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ALLERGAN

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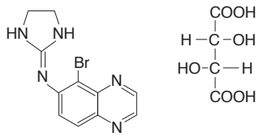
ALPHAGAN® P

(brimonidine tartrate ophthalmic solution) 0.15%
sterile

DESCRIPTION

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15% is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It is an off-white to pale yellow powder. It has a molecular weight of 442.24 as the tartrate salt, and is both soluble in water (1.5 mg/mL) and in the product vehicle (3.0 mg/mL) at pH 7.2.
The structural formula is:

Formula: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$
CAS Number: 59803-98-4



In solution, ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15% has a clear, greenish-yellow color. It has an osmolality of 250-350 mOsmol/kg and a pH of 6.6-7.4.

Each mL of ALPHAGAN® P contains:

Active ingredient: brimonidine tartrate 0.15% (1.5 mg/mL)

Preservative: PURITE® 0.005% (0.05mg/mL)

CLINICAL PHARMACOLOGY

Mechanism of action:
ALPHAGAN® P is an alpha adrenergic receptor agonist. It has 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.

Pharmacokinetics:
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. In humans, systemic metabolism of brimonidine is extensive. It is metabolized primarily by 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.

Clinical Evaluations:
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.

Two clinical studies were conducted to evaluate the safety, efficacy, and acceptability of ALPHAGAN® P (brimonidine tartrate ophthalmic 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 ophthalmic solution) 0.15% is comparable in IOP lowering effect to ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2-5 mmHg.

INDICATIONS AND USAGE

ALPHAGAN® P is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

ALPHAGAN® P is 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.

PRECAUTIONS

General:
Although ALPHAGAN® P had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

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

ALPHAGAN® P should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for Patients:
As with other drugs in this class, ALPHAGAN® P may cause fatigue and /or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Drug Interactions:
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. Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), anti-hypertensives and/or cardiac glycosides is advised.

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. No data on the level of circulating catecholamines after ALPHAGAN® P administration are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
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 1.0 mg/kg/day in rats achieved 86 and 55 times, respectively, the plasma drug concentration estimated in humans treated with one drop of ALPHAGAN® P into both eyes 3 times per day.

Brimonidine tartrate was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies including the Ames test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.

Pregnancy: Teratogenic effects: Pregnancy Category B.
Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility or harm to the fetus due to ALPHAGAN® P. Dosing at this level produced an exposure that is 189 times higher than the exposure seen in humans following multiple ophthalmic doses.

There are no adequate and well-controlled studies in pregnant women. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. ALPHAGAN® P should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers:
It is not known whether this drug is excreted in human milk; although in animal studies brimonidine tartrate was excreted in breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established. Agitation, apnea, bradycardia, convulsions, cyanosis, depression, dyspnea, emotional instability, hypotension, hypothermia, hypotonia, hypoventilation, irritability, lethargy, somnolence, and stupor have been reported in pediatric patients receiving brimonidine tartrate 0.2%.

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

ADVERSE REACTIONS

Adverse events occurring in approximately 10-20% of the subjects included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritus.

Adverse events occurring in approximately 5-9% of the subjects included: burning sensation, conjunctival folliculosis, hypertension, oral dryness, and visual disturbance.

Events occurring in approximately 1-4% of subjects included: allergic reaction, asthenia, blepharitis, bronchitis, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, flu syndrome, follicular conjunctivitis, foreign body sensation, headache, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, stinging, superficial punctate keratopathy, visual field defect, vitreous floaters, and worsened visual acuity.

The following events were reported in less than 1% of subjects: corneal erosion, insomnia, nasal dryness, somnolence, and taste perversion.

OVERDOSAGE

No information is available on overdosage in humans. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15% in the affected eye(s) three times daily, approximately 8 hours apart.

HOW SUPPLIED:

ALPHAGAN® P is supplied sterile in opaque teal LDPE plastic bottles with droppers with purple high impact polystyrene (HIPS) caps as follows:

3 mL in 10 mL bottle
5 mL in 10 mL bottle
10 mL in 10 mL bottle
15 mL in 15 mL bottle

NOTE: Store below 25°C. Keep out of reach of children.

Rx Only

Manufactured by:
Allergan Sales, LLC
Waco, Texas, USA

ROC(Taiwan) Invention Patent No. I287992
ROC(Taiwan) Invention Patent No. I287998

ALLERGAN

*** ARTWORK IS ACTUAL SIZE**
*** DROP TEMPLATE AND NOTES BEFORE PROCESSING**
*** PAGE 1 OF 2**

Part Number:	**71726UT12C**
Drawing Number:	**0218401**
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艾弗目®P無菌眼用液劑0.15%

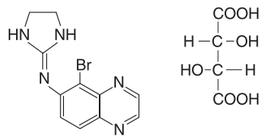
ALPHAGAN® P Ophthalmic Solution 0.15%

衛署藥輸字第023695號

性狀

ALPHAGAN® P 0.15%無菌眼用液劑0.15%，為供眼用，具有相對選擇性的α-2腎上腺激素促進作用劑。本品的化學名為5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate，呈灰白至灰黃粉末，酒石酸鹽的分子量為442.24，可溶於水(1.5 mg/mL)，也可溶解於pH 7.2的本品媒液(3.0 mg/mL)中。

結構式：



化學式：$C_{11}H_{10}BrN_5C_4H_6O_6$

於溶液中，本藥呈澄清綠黃色，滲透壓為250-350 mOsmol/kg，pH值介於6.6至7.4。

本藥每mL含有：

活性成分：brimonidine tartrate 15%(1.5 mg/mL)

保存劑：PURITE 0.005% (0.05 mg/mL)

臨床藥理

作用機轉：

本藥是一種α腎上腺激素作用促進劑，給藥後兩小時出現降眼壓效果的峰值。於動物和人體進行螢光光度計量研究(Fluorophotometric studies)顯示，本品經由減少水樣液的產生，並能增加葡萄膜鞏膜的流出液，來達到雙重的作用機轉。

藥物動力學：

眼內投予0.1%或0.2%的活性成分溶液後，於0.5至2.5小時內出現血漿濃度峰值後，血漿濃度以全身半衰期約兩小時的速度降低。本藥主要經由肝臟代謝，藥物和藥物代謝產物的主要排除路徑是經由尿路排泄，約87%的經口投與放射性標記劑量，於120小時以內被清除，而其中有74%出現於尿液中。

臨床評估：

眼內壓升高是造成青光眼性視野喪失的一大風險因子；眼內壓愈高，則視神經受損與視野喪失的可能性愈高。本品具有降低眼內壓效果，而極少對心血管和肺參數造成影響。

進行兩項臨床研究，評估ALPHAGAN® P 0.15%，相對於ALPHAGAN®，每日三次投與患有開放隅角性青光眼或高眼壓病人的安全性、有效性和接受程度，結果顯示ALPHAGAN® P 0.15%，具有可媲美ALPHAGAN®0.2%的眼內壓下降效果，可有效降低患有開放隅角性青光眼或高眼壓病人的眼內壓，約達2-5毫米汞柱。

適應症

開放角隅青光眼或高眼壓。

禁忌

ALPHAGAN® P禁忌用於對brimonidine tartrate或本藥任何成分過敏病人，也禁忌用於正在接受單胺氧化酶(MAO)抑制劑治療病人。

警語

一般方面：

雖然臨床研究顯示，ALPHAGAN® P極少對病人血壓造成影響，但用於治療患有重度心血管疾病病人時，仍應審慎。

尚未有ALPHAGAN® P用於肝或腎功能受損病人的研究，故用於此類病人時應審慎注意。

ALPHAGAN® P用於患有憂鬱症、腦血管或冠狀血管機能不全、雷氏症候群、姿態性低血壓、或血栓閉鎖性血管炎病人時應審慎。接受降眼內壓處方藥物的病人，應例行性地監測眼內壓。

病人資訊：

如同其它此類藥物般，ALPHAGAN® P可能在某些病人身上會引起倦怠感和(或)嗜睡，從事危險性活動或工作病人，應注意可能有注意力和警覺性降低等的問題。

藥物交互作用：

雖然尚未對ALPHAGAN® P進行與特定藥物的藥物交互作用研究，但須考慮ALPHAGAN® P具有增強或加成中樞神經系統抑制劑(酒精、巴比妥酸鹽、鴉片劑、鎮定劑、或麻醉劑）效果的可能。α促進作用劑這一類藥物可能會減低脈搏和降低血壓，因此當α促進作用劑類藥物合併使用β作用阻斷劑(包括眼用和全身性使用)、抗高血壓劑、和(或)心臟作用糖苷等藥物使用時應審慎。

三環抗鬱劑，已有報告指出會減低全身性投與clonidine的降血壓效果，但未知同時使用三環抗鬱劑與ALPHAGAN® P於人體,是否可能導致干擾眼內壓下降的效果。目前尚無任何投與ALPHAGAN® P後的catecholamines血中濃度的資料，但建議病人於併服可能會影響血循環胺類(amines)的代謝和攝取的三環抗鬱劑時應審慎。

致癌性，致突變性，和生育力受損：

小鼠和大鼠分別經過21個月和24個月的用藥後，未觀察得本藥引起的致癌效應：研究中，經膳食投與小鼠高達2.5mg/kg/日劑量和大鼠高達1.0mg/kg/日劑量的brimonidine tartrate，所致的血漿藥物濃度，分別是人類使用每日三次，每次兩眼各滴一滴ALPHAGAN® P治療時，預估所得血漿藥物濃度的86倍與55倍。

本藥用於一系列試管試驗和活體試驗研究，包括Ames試驗、中國倉鼠卵巢(Chinese Hamster Ovary; CHO)細胞染色體迷失檢定分析(chromosomal aberration assay)、小鼠的宿主媒介檢定分析(host-mediated assay)和細胞新生研究(cytogenic studies)、和顯著致命檢定分析(dominant lethal assay)，不具致突變發生或致細胞新生作用。

用於孕婦：致畸胎作用：妊娠用藥級數B。

大鼠每日口服投與0.66 mg的brimonide tartrate進行生殖研究，未見任何因本藥造成的生育力受損、或胚胎損傷，這種用量比人類經多次眼用劑量投與後，病人所得的劑量高189倍。

目前尚無足夠且經充分對照的孕婦研究，而於動物實驗，brimonidine某種程度會通過胎盤，進入胎兒血循環。ALPHAGAN® P唯有在經權衡後，對母體的潛在效益超過可能對胎兒的風險時，方可用於孕婦。

用於哺乳婦：

未知本藥是否會分泌於乳汁，但於動物實驗，brimonidine tartrate會分泌於動物乳汁。基於藥物對母體重要性的考慮，應在停止哺乳與停止用藥，擇一而為。

用於小兒：

本品用於小兒病人的安全性和有效性尚未確立。小兒病人使用brimonidine tartrate 0.2%，曾報告有躁動不安、窒息、心搏減慢、抽搐、發紺、憂鬱、呼吸困難、情緒不穩、低血壓、體溫過低、肌肉張力不足、換氣不足、興奮易怒、不活潑、嗜睡、和木僵等副作用。

用於老人：

用於老人與用於其它成年病人的安全性或有效性間，整體上來說，未見任何差異。

不良反應

發生率約10-20%的不良反應，包括：過敏性結膜炎、結膜充血、和眼睛搔癢。

發生率約5-9%的不良反應，包括：灼燒感、結膜毛囊炎、高血壓、口乾、和視覺模糊。

發生率約1-4%的不良反應，包括：過敏反應、全身無力、眼瞼緣炎、支氣管炎、結膜水腫、結膜出血、結膜炎、咳嗽、頭昏眼花、消化不良、呼吸困難、淚漏、流淚、眼乾、眼睛刺激感、眼痛、眼瞼水腫、眼瞼紅斑、流感症狀、毛囊性結膜炎、異物感、頭痛、咽炎、畏光、發疹、鼻炎、鼻竇感染、竇炎、刺痛感、表淺小點狀角膜病變、視野缺損、玻璃體漂浮物、和視銳度惡化。

發生率低於1%的不良反應，包括：角膜糜爛、失眠、鼻乾、思睡、和味覺倒錯。

用藥過量

並無任何人體使用本品用藥過量之相關資訊。口服用藥過量的處置，包括支持性療法和症候性療法，須隨時維持病人呼吸道的暢通。

用法用量：本藥須由醫師處方使用

建議劑量每日三次，每次患眼滴一滴，間隔約8小時。

包裝

本品為不透明無菌塑膠滴瓶，有3公撮，5公撮，10公撮，15公撮等包裝。

註：低於25°C溫度下儲存，置於兒童不能及之處。

ALLERGAN

Manufactured by:
Allergan Sales, LLC
Waco, Texas, U.S.A.

藥商
台灣愛力根藥品股份有限公司
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中華民國發明專利第I287992號
中華民國發明專利第I287998號

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* ARTWORK IS ACTUAL SIZE * DROP TEMPLATE AND NOTES BEFORE PROCESSING * PAGE 2 OF 2	
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