Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alphagan 0.2% *w/v* (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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.

Product imported from Greece
Clear, greenish-yellow to light greenish-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 Alphagan 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
Alphagan 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).

Alphagan 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 Alphagan 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 Alphagan (see section 4.8 for details). If allergic reactions are observed, treatment with Alphagan should be discontinued.

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

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

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

The preservative in Alphagan, 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

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

Although specific drug interactions studies have not been conducted with Alphagan, 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 Alphagan 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 Alphagan, 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 Alphagan.

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).

4.6 Fertility, 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.

Alphagan 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. Alphagan should not be used by women nursing infants.

4.7 Effects on ability to drive and use machines

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

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 Alphagan 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 Alphagan 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 (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 Alphagan by paediatric subjects have been published or reported to Allergan. 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 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.

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

Clinical trials show that Alphagan is effective in combination with topical beta-blockers. Shorter term studies also suggest that Alphagan 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 Cmax 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 Alphagan 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 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 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
Poly (vinyl alcohol)
Sodium chloride
Sodium citrate
Citric acid monohydrate
Purified water
Hydrochloric acid (for pH-adjustment) or
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.
After first opening: use within 28 days.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

5ml white plastic dropper bottle with a purple screw cap in an over labeled carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

G & A Licensing Ltd
Ballymurray
Co. Roscommon

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1447/85/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th December 2010

10 DATE OF REVISION OF THE TEXT