1 NAME OF THE MEDICINAL PRODUCT

ALPHAGAN® P

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

brimonidine tartrate 0.15% w/v
For the full list of excipients, see section 12.

3 PHARMACEUTICAL FORM

Eye drops, solution

4 INDICATIONS AND USAGE

ALPHAGAN P is indicated for lowering intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

5 DOSAGE AND ADMINISTRATION

The recommended dosage is one drop of **ALPHAGAN P** in the affected eye(s) three times daily, approximately 8 hours apart. **ALPHAGAN P** eye drops, solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart.

6 CONTRAINDICATIONS

6.1 Neonates and Infants (pediatric patients younger than 2 years old)

ALPHAGAN P is contraindicated in neonates and infants (pediatric patients younger than 2 years old) *[see Use in Specific Populations (10.3)]*.

6.2 Hypersensitivity Reactions

ALPHAGAN P is contraindicated in case of hypersensitivity to the active substance or to any of the excipients listed in section 12.

7 WARNINGS AND PRECAUTIONS

7.1 Potentiation of Vascular Insufficiency

ALPHAGAN P may potentiate syndromes associated with vascular insufficiency. **ALPHAGAN P** should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

7.2 Severe Cardiovascular Disease

Although brimonidine tartrate ophthalmic solution had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

7.3 Contamination of Topical Ophthalmic Products After Use

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. Do not touch the tip of the dispensing container to the eye or surrounding structures. Serious damage to the eye and

subsequent loss of vision may result from using contaminated solutions.

7.4 Effects on ability to drive and use machines

As with other similar medications, Alphagan P may cause fatigue and/or drowsiness in some patients. Patients who engage in activities such as driving and operating machinery should be cautioned of the potential for a decrease in mental alertness. Alphagan P may also cause blurred vision or visual disturbance in some patients. The patient should wait until these symptoms have cleared before driving or using machinery.

8 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Potentiation of Vascular Insufficiency *[see Warnings and Precautions (7.1)]*
- Severe Cardiovascular Disease *[see Warnings and Precautions (7.2)]*
- Contamination of Topical Ophthalmic Products after Use *[see Warnings and Precautions (7.3)]*
- Neonates and Infants (Pediatric Patients Younger than 2 Years Old) *[see Contraindications (6.1)]*

8.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions occurring in approximately 10% to 20% of the subjects receiving brimonidine ophthalmic solution (0.1% to 0.2%) included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritus. Adverse-reactions occurring in approximately 5% to 9% included: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.

Adverse reactions occurring in approximately 1% to 4% of the subjects receiving brimonidine ophthalmic solution (0.1% to 0.2%) included: abnormal taste, allergic reaction, asthenia, blepharitis, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, fatigue, flu syndrome, follicular conjunctivitis, foreign body sensation, gastrointestinal disorder, headache, hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), insomnia, keratitis, lid disorder, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, somnolence, stinging, superficial punctate keratopathy, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity.
The following reactions were reported in less than 1% of subjects: corneal erosion, hordeolum, nasal dryness, and taste perversion.

8.2 Postmarketing Experience

The following reactions have been identified during postapproval use of brimonidine tartrate ophthalmic solutions. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Bradycardia, depression, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), syncope, and tachycardia.
- Apnea, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

9 DRUG INTERACTIONS

9.1 Antihypertensives/Cardiac Glycosides

Because **ALPHAGAN P** may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with **ALPHAGAN P** is advised.

9.2 CNS Depressants

Although specific drug interaction studies have not been conducted with **ALPHAGAN P**, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

9.3 Tricyclic Antidepressants

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with **ALPHAGAN P** in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

9.4 Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary
There are no adequate and well-controlled studies with **ALPHAGAN P** in pregnant women.

In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent (see Data). Because animal reproduction studies are not always predictive of human response, **ALPHAGAN P** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Data
Human Data
Limited available data from postmarketing safety reports and published literature with topical use of brimonidine ophthalmic solution in pregnant women are insufficient to inform a drug-associated risk of pregnancy-related adverse outcomes including miscarriage, stillbirth, congenital anomaly, and events experienced by offspring while breastfeeding.

Animal Data
Embryofetal studies were conducted in pregnant rabbits administered brimonidine tartrate by daily oral gavage on gestation days 6 to 18, to target the period of organogenesis. Brimonidine caused miscarriage at 5 mg/kg/day (approximately 50-times the recommended human ophthalmic dose [RHOD] based on

AUC, for brimonidine tartrate 0.15%). The no observed adverse effect level (NOAEL) for developmental toxicity in rabbits was 1 mg/kg/day (approximately 6-fold the RHOD based on AUC, for brimonidine tartrate 0.15%). No treatment-related malformations were observed in rabbits. Signs of maternal sedation and fatigue were observed at all dose levels; the lowest observed adverse effect level (LOAEL) for maternal toxicity was 5 mg/kg/day, based on the dose response for these signs.

Embryofetal studies were conducted in pregnant rats administered brimonidine tartrate by daily oral gavage on gestation days 6 to 15, to target the period of organogenesis. The NOAEL for developmental toxicity was 2.5 mg/kg/day (approximately 750-fold the RHOD based on AUC, for brimonidine tartrate 0.15%). No treatment-related malformations were observed in rats. The LOAEL for maternal toxicity was 2.5 mg/kg/day, based on signs of sedation and fatigue. The maternal NOAEL was 1.0 mg/kg/day (180-fold the RHOD based on AUC, for brimonidine tartrate 0.15%).

After pregnant rats received a single oral dose of ^{14}C-brimonidine tartrate, brimonidine and metabolites crossed the placenta and were detectable in fetal blood and organs.

10.2 Lactation

Risk Summary

It is not known whether brimonidine tartrate is excreted in human milk. In animal studies, brimonidine tartrate has been shown to cross the blood-brain barrier and is excreted into breast milk after oral administration to lactating rats *(see Data)*. Because of the potential for serious adverse reactions, including central nervous system depression and apnea, from **ALPHAGAN P** in nursing infants, ALPHAGAN P is not recommended for use during lactation.

Data

Animal Data

After a single oral dose of ^{14}C-labeled brimonidine tartrate to lactating rats, brimonidine and metabolites were detected in milk. After male and female rats received a single oral dose of ^{14}C-brimonidine tartrate, brimonidine crossed the blood-brain barrier. Radiolabel was detected in the cerebellum, cerebrum, and spinal cord.

10.3 Pediatric Use

ALPHAGAN P is contraindicated in pediatric patients younger than 2 years old *[see Contraindications (6.1)]*. During postmarketing surveillance, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate have not been studied in children below the age of 2 years.

In a well-controlled clinical study conducted in pediatric glaucoma patients aged 2 to 7 years old, the most commonly observed adverse reactions with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50% to 83% in pediatric patients aged 2 to 6 years old) and decreased alertness. In pediatric patients aged 7 years and older (greater than 20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of pediatric patients on brimonidine tartrate ophthalmic solution 0.2% discontinued from the study due to somnolence.

10.4 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

10.5 Special Populations

ALPHAGAN P has not been studied in patients with hepatic impairment.

ALPHAGAN P has not been studied in patients with renal impairment. The effect of dialysis on brimonidine pharmacokinetics in patients with renal failure is not known.

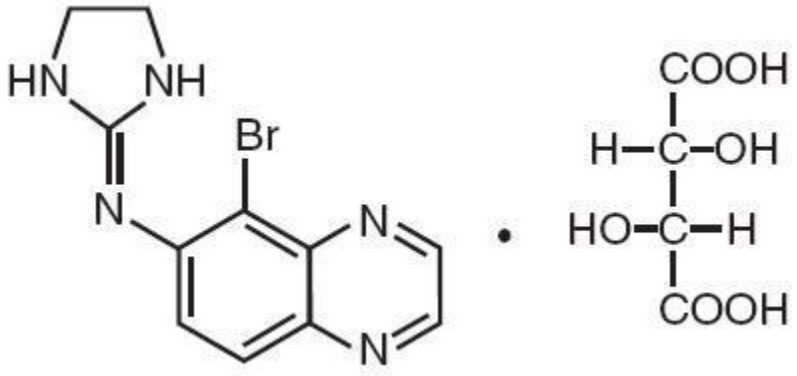
11 OVERDOSAGE

Limited information exists on accidental ingestion of brimonidine in adults; the only adverse reaction reported to date has been hypotension. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving **ALPHAGAN P** as part of medical treatment of congenital glaucoma or by accidental oral ingestion *[*see *Use in Specific Populations (10.3)]*. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

12 DESCRIPTION

ALPHAGAN P (brimonidine tartrate eye drops, solution), sterile, is a relatively selective alpha-2 adrenergic receptor agonist for topical ophthalmic use.

The structural formula of brimonidine tartrate is:



5- Bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate; MW= 442.24

In solution, **ALPHAGAN P** (brimonidine tartrate eye drops, solution) has a clear, greenish-yellow color. It has an osmolality of 250-350 mOsmol/kg and a pH of 6.9-7.4.

Brimonidine tartrate appears as an off-white to pale-yellow powder and is soluble in both water (0.6 mg/mL) and in the product vehicle (1.4 mg/mL) at pH 7.7.

ALPHAGAN P contains the active ingredient brimonidine tartrate 0.15% w/v with the inactive ingredients sodium chloride; sodium carboxymethylcellulose; boric acid; potassium chloride; sodium borate decahydrate; calcium chloride dihydrate; magnesium chloride hexahydrate; Purite® (stabilized oxychloro complex, 2% sol) 0.005% (0.05mg/mL) as a preservative; hydrochloric acid and/or sodium hydroxide to adjust pH and purified water.

13 CLINICAL PHARMACOLOGY

13.1 Mechanism of Action

ALPHAGAN P is a relatively selective alpha-2 adrenergic receptor agonist with a peak ocular hypotensive effect occurring at two hours post-dosing.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

13.2 Pharmacokinetics

Absorption

After ocular administration of either a 0.1% or 0.2% solution, plasma concentrations peaked within 0.5 to 2.5 hours and declined with a systemic half-life of approximately 2 hours.

Distribution

Brimonidine was approximately 29% bound to plasma proteins in healthy subjects.

Elimination

Metabolism

In humans, brimonidine is extensively metabolized by the liver.

Excretion

Urinary excretion is the major route of elimination of brimonidine and its metabolites. Approximately 87% of an orally-administered radioactive dose of brimonidine was eliminated within 120 hours, with 74% found in the urine.

14 NONCLINICAL TOXICOLOGY

14.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1 mg/kg/day in rats achieved approximately 93 and 76 times the recommended human ophthalmic dose (RHOD) based on C_{max} respectively for brimonidine tartrate 0.15%.

Mutagenesis

Brimonidine tartrate was not mutagenic or clastogenic in a series of *in vitro* and *in vivo* studies including the Ames bacterial reversion test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three *in vivo* studies in CD-1 mice: a host-mediated assay, cytogenetic study, and dominant lethal assay.

Impairment of Fertility

A reproduction and fertility study in rats with brimonidine tartrate demonstrated no adverse effect on male or female fertility at oral doses up to 1 mg/kg (approximately 180 times the recommended human ophthalmic dose [RHOD] based on estimated AUC) for brimonidine tartrate 0.15%.

15 CLINICAL STUDIES

Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Brimonidine tartrate has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters.

Clinical studies were conducted to evaluate the safety, efficacy, and acceptability of **ALPHAGAN P** (brimonidine tartrate eye drops, solution) 0.15% compared with **ALPHAGAN** administered three-times-daily in patients with open-angle glaucoma or ocular hypertension. Those results indicated that **ALPHAGAN P** (brimonidine tartrate eye drops, solution) 0.15% is comparable in IOP lowering effect to

ALPHAGAN (brimonidine tartrate eye drops, solution) 0.2%, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2-6 mmHg.

16 HOW SUPPLIED/STORAGE AND HANDLING

ALPHAGAN P is supplied sterile, in teal opaque plastic LDPE bottles and tips, with purple high impact polystyrene (HIPS) caps, containing 5 ml, 10 ml or 15 ml.
Not all packages may be marketed.

Storage: Store below 25ºC

Shelf life
The expiry date of the product is indicated on the packaging materials.
Shelf life after first openning: 28 days, and no later than the expiry date on the product.

17 MANUFACTURER

Allergan, Inc. USA, 2525 Dupont Drive, Irvine, California, USA.

18 REGISTRATION HOLDER

AbbVie Biopharmaceuticals Ltd., 4 Haharash St., Hod Hasharon, Israel.

19 MARKETING AUTHORIZATION NUMBER

131-06-30961

20 DATE OF REVISION OF THE TEXT

Revised in December 2025.