SUMMARY OF PRODUCT CHARACTERISTICS

BROMOLON

(Brimonidine Tartrate 0.2% w/v Eye Drops)

1. Name of the medicinal product

BROMOLON

2. Qualitative and quantitative composition

Brimonidine Tartrate Ph. Eur. ……0.2 % w/v

Aqueous vehicle…….q.s.

Benzalkonium Chloride (As preservative)……Ph. Eur. (0.005 % w/v)

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Eye Drops, solution.

Clear, greenish-yellow solution, free from visible particulate matter.

4. Clinical particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Paediatric population

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)

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.

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 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.

The Brimonidine eye drops contain benzalkonium chloride as preservative, which may cause eye irritation. Remove contact lenses prior to application and wait at least 15minutes before reinserting. Known to discolour soft contact lenses.

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 noradrenergic transmission (e.g. tricyclic antidepressants and miaserin).

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 antihypertensive 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 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. Brimonidine eye drops should only be used during pregnancy if the potential benefit to the mother outweighs the potential risk to the foetus.

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.

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.

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%).

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 micro vessels associated with human retinal xenografts.

Topical administration of brimonidine tartrate decreases intraocular pressure in humans with minimal effect on cardiovascular or pulmonary parameters.

5.2 Pharmacokinetic properties

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). AUC0-12h 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%.

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

Polyvinyl alcohol

Sodium citrate

Citric acid anhydrous

Sodium chloride

Sodium hydroxide (to adjust pH)

Water for injection

6.2 Incompatibilities

Benzalkonium chloride may be deposited in and is known to discolour soft contact lenses. These lenses should therefore be removed before instillation of the eye drops and not reinserted earlier than 15 minutes after use.

6.3 Shelf life

Unopened: 2 years.

Opened: 28 days

6.4 Special precautions for storage

Store in dry place below 30°C, Protect from light.

6.5 Nature and contents of container

Clear, greenish-yellow solution, free from visible particulate matter, is filled in 5 mL labelled LDPE vial provided with spike HIPS cap packed in an overprinted carton with leaflet.

Special precautions for disposal and other handling

No special instructions.

7 MARKETING AUTHORISATION HOLDER

Bliss GVS Pharma Ltd.

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