SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Brimonidine Tartrate 0.2% w/v Eye Drops.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Brimonidine tartrate 0.2% w/v (2.0 mg/ml).

Excipient with known effect

Benzalkonium chloride 0.005% w/v.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.

Clear, greenish-yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For 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 contra-indicated.

- As adjunctive therapy to other intraocular pressure lowering medications when the target intraocular pressure is not achieved with a single agent. (See section 5.1)

4.2 Posology and method of administration

Posology

Paediatric population

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

Brimonidine eye drops should not be used in children aged below 12 years and are contraindicated in neonates and infants (less than 2 years of age) (see sections 4.3, 4.4 & 4.9). It is known that severe adverse reactions can occur in neonates. The safety and efficacy of brimonidine has not been established in children.

Adults including the elderly:

One drop into the affected eye(s) twice daily, approximately 12 hours apart. No dosage adjustment is required in elderly patients.

To reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctal occlusion) for one minute immediately after the instillation of each drop.

If more than one topical ophthalmic drug is to be administered, they should be instilled 5 to 15 minutes apart.

Patients with renal and hepatic impairment:

Brimonidine eye drops have not been studied in patients with renal or hepatic impairment (see section 4.4).

Method of administration

Precautions to be taken before handling or administering the medicinal product

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

Contraindicated in neonates and infants.(See section 4.8)

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

4.4 Special warnings and precautions for use

Paediatric population

Children of 2 years of age and above, especially those in the 2 to 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 is required in treating patients with:

- severe or unstable and uncontrolled cardiovascular disease.
- depression
- cerebral or coronary insufficiency
- Raynaud's phenomenon
- orthostatic hypotension
- thromboangiitis obliterans

The use of Brimonidine Eye Drops has not been studied in patients with hepatic or renal impairment, therefore, caution should be exercised when treating such patients.

It is reported that some patients (12.7%) in clinical trials experienced ocular allergic type reaction with brimonidine eye drops (see section 4.8); if allergic reactions are apparent, treatment should be discontinued.

Delayed ocular hypersensitivity reactions have been reported with Brimonidine Eye Drops, with some reported to be associated with an increase in IOP.

Contact lenses

Brimonidine eye drops contain 0.05mg/ml benzalkonium chloride as preservative which may be deposited in soft contact lenses. Hence, Brimonidine eye drops should not be used while wearing these lenses. The lenses should be removed before instillation of the drops and not reinserted earlier than 15 minutes after use.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenagic transmission (e.g. tricyclic antidepressants and miaserin), (see section 4.3).

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

Although no actual data on the level of circulating catecholamines after administration of brimonidine eye drops are available, caution is advised when using the eye drops in patients who are taking medications which can affect the metabolism and uptake of circulating amines, eg. chlorpromazine, methylphenidate, reserpine.

After application of brimonidine eye drops, clinically insignificant decreases in blood pressure have been reported in some patients. Caution is therefore advised when using drugs such as antihypertenstives and/or cardiac glycosides concomitantly with brimonidine eye drops.

Caution is advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of pharmaceutical form) which may interact with α-adrenergic agonists or interfere with their activity, ie. agonists or antagonists of the adrenergic receptor, eg. 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. Brimonidine eye drops should only be used during pregnancy if the potential benefit to the mother outweighs the potential risk to the foetus.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

Brimonidine eye drops may cause fatigue and/or drowsiness which may impair the ability to drive or to use machinery. They may also 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 operating machinery.

4.8 Undesirable effects

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 nature serious enough to require discontinuation of treatment.

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

The following convention has been used for classification of frequency of undesirable 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.

Not known (cannot be estimated from the available data)

Within each frequency grouping, undesired 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, allergic blepharitis, allergic blepharoconjuctivitis, 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 (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.

The following adverse reactions have been identified during post-marketing use of Brimonidine eye drops 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 reaction including erythema, face oedema, pruritus, rash and vasodilation
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 apnoea, lethargy, somnolence, pallor and respiratory depression have been reported in neonates and infants receiving brimonidine (see section 4.3).

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 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 ≤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 www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google Play or Apple App Store.

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, apnoea, hypotonia, hypothermia, respiratory depression and seizure

Paediatric population

Reports of serious adverse effects following inadvertent ingestion of brimonidine eye drops have been published/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 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.

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code, S01E A 05. Sympathomimetics in glaucoma therapy.

Brimondine 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 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 seen at 2 hours post-dosing. In two 1 year studies, brimonidine has been shown to lower intraocular pressure by mean values of approximately 4-6 mmHg.

Flourophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action. It is thought that it may lower intraocular pressure by reducing aqueous humour formation and enhancing uveoscleral outflow.

Clinical trials 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 additive effect in combination with travoprost (6 weeks) and latanoprost (3 months).

5.2 Pharmacokinetic properties

a) General characteristics:

It is reported that after ocular administration of a 0.2% solution twice daily for 10 days, plasma concentrations are low (mean Cmax 0.06 ng/ml). There is a slight accumulation in the blood after multiple instillations (twice daily for 10 days). $AUC_{0\text{-}12h}$ at steady stated is reported as 0.31 nghr/ml, compared to 0.23 nghr/ml after the initial dose. The mean apparent half-life in the systemic circulation was approximately 3 hours in humans after topical dosing. 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. It is reported that 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.

Kinetics profile:

No great deviation from dose proportionality for plasma Cmax and AUC has been observed following a single topical dose of 0.08%, 0.2% and 0.5%.

b) Characteristics in patients:

The C_{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 months clinical study, which included elderly patients, it is reported that 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, genotoxicty, carcinogenic potential, toxicity to reproduction.

6. Pharmaceutical particulars

6.1 List of excipients

Benzalkonium chloride

Polyvinyl alcohol

Sodium citrate

Citric acid anhydrous

Sodium chloride

Sodium hydroxide (to adjust pH)

Water for injection

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Before first opening : 2 years.

After first opening : 28 days.

6.4 Special precautions for storage

For storage conditions before and after first opening of the medicinal product, see section 6.3. Do not store above 25ºC.

6.5 Nature and contents of container

5 ml low density polyethylene dropper bottle with polystyrene cap.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 15872/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/10/2024

10 DATE OF REVISION OF THE TEXT

21/10/2024