

## Summary of Product Characteristics

### 1 NAME OF THE MEDICINAL PRODUCT

Brimon 2 mg/ml Eye Drops, Solution

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2 mg brimonidine tartrate (equivalent to brimonidine base 1.3 mg/ml).

Excipient(s) 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, colourless to 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

*Recommended dosage in adults (including the elderly)*

The recommended dose is one drop of Brimon 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 population*

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 section 4.3, section 4.4 and section 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

- Neonates and infants (see section 4.8)
- Hypersensitivity to brimonidine tartrate or to any of the excipients listed in section 6.1.
- Concomitant treatment with monoamine oxidase (MAO) inhibitor therapy
- Concomitant treatment with antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).

### 4.4 Special warnings and precautions for use

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 Brimon should be discontinued.

Delayed ocular hypersensitivity reactions have been reported with brimonidine 0.2% reference product, with some reported to be associated with an increase in IOP.

Brimon 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; such patients should be treated with caution.

#### *Paediatric population*

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 of somnolence (see section 4.8).

The preservative in Brimon, benzalkonium chloride, may cause eye irritation.

Avoid contact with soft contact lenses. Contact lenses should be removed prior to application. It has to be waited at least 15 minutes before reinsertion. Known to discolour soft contact lenses.

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

Brimon 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 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. Brimon should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the foetus.

Breastfeeding

It is unknown whether brimonidine is excreted in human milk. Animal studies have shown excretion of brimonidine in rat’s breast milk. Brimon 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. It 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 ( ≥1/10); Common (≥ 1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very rare (<1/10,000), not known (cannot be estimated from the available data).

<u>Immune system disorders</u>	<i>Uncommon:</i> (≥1/1,000 to <1/100)	- Systemic allergic reactions
<u>Psychiatric disorders</u>	<i>Uncommon:</i> (≥1/1,000 to <1/100)	- Depression
	<i>Very Rare:</i> (<1/10,000)	- Insomnia
<u>Nervous system disorders</u>	<i>Very Common:</i> (≥1/10)	- Headache - Drowsiness
	<i>Common:</i> (≥1/100 to <1/10)	- Dizziness - Abnormal taste
	<i>Very Rare:</i> (<1/10,000)	- Syncope
<u>Eye disorders</u>	<i>Very Common:</i> (≥1 /10)	- Ocular irritation including allergic reactions (hyperaemia, burning and stinging, pruritis, foreign body sensation, conjunctival follicles). - Blurred vision. - allergic blepharitis, allergic blepharoconjunctivitis, allergic conjunctivitis, ocular allergic reaction, and follicular conjunctivitis
	<i>Common:</i> (≥1/100 to <1/10)	- Local irritation (eyelid hyperaemia and oedema, blepharitis, conjunctival oedema and discharge,

		ocular pain and tearing). <ul style="list-style-type: none"><li>- Photophobia</li><li>- Corneal erosion and staining</li><li>- Ocular dryness</li><li>- Conjunctival blanching</li><li>- Abnormal vision</li><li>- Conjunctivitis.</li></ul>
	<i>Very Rare:</i> ( $<1/10,000$ )	<ul style="list-style-type: none"><li>- Iritis (anterior uveitis)</li><li>- Miosis</li></ul>
<u>Cardiac disorders</u>	<i>Uncommon:</i> ( $\geq 1/1,000$ to $<1/100$ )	<ul style="list-style-type: none"><li>- Palpitations/arrythmias (including bradycardia and tachycardia)</li></ul>
<u>Vascular disorders</u>	<i>Very Rare:</i> ( $<1/10,000$ )	<ul style="list-style-type: none"><li>- Hypertension</li><li>- Hypotension</li></ul>
<u>Respiratory, thoracic and mediastinal disorders</u>	<i>Common:</i> ( $\geq 1/100$ to $<1/10$ )	<ul style="list-style-type: none"><li>- Upper respiratory symptoms</li></ul>
	<i>Uncommon:</i> ( $\geq 1/1,000$ to $<1/100$ )	<ul style="list-style-type: none"><li>- Nasal dryness</li></ul>
	<i>Rare:</i> ( $\geq 1/10,000$ to $<1/1,000$ )	<ul style="list-style-type: none"><li>- Dyspnoea</li></ul>
<u>Gastrointestinal disorders</u>	<i>Very Common:</i> ( $\geq 1/10$ )	<ul style="list-style-type: none"><li>- Oral dryness</li></ul>
	<i>Common:</i> ( $\geq 1/100$ to $<1/10$ )	<ul style="list-style-type: none"><li>- Gastrointestinal symptoms</li></ul>
<u>General disorders and administrative site conditions</u>	<i>Very Common:</i> ( $\geq 1/10$ )	<ul style="list-style-type: none"><li>- Fatigue</li></ul>
	<i>Common:</i> ( $\geq 1/100$ to $<1/10$ )	<ul style="list-style-type: none"><li>- Asthenia</li></ul>

The following adverse reactions have been identified during post-marketing use of brimonidine 0.2% reference product 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, hypotension, hypotonia, bradycardia, hypothermia, cyanosis 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, apnea, 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. 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: S01EA05

Brimonidine is an alpha-2 adrenergic receptor agonist that is 1000-fold more selective for the alpha-2 adrenoceptor than the alpha-1 adrenoreceptor. 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 eye drops have a rapid onset of action, with peak ocular hypotensive effect seen at two hours post-dosing. In two 1 year studies, these 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 brimonidine may lower IOP 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 these 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 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, dihydrate  
Citric acid, monohydrate  
Water for injection  
Hydrochloric acid and sodium hydroxide to adjust pH.

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

Unopened: 2 years.

After first opening: Chemical, physical and microbiological in use stability has been demonstrated for 28 days.

## **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions

## **6.5 Nature and contents of container**

White, opaque, sterile, plastic bottle for ophthalmic made of polyethylene with sterile plastic dropper and sterile cap made of polyethylene: 5 ml x1, 5 ml x 2, 5 ml x3 and 5 ml x6.

Not all pack sizes may be marketed.

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

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Rowex Ltd  
Newtown  
Bantry  
County Cork

## **8 MARKETING AUTHORISATION NUMBER**

PA 711/119/1

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

Date of First Authorisation: 12th October 2007

Date of last renewal: 8th June 2012

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

April 2013