pressure, caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), antihypertensives 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® can lead to an interference in IOP lowering effect. No data on the level of circulating catecholamines after ALPHAGAN® is instilled are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Carcinogenesis, mutagenesis, 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 (as the free base) and 1.0 mg/kg/day, respectively (~77 and 118 times, respectively, the human plasma drug concentration following the recommended ophthalmic dose).

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

Pregnancy: Reproduction 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®. Dosing at this level produced 100 times the plasma drug concentration level seen in humans following multiple ophthalmic doses.

There are no studies of ALPHAGAN® in pregnant women, however in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. ALPHAGAN® 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 ALPHAGAN® is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be 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. Symptoms of bradycardia, hypotension, hypothermia, hypotonia and apnea have been reported (rarely) in neonates receiving brimonidine.

PAGE 4

ADVERSE REACTIONS

Adverse events occurring in approximately 10-30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions and ocular pruritus.

Events occurring in approximately 3-9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations, nasal dryness and syncope.

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® in the affected eye(s) two times daily. For those patients whose IOP peaks in the afternoon or need additional IOP control, an additional drop of brimonidine in the afternoon can be added.

HOW SUPPLIED

ALPHAGAN® ophthalmic solution is supplied sterile in white opaque plastic dropper bottles as follows:
5 mL, 10 mL, 15 mL.

NOTE: Store at or below 25C (77F). On prescription only. Keep out of the reach of children.

ALLERGAN®

Manufactured by:
Allergan Pharmaceuticals Ireland,
Westport, Ireland
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艾弗目®眼藥水 0.2%
ALPHAGAN® Ophthalmic Solution 0.2%
(brimonidine tartrate)

衛署藥輸字第 022635 號

性狀：

本品 1 ml 含有：brimonidine tartrate 2 mg (相當於 1.32 mg brimonidine 游離基)，benzalkonium chloride 0.05 mg，聚乙烯醇 14 mg，氯化鈉，檸檬酸鈉，檸檬酸及純水。

臨床藥理學：

本品乃相對上具有選擇性之 α-2 腎上腺激性作用劑(α-2 adrenergic agonist)，給藥後兩小時出現尖峰降眼壓效果，於動物及人體進行螢光光譜研究顯示 brimonidine tartrate 藉由減少眼房水產量與增加葡萄膜鞏膜流出量，具有雙重作用機轉。

眼部投予 0.2%眼藥水後，1 至 4 小時後達到血漿濃度峰值，隨後下降，全身性半衰期約 3 小時。

於人體 brimonidine 全身性之代謝作用完全，主要係由肝臟代謝，藥物及其代謝產物之主要清除路徑係由尿液排出，約 87%經口投藥之放射性劑量於 120 小時內清除，而其中 74%出現於尿液。

眼內壓（Intraocular Pressure, IOP）升高為青光眼視野喪失之一大風險因子，IOP 越高則視神經受損及視野喪失可能性越高，本品可降低眼內壓而對心血管及肺臟功能極少造成影響。

在為期長達一年與 timolol 0.5%相比較的臨床試驗中，相較於 timolol 約 6 mm Hg 之 IOP 降低效果，本品可降低約 4-6 mm Hg 之 IOP。有 8%的參與本試驗之病患由於眼內壓控制不當而停止繼續研究，其中 30%係發生於治療之第一個月，約 20%因副作用而停止繼續研究。

PAGE 1

適應症：開放角隅青光眼或高眼壓。

說明：適用於患有開放角隅青光眼或高眼壓病人降低眼內壓，用於某些病人，本品之 IOP 降低效果隨著時間而消失，此種喪失效果的開始時間因人而異，故須密切監視。

禁忌症：

禁用於對 brimonidine tartrate 或本品之任一種成分過敏病人，也禁用於接受單胺氧化酵素(monoamine oxidase，MAO)抑制劑治療病人。

注意事項：

一般方面：

雖然本品於臨床研究中對病人血壓影響極小，但用於治療患有嚴重心血管疾病病人時應審慎。

本品未曾用於肝或腎機能受損病人進行研究，用於治療此等病人應審慎。

本品應小心用於患有抑鬱、腦部或冠狀機能不全、雷氏症候群(Raynaud's phenomenon)、姿勢性低血壓(orthostatic hypotension)或血栓閉鎖血管炎(thromboangiitis obliterans)等病人。

研究期間，有些病人的效果喪失，使用本品治療第一個月觀察得的 IOP 降低效果不一定能反映出長期 IOP 降低程度；對於每日投藥兩次無法適當控制 IOP 的病人，必須於下午再加滴一滴 brimonidine，使用降低眼內壓藥物的病人必須經常性監視其 IOP 的變化。

病人資訊：

本品的保存劑 benzalkonium chloride 可能被軟式隱形眼鏡吸收，配戴軟式隱形眼鏡病人須指導他們於滴注本品後，至少須等候 15 分鐘才能配戴隱形眼鏡。

如同此類型的其它藥物般，本品可能於某些病人造成疲倦及(或)嗜睡，從事危險性活動病人須注意警覺性降低的可能。

藥物交互作用：

雖然未曾使用本品進行特定藥物交互作用研究，但須考慮與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)產生加成作用增強效果的可能，本品於臨床研究對脈搏及血壓不會造成顯著影響，但因 α-促效劑類別藥物可能降低脈搏及血壓，故建議合併使用乙型遮斷劑 β–blockers(眼用及全身性使用)、抗高血壓劑及/或強心配糖體(cardiac glycosides)等藥物時應審慎。

據報告三環抗抑鬱劑會減弱全身性 clonidine 之降血壓效果，但未知合併使用此等藥劑與本品是否導致干擾 IOP 降低效果；目前並無有關滴注本品後的血循環兒茶酚胺(catecholamines)濃度資料，但建議使用三環抗抑鬱劑病人應審慎，原因是該種藥物可能影響循環性胺類(amines)代謝及攝取。

PAGE 2

致癌性，致突變性，危害生育力：

於小鼠及大鼠之為期 21 個月及 2 年研究期間，分別口服投予 25 mg/kg/日(以游離基計)及 10 mg/kg/日(分別高達使用推薦眼用劑量後人類血漿藥物濃度之 77 倍及 118 倍)，並未觀察得化合物相關之致癌作用。

本品於一系列試管試驗及活體研究，包括 Ames 試驗，寄主媒介檢定分析(host-mediated assay)，中國倉鼠卵巢(CHO)細胞之染色體畸型分析(chromosomal aberration assay)，小鼠細胞遺傳學研究及致死量檢定分析(lethal assay)中，不具有突變發生作用或細胞再生作用。

用於孕婦：

大鼠使用口服劑量 0.66 mg 游離基/kg 進行生殖研究，並未危害生育力或對胚胎造成傷害，此種劑量為可產生人類使用多劑眼用劑量後血漿藥物濃度的百倍。

並無任何本品用於孕婦之研究，但動物研究中 brimonidine 會穿過胎盤進入胎兒血循環至一定相當程度，除非對母體可能的效益超過對胚胎潛在的風險時才可用於孕婦。

用於哺乳婦：

未知本品是否分泌於人類乳汁，但動物研究中 brimonidine tartrate 顯然分泌於乳汁，故須考慮藥物對母體的重要性，決定是否停止哺乳或停止用藥。

用於小兒：用於小兒科之安全性及效果尚未確立。此外，心跳減慢、低血壓、體溫降低、肌張力減弱及呼吸弛緩等症候，也曾罕見於投與 brimonidine 的新生兒。

副作用：

發生率約 10-30%的副作用，以發生率遞減順序表示，包括：口乾，眼部充血，燒灼感及針刺感，頭痛，視力模糊，異物感，疲勞/嗜睡，結膜濾泡，眼部過敏反應及眼部搔癢。

發生率約 3-9%的副作用，以遞減順序表示，包括：角膜染色/糜爛，畏光，眼皮紅斑，眼痛，眼乾，流淚，上呼吸道症狀，眼皮水腫，結膜水腫，昏眩，眼瞼炎，眼部刺激，胃腸道症狀，虛弱無力，結膜變白，視力異常及肌肉痛。

下列副作用發生率低於 3%：眼皮結痂，結膜出血，味覺異常，失眠，結膜分泌物，抑鬱，高血壓，焦慮不安，心悸，鼻乾及昏厥。

過量：

並無有關人類用藥過量的資訊，口服用藥過量之處理，包括支持性及症候性治療，須維持病人呼吸道的暢通。

用法用量：本藥限由醫師處方使用

推薦劑量為每日兩次，每次滴注一滴艾弗目® 眼藥水於患部；對於下午達到 IOP 峰值或需要額外控制 IOP 病人，可於下午增加一滴劑量。

包裝：

艾弗目® 眼藥水 0.2%(ALPHAGAN® ophthalmic solution)係白色不透明無菌塑膠滴瓶，包裝如下：5 ml，10 ml，15 ml。

註：儲存於 25℃(77℉)或以下溫度，限處方調劑，置於兒童不能及之處。

製造廠
Allergan Pharmaceuticals Ireland
Castlebar Road, Westport, County Mayo, Ireland.
藥商

香港商愛力根有限公司台灣分公司
台北市羅斯福路二段 102 號 9 樓
電話：(02)2366-9888

ALPHAGAN®
Brimonidine tartrate ophthalmic solution 0.2%

ALLERGAN®

DESCRIPTION

Each mL contains: brimonidine tartrate 2 mg (equivalent to 1.32 mg as brimonidine free base) with: benzalkonium chloride 0.05 mg, polyvinyl alcohol 14 mg; sodium chloride; sodium citrate; citric acid and purified water.

CLINICAL PHARMACOLOGY

ALPHAGAN® is a relatively selective alpha-2 adrenergic 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.

After ocular administration of a 0.2% solution, plasma concentrations peaked within 1 to 4 hours and declined with a systemic half-life of approximately 3 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.

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. ALPHAGAN® has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters.

In comparative clinical studies with timolol 0.5%, lasting up to one year, the IOP lowering effect of ALPHAGAN® was approximately 4-6 mm Hg compared with approximately 6 mm Hg for timolol. Eight percent of subjects were discontinued from studies due to inadequately controlled intraocular pressure, which in 30% of these patients occurred during the first month of therapy. Approximately 20% were discontinued due to adverse experiences.

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INDICATIONS AND USAGE

ALPHAGAN® is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The IOP lowering efficacy of ALPHAGAN® ophthalmic solution diminishes over time in some patients. This loss of effect appears with a variable time of onset in each patient and should be closely monitored.

CONTRAINDICATIONS

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

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

ALPHAGAN® 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 ALPHAGAN® ophthalmic solution during the first month of therapy may not always reflect the long-term level of IOP reduction. For those patients whose IOP is not adequately controlled with twice-daily dosing, an additional drop of brimonidine in the afternoon can be added. Patients prescribed IOP-lowering medication should be routinely monitored for IOP.

Information for Patients: The preservative in ALPHAGAN®, benzalkonium chloride, may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling ALPHAGAN® to insert soft contact lenses.

As with other drugs in this class, ALPHAGAN® 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®, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives or anesthetics) should be considered. ALPHAGAN® did not have significant effects on pulse and blood pressure in clinical studies. However, since alpha-agonists, as a class, may reduce pulse and blood

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