BRIMONIDINE TARTRATE 0.2%W/V/EYE DROPS

PL 15872/0018

UKPAR

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LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted FDC International Limited a Marketing Authorisation (licence) for the medicinal product Brimonidine Tartrate 0.2%w/v Eye Drops (PL 15872/0018) on 26th March 2010. This is a prescription-only medicine (POM).

Brimonidine Tartrate 0.2%w/v Eye Drops are a sterile, preserved solution used as eye drops. The active ingredient brimonidine tartrate works by reducing pressure within the eyeball. It is used to reduce pressure in the eye in the conditions of glaucoma or ocular hypertension. The medicine may be used alone or in conjunction with another eye drop that reduces pressure in the eye.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Brimonidine Tartrate 0.2%w/v Eye Drops outweigh the risks; hence a Marketing Authorisation has been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a Marketing Authorisation for the medicinal product Brimonidine Tartrate 0.2% w/v Eye Drops to FDC International Limited on 26th March 2010. This product is a prescription-only medicine.

This application was submitted as an abridged application according to Article 10(1) of Directive 2001/83/EC. The products are claimed to be generic medicinal products of the original, Alphagan 0.2% w/v (2 mg/ml) eye drops, solution (PL 00426/0088), which has been licensed to Allergan in the UK for more than 10 years (18th March 1997).

The product contains the active ingredient brimonidine tartrate. Brimonidine tartrate lowers high pressure in the eye, a problem caused by the condition known as open-angle glaucoma. It reduces production of the liquid that fills the eye ball, and it promotes drainage of this liquid.

No new clinical data are submitted. The requirements for applications for this type of are set out in the EMEA Note for Guidance 239/95 (on locally applied, locally acting products).

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP) and Environmental Risk Assessment (ERA). The lack of ERA is justified since the application is for a generic version of an approved product and it is not likely to change the total market of brimonidine tartrate.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Brimonidine Tartrate

INN: Brimonidine Tartrate

Structure

Molecular weight: 442.26
Molecular formula: $\text{C}_{11}\text{H}_{10}\text{BrN}_{5}\text{C}_{4}\text{H}_{6}\text{O}_{6}$
Chemical name: 5-Bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxaline tartrate
5-Bromo-6-(2-imidazolin-2-yl-amino)quinoxaline tartrate

Appearance: A white to yellowish crystalline substance.

The active substance brimonidine tartrate, is not subject to a European Pharmacopoeia monograph.

Manufacture

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance brimonidine tartrate.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active substance.

An appropriate specification is provided for the active substance brimonidine tartrate, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided for 3 consecutive batches and comply with the proposed specification. Suitable Certificates of Analysis have been provided for all reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in two low density polyethylene bags. Each bag is sealed with Nylon twist ties. Structural support is provided by a polyethylene drum that is not in
contact with the product. Appropriate declarations have been provided stating that
the primary packaging components comply with the food contact requirements of

Satisfactory specifications and certificates have been provided for all aspects of the
container-closure system.

Appropriate stability data have been generated for the drug substance and supports an
appropriate retest period when stored in the proposed packaging.

**DRUG PRODUCT**

**Other ingredients**
The drug product is presented as a clear, greenish-yellow solution.
Other ingredients consist of pharmaceutical excipients, benzalkonium chloride, polyvinyl alcohol,
sodium citrate, citric acid anhydrous, sodium chloride, sodium hydroxide (to adjust pH) and
purified water (water for injection). An appropriate justification for the inclusion of each
excipient has been provided.

All excipients used comply with their respective Ph.Eur monograph. Satisfactory certificates of
analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.

There were no novel excipients used and no overages.

**Product development**
The objective of the development programme was to produce a product that could be
considered a generic medicinal product of the brand leader Alphagan 0.2% w/v (2mg/ml)
eye drops solution which has been licensed to Allergan since March 1997. The excipients
are standard to eye drop formulations. The formulation is qualitatively the same as the
brand leader with the absence of HCL as a pH adjuster, but different quantitatively.
Appearance, pH and osmolality were selected as factors contributing to the design of the
proposed formulation.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of the product, along
with an appropriate account of the manufacturing process. Process validation data on three
batches of the finished product and have been provided and demonstrate compliance with
the release specification.

**Finished product specification**
The finished product specification is satisfactory. Acceptance limits have been justified
with respect to conventional pharmaceutical requirements and, where appropriate, safety.
Test methods have been described and have been adequately validated, as appropriate.
Batch data have been provided and comply with the release specification. Certificates of
Analysis have been provided for any working standards used.
Container Closure System
The product is filled in 5 ml low density polyethylene dropper (LDPE) bottle with polystyrene cap. Secondary packaging of the bottles is in white cardboard cartons.
Specifications and Certificates of Analysis for all packaging types used have been provided. The LDPE has shown compliance with the Ph Eur. monograph for polyethylene.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years, before first opening has been set, with the following special storage precautions, “Do not store above 25°C. Do not refrigerate”. After the first opening, the product has a shelf-life of 28 days. The same storage conditions apply as stated above.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA form
The MAA form is pharmaceutically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

This application for Brimonidine Tartrate 0.2% w/v Eye Drops was submitted as national abridged application, according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal product of Alphagan 0.2% eye Drops PL 00426/0088, first authorised to Allergan in the UK on the 18/03/97.

No new preclinical data have been supplied with this application and none are required for an application of this type.

A preclinical expert report has been written by a suitably qualified person and is satisfactory.

The Marketing Authorisation Holder has been provided adequate justification for not submitting an Environmental Risk Assessment.
CLINICAL ASSESSMENT

1. BACKGROUND
Brimonidine is an alpha2adrenoceptor agonist used to lower intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension (1). Brimonidine 0.2% (2 mg/ml) Eye Drops, like Alphagan® 0.2% Eye Drops, is proposed to be indicated for reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension as monotherapy when beta-blocker therapy is contraindicated and as adjunctive therapy to other IOP lowering medications when the target IOP is not achieved with a single agent.

Brimonidine 0.2% (2 mg/ml) Eye Drops are well established in the requested indication.

2. INDICATIONS
The applicant has submitted the following:

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.

The above is consistent with the indications licensed for the reference product and is satisfactory.

3. DOSE & DOSE SCHEDULE
The applicant has submitted the following:

Adolescents 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 (punctul 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.

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

Use in paediatric subjects:
No clinical studies have been performed in adolescents (12 to 17 years).
Brimonidine eye drops are not recommended for use in children 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.
The above is consistent with the posology licensed for the reference product and is satisfactory.

4. TOXICOLOGY
No new data are submitted and none are required for this type of application.

5. CLINICAL PHARMACOLOGY
No new data are submitted. The medical assessor agrees that no pharmacokinetic data are required for this product.

6. EFFICACY
No new data are submitted. The requirements for applications for this type of are set out in the EMEA Note for Guidance 239/95 (on locally applied, locally acting products). In principle clinical data are in principle necessary for such products unless an exemption can be justified.

The applicant states the following:

The FDC generic ophthalmic formulation of brimonidine 0.2% is an aqueous solution and contains the same active substance in the same concentration and the same excipients, benzalkonium chloride, polyvinyl alcohol, sodium citrate, citric acid anhydrous, sodium chloride, sodium hydroxide and water for injections, as those of the reference product, Alphagan 0.2% Eye Drops, licensed by Allergan Limited. These excipients are widely used, standard eye drop constituents of pharmacopoeial quality. In view of this no comparative bioavailability or bioequivalence studies have been conducted.

Brimonidine is a relatively lipophilic molecule and absorption into the cornea is rapid. Sufficient concentrations to activate $\alpha_2$-adrenoceptors are found in the anterior segment, aqueous humour and vitreous from the second hour (6). Following 2 weeks of treatment, concentrations of brimonidine in the iris, ciliary body and choroid retina have been reported to be 3-17 times greater than those observed after a single dose. Accumulation does not occur in the absence of melanin

Comparative analytical studies with the FDC and Allergan formulations have confirmed the appearance i.e. clear, greenish-yellow solution to be the same for both. The results of pH testing demonstrated the pH to be 6.3 for all three batches of the FDC formulation and close to that of 6.2 for one batch of Alphagan® 0.2% Eye Drops. Osmolality testing showed values of 302, 298 and 304 mOsm for the FDC formulation and 302 mOsm for Alphagan® 0.2% Eye Drops confirming their closeness. The similar pH and osmolality to that of the Allergan formulation should ensure the equally good local tolerability of the FDC formulation.

The active substance is in aqueous solution and in principle, as for orally and parenterally administered oral solutions, clinical trial data will not be required provided that there is no risk of any difference from the reference product in terms of safety or efficacy arising from any differences in excipients (e.g. affecting retention of the product at the cornea). The applicant has established that the physical properties of the two products are sufficiently comparable for this requirement to be met.
The medical assessor agrees that no clinical data are required for this product.

7. SAFETY
No new data are submitted. Similar issues to those relevant to efficacy apply. As the applicant has established that the physical properties of the two products are comparable it can be concluded that there are no safety issues.

8. EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory. It adequately addresses the issue of any differences in formulation that might affect the physical properties and performance of the product, supporting the assertion that clinical trials are not required.

9. SUMMARY OF PRODUCT CHARACTERISTICS, PATIENT INFORMATION LEAFLET (PIL) AND LABELS.
The SmPC, PIL and labelling are medically acceptable.

10. APPLICATION FORM (MAA)
The MAA is medically satisfactory.

11. DISCUSSION
The applicant has established that the physical properties of the two aqueous solution products are sufficiently comparable for there to be no requirement for clinical trial data as there is no risk of any difference from the reference product in terms of safety or efficacy arising from any differences in excipients (e.g. affecting retention of the product at the cornea).

12. MEDICAL CONCLUSION
It is recommended that a Marketing Authorisation is granted for this application.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Brimonidine Tartrate 0.2%w/v Eye Drops (PL 15872/0018) are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
Brimonidine tartrate is a well-known drug and has been used for many years. No bioequivalence studies have been performed and none are required for this application, as the product is an optical aqueous solution that is administered locally as well as acting locally.

No formal data on clinical efficacy or safety have been presented for this application and none are required.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is qualitatively the same as the brand leader with the absence of HCL as a pH adjuster, but different quantitatively. Extensive clinical experience with brimonidine tartrate, is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

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<td>1</td>
<td>The MHRA received the marketing authorisation application on 24&lt;sup&gt;th&lt;/sup&gt; June 2008.</td>
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<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 27&lt;sup&gt;th&lt;/sup&gt; June 2008.</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 27&lt;sup&gt;th&lt;/sup&gt; February 2009 and 5&lt;sup&gt;th&lt;/sup&gt; August 2009.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 30&lt;sup&gt;th&lt;/sup&gt; July 2009, 24&lt;sup&gt;th&lt;/sup&gt; September 2009 and 5&lt;sup&gt;th&lt;/sup&gt; March 2010.</td>
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<td>5</td>
<td>The application was determined on 26&lt;sup&gt;th&lt;/sup&gt; March 2010.</td>
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# STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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BRIMONIDINE TARTRATE 0.2% W/V/EYE DROPS
PL 15872/0018

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).
Excipients include Benzalkonium chloride 0.005% w/v. See section 6.1 for full list of excipients.

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

4.2 Posology and method of administration
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 (punctul 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.
Use in renal and hepatic impairment:
Brimonidine eye drops have not been studied in patients with renal or hepatic impairment (see section 4.4).
Use in paediatric subjects:
No clinical studies have been performed in adolescents (12 to 17 years).
Brimonidine eye drops are not recommended for use in children 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.

4.3 Contraindications
Contraindicated in neonates and infants.
Contraindicated in patients with known hypersensitivity to brimonidine tartrate or to any of the other ingredients.
Contraindicated in patients receiving monoamine oxidase inhibitor (MAOI) therapy or those on antidepressants which affect noradrenergic transmission (eg. 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 to 7 age range and/or weighing less than 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

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 bimonidine eye drops, clinically insignificant decreases in blood pressure have been reported in some patients. Caution is therefore advised when using drugs such as antihypertensives 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.

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.

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.
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.

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 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).

4.9 Overdose

Ophthalmic overdose:
There is no experience in adults, as it is unlikely that overdose would be experienced via the ophthalmic route. However, symptoms of brimonidine overdose (including loss of consciousness, hypotension, hypotonia, bradycardia, hypothermia, cyanosis and apnoea) have been reported in neonates and infants receiving brimonidine eye drops as part of medical treatment of congenital glaucoma.

Systemic overdose resulting from accidental ingestion:
Two cases of adverse effects following inadvertent ingestion of 9-10 drops of a brimonidine eye drop by adults have been reported; the subjects experienced a hypotensive episode, followed in one instance by rebound hypertension approximately 8 hours after ingestion. Both subjects were reported to have made a full recovery within 24 hours. No adverse effects were noted in a third subject who also ingested an unknown amount of brimonidine eye drops orally.

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, hypotonia, bradycardia, hypothermia 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.

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.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code, S01E A 05. Sympathomimetics 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 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.

Fluorophotometric 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_0-12h at steady state 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 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 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, 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)
Purified Water (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
Before and after first opening (see section 6.3): Do not store above 25°C. Do not refrigerate.

6.5 Nature and contents of container
5 ml low density polyethylene dropper bottle with polystyrene cap.

6.6 Special precautions for disposal
None.

7 MARKETING AUTHORISATION HOLDER
FDC International Ltd
Unit 6, Fulcrum 1
Solent Way, Whiteley
Fareham
Hampshire
PO15 7FE

8 MARKETING AUTHORITY NUMBER(S)
PL 15872/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26/03/2010

10 DATE OF REVISION OF THE TEXT
26/03/2010
PATIENT INFORMATION LEAFLET

BRIMONIDINE TARTRATE 0.2% W/V/EYE DROPS
PL 15872/0018

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Brimonidine tartrate

Please read this leaflet carefully before you start using this medicine.

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1. BEFORE YOU USE BRIMONIDINE

- Have your doctor or pharmacist
- Read the information leaflet
- Make sure you understand how to use it

2. IMPORTANT INFORMATION

- Store in a cool, dry place away from children
- Do not exceed the recommended dose
- If you have any doubts, consult your doctor or pharmacist

3. DIRECTIONS FOR USE

- Place one drop into the affected eye
- Repeat at the same time each day
- Do not use if the bottle is not clear
- Do not use if the solution is cloudy

4. POSSIBLE SIDE EFFECTS

- Redness or irritation
- Eye pain or discomfort
- Blurred vision
- Changes in vision

5. OVERDOSE

- Call your doctor or pharmacist
- Go to the nearest hospital

6. ADDITIONAL INFORMATION

- Do not use if the bottle is not clear
- Do not use if the solution is cloudy
- Do not use if you are allergic to any ingredient

7. LEGAL INFORMATION

- This leaflet is a summary of the safety and effectiveness of the product
- For full details, please refer to the product information leaflet

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If you use more Brimonidine than you should: In adults an overdose due to the use of the eye drops is unlikely. In children overdose has been reported in those receiving brimonidine as part of treatment for glaucoma. Contact your doctor immediately if a child develops signs of sleepiness, weakness, low temperature or breathing difficulties. If you use too many drops or if the eye drops are swallowed, seek medical attention. You should contact your doctor.

If you forget to use Brimonidine: Apply the drops as soon as you remember. However, if it is almost time for your next dose, do not double your dose and carry on with the normal schedule dose.

4. POSSIBLE SIDE EFFECTS
   Like all medicines, Brimonidine can cause side effects, although not everybody gets them. If you experience a rare or serious side effect, tell your doctor immediately.

   - Very common: these may affect more than 1 in 10 patients
     - allergic reaction in the eye causing eye redness, burning, stinging, itching or white spots on the membrane covering the inside of the eyelids or the eye, blurring vision, feeling or something in the eye, itching
     - nightshade, tiredness, dryness and dry mouth

   - Common: these may affect between 1 in 10 and 1 in 100 patients
     - changes in the surface of the eye, swollen or red eyelids, abnormal vision, sticky, weepy or watery eyes, sensitivity to light irritation, pain, swelling of the membrane covering the inside of the eyelids or the eye
     - dizziness, feeling or being sick, general weakness
     - cold-like symptoms or abnormal taste

   - Rare: these may affect between 1 in 100 and 1 in 1,000 patients
     - depression
     - palpitations or changes in heart rate
     - dry nose or general dryness

   - Very rare: these may affect less than 1 in 10,000 patients
     - eye inflammation or a reduction in pupil size
     - trouble, higher or lower blood pressure or sleeplessness

   If any of these affects are serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE BRIMONIDINE
   Do not store above 25°C. Do not refrigerate.
   Discontinue within 30 days of opening.
   Keep out of the reach of children.
   The product should not be used after the expiry date. (This is printed on both the bottle label and on the carton of the bottle is packed in)

6. FURTHER INFORMATION
   What Brimonidine contains
   Active ingredient is brimonidine tartrate 0.2% (0.2 mg/mL). Also contains: 0.065% benzalkonium chloride (as preservative), polyvinyl alcohol, sodium chloride, disodium phosphate, sodium bicarbonate and water for injection.

   What Brimonidine looks like and contents of the pack
   Each bottle contains 5 ml of the clear, greenish yellow solution, eye drops solution.

   Marketing Authorisation Holder and Manufacturer
   FDC International Ltd, Al-Unit 9, Pulman Industrial Estate, Newbury, Berkshire, RG40 9JE
   PL number: 15872/0018
   Hard to see or read the leaflet? Call +44(0) 1488 985222 for help.
   This leaflet was last approved in: 2011

   MODE OF USE
   (1) Cap with a spike
   (2) Bottle as received
   (3) Tighten the cap on the nozzle till the cap touches the shoulder.
   (4) Pierce bottle
   (5) The spike in the cap will pierce the tip of the bottle.
   (6) The spike in the cap will pierce the tip of the bottle.