – BRIMONIDINE should not be used by women nursing infants.

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

ARROW - BRIMONIDINE may cause fatigue and/or drowsiness which may impair the ability to drive or operate machinery. ARROW – BRIMONIDINE 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.

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## **Adverse Effects**

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The most commonly reported ADRs are oral dryness, ocular hyperaemia and burning/stinging, all occurring in 22% to 25% of patients. They are usually transient and not commonly of a severity requiring discontinuation of treatment.

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

The following terminologies have been used for classification of frequency of adverse effects:

Very common:	≥1 in 10
Common:	≥1 in 100 and <1 in 10
Uncommon:	≥1 in 1,000 and <1 in 100
Rare:	≥1 in 10,000 and <1 in 1,000
Very rare:	< 1 in 10,000

Within each frequency grouping, adverse effects are presented in order of decreasing seriousness.

### *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 including allergic reactions (hyperaemia, burning, stinging, pruritis, foreign body sensation, conjunctival follicles); blurred vision.

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 (anterior uveitis); miosis.

*Respiratory, thoracic and mediastinal disorders:*

Common: Upper respiratory symptoms.

Uncommon: Nasal dryness.

Rare: Dyspnoea

*Gastrointestinal disorders:*

Very common: Oral dryness.

Common: Gastrointestinal symptoms.

*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.

In cases where brimonidine has been used as part of the medical treatment of congenital glaucoma, symptoms of brimonidine overdose such as loss of consciousness, hypotension, hypotonia, bradycardia, hypothermia, cyanosis and apnoea have been reported in neonates and infants receiving brimonidine (see Contraindications).

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 eye drops as adjunctive treatment. In 8% of 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-year-old age group (25%), but was more affected by weight, occurring more frequently in those children weighing  $\leq 20$  kg (63%) compared to those weighing  $>20$  kg (25%) (see Warnings and Precautions).

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## Interactions

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

After the application of brimonidine tartrate eye drops, clinically insignificant decreases in blood pressure were noted in some patients. Caution is advised when using drugs such as antihypertensives and/or cardiac glycosides concomitantly with ARROW - BRIMONIDINE.

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 eg. isoprenaline, prazosin.

No actual data on the level of circulating catecholamines after administration of brimonidine tartrate eye drops are available. Caution, however, is advised in patients who are taking medications which can affect the metabolism and uptake of circulating amines eg. chlorpromazine, methylphenidate, reserpine.

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## Overdosage

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### ***Ophthalmic overdose***

There is no experience in adults, as it is unlikely that overdose would be experienced via the ophthalmic route. However, symptoms of brimonidine overdose (including loss of consciousness, hypotension, hypotonia, bradycardia, hypothermia, cyanosis and apnoea) have been reported in neonates and infants receiving brimonidine tartrate eye drops as part of medical treatment of congenital glaucoma.

### ***Systemic overdose resulting from accidental ingestion***

Two cases of adverse effects following inadvertent ingestion of 9-10 drops of brimonidine tartrate eye drops by adults have been reported. The subjects experienced a hypotensive episode, followed in one instance by rebound hypertension approximately 8 hours after ingestion. Both subjects were reported to have made a full recovery within 24 hours. No adverse effects were noted in a third subject who also ingested an unknown amount of brimonidine tartrate eye drops orally.

Reports of serious adverse effects following inadvertent ingestion of brimonidine tartrate eye drops have been published/reported. The subjects experienced symptoms of CNS depression, typically temporary coma or low level of consciousness, hypotonia, bradycardia, hypothermia and 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.

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.

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## **Pharmaceutical Precautions**

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Store below 25°C. Discard 4 weeks after opening.

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## **Medicine Classification**

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Prescription Medicine

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## **Package Quantities**

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ARROW - BRIMONIDINE 0.2% w/v solution – 5 mL dropper bottle

### ***List of excipients***

PRESERVATIVE: benzalkonium chloride

INACTIVES: polyvinyl alcohol, sodium citrate, citric acid anhydrous, sodium chloride, sodium hydroxide (to adjust pH) and purified water.

### ***Preclinical safety data***

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

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## **Name and Address**

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## **Date of Preparation**

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10 October 2011