

AUSTRALIAN PRODUCT INFORMATION – ENIDIN® (brimonidine tartrate) Eye Drops

1 NAME OF THE MEDICINE

Brimonidine tartrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of ENIDIN® 0.2% Eye Drops contains 2.0 mg brimonidine tartrate (equivalent to 1.32 mg as brimonidine free base).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Eye drops, solution.

ENIDIN® 0.2% is a sterile ophthalmic solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ENIDIN® eye drops are effective in lowering elevated intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension. ENIDIN® eye drops can be used in the treatment of glaucoma as either monotherapy or in combination with topical beta-blockers.

4.2 DOSE AND METHOD OF ADMINISTRATION

Monotherapy: The recommended dose is one drop of ENIDIN® eye drops in the affected eye(s) twice daily, approximately 12 hours apart.

Combination Therapy: The recommended dose is one drop of ENIDIN® eye drops in the affected eye(s) twice daily, approximately 12 hours apart.

In order to minimise systemic absorption of ENIDIN® eye drops, apply pressure to the tear duct immediately following administration of the drug.

As with all eye drops containing benzalkonium chloride as a preservative, there is potential for incompatibility with other topical ophthalmic medications. If more than one topical ophthalmic drug is to be used, other eye drops should not be used within five to ten minutes of using ENIDIN® eye drops.

4.3 CONTRAINDICATIONS

ENIDIN[®] eye drops are contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. This product is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

ENIDIN[®] eye drops are also contraindicated in neonates and infants (children under the age of 2 years)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Brimonidine eye drops should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangitis obliterans.

During the studies there was a loss of effect in some patients. The IOP-lowering efficacy observed with brimonidine eye drops during the first month of therapy may not always reflect the long-term level of IOP reduction. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Cardiovascular disease

Although brimonidine 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.

Hypersensitivity

Delayed ocular hypersensitivity reactions have been reported with ENIDIN[®], with some reported to be associated with an increase in IOP.

Use in hepatic or renal impairment

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

Use in the elderly

No data available.

Paediatric use

Symptoms of bradycardia, coma, hypotension, lethargy, pallor, respiratory depression, somnolence, hypothermia, hypotonia and apnoea have been reported in neonates, infants and children receiving brimonidine either for congenital glaucoma or by accidental oral ingestion. [See Section 4.3 CONTRAINDICATIONS.]

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

Information for Patients

The preservative in ENIDIN[®] eye drops, benzalkonium chloride, may be absorbed by and cause discolouration of soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after using ENIDIN[®] eye drops to insert soft contact lenses.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures to avoid eye injury and contamination of eye drops.

Effects on the laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Specific drug interaction studies have not been conducted with brimonidine eye drops. The possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered. Because brimonidine eye drops may reduce blood pressure, caution using drugs such as beta-blockers (ophthalmic and systemic), 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 (i.e. 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 eye drops can lead to an interference in IOP lowering effect. No data on the level of circulating catecholamines after brimonidine 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.

As brimonidine is metabolised primarily by the liver, most likely by cytochrome P450 and aldehyde oxidase, this may affect the metabolism of other drugs that utilise the cytochrome P450 pathway.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Brimonidine did not have a significant effect on fertility in a reproductive performance study in rats at oral doses of up to 0.66 mg/kg/day.

Use in pregnancy – Pregnancy Category B3

There are no studies of brimonidine in pregnant women, but in rats the drug crosses the placenta and enters the foetal circulation.

Because animal reproductive studies are not always predictive of human response, ENIDIN[®] should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

In pregnant rats, brimonidine was associated with maternotoxicity and increased early resorptions/post-implantation losses and decreased pup viability and bodyweights at exposures (based on AUC) of 180 times greater than expected exposures in humans treated therapeutically. The drug was also maternotoxic in rabbits and caused abortions at exposures about 12 times greater than those expected in humans. In both rats and rabbits, brimonidine was not teratogenic.

Use in lactation.

It is not known whether brimonidine is excreted in human milk. Therefore a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. In lactating rats, levels of the drug in milk were up to 12 times higher than those in maternal plasma; and in a peri- and postnatal study in rats, brimonidine was associated with decreased pup viability and pup weights during lactation at maternal plasma exposures of about 55 times greater than those expected in humans.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with other alpha-agonists, brimonidine can potentially cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities requiring mental alertness, such as driving and operating machinery, should be cautioned of the potential for a decrease in mental alertness.

ENIDIN[®] may also cause blurred vision or visual disturbance. The patient should wait until these symptoms have cleared before driving or using machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

A: Clinical Trials - Frequency of adverse events occurring in pivotal monotherapy studies

	<i>brimonidine 0.2%</i> (n=822) %	<i>timolol 0.5%</i> (n=521) %	<i>betaxolol 0.25%</i> (n=196) %
<i>OCULAR</i>			
<i>ocular hyperaemia</i>	20	21	7.7
<i>burning/stinging</i>	19	35.5	7.1
<i>foreign body sensation</i>	12	13	0
<i>blurring</i>	12	18	2.6
<i>ocular allergic reaction</i>	8.9	0.2	0
<i>conjunctival follicles</i>	8.5	4.4	1.0
<i>ocular pruritus (itching)</i>	7.8	8.8	1.0
<i>corneal staining/erosion</i>	6.8	9.2	4.1
<i>conjunctival oedema</i>	6.3	5.0	3.1
<i>photophobia</i>	6.0	8.4	0.5
<i>eyelid erythema</i>	5.2	4.4	0
<i>ocular dryness</i>	5.2	8.3	0.5
<i>ocular ache/pain</i>	5.1	4.2	2.6
<i>SYSTEMIC</i>			
<i>oral dryness</i>	21	13	1.0
<i>headache</i>	13	17	5.6
<i>fatigue/drowsiness</i>	12	13	1.0
<i>upper respiratory symptoms</i>	6.7	7.1	4.1

Brimonidine eye drops - adverse events occurring at 1-5%

Ocular: eyelid oedema, abnormal vision, blepharitis, ocular irritation, conjunctival blanching, conjunctival discharge.

Systemic: dizziness, gastrointestinal symptoms, asthenia, abnormal taste.

Brimonidine eye drops - adverse events occurring at <1%

Ocular: conjunctival papillae, tearing.

Systemic: depression, systemic allergic reaction, nasal dryness, palpitations.

B: Clinical Trials - Frequency of adverse events occurring in combination therapy studies

As adjunctive therapy, assigning causality of adverse events cannot be reliable because both agents are administered concurrently. However, the most common adverse events have been tabulated below.

	<i>brimonidine 0.2% in combination with various beta blockers (n=185) %</i>	<i>pilocarpine 2.0% in combination with various beta blockers (n=66) %</i>	<i>dipivefrine 0.1% in combination with various beta blockers (n=69) %</i>
<i>OCULAR</i>			
<i>Burning/stinging</i>	8.6	4.5	18.8
<i>Conjunctival blanching</i>	4.3	0	34.8
<i>Ocular allergic reaction</i>	10.3	0	11.6
<i>Ocular ache/pain</i>	3.8	6.1	1.4
<i>Ocular hyperaemia</i>	9.7	0	37.7
<i>Conjunctival follicles</i>	1.6	0	5.8
<i>SYSTEMIC</i>			
<i>Oral dryness</i>	9.7	0	5.8
<i>Headache</i>	6.5	24.2	5.8

Post Marketing Experience

During post-marketing surveillance, apnoea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in neonates, infants, and children receiving brimonidine either for congenital glaucoma or by accidental ingestion.

The following adverse reactions have been identified during postmarketing use of ENIDIN[®] 0.2% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Eye disorders

Iritis, iridocyclitis (anterior uveitis), miosis, conjunctivitis, eyelids pruritus.

Immune system disorders

Hypersensitivity, skin reaction (including erythema, face oedema, pruritus, rash, and vasodilatation)

Cardiac disorders

Palpitations/arrhythmias (including bradycardia or tachycardia).

Psychiatric disorders

Depression.

Vascular disorders

Hypotension, syncope

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Ophthalmic overdose:

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

Systemic overdose resulting from accidental ingestion:

There is very limited information regarding accidental ingestion of brimonidine in adults. The only adverse event reported to date was hypotension. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

Symptoms of brimonidine overdose such as apnoea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in neonates, infants, and children receiving ENIDIN[®] as part of medical treatment of congenital glaucoma or by accidental oral ingestion.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Brimonidine tartrate is an alpha-2 adrenergic agonist that is 1000-fold more selective for the alpha-2 adrenoreceptor than the alpha-1 adrenergic receptor. Affinity at human alpha-1 and alpha-2 adrenoreceptors 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 solution decreases intraocular pressure (IOP) in humans. When used as directed, brimonidine eye drops have the action of reducing elevated IOP with minimal effect on cardiovascular parameters.

Brimonidine has 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 solution has a dual mechanism of action. Brimonidine lowers IOP by reducing aqueous humor production and enhancing uveoscleral outflow.

Clinical trials

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 has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters.

Monotherapy:

The efficacy of brimonidine eye drops was demonstrated in two multicentre studies comparative with timolol 0.5% lasting up to one year in subjects with glaucoma or ocular hypertension. A total of 513 subjects received brimonidine eye drops in the two studies.

The overall mean decrease ($\pm$ SD) in IOP from baseline at 12 months, as measured at peak response, was 6.20 ± 4.08 mmHg for brimonidine monotherapy and 5.56 ± 3.65 mmHg for timolol monotherapy. At trough response, these figures were 3.74 ± 3.83 mmHg for brimonidine and 5.80 ± 3.35 mmHg for timolol.

These results represent approximately 16% - 26% mean reduction from baseline measurements. IOP decreases were maintained for up to one year; no tachyphylaxis was observed. 9.4% of subjects treated with brimonidine eye drops and 5.1% of subjects treated with timolol 0.5% were discontinued because of inadequately controlled intraocular pressure. 30% of these patients withdrew during the first month of therapy.

Adjunctive Therapy:

The ability of brimonidine eye drops to lower IOP when used in combination with other anti-glaucoma agents has been evaluated in two large scale multicentre, randomised studies, involving 321 patients, 150 of which received brimonidine.

In the first study, brimonidine 0.2% twice daily as an adjunct to β -blocker therapy was compared with pilocarpine 2% administered three times daily, as an adjunct to β -blocker therapy. The overall mean decrease ($\pm$ SD) in IOP from baseline at 3 months, as measured at

peak response, was 4.92 ± 3.02 mmHg for brimonidine adjunctive therapy and 5.52 ± 3.08 mmHg for pilocarpine adjunctive therapy. At trough response, these figures were 3.95 ± 2.67 mmHg for brimonidine adjunctive therapy and 3.81 ± 2.75 mmHg for pilocarpine adjunctive therapy. These results represent a mean additional decrease in IOP for brimonidine eye drops adjunctive therapy of 17% - 22%.

The second study was an 8 month comparison of the additive IOP lowering effect to an already established β -blocker eye drop regimen, of brimonidine 0.2% eye drops or dipivefrine 0.1% eye drops. Adjunctive brimonidine eye drops was shown to be superior to adjunctive dipivefrine 0.1% at peak effect and equivalent in efficacy to adjunctive dipivefrine at trough at most time points.

The overall mean decrease ($\pm$ SD) in IOP from baseline at 3 months, as measured at peak response, was 3.26 ± 3.16 mmHg for brimonidine adjunctive therapy and 2.33 ± 3.13 mmHg for dipivefrine adjunctive therapy. At trough response, these figures were 2.89 ± 3.14 mmHg for brimonidine adjunctive therapy and 3.31 ± 3.69 mmHg for dipivefrine adjunctive therapy. These results represent a mean additional decrease in IOP for brimonidine adjunctive therapy of 12% - 15%.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After ocular administration of a 0.2% solution twice daily in normal healthy subjects for 10 days, plasma concentrations were measured as (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.

Metabolism

Brimonidine is metabolised primarily by the liver.

Excretion

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Brimonidine was non-genotoxic in assays for chromosomal damage (Chinese hamster cells in vitro, in vivo bone marrow cytogenetic assay and a dominant lethal assay). In assays for gene mutations in *S. typhimurium* and *E. coli*, brimonidine gave a positive response in one *S. typhimurium* strain without metabolic activation. Other strains gave negative results.

Carcinogenicity

No compound-related carcinogenic effects were observed in 21 month and 2 year studies in mice and rats given oral doses of 2.5 and 1 mg/kg/day respectively as the free base. Plasma concentrations of brimonidine in mice and rats in the high-dose groups were > 60 times greater than those expected in humans dosed therapeutically.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each mL of ENIDIN[®] 0.2% solution contains:

ACTIVE: brimonidine tartrate 2.0 mg (equivalent to 1.32 mg as brimonidine free base)

PRESERVATIVE: benzalkonium chloride 0.05 mg

INACTIVES: polyvinyl alcohol; sodium chloride; sodium citrate dihydrate; citric acid monohydrate; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH (6.3-6.5).

6.2 INCOMPATIBILITIES

As with all eye drops containing benzalkonium chloride as a preservative, there is potential for incompatibility with other topical ophthalmic medications. If more than one topical ophthalmic drug is to be used, other eye drops should not be used within five to ten minutes of using ENIDIN[®] eye drops.

The preservative in ENIDIN[®] eye drops, benzalkonium chloride, may be absorbed by and cause discolouration of soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after using ENIDIN[®] eye drops to insert soft contact lenses.

6.3 SHELF LIFE

30 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

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.

6.5 NATURE AND CONTENTS OF CONTAINER

ENIDIN[®] (brimonidine tartrate ophthalmic solution) 0.2% sterile solution is supplied in white opaque plastic dropper bottles. Each bottle contains 5mL.

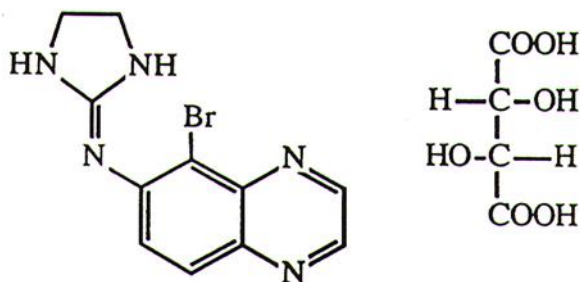
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Discard contents 4 weeks after opening the bottle.

6.7 PHYSICOCHEMICAL PROPERTIES

Brimonidine tartrate is an off-white, pale yellow to pale pink powder and is water soluble (34 mg/mL). In solution, brimonidine tartrate has a clear, greenish-yellow colour.

Chemical structure



Chemical name: 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate.

Molecular weight: 442.24 as the tartrate salt.

Empirical formula: $C_{11}H_{10}BrN_5$, $C_4H_6O_6$

CAS Number: 79570-19-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

AUST R 81531

8 SPONSOR

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A.B.N.: 85 000 612 831

9 DATE OF FIRST APPROVAL

24 April 2002

10 DATE OF REVISION

19 January 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	The PI has been reformatted in line with the TGA's approved form for PIs.

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