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 with known effect
Contains benzalkonium chloride 0.05 mg/ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution (eye drops)
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

Posology

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.

Use in renal and hepatic impairment
Alphagan has not been studied in patients with hepatic or renal impairment (see section 4.4).

Paediatric population

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 aged 2 to 12 years.

Method of administration

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. This may result in a decrease of systemic side effects and an increase in local activity. To avoid contamination of the eye or eye drops do not allow the dropper tip to come into contact with any surface.

If more than one topical ophthalmic drug is to be used, the different drugs should be instilled 5-15 minutes apart

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Neonates and infants (less than 2 years of age) (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

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

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.

Vascular disorders

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

Hepatic and renal insufficiency

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

Benzalkonium chloride

The preservative in Alphagan, 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.

Alphagan 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 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

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. Alphagan should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the foetus. To reduce the systemic absorption, see section 4.2

Breast-feeding

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 25.9-31.2% 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).

Table 1: Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse reaction
Immune system disorders	Uncommon	Allergic reactions
Psychiatric disorders	Uncommon	Depression
	Very rare	Insomnia
Nervous system disorders	Very common	Headache
	Common	Dizziness Abnormal taste
Eye disorders	Very common	Ocular hyperaemia Burning and stinging Blurred vision Foreign body sensation Conjunctival folliculosis Pruritus Ocular allergic reaction (includes allergic blepharitis, allergic blepharoconjunctivitis, allergic conjunctivitis and follicular conjunctivitis)
	Common	Eyelid hyperaemia Eyelid oedema Blepharitis Conjunctival oedema Conjunctival discharge Eye pain Tearing Photophobia Eyelid erythema Corneal erosion and staining Eye dryness Conjunctival blanching Abnormal vision Conjunctivitis Eye irritation Conjunctival papillae
	Very rare	Iritis Miosis
Cardiac disorders	Uncommon	Palpitations/arrhythmias (including bradycardia and tachycardia)
Vascular disorders	Very rare	Hypertension Hypotension
Respiratory, thoracic and mediastinal disorders	Common	Upper respiratory symptoms
	Uncommon	Nasal dryness
	Rare	Dyspnoea

Gastrointestinal disorders	Very common	Oral dryness
	Common	Gastrointestinal symptoms
General disorders and administration site conditions	Very common	Fatigue/drowsiness
	Common	Asthenia

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.

Table 2: Adverse reactions identified during post-marketing use

System organ class	Adverse reaction
Eye disorders	Iritis Iridocyclitis (anterior uveitis) Miosis Conjunctivitis Eyelid pruritus
Skin and subcutaneous tissue disorders	Hypersensitivity Skin reaction including erythema, face oedema, pruritus, rash and vasodilatation
Cardiac disorders	Palpitations/arrhythmias (including bradycardia or tachycardia)
Psychiatric disorders	Depression
Vascular disorders	Hypotension Syncope

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).

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 medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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. 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

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; less than 5% unchanged drug was detected in urine based on semi-quantitative thin layer chromatography analysis. 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%.

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 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 dihydrate
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

Before first opening: 2 years for the 2.5 ml container.
3 years for the 5 ml and 10 ml containers.
After first opening: 28 days.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

White low density polyethylene dropper bottles with a 35 microlitre tip. The cap is either a conventional polystyrene screw cap or a Compliance Cap (C-Cap).

2.5 ml, 5 ml and 10 ml bottles in packs of 1, 3 or 6. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

AbbVie Ltd.
Maidenhead
SL6 4UB
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 41042/0052

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/09/2006

10 DATE OF REVISION OF THE TEXT

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