

# Data Sheet

## ENIDIN<sup>®</sup> P 1.5

*brimonidine tartrate 1.5 mg/mL eye drops*

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### Presentation

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ENIDIN<sup>®</sup> P 1.5 eye drops are a clear, greenish-yellow, sterile ophthalmic solution. Brimonidine tartrate is an off-white to pale yellow powder and is both soluble in water (1.5mg/mL) and the product vehicle (3.0 mg/mL) at pH 7.2.

### USES

#### *Actions*

Brimonidine is an alpha-2 adrenergic agonist that is 1000-fold more selective for the alpha-2 adrenoceptor than the alpha-1 adrenoceptor. Affinity at human alpha-1 and alpha-2 adrenoceptors are ~2000 nM and ~2 nM, respectively. This selectivity results in no mydriasis and the absence of vasoconstriction in microvessels associated with human retinal xenografts.

Topical administration of brimonidine decreases intraocular pressure (IOP) in humans. When used as directed, brimonidine has the action of reducing elevated IOP with minimal effect on cardiovascular parameters.

Brimonidine has a rapid onset of action, with the peak ocular hypotensive effect occurring at two hours post-dosing. The duration of effect is at least 12 hours.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action. ENIDIN<sup>®</sup> P 1.5 eye drops lower IOP by reducing aqueous humor production and enhancing uveoscleral outflow.

#### *Pharmacokinetics*

After ocular administration of a 0.1% and 0.2% solution of ENIDIN<sup>®</sup> P 1.5 eye drops three times daily for 7 days, plasma concentrations were low (mean C<sub>max</sub> was 0.03 ng/mL and 0.06ng/mL for the 0.1% and 0.2% solutions, respectively). There was a slight accumulation in plasma after multiple instillations. The area under the plasma concentration-time curve over 8 hours at steady state (AUC<sub>0-8h</sub>) was 0.14 ng.hr/mL and 0.25 ng.hr/mL for the 0.1% and 0.2% solutions, respectively. The mean apparent half-life in the systemic circulation was approximately 2 hours in humans after topical dosing.

Peak plasma brimonidine concentration (C<sub>max</sub>) is predicted to be 0.03 ng/mL when ENIDIN<sup>®</sup> P 1.5 is administered twice daily for 7 days. Systemic accumulation is unlikely after twice daily administration of a 0.15% solution given the short elimination half-life of brimonidine.

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

The pharmacokinetics of ENIDIN® P 1.5 eye drops have not been specifically studied in patients with hepatic or renal disease (see Warnings and Precautions) or in paediatric patients (see Contraindications and Dosage and Administration).

### **Indications**

ENIDIN® P 1.5 eye drops are effective for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

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## **Dosage and Administration**

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The recommended dose is one drop of ENIDIN® P 1.5 eye drops in the affected eye(s) twice daily, approximately 12 hours apart.

If more than one topical ophthalmic medicine is to be used, other eye drops should not be used within five to ten minutes of using ENIDIN® P 1.5 eye drops.

In order to minimise systemic absorption of ENIDIN® P 1.5 eye drops, apply pressure to the tear duct immediately following administration.

### **Paediatric Use**

ENIDIN® P 1.5 Safety and effectiveness of ENIDIN® P 1.5 eye drops in children has not been established. During post-marketing surveillance, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in neonates, infants, and children receiving brimonidine either for congenital glaucoma or by accidental ingestion. Also see Contraindications section.

### **Use in Patients with Renal or Hepatic Disease**

ENIDIN® P 1.5 eye drops have not been studied in patients with hepatic or renal impairment (see Warnings and Precautions).

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## **Contraindications**

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ENIDIN® P 1.5 eye drops are contraindicated in patients with hypersensitivity to brimonidine tartrate or any component of this medication. It is also contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

ENIDIN® P 1.5 eye drops are contraindicated in infants and children <2 years of age.

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## **Warnings and Precautions**

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Although ENIDIN® P 1.5 eye drops had minimal effect on blood pressure and heart rate of patients in clinical studies, caution should be observed in treating patients with severe, uncontrolled cardiovascular disease.

ENIDIN® P 1.5 eye drops have not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

ENIDIN<sup>®</sup> P 1.5 eye drops should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

During the studies there was a loss of effect in some patients. The IOP-lowering efficacy observed with brimonidine eye drops during the first month of therapy may not always reflect the long-term level of IOP reduction. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

### ***Carcinogenesis, mutagenesis and impairment of fertility***

No compound-related carcinogenic effects were observed in 21 month and 2 year studies in mice and rats given oral doses of 2.5 mg/kg/day and 1.0 mg/kg/day brimonidine respectively. Plasma concentrations of brimonidine in mice and rats in the high dose groups were at least 110 times greater than those expected in humans dosed therapeutically.

Brimonidine tartrate was non-genotoxic in assays for chromosomal damage (Chinese hamster cells *in vitro*, *in vivo* bone marrow cytogenetic assay and a dominant lethal assay). In assays for gene mutations in *Salmonella typhimurium* and *Escherichia coli*, brimonidine gave a positive response in one *S.typhimurium* strain without metabolic activation. Other strains gave negative results.

Brimonidine did not have a significant effect on fertility in rats at oral doses of up to 0.66 mg/kg/day (ca 115 times the anticipated AUC in patients).

ENIDIN<sup>®</sup> P 1.5 eye drops are the only IOP-lowering product preserved with Purite<sup>®</sup>. *In vitro* and *in vivo* studies demonstrate a lower rate of corneal epithelial cytotoxicity (an indicator of ocular surface health) and increased cell viability for Purite<sup>®</sup>-preserved ophthalmic solutions compared to use of other preservatives.

### ***Pregnancy and Lactation***

Pregnancy Category B3

There are no studies of brimonidine in pregnant women. In rats, the drug crosses the placenta and enters the fetal circulation. In pregnant rats, brimonidine was associated with maternotoxicity and increased early resorptions/post-implantation losses and decreased pup viability and body weights at estimated exposures (based on AUC) of 390 times the expected exposures in humans treated therapeutically. The drug was also maternotoxic in rabbits and caused abortions at exposures about 26 times greater than those expected in humans. In both rats and rabbits, brimonidine was not teratogenic.

It is not known whether brimonidine is excreted in human milk. In lactating rats, levels of the drug in milk were up to 12 times higher than those in maternal plasma; and in a perinatal and postnatal study in rats, brimonidine was associated with decreased pup viability and pup weights during lactation at maternal plasma exposures of about 116 times greater than those expected in humans.

### ***Effects on ability to drive and use machines***

As with other alpha-agonists, ENIDIN<sup>®</sup> P 1.5 eye drops can potentially cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities requiring mental alertness, including driving, should be cautioned of the potential for a decrease in mental alertness.

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## Adverse Effects

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The most commonly reported adverse reaction is conjunctival hyperaemia, occurring in 18.2% of patients. This is usually transient and does not normally require discontinuation of treatment.

Allergic conjunctivitis occurred in 9.2% of subjects (causing withdrawal in 7.4% of subjects) in clinical trials, with the onset between 3 and 9 months in the majority of patients.

The following undesirable effects considered to be at least possibly related to treatment were reported during two 12-month clinical trial studies where ENIDIN<sup>®</sup> P 1.5 eye drops were administered three times daily:

### **Ocular effects:**

Very common	Conjunctival hyperaemia
Common	Allergic conjunctivitis, ocular irritation (ocular burning and stinging sensation, eye pruritus, foreign body sensation, follicular conjunctivitis, conjunctival folliculosis, conjunctival oedema), local irritation (eyelid oedema and erythema, eye discharge, eye irritation, blepharitis, eye pain), eye dryness, epiphora, photophobia, superficial punctate keratitis, visual disturbance, visual acuity worsened
Uncommon	Eye oedema, eyelid pruritus, conjunctivitis, papillary hypertrophy, iritis

### **Systemic effects:**

Common	<i>Body as a whole:</i>	Asthenia, headache
	<i>Gastrointestinal:</i>	Oral dryness
	<i>Respiratory system:</i>	Rhinitis
Uncommon	<i>Nervous system:</i>	Somnolence, dizziness
	<i>Respiratory system:</i>	Pharyngitis
	<i>Special senses:</i>	Taste perversion

In another 3-month clinical study in patients whose IOP was already controlled with ALPHAGAN<sup>®</sup> eye drops, ENIDIN<sup>®</sup> P 1.5 eye drops dosed twice daily was evaluated. The undesirable effects considered to be at least possibly related to treatment were similar to those seen in the 12-month three times daily studies, but the incidence rates were generally lower.

The following adverse reactions have been identified during post-marketing use of ALPHAGAN<sup>®</sup> in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

#### *Immune system disorders*

Not known: Hypersensitivity

#### *Eye disorders*

Not known: Vision blurred

*General disorders and administration site conditions*  
Not known: Fatigue

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## **Interactions**

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Although specific drug interaction studies have not been conducted with ENIDIN<sup>®</sup> P 1.5 eye drops, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

Because ENIDIN<sup>®</sup> P 1.5 eye drops may reduce blood pressure, caution using drugs such as antihypertensives and/or cardiac glycosides is advised.

Caution is advised when initiating or changing the dose of a concomitant systemic agent which may interact with alpha-adrenergic agonists or interfere with their activity (ie. sympathomimetic agents, agonists or antagonists of the adrenergic receptor).

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 ENIDIN<sup>®</sup> P 1.5 eye drops can lead to an interference in IOP lowering effect, although in rabbit experiments, tricyclic antidepressants did not alter the IOP response to brimonidine. No data on the level of circulating catecholamines after ENIDIN<sup>®</sup> P 1.5 eye drops are instilled are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

As brimonidine is metabolised primarily by the liver, most likely by cytochrome P450 and aldehyde oxidase, this may affect the metabolism of other drugs that utilise the cytochrome P450 pathway.

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## **Overdosage**

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### **Adults**

Ophthalmic overdose:

In those cases received, the events reported have generally been those already listed as adverse reactions.

Systemic overdose resulting from accidental ingestion:

There is very limited information regarding accidental ingestion of brimonidine in adults. The only adverse event reported to date was hypotension.

Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

### **Paediatric population**

Symptoms of brimonidine overdose such as apnoea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in neonates, infants, and children receiving ALPHAGAN<sup>®</sup> as part of medical treatment of congenital glaucoma or by accidental oral ingestion.

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.

Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

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In the event of a topical overdosage, flush eye with a topical ocular irrigant.

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## Pharmaceutical Precautions

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To avoid contamination of the solution, keep container tightly closed. Do not touch dropper tip to any surface. Contents are sterile if seal is intact.

Shelf life: 18 months

Storage: Store below 25°C

Discard contents 4 weeks after opening the bottle.

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## Medicine Classification

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Prescription Medicine

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## Package Quantities

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ENIDIN<sup>®</sup> P 1.5 eye drops are supplied in opaque plastic dropper bottles (5 mL).

### Further Information

Each mL of ENIDIN<sup>®</sup> P 1.5 eye drops contains 1.5 mg brimonidine tartrate, equivalent to 0.99mg as brimonidine free base.

### List of excipients

PRESERVATIVE: sodium chlorite (as Purite<sup>®</sup>) (stabilized oxychloro complex, solution)

INACTIVES: carmellose sodium, boric acid, borax, sodium chloride, potassium chloride, calcium chloride, magnesium chloride and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH (6.6-7.4).

### Clinical trial results

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. ENIDIN<sup>®</sup> P 1.5 eye drops have the action of lowering IOP with minimal effect on cardiovascular and pulmonary parameters.

ENIDIN<sup>®</sup> P 1.5 eye drops were developed based on the clinical efficacy and tolerability of ALPHAGAN<sup>®</sup> eye drops. ALPHAGAN<sup>®</sup> eye drops contain brimonidine tartrate 0.2% and are preserved with benzalkonium chloride. ENIDIN<sup>®</sup> P 1.5 eye drops contain brimonidine tartrate 0.15%, are formulated to a physiological pH, contain key electrolytes present in tears (sodium, potassium, calcium, magnesium) and are preserved with Purite<sup>®</sup>. Data indicate that the substitution of benzalkonium chloride with Purite<sup>®</sup> decreases the risk of corneal disruption and inflammation, particularly when administered in higher doses (eg. use of multiple eye drops) and/or chronically. Furthermore, based on non-clinical pharmacokinetic data, Purite<sup>®</sup> increases the pH and thus enhances the ocular penetration of brimonidine, effectively reducing IOP with lower concentrations of active ingredient, further reducing the potential for adverse reactions. This is confirmed by clinical trials comparing ALPHAGAN<sup>®</sup> eye drops with ENIDIN<sup>®</sup> P 1.5 eye drops (see Studies with ENIDIN<sup>®</sup> P 1.5 eye drops below).

### *Studies with ALPHAGAN® eye drops*

The long term efficacy of ALPHAGAN® eye drops was demonstrated in two multicentre studies, one of 12 months and the other of 6 months duration, in subjects with glaucoma or ocular hypertension. The IOP lowering effect of ALPHAGAN® eye drops ranged from an overall mean reduction of 4.1 mm Hg at trough to a peak effect of 6.4 mm Hg. These results represent approximately 16% - 26% mean reduction from baseline measurements. IOP decreases were maintained for up to one year; no tachyphylaxis was observed. Eight percent of subjects were discontinued from the studies due to inadequately controlled IOP.

Analyses of the proportion of subjects who exhibited decreases of  $\geq 3$  mm Hg at two consecutive visits within the first month of treatment were performed. This subgroup represents 66% of subjects. In these subjects, the overall mean reduction of IOP with ALPHAGAN® eye drops ranged from 5.3 mm Hg at trough to a peak effect of 7.2 mm Hg. These results represent approximately 20% - 30% mean reduction from baseline measurements. At the end of one year, greater than 50% of subjects had IOP reductions of  $\geq 5$  mm Hg.

### *Studies with ENIDIN® P 1.5 eye drops*

The efficacy and safety of ENIDIN® P 1.5 eye drops was demonstrated by comparison with that of ALPHAGAN® eye drops in a 3 month multicentre study involving 391 patients with glaucoma or ocular hypertension already controlled with ALPHAGAN® eye drops (study 017). ENIDIN® P 1.5 eye drops twice daily was found to provide equivalent efficacy compared to ALPHAGAN® eye drops twice daily with the mean IOP change from baseline between ENIDIN® P 1.5 and ALPHAGAN® being no more than 0.79 mm Hg at any timepoint (NS). ENIDIN® P 1.5 eye drops also tended towards less overall adverse reactions than ALPHAGAN® eye drops (16.7% vs 22.1%) and less allergic conjunctivitis (3.9% vs 4.4%).

The long-term safety of ENIDIN® P 1.5 eye drops was confirmed by comparison with that of ALPHAGAN® eye drops in two multicentre studies of 12 months duration. In these studies, patients were randomized to brimonidine 0.15% (ALPHAGAN® P) eye drops three times daily, brimonidine-Purite® 0.2% eye drops three times daily, or brimonidine 0.2% (ALPHAGAN®) eye drops three times daily. Pooled data from these studies demonstrated that ENIDIN® P 1.5 eye drops were associated with significantly less adverse reactions than ALPHAGAN® eye drops overall (49.7% vs 62.4%), as well as in terms of the following specific adverse reactions: allergic conjunctivitis (9.2% vs 15.7%), eye discharge (1.3% vs 3.9%), conjunctival hyperaemia (18.2% vs 25.6%) and oral dryness (5.3% vs 10.4%). Similarly, ENIDIN® P 1.5 eye drops were associated with significantly less adverse reactions than brimonidine-Purite® for allergic conjunctivitis (9.2% vs 14.6%) and oral dryness (5.3% vs 9.4%). Brimonidine-Purite® eye drops were also associated with significantly less adverse reactions than ALPHAGAN® eye drops for allergic conjunctivitis (14.6% vs 15.7%) and oral dryness (9.4% vs 10.4%) demonstrating a safety benefit from Purite® substitution, even when brimonidine concentration was unchanged. These safety data support those of study 017, and demonstrate that ENIDIN® P 1.5 eye drops provide the most favourable safety profile with the lowest effective dose of brimonidine.

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