

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Brimogen 2 mg/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains 2.0 mg brimonidine tartrate, equivalent to 1.3 mg of brimonidine.

Excipient with known effect: benzalkonium chloride 0.05 mg/ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear, slightly yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

- As monotherapy in patients in whom topical beta-blocker therapy is contraindicated.
- As adjunctive therapy to other intraocular pressure lowering medications when the target IOP is not achieved with a single agent (see section 5.1).

4.2 Posology and method of administration

Posology

Recommended dosage in adults (including the elderly)

The recommended dose is one drop of Brimogen in the affected eye(s) twice daily, approximately 12 hours apart. No dosage adjustment is required for the use in elderly patients.

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

If more than one topical ophthalmic drug is to be used, the different drugs should be instilled 5-15 minutes apart.

Use in renal and hepatic impairment

Brimogen has not been studied in patients with hepatic or renal impairment (see section 4.4).

Paediatric population

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

Brimogen is not recommended for use in children below 12 years and it is contraindicated in neonates and infants (less than 2 years of age) (see sections 4.3, 4.4 and 4.9). It is known that severe adverse reactions can occur in neonates.

The safety and efficacy in children have not been established.

Method of administration

Ocular use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Neonates and infants (less than 2 years of age) (see section 4.8).
- Patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).

4.4 Special warnings and precautions for use

Children of 2 years of age and above, especially those in the 2-7 age range and/or weighing ≤ 20 kg, should be treated with caution and closely monitored due to the high incidence and severity of somnolence (see section 4.8).

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

Some (12.7%) patients in clinical trials experienced an ocular allergic type reaction (see section 4.8 for details). If allergic reactions are observed, treatment with Brimogen should be discontinued.

Delayed ocular hypersensitivity reactions have been reported with brimionidine tartrate containing eye drops with some reported to be associated with an increase in IOP.

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

Brimogen has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

Preservative

Brimogen eye drops, solution contains 0.05 mg benzalkonium chloride in each ml.

Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. Patient should remove contact lenses before using this medicine and put them back 15 minutes afterwards.

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

From the limited data available, there is no difference in the adverse event profile in children compared to adults.

Generally, however, eyes in children show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children.

4.5 Interaction with other medicinal products and other forms of interaction

Brimogen is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin), (see section 4.3).

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

No data on the level of circulating catecholamines after Brimogen administration are available. Caution, however, is advised in patients taking medications which can affect the metabolism and uptake of circulating amines e.g. chlorpromazine, methylphenidate, reserpine.

After the application of brimonidine tartrate containing 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 Brimogen.

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).

4.6 Fertility, pregnancy and lactation

Pregnancy

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. Brimogen should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus.

Lactation

It is not known if brimonidine is excreted in human milk. The compound is excreted in the milk of the lactating rat. Brimogen should not be used by women nursing infants.

4.7 Effects on ability to drive and use machines

This product may cause fatigue and/or drowsiness, which may impair the ability to drive or operate machinery. This product 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.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

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	($\geq 1/10$)
Common	($\geq 1/100$ to $< 1/10$)
Uncommon	($\geq 1/1,000$ to $< 1/100$)
Rare	($\geq 1/10,000$ to $< 1/1,000$)
Very rare	($< 1/10,000$)

Not known	(Frequency cannot be estimated from the available data)
-----------	---

System Organ Class	Frequency	Adverse Reaction
Immune system disorders	Uncommon	Systemic allergic reactions
Psychiatric disorders	Uncommon	Depression
	Very rare	Insomnia
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.
Cardiac disorders	Uncommon	Palpitations/arrhythmias (including bradycardia and tachycardia).
Vascular disorders	Very rare	Hypertension, hypotension.
Respiratory, thoracic and mediastinal disorders	Common	Upper respiratory symptoms
	Uncommon	Nasal dryness
	Rare	Dyspnoea
Gastrointestinal disorders	Very common	Oral dryness
	Common	Gastrointestinal symptoms
General disorders and administration site conditions	Very common	Fatigue
	Common	Asthenia

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

System Organ Class	Frequency	Adverse Reaction
Eye disorders	Not known	Iridocyclitis (anterior uveitis), eyelid pruritus.
Skin and subcutaneous tissue disorders	Not known	Skin reaction including erythema, face oedema, pruritus, rash and vasodilatation.

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, lethargy, somnolence, hypotension, hypotonia, bradycardia, hypothermia, cyanosis, pallor, respiratory depression and apnea have been reported in neonates and infants receiving brimonidine (see section 4.3).

In a 3-month, phase 3 study in children aged 2-7 years with glaucoma, inadequately controlled by beta-blockers, a high prevalence of somnolence (55%) was reported with brimonidine 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 ≤ 20 kg (63%) compared to those weighing > 20 kg (25%) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

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.

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, apnea, hypotonia, hypothermia, respiratory depression and seizure.

Paediatric population

Reports of serious adverse effects following inadvertent ingestion of brimonidine eye drops by paediatric subjects have been published or reported. The subjects experienced symptoms of CNS depression, typically temporary coma or low level of consciousness, lethargy, somnolence, hypotonia, bradycardia, hypothermia, pallor, respiratory depression and apnea, 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sympathomimetics in glaucoma therapy, ATC code: S01EA05.

Brimonidine is an alpha-2 adrenergic receptor agonist that is 1000-fold more selective for the alpha-2 adrenoceptor than the alpha-1 adrenoceptor.

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.

Topically applied brimonidine tartrate has a rapid onset of action, with peak ocular hypotensive effect seen at two hours post-dosing. In two 1-year studies, brimonidine tartrate containing eye drops 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 Brimogen may lower IOP by reducing aqueous humour formation and enhancing uveoscleral outflow.

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

5.2 Pharmacokinetic properties

a) General characteristics

After ocular administration of a 0.2% solution twice daily for 10 days, plasma concentrations were low (mean C_{max} was 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 tartrate containing eye drops for up to one year, nor was significant ocular toxicity found during a one year ocular safety study in monkeys given approximately four times the recommended dose of brimonidine tartrate.

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

Kinetics profile:

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

b) Characteristics in patients

Characteristics in elderly patients:

The C_{max} , AUC, and apparent half-life of brimonidine are similar in the elderly (subjects aged 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.

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Poly(vinyl alcohol)
Sodium chloride
Sodium citrate
Citric acid monohydrate
Hydrochloric acid (for pH-adjustment) or
Sodium hydroxide (for pH-adjustment)
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 2 years
After first opening: 28 days

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

White low density polyethylene dropper bottles with low density polyethylene dropper tips and white high density polyethylene screw caps.

Each bottle contains 5 ml solution.
Pack sizes: 1 x 5 ml, 3 x 5 ml and 6 x 5 ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

Date of latest renewal: {DD month YYYY}

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

<[To be completed nationally]>