Professional Information for Medicines for Human Use

APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

AGOBRIM EYE DROPS 0,2 % *w/v* EYE DROPS.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AGOBRIM EYE DROPS 0,2 % *w/v* EYE DROPS.

Each vial contains Brimonidine tartrate 0,2 % w/v equivalent to (2,0 mg/mL) of AGOBRIM EYE DROPS Ophthalmic solution.

Excipients with known effect: Preservative: Benzalkonium Chloride 0,005 % *w/v*.

For full list of excipients, (See section 6.1)

3. PHARMACEUTICAL FORM

AGOBRIM EYE DROPS (Brimonidine Tartrate Eye Drops 0,2 % *w/v* BP) is clear greenish yellow solution, practically free from visible particle.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

AGOBRIM EYE DROPS is indicated for the lowering of intraocular pressure in patients with open angle glaucoma or ocular hypertension.

4.2. Posology and method of administration

The recommended dose is one drop of AGOBRIM EYE DROPS in the affected eye(s) twice daily, approximately 12 hours apart.

AGOBRIM EYE DROPS may be used concomitantly with other topical ophthalmic medicinal products to lower intraocular pressure. If more than one topical ophthalmic product is being used, the product should be administered at least 5 minutes apart.

Method of administration:

Ocular use.

4.3. Contraindications

AGOBRIM EYE DROPS is contraindicated in patients who have exhibited a hypersensitivity to brimonidine tartrate, benzalkonium chloride or to any of the excipients listed in section 6.1.

AGOBRIM EYE DROPS is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

Safety and efficacy of AGOBRIM EYE DROPS in children younger than 2 years of age has not been established. However due to potentially serious adverse central nervous system effects, including apnoea and lethargy, reported in infants treated with topical brimonidine tartrate, the use of AGOBRIM EYE DROPS is not recommended for use in paediatric patients under the age of two. (see section 4.8).

4.4. Special warnings and precautions for use

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 and severity of somnolence (see section 4.8).

Cardiac disorders

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

Eye disorders

If allergic reactions are observed, treatment with AGOBRIM EYE DROPS should be discontinued.

Delayed ocular hypersensitivity reactions have been reported with brimonidine, as contained in AGOBRIM EYE DROPS**,** with some reported to be associated with an increase in IOP.

The use of AGOBRIM EYE DROPS may result in dry eyes and therefore should be used with caution in patients with dry eye syndrome.

Vascular disorders

Brimonidine, as contained in AGOBRIM EYE DROPS should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangitis obliterans.

Hepatic and renal insufficiency

Brimonidine , as contained in AGOBRIM EYE DROPS has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

Benzalkonium chloride

The preservative in AGOBRIM EYE DROPS, benzalkonium chloride, may cause eye irritation, symptoms of dry eyes, and may affect the tear film and corneal surface. Patients should remove contact

lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses. Patients should avoid contact with soft contact lenses.

AGOBRIM EYE DROPS 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 medicines and other forms of interaction

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

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

There is no information available regarding the level of circulating catecholamines after AGOBRIM EYE DROPS administration. Caution, however, is advised in patients taking medications which can affect the metabolism and uptake of circulating amines e.g., chlorpromazine, methylphenidate, reserpine and tricyclic antidepressants may affect the metabolism and uptake of circulating amines.

After the application of AGOBRIM EYE DROPS, insignificant decreases in blood pressure were noted in some patients.

Caution is advised when using medicines such as antihypertensives and/or cardiac glycosides (i.e digoxin) concomitantly with AGOBRIM EYE DROPS.

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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 i.e., agonists or antagonists of the adrenergic receptor e.g. (isoprenaline, prazosin, beta-blockers, anti-hypertensives). Alpha-agonists, as a class, may reduce pulse and blood pressure.

4.6. Fertility, pregnancy, and lactation

Pregnancy

The safety of use during human pregnancy has not been established.

AGOBRIM EYE DROPS should not be used during pregnancy.

Breast-feeding

It is not known if brimonidine is excreted in human milk. AGOBRIM EYE DROPS should not be used by women nursing infants.

Fertility

No data is available

4.7. Effects on ability to drive and use machines

AGOBRIM EYE DROPS may cause fatigue and/or drowsiness, which may impair the ability to drive or operate machinery. AGOBRIM EYE DROPS 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 reported ADRs are oral dryness, ocular hyperaemia, and burning/stinging. They are usually transient and not commonly of a severity requiring discontinuation of treatment.

Adverse reactions reported are included in the table below.

a. Tabulated list of adverse reactions

Skin and subcutaneous tissue disorders	
• Eyelid erythema, • Eyelid oedema, • Rash	Frequent
• Eye Pruritus, • Vasodilatation	Frequency not known
Immune system disorders	
• Allergic reactions	Frequent
Psychiatric disorders	
• Insomnia, depression, anxiety, syncope.	Less frequent

Nervous system disorders	
• Headache, • Dizziness	Frequent
• Taste perversion, • Somnolence in adults and infants.	Less frequent
Eye disorders	
• Conjunctival hyperaemia, Eye pruritus, Allergic conjunctivitis. • Burning sensation, • Stinging, foreign body sensation, • Follicular conjunctivitis, • Photophobia, • Eye pain, • Eye dryness, • Conjunctival oedema, • Blepharitis, • Eye irritation, • Eye discharge, • Conjunctival haemorrhage. • Conjunctival folliculosis, • Conjunctivitis, • Epiphora, • Visual field defects, visual disturbances, • Worsened visual acuity, • Superficial punctate keratopathy, • Vitreous floaters.	Frequent
• Corneal erosion.	Less frequent
• Iritis, • Miosis	Frequency not known

Cardiac disorders	
• Palpitations	Less frequent
• Bradycardia in adults and infants, tachycardia.	Frequency not known
Vascular disorders	
• Hypertension	Frequent
• Hypotension in adults and infants.	Frequency not known
Respiratory, thoracic, and mediastinal disorders	
• Cough, dyspnoea	Frequent
• Nasal dryness	Less frequent
• Apnoea in infants.	Frequency not known
Infections and infestations	
• Sinusitis, • Sinus infection, • Flu syndrome, • Bronchitis, • Rhinitis, • Pharyngitis	Frequent
General disorders and administration site conditions	
• Asthenia	Frequent
• Hypothermia in infants	Frequency not known
Musculoskeletal disorders	
• Hypotonia in infants	Frequency not known

f. 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 medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: ttps://www/sahpra.org.za/Publications/Index/8

4.9. Overdose

Treatment, in the event of an oral overdose, includes supportive and symptomatic therapy. A patent airway should be maintained.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological Classification: A.15.4 Ophthalmic preparations. Other.

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 adrenoreceptor.

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 (IOP) in humans with minimal effect on cardiovascular or pulmonary parameters.

Limited data are available for patients with bronchial asthma showing no adverse effects.

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

5.2 Pharmacokinetic properties

a) General characteristics

After ocular administration of either 0,1 % or a 0,2 % solution twice daily for 10 days, plasma

concentrations were low (mean C_{max} was 0.06 ng/mL). Peak ocular hypotensive effect occurs at two hours post-dosing. 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 (AUC0-12h) 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 bio microscopic examination of eyes in patients treated with AGOBRIM 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. A major part of the dose (around 75 % of the dose) was excreted as metabolites in urine within five days; no unchanged medicine 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 was observed following a single topical dose of 0,08 %, 0,2 % and 0,5 %.

b) Characteristics in patients

Characteristics in elderly patients:

The Cmax, 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 extremely low.

Following topical ocular administration of 0.2 % brimonidine solution, plasma concentrations peaked within 0,5 to 2,5 hours and declined with a systemic half life of approximately 2 hours. Systemic

metabolism of brimonidine in humans is extensive and occurs primarily by the liver. The major route of elimination of the medicine and its metabolites is by urinary excretion.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Benzalkonium chloride Ph. Eur.

Polyvinyl alcohol Ph. Eur.

Sodium citrate Dihydrate Ph. Eur.

Citric acid Ph. Eur.

Sodium chloride Ph. Eur.

Sodium hydroxide Ph. Eur.

Water for injection Ph. Eur.

6.2. Incompatibilities

Not Applicable

6.3. Shelf life

Proposed shelf-life for unopened vial: 24 months.

Proposed shelf-life for opened vial: 28 days

6.4. Special precautions for storage

Store at or below 30 °C.

Protect from light.

Discard after 28 days of opening the vial.

Keep all medicines out of the reach and sight of children.

6.5. Nature and contents of container

LDPE vial

A clear greenish yellow solution, practically free from visible particle.

5mL solution filled in 5mL clear translucent LDPE vial with white HIPS cap.

6.6. Special precautions for disposal and handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Discard after 28 days of opening the vial.

7. HOLDER OF CERTIFICATE OF REGISTRATION

FDC SA (PTY) LTD

Unit J3, Willows Office Park

Farm Road, The Willows

Pretoria, 0081

South Africa

8. REGISTRATION NUMBER (S):47/15.4/0706

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