

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Brimonidine 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(s): Contains benzalkonium chloride 0.05 mg/ml.

For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear, colourless to pale yellow 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

*Recommended dosage in adults (including the elderly)*

The recommended dose is one drop of Brimonidine 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 (punctal 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*

Brimonidine has not been studied in patients with hepatic or renal impairment (see section

4.4).

#### *Use in paediatric subjects*

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

Brimonidine is not recommended for use in children below 12 years and 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 of Brimonidine have not been established in children.

### **4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- Neonates and infants (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 with Brimonidine (see section 4.8 for details). If allergic reactions are observed, treatment with Brimonidine should be discontinued.

Delayed ocular hypersensitivity reactions have been reported with Brimonidine 2 mg/ml, with some reported to be associated with an increase in IOP

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

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

The preservative in Brimonidine, benzalkonium chloride, 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.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Brimonidine 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 Brimonidine, 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 Brimonidine 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, 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 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 e.g. (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 should be used during pregnancy only 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 should not be used by women nursing infants.

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

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

#### **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 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.

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 (cannot be estimated from the available data).

### *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 (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

### *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 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 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 apnoea 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  $\leq 20$  kg (63%) compared to those weighing  $>20$  kg (25%) (see section 4.4).

## **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 an oral overdose includes supportive and symptomatic therapy; patient's airway 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 by paediatric subjects have been published or reported to Marketing Authorization Holder. 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**

Pharmacotherapeutic group: Sympathomimetics in glaucoma therapy, ATC code = S01EA 05.

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.

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

Clinical trials show that Brimonidine is effective in combination with topical beta-blockers. Shorter term studies also suggest that Brimonidine has 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<sub>max</sub> 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 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 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

Polyvinyl alcohol

Sodium chloride

Sodium citrate

Citric acid monohydrate

Sodium hydroxide (for pH-adjustment) or

Hydrochloric acid (for pH-adjustment)

Water for injections

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

Before first opening: 3 years

After first opening: 4 weeks

## **6.4 Special precautions for storage**

Before first opening of the bottle: This medicinal product does not require any special storage conditions

After first opening of the bottle: Do not store above 30°C

## **6.5 Nature and contents of container and special equipment for use, administration or implantation**

5ml BFS (Blow Fill Seal) low density polyethylene bottle with a purple polypropylene spiked screw cap. Upon piercing, the bottle delivers a drop size of approximately 35 microlitres

10ml BFS (Blow Fill Seal) low density polyethylene bottle with a blue polypropylene spiked screw cap. Upon piercing, the bottle delivers a drop size of approximately 35 microlitres

Pack sizes of 1, 3 and 6 bottles.

For the 3 or 6 pack sizes, there will be 3 or 6 cartons, each containing a single bottle of Brimonidine eye drops, packaged in a larger outer carton.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**



No special requirements.

*Using the drops for the first time:* These eye drops come in a bottle with a screw cap. The inside of the screw cap contains a spike. The screw cap is fitted to the bottle in such a way that there is no contact between the spike and the top of the bottle. In order to open the bottle it is necessary to tighten the screw cap further, so that the edge of the screw cap and the bottle edge are totally aligned. At this point the screw cap spike will pierce the top of the bottle which will open the bottle. Once the bottle has been opened in this way, unscrew the screw cap fully to remove it from the bottle and apply the eye drops.

## **7. MARKETING AUTHORISATION HOLDER**

Brown & Burk UK Ltd

5, Marryat Close

Hounslow West

Middlesex

TW4 5DQ

UK

## **8. MARKETING AUTHORISATION NUMBER(S)**

Uk: PL 25298/0045

SE: MTnr 43698

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

2011-06-08

## **10. DATE OF REVISION OF THE TEXT**

2012-04-27