Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Brimonidine

Proprietary Product Name: Alphagan P; Enidin Prso

Sponsor: Allergan Australia Pty Ltd

August 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New strength, Change in formulation and Two new trade names.
Decision:	Approved
Date of Decision:	24 May 2010
Active ingredient(s):	Brimonidine tartrate
Product Name(s):	Alphagan P and Enidin P
Sponsor's Name and Address:	Allergan Australia Pty Ltd Locked Bag 1514, Pymble NSW 2073
Dose form(s):	Solution (eye drops)
Strength(s):	1.5 mg/mL (0.15%)
Container(s):	Teal coloured LDPE bottle with a teal green coloured LDPE control dropper tip and a purple coloured, high impact polystyrene (HIPS) cap
Pack size(s):	5 ml Fill in a 10 mL Container
Approved Therapeutic use:	'Alphagan P/Enidin P eye drops are effective in lowering elevated intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension. Alphagan P/Enidin P eye drops can be used in the treatment of glaucoma either as a monotherapy or in combination with topical beta-blockers'.
Route(s) of administration:	Eye drops
Dosage:	The recommended dose is one drop of Alphagan P eye drops in the affected eye(s) twice daily, approximately 12 hours apart.
ARTG number(s):	158888 and 158893

Product Background

Glaucoma is a leading cause of blindness. The common end-point of glaucoma is optic neuropathy ('glaucomatous optic neuropathy') with the progressive destruction of retinal ganglion cells of the neural retina. The major known risk factor is elevated intra-ocular pressure (IOP). While the goal of treatment is to preserve visual function, the common surrogate endpoint is to lower IOP (although there is no single, safe level of IOP applicable to all patients; some glaucomatous pathology may occur within the normal pressure range). Open-angle glaucoma (OAG) accounts for 90% of glaucoma in Western societies. It may be asymptomatic until irreversible visual loss has occurred. Major detectable pathologies in chronic glaucoma are: raised IOP; excavation and atrophy of the optic nerve head; and loss of visual field in advanced cases.

Treatments to reduce IOP include: topical eye drops (parasympathomimetics; carbonic anhydrase inhibitors; sympathomimetics; topical a-agonists; topical non-selective beta blockers; and topical prostaglandins); systemic medications; laser therapy; surgery. Medical therapy aims to reduce aqueous production or facilitate outflow. It has also been speculated

that brimonidine has a protective effect (against glaucomatous damage to retinal ganglion cells) independent of pressure reduction[1].

Clinical studies distinguished between ocular hypertension (that is, IOP above normal) and glaucoma (where there is also evidence of visual field loss or optic nerve damage).

Brimonidine, the active ingredient in Alphagan P, is structurally and pharmacologically related to clonidine and apraclonidine (p-aminoclonidine).

Brimonidine is a relatively selective a_2 adrenoceptor agonist, according to the sponsor's Clinical Overview "1000-fold more selective for the a-2 adrenoceptor than the a-1 adrenoceptor". Of relevance to Alphagan P (and the additional tradename Enidin P), the a_2 adrenoceptor is located in the central nervous system (CNS) and the ocular ciliary body. The sponsor states that stimulation of this receptor "can lead to CNS depression; in the eye, there is decreased aqueous production, and depending on the degree of a_2 activity, enhancement of uveoscleral outflow". Thus, brimonidine's intended effect requires penetration of the cornea. Typical systemic effects of a_2 adrenoceptor agonism include systemic hypotension, sedation and bradycardia. Typical ocular effects of a_1 agonism include conjunctival blanching, mydriasis and eyelid retraction.

Brimonidine may interact with imidazoline receptors; the sponsor did not discuss this.

Alphagan P eye drops were developed as a line extension to Alphagan, "to optimise ocular comfort for the patient while maintaining clinical efficacy". There are two broad differences in formulation between Alphagan and Alphagan P:

(1) dose strength of brimonidine tartrate (0.20% for Alphagan; 0.15% for Alphagan P)
(2) excipients (most notably, the preservative used: benzalkonium chloride (BAK) 0.005% for Alphagan, and Purite 0.005% for Alphagan P)

The latter difference is stated by the sponsor to alter the pH of the product. The sponsor further states that the increase in pH with Alphagan P improves ocular bioavailability of brimonidine. (It is stated that brimonidine Purite solution is buffered at pH 7.1-7.3, whereas Alphagan is buffered between pH 6.3-6.5. "Because the coefficient of absorption (pK_a) of brimonidine base is approximately 7.2, the higher pH of brimonidine Purite solution increases the equilibrium concentration of unionised drug, promoting ocular permeability of the non-polar moiety, with resulting enhanced ocular drug absorption".) This claim is used to justify reducing the amount of active ingredient in Alphagan P.

Purite is essentially sodium chlorite. According to the sponsor, the latter compound has cidal activity due to oxidative action. (This contrasts with BAK, which has detergent action. The sponsor argues that mammalian cells have multiple anti-oxidant pathways and are "able to cope with oxidative stress" whereas mammalian cells are as vulnerable as prokaryotic cells to detergent effects.) Purite is described variously as a stabilised oxychloro complex, or an equilibrium mixture of oxychloro species.

The sponsor states that "the formulation of Alphagan P eye drops is virtually identical to that of Refresh Tears Plus (ARTG No. 127559) with the addition brimonidine tartrate". The Allergan product with that ARTG number, classified as a medical device, has the following excipients: calcium chloride; magnesium chloride; potassium chloride; sodium carboxymethyl cellulose; sodium chloride; sodium lactate; water, purified in required

[1]Galanopolous A and Goldberg I. Clinical efficacy and neuroprotective effects of brimonidine in the management of glaucoma and ocular hypertension. Clinical Ophthalmology 2009: 3; 117–122.

quantity (QS). Thus Alphagan P is not identical to the eye lubricant with ARTG No. 127559, in that it also contains Purite. The sponsor's justification for not providing nonclinical documentation was that the safety of the ingredients in Alphagan P has been well established with Alphagan and Refresh Tears Plus.

The sponsor, in its Clinical Overview, also claims that Purite is the preservative in several other current Allergan products: "Refresh Contacts" contains Purite and is widely sold in the European Union (EU), North America, Australia and New Zealand". No information about this device was obtainable from the ARTG by searching under all entries for 'Refresh' or by looking under current products by sponsor (Allergan Australia).

According to the Quality evaluator, calcium chloride, magnesium chloride and carmellose sodium and the preservative Purite have not been used in any registered in Australia eye products (and Purite has not been used in any registered product).

Preservative integrity Sterility aspects of the proposed products evaluated by the Office of Laboratories and Scientific Services (OLSS, TGA) were acceptable provided that the closed shelf life was reduced from 24 months to 18 months when stored below 25 °C. Thus, although the chemical and physical data provided in the submissionwere said to support an unopened shelf life of 24 months when stored below 25ºC, the final assigned shelf life is 18 months. In addition, like the majority of eye drops the product must be discarded 4 weeks after opening.

The microbiological aspects of manufacture were adequately controlled. The bottles are different from the previously registered product, and container safety was evaluated by OLSS and found to be satisfactory.

Regulatory Status

Brimonidine tartrate ('Alphagan') eye drops were first registered by Allergan in November 1997, and in Australia in November 1999 (AUST R 60297). The same product with the additional trade name of 'Enidin' (AUST R 81531) was registered in 2002. These products contain 2 mg/mL of brimonidine tartrate in a citrate buffer using benzalkonium chloride (BAK) as the preservative. This meets the preservative efficacy criteria of the British Pharmacopoeia/ European Pharmacopoeia (BP/Ph.Eur).

In USA, 0.15% strength Alphagan P was approved in March 2001, while 0.10% strength Alphagan P was approved in August 2005. In the US PI, three times a day (TID**) dosing is recommended** (and use of the 0.15% strength product and the 0.10% strength product should be viewed in that context) compared with twice daily in Australia. The Alphagan product is registered but not marketed.

Alphagan P has also obtained marketing approval in Canada (November 2003; 0.15% and TID dosing, although it is inferred in the Dossier that Alphagan was registered for twice a day, BID, use), NZ (November 2006; 0.15% BID dosing) and other countries.

There has been no application to register Alphagan P in the Netherlands, Sweden or the UK.

The clinical sections of the US and Canadian dossiers comprised studies 190342-004, -005, -007 and -008, but not -017.

No marketing application for Alphagan P has been rejected in USA or Canada.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

All details are identical to that in the approved Alphagan and Enidin. The drug substance brimonidine tartrate is the same as that described in the registered Alphagan. The tartrate form enhances water solubility.

Excipients

A novel preservative, 'Purite', is used at a concentration of 0.05 mg/mL in the proposed product to replace benzalkonium chloride 0.05 mg/ml as a preservative in the registered products. Purite has not been used in any registered eye products, or any registered products in the ARTG. Thus a brief evaluation of this novel preservative based on the submitted information is included at the end of this section.

The chlorite and chlorine in Purite are oxidants and may potentially react with the drug substance, which may increase the amounts of known and unknown impurities. The sponsor has not discussed this potential incompatibility and is requested to do so or to justify the omission of this consideration.

The sponsor has indicated that Purite 0.05 mg/mL was chosen because it met the USP criteria for preservative efficacy (effective at equal or great than 0.001 mg/mL), provided an adequate safety margin. It is said to be supported by the results of several preservative efficacy studies in conjunction with the Purite stability in finished products. The evaluation of Purite as a preservative was referred to the Microbiology Section of Office of Laboratories and Scientific Services (OLSS), TGA.

Excipients calcium chloride, magnesium chloride and carmellose sodium are also proposed in the proposed formulation. Although the sponsor has claimed that these excipients have been used in a current Refresh Tears Plus (ARTG 127559) eye product, this is in fact a listed device in the ARTG and thus it is not a registered eye product and no toxicological data would have been provided or evaluated for this listed product. The search in the ARTG indicates that calcium chloride, magnesium chloride and carmellose sodium have not been used in any registered eye drop products. Furthermore, the amount of potassium chloride in the proposed product is higher than in any other registered eye products and the amounts of boric acid, borax and sodium chloride are less than in some registered eye products.

A Brief Evaluation of Purite (also called Oxychloro Complex)

Purite is the registered trademark of Allergan.

There are no BP/Ph. Eur. or USP/NF monographs for Purite (or sodium chlorite or chlorite) or products containing it. The specifications were set on the basis of stability studies. All test methods for the parameters in the specification have been described.

Stability

Results of batch stability testing were cosnidered acceptable.

Drug Product

Formulation and manufacture

The formulation contains a novel proprietary preservative Purite, which has not been used in any registered products in the ARTG, though Alphagan P containing Purite has been approved and marked in the USA. Purite is not simply a stabilised solution of sodium chlorite. There are a number of issues related to the use of Purite such as its composition,

instability, potential reactivity and preservative integrity, which have been identified in the evaluation reports.

Specifications

There were some issues relating to the limits of some parameters tested at release and expiry, and in particular several impurity limits. These were subsequently resolved.

Stability

The proposed product is formulated as an isotonic, preserved, sterile solution in a multi-dose eye drop bottle. Purite is known to be degraded by exposure to light. The use of yellow light in some stages of manufacturing is required.

The presence of Purite in the product contributed to the formation of new degradation products and the increased levels of known impurities, when compared with that in the approved Alphagan and Enidin, which do not contain Purite.

Bioavailability

This product is for ocular use only and is intended to act without systemic absorption. As a consequence it is not required that the company provide bioavailability data to the quality evaluator. This is in accordance with the ICH Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98).

Clinical trial formulations

There are 0.1% and 0.15% Phase III formulations and a proposed commercial formation. The 0.15% Phase III formulation used in clinical trial studies is the same as the proposed commercial formulation.

Quality Summary and Conclusions

Approval of the company's application is recommended with respect to chemistry, quality control and bioavailability.

III. Nonclinical Findings

Introduction

Allergan Australia Pty Ltd applied to register Alphagan P/Enidin P, a new formulation and new strength of Alphagan eye drops (containing brimonidine as the active ingredient) for the same indication, the lowering of intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension. The new formulation contains the preservative Purite as a replacement for benzalkonium chloride (BAK). Purite is a novel ingredient in a registered product; as such, the focus of this evaluation is the safety of Purite. The nonclinical data contained single-dose and repeat-dose toxicity, genotoxicity and local tolerance studies with Purite. BAK was used as a comparator in a number of the toxicity studies. The quality of the studies was high, with the majority of these studies conducted under GLP conditions. Nonclinical data also included published literature on the oral toxicity of chlorite, chlorine dioxide and chlorate, the components of Purite. Although studies with brimonidine and Purite in combination were not submitted with this application or referred to by the sponsor, such studies have been submitted previously by the sponsor to support the registration of Combigan. As brimonidine has been assessed previously, and its clinical dose is not increased, discussion of its toxicity in this report is limited to these combination studies.

Seven repeat-dose studies with Purite of up to 6 months duration were submitted. All studies involved topical ocular administration to rabbits, either *via* pre-treated lenses or instillation of eye drops. Previously submitted studies with brimonidine-Purite were included in this

evaluation report to assess the local and systemic effects of the combination. The majority of studies were conducted under GLP conditions. Histopathological analyses were performed on ocular tissues in all of studies with systemic tissues examined in the 6-month studies. The concentration of Purite tested ranged from 50 ppm (the proposed clinical concentration) up to 1000 ppm (Table 3). BAK (100 ppm) was included as a comparator in two studies (Studies TX01062 and TX03045), up to 1 month duration. The dosing regimen used in these studies exceeded the one-drop twice-daily clinical regimen, with at least 3 drops administered per day.

Pharmacology

Purite is included in the formulation as an antimicrobial agent. Purite consists of chlorite (~99.5%) and lesser amounts of chlorate (~0.5%) and chlorine dioxide (trace), and is an oxidising solution that generates free radicals in saline. The free radicals penetrate cell membranes and disrupt cellular function by oxidising lipids and modifying proteins and DNA (reviewed in Noecker, 2001[2]). As eukaryotic cells have antioxidants, oxidases and catalases, it has been reported that they are better able to cope with oxidative preservatives compared with prokaryotic cells. In contrast, detergent preservatives, such as BAK, have equivalent cytotoxicity to eukaryotic and prokaryotic cells (Noecker, 2001)[2]. *In vitro*, Purite produced less cellular damage than BAK to dog kidney epithelial cells with consistent *in vivo* findings seen in the toxicity studies.

Pharmacokinetics

No studies investigating the fate of topically-applied Purite were submitted. Published papers suggest that after ocular administration, Purite is converted to natural tear components (Na^+, Cl^-, O_2 and H_2O) by reactions involving tear-film chemicals combined with photolytic reactions (reviewed in Noecker, 2001).

Relative Exposure

No toxicokinetic data were obtained for Purite. For consideration of systemic effects, relative exposures in submitted studies were calculated based on animal: human doses adjusted for body surface area (BSA). For consideration of local effects, exposure ratios were based on animal: human dose per eye. Relative doses of Purite are tabulated below (Table 3). This is a conservative approach, recognising that the rabbit has a number of anatomical and physiological differences compared with humans that increases its sensitivity to ocular toxicity by predisposing its eyes to longer contact with topical ocular products compared with humans. These include low tear flow, a very low blinking frequency, a large nictitating membrane and a large cul-de-sac which may serve as a reservoir (Lee and Robinson, 1986[3]). Studies using pre-treated lenses are not included in the table. Administered doses exceeded the clinical dose in terms of both systemic and local exposure.

[2] Noecker, R. (2001) Effects of common ophthalmic preservatives on ocular health. *Adv. Ther.* **18:** 205–215.

[3] Lee, V.H.L. and J.R. Robinson. (1986) Review: topical ocular drug delivery: recent developments and future challenges. *J. Ocul. Pharmacol.* **2:** 67–108.

Table 3. Relative doses of Purite used in rabbit repeat-dose studies

Study	Treatment		Daily dose[a]				Relative dose	
	Daily dosing regimen; study duration	ppm	per eye (µg)	Total (µg)	per bw (µg/kg)	per BSA ($\mu g/m^2$)	Systemic	Local
1634-1430-AS5	16 × 35 µL [*single eye*] 1 day	50	28	28	9	108	23	8
1381-1089-3		1000	560	560	187	2244	488	160
TX01062	6 × 70 µL [*single eye*] 7 days	150	63	63	21	252	55	18
		250	105	105	35	420	91	30
		500	210	210	70	840	183	60
TX03045	3 × 70 µL [*single eye*[b]] 1 month	50	10.5	42	14	168	37	3
		150	31.5					9
		300	63	63	21	252	55	18
		1000	210	210	70	840	183	60
1634-1302-1	4 × 35 µL [*single eye*] 6 months	50	7	7	2.3	28	6	2
TX97053	3 × 35 µL [*single eye*] 6 months	70	7.4	7.4	2.5	30	6.5	2
Human	2 × 35 µL[c] [*to each affected eye*]	50	3.5	7	0.14	4.6	–	–

[a] *assuming bodyweights of 3 and 50 kg for rabbits and humans, respectively, and using µg/kg to* $\mu g/m^2$ *conversion factors of 12 and 33 for rabbits and humans, respectively;* [b] *the same animals received 50 ppm in the right eye and 150 ppm in the left eye;* [c] *maximum recommended human dose.*

Clinical studies on the plasma kinetics of brimonidine from brimonidine-Purite 0.15% BID were not performed. However, the plasma kinetics of brimonidine at higher and lower doses (0.1% and 0.2%, respectively) administered TID to both eyes were determined (Clinical Study 190342-006). From the area under the concentration–time curve from 0 h to 8 h ($AUC_{0–8h}$) of 0.14 ng.h/mL and 0.25 ng.h/mL for the 0.1% and 0.2% doses, respectively, the predicted $AUC_{0–12h}$ for brimonidine with the clinical formulation was 0.147 ng.h/mL, and the maximum concentration of drug in serum (C_{max}) 0.032 ng/mL. Doses used in nonclinical combination studies resulted in systemic exposures up to 12-fold the clinical exposure, while local exposures were at or below that expected clinically (Table 4).

Table 4. Relative exposure of brimonidine in repeat-dose studies

Species; Study	Treatment		Daily dose[a]				Relative dose based on:	
	Daily dosing regimen; study duration	%	per eye (µg)	Total (µg)	per bw (µg/kg)	AUC_{0-24h} (ng.h/mL)	AUC	Local dose
Rabbit (NZW) TX97053	3 × 35 µL [*single eye*] 6 months	0.065	68	68	23	1.5	5	0.65
		0.13	137	137	46	3.4	12	1.3
Human	2 × 35 µL[b] [*to each affected eye*]	0.15	105	210	4.2	0.294	–	–

[a]*assuming bodyweights of 3 and 50 kg for rabbits and humans, respectively;* [b]*maximum recommended human dose (both eyes treated twice daily with 1 drop)*

Toxicology

Local toxicity

Solutions containing Purite and carboxymethyl cellulose (CMC; present as an excipient in Alphagan P/Enidin P) were well-tolerated and not associated with any ocular toxicity at Purite concentrations up to 250 ppm and 30 times the clinical local dose (in a 7-day study; see Table 3) or 50 ppm and 3 times the clinical local dose (in a 1-month study; see Table 3). At ≥150 ppm (≥9-times the clinical local dose; 1-month study), mild conjunctival congestion was occasionally seen, and signs of ocular discomfort were observed at≥300 ppm (18 -times the local clinical dose. See Table 3). After 7 days of daily treatment with 60 times the clinical local dose (500 ppm formulation), there was no evidence of corneal or conjunctival damage, however minimal corneal epithelial degeneration was observed in a single animal (of 4 treated) at 1000 ppm (60 times the daily clinical local dose; see Table 3) for 1 month. Greater ocular discomfort and damage was observed with Purite in the absence of CMC; evident as ocular discomfort with depletion of conjunctival goblet cells at 150 ppm (and 18 times the clinical local dose; 7-day study. See Table 3). At 1000 ppm in a 1-day study (the next highest tested concentration; 160 times the local dose) there was an increased incidence of hyperaemia, discharge, conjunctival congestion and swelling after only a single day of treatment. CMC may affect the mucin layer overlying the corneal epithelial membrane, moderating the toxicity of Purite. Similar effects have been reported for BAK (reviewed in Lee and Robinson, 1986[3]).

There were no apparent cumulative toxicity effects with Purite, with no significant corneal damage observed in rabbits with 4-times daily applications of 50 ppm Purite for up to 6 months (2 times the clinical local dose; see Table 3). In a 6 month study in which lenses were treated either with Purite or Purite spiked with higher levels of chlorine dioxide (up to 5.9 ppm compared with ~0.15 ppm), there was no difference in ocular discomfort or toxicity between the two groups.

Greater toxicity was observed with 100 ppm BAK (circa 6 times the local clinical dose in Alphagan) than with 1000 ppm Purite/CMC or 150 ppm Purite without CMC (60 times and 18 times the local clinical dose, respectively). This included a greater incidence, duration and severity of ocular discomfort, together with microscopic evidence of ocular tissue damage (corneal epithelial degeneration and endothelial atrophy as well as a minimal to mild

depletion of conjunctival goblet cells). This is consistent with the detergent properties of BAK, which can cause lysis of cytoplasmic membranes and solubilisation of the intercellular cement of the corneal epithelium (Noecker, 2001[2]) and consistent with *in vitro* cytotoxicity findings. Both CMC (in Alphagan P/Enidin P) and polyvinyl alcohol (present in the Alphagan formulation) have been shown to attenuate the corneal membrane toxicity of BAK (reviewed in Lee and Robinson, 1986[3]). Ideally, to compare the safety of the new formulation with that of the previous one, the comparison should be between Purite/CMC and BAK/polyvinyl alcohol. Nonetheless, sufficient evidence has been presented to suggest that Purite has milder effects on ocular tissue than BAK, particularly in the presence of CMC.

There were no apparent novel or exaggerated ocular toxicities observed with a mixture of brimonidine-Purite/CMC (that is, similar to the clinical formulation) compared with Purite/CMC in a study of 6 months duration. The local doses achieved were 1.3 and 2 times the clinical local dose of brimonidine and Purite, respectively. Though these doses appear low, the actual exposure is likely to be higher in rabbits and therefore there are no additional adverse ocular effects expected for the combination brimonidine-Purite/CMC mixture compared with Purite CMC.

Systemic toxicity

There was no evidence of systemic toxicity after ocular administration of Purite (with or without CMC) at doses up to >480-fold the anticipated clinical exposure on a BSA basis. Rabbits that had received ocular instillations of brimonidine- Purite/CMC, similar to the clinical formulation, displayed a dose-related and transient sedation, consistent with other brimonidine studies. There was also a dose-related, reproducible increase in serum glucose levels at 5 fold the clinical AUC. This brimonidine-induced hyperglycaemia started to occur at 0.5h after dosing, peaked at 1h post-dose and persisted for about 4h. As brimonidine is an a_2-adrenergic receptor agonist, systemic brimonidine may have caused an inhibition of insulin release through receptors on pancreatic islet b cells thereby inducing the observed hyperglycaemia. Hyperglycaemia was also observed with ocular administration of brimonidine-BAK formulations in previously evaluated studies.

As systemic exposure with Purite may occur in the event of a defective epithelium or corneal ulcers, oral toxicity studies with chlorite and chlorine dioxide (the main components of Purite) submitted by the Sponsor were examined. The toxicities observed in rats and monkeys after oral administration were consistent with the oxidative nature of chlorite; reduced blood glutathione and red blood cell parameters (erythrocytes, haemoglobin and haematocrit) and increased methaemoglobin; as well as decreased serum thyroxine levels in monkeys, of unknown aetiology. The No Observed Effect Level (NOEL) was established at 10 mg/kg/day chlorite orally (PO) in both rats and monkeys (Harrington *et al.*, 1995; Bercz *et al.*, 1982[4]). This is circa 13,000 and 26,000 times, respectively, the clinical dose on a BSA basis, assuming equivalent bioavailability by the two administration routes.

[4] Harrington, R.M., R.R. Romano, D. Gates and P. Ridgway. (1995) Subchronic toxicity of sodium chlorite in the rat. *J. Am. College Toxicol.* **14:** 21–33. and Bercz, J.P., L. Jones, L. Garner, D. Murray, D.A. Ludwig and J. Boston. (1982) Subchronic toxicity of chlorine dioxide and related compounds in drinking water in the nonhuman primate. *Environ. Health Perspect.* **46:** 47–55.

Genotoxicity and carcinogenicity

Purite was tested for mutagenicity in an Ames test. The set of bacterial strains used and the concentrations tested were appropriate and the test was adequately validated. There was no evidence of genotoxicity in the submitted study. Previously, both sodium chlorite and chlorine dioxide have given variable results in bacterial mutagenicity and *in vivo* clastogenicity tests, while only sodium chlorite appeared clastogenic in a Chinese hamster fibroblast cell line (reviewed in Harrington *et al.*, 1989[5]). Based on the weight of evidence, Purite is likely to have a low genotoxic potential. Of particular interest though, in the submitted Ames test, there was a lack of any apparent antimicrobial activity at the highest concentration of Purite (10 mg/plate). This was unexpected as Purite is added to the formulation as a preservative and antimicrobial agent. Purite has lower antimicrobial activity than BAK and it has been suggested that it may also be less effective as a preservative (Charnock, 2006[6]). The efficacy of Purite as a preservative, however, is an issue for the quality evaluator.

Carcinogenicity studies with Purite administered by the clinical route were not submitted. However, published papers indicated no test-item related tumours were observed after oral administration of sodium chlorite (100 and 60 mg/kg/day PO, respectively; ER >48,000[7]) in mice and rats treated for up to 85 weeks (Kurokawa *et al.*, 1986[8]). Similarly, no treatment-related skin tumours were observed in mice that had been topically dosed with sodium chlorite (4 mg/mouse; ER >77,000 on a BSA basis) twice a week for 51 weeks (Kurokawa *et al.*, 1984[9]). While dermally-applied sodium chlorite (4 mg/mouse) was suggested to be a possible tumour promoter (Kurokawa *et al.*, 1984[9]), SC-administered chlorine dioxide (0.63 mg/mouse[10]; ER >16,000) was not (Bull, 1980[11]). Taken together, there are unlikely to be carcinogenic concerns at the proposed clinical dose of Purite.

[5] Harrington, R.M., D. Gates and R.R. Romano. (1989) A review of the uses, chemistry and health effects of chlorine dioxide and the chlorite ion. *Chemical Manufacturers Association, Washington, DC.*

[6] Charnock, C. (2006) Are multidose over-the-counter artificial tears adequately preserved? *Cornea* **4:** 432–437.

[7] ER = animal: human dose ratio for chlorite based on body surface area; sodium chlorite is 74.6% chlorite by weight

[8] Kurokawa, Y., S. Takayama, Y. Konishi, Y. Hiasa, S. Asahina, M. Takahashi, A. Maekawa and Y. Hayashi. (1986) Long-term *in vivo* carcinogenicity tests of potassium bromate, sodium hypochlorite, and sodium chlorite conducted in Japan. *Environ. Health Perspect.* **69:** 221–235.

[9] Kurokawa, Y., N. Takamura, Y. Matsushima, T. Imazawa and Y. Hayashi. (1984) Studies on the promoting and complete carcinogenic activities of some oxidising chemicals in skin carcinogenesis. *Cancer Lett.* **24:** 299–304.

[10] A 2–2.5 mg/L chlorine dioxide solution was concentrated 168× to 420 mg/L and 1.5 mL applied SC (Bull, 1980)

[11] Bull, B.J. (1980) Health effects of alternate disinfectants and their reaction products. *Am. Water Works Assoc. J* **72:** 299–303.

Reproductive toxicity

No effect on male or female fertility was observed in Long-Evans rats treated orally with 10 mg/kg/day chlorine dioxide prior to mating (Carlton *et al.*, 1991[12]). However, in female A/J mice treated orally with 2 mg/kg/day sodium chlorite (ER ~970), *ca* 17% lower conception rates were observed (Moore *et al.*, 1980[13]). In a published embryofetal study, SD rats received sodium chlorite (PO or IP) during the period of organogenesis (GD 8–15) (Couri *et al.*, 1982[14]). At ≥20 mg/kg/day IP, there was a significant increase in the number of stillbirths and resorptions with a concomitant reduction in litter size. However, there were no significant gross soft tissue or skeletal malformations at doses up to 50 mg/kg/day intraperitoneally (IP) or 200 mg/kg/day PO. There was no effect on gestation duration or litter size in A/J mice that had received 2 mg/kg/day PO (100 ppm in drinking water; ER ~970) sodium chlorite through gestation and lactation (Moore *et al.*, 1980[13]). However, lower birth weights and post-natal body weight gain were observed in the F_1 progeny of treated dams (Moore *et al.*, 1980[13]). Based on adverse reproductive effects only occurring at doses of chlorite far exceeding that expected clinically with Alphagan P, there are unlikely to be reproductive concerns.

Skin sensitisation

Purite was not a skin sensitiser in an adequately conducted and validated guinea pig maximisation test.

Nonclinical Summary and Conclusions

The toxicity of Purite was assessed in repeat-dose topical ocular studies in rabbits. Dosing frequency exceeded the twice daily regimen in patients. Treated rabbits had a greater tolerance of Purite/CMC solutions than Purite solutions lacking CMC. No ocular toxicity was evident with Purite (+CMC) solutions at 50 ppm and 3 times the clinical local daily dose, while mild conjunctival congestion was occasionally seen at 150 ppm (and 9 times the clinical local dose) and signs of ocular discomfort were observed at≥300 ppm (and 18 times the clinical local dose). There was no evidence of corneal or conjunctival damage after 7 daily treatments with a 500 ppm formulation (60 times the clinical local dose), but after 1 month with treatment with a 1000 ppm formulation at an equivalent local dose, minimal corneal epithelial degeneration was observed in a single animal. In the absence of CMC, ocular discomfort was apparent with Purite at 150 ppm (18 times the clinical local dose), together with depletion of conjunctival goblet cells, and at 1000 ppm in a 1-day study (160 times the clinical local dose), conjunctival congestion and swelling with hyperaemia were observed.

Greater ocular damage was observed with 100 ppm BAK than 1000 ppm Purite/CMC or 150 ppm Purite without CMC. This included greater incidence, duration and severity of

[12] Carlton, B.D., A.H. Basaran, L.E. Mezza, E.L. George and M.K. Smith. (1991) Reproductive effects in Long-Evans rats exposed to chlorine dioxide. *Environ. Res.* **56:** 170–177.

[13] Moore, G.S., E.J. Calabrese and D.A. Leonard. (1980) Effects of chlorite exposure on conception rate and litters of A/J strain mice. *Bull. Environ. Contam. Toxicol.* **25:** 689–696.

[14] Couri, D., C.H. Miller, Jr, R.J. Bull, J.M. Delphia and E.M. Ammar. (1982) Assessment of maternal toxicity, embryotoxicity and teratogenic potential of sodium chlorite in Sprague-Dawley rats. *Environ. Health Perspect.* **46:** 25–29.

ocular discomfort, corneal epithelial degeneration and endothelial atrophy and depletion of conjunctival goblet cells. BAK had greater epithelial cytotoxicity *in vitro* than Purite.

There was no evidence of systemic toxicity with ocularly-applied Purite up to >480 times the clinical dose, based on body surface area.

In two previously-submitted studies with eye drop formulations containing brimonidine and Purite/CMC in combination, there was no evidence of ocular toxicity in rabbits that received 1.3 and 2 times the clinical local dose of brimonidine and Purite, respectively, for 6 months. Brimonidine-induced hyperglycaemia was observed at 5 times the anticipated clinical AUC.

Purite and its components were not apparently genotoxic or carcinogenic.

Reduced fertility was observed in female mice treated orally with 2 mg/kg/day sodium chlorite, almost 1000 times the clinical dose based on BSA. At doses≥20 mg/kg/day IP to pregnant rats during the period of organogenesis, there was a significant increase in the number of stillbirths and resorptions but no evidence of teratogenicity. In a pre/postnatal study in mice, lower birth weights and postnatal growth were observed in progeny from dams that had received 2 mg/kg/day sodium chlorite, *ca* 970 times the anticipated clinical exposure.

Purite was not a skin sensitiser in a guinea pig maximisation test.

Nonclinical data indicated that Purite/CMC was milder on ocular tissues and had lower epithelial cytotoxicity than BAK, supporting the use of this alternative preservative.

Adverse effects on reproductive parameters occurred at sufficiently high chlorite exposures to be not of particular concern for the proposed dose and administration route.

There are no objections on nonclinical grounds to the registration of Alphagan P/Enidin P for the proposed indication.

IV. Clinical Findings

Introduction

Overview of submitted data

Phase 3 studies were:

- Study 190342-017 ('Study 017'): a pivotal, three month study of brimonidine 0.15% in Purite-containing vehicle versus Alphagan, using BID dosing, in 391 patients with IOP already controlled by use of Alphagan for at least 6 weeks. This was the only study to use the proposed dosing regimen.
- Two supportive, double-blind, randomised, parallel group, active control 12 month studies of brimonidine 0.15% in Purite-containing vehicle versus brominidine 0.2% in Purite-containing vehicle versus Alphagan; TID dosing was used.
    - Study 190342-007 (Study 007): n=593
    - Study 190342-008 (Study 008): n=554

  Pooled data were also presented.

The Phase 3 studies used a non-inferiority margin of a difference of <1.5 mm of mercury (Hg) in IOP. Additional studies were:

- Two dose-ranging, Phase 2, one month efficacy/safety studies (n=103; 122) using TID (Study 190342-004) or BID (Study 190342-005) dosing of brimonidine 0.1% and 0.2% in the Purite-containing vehicle, versus a third arm given vehicle only, and versus a fourth arm as follows:
  - in Study 004 (TID dosing): Alphagan
  - in Study 005 (BID dosing): Timoptic (timolol maleate)

  The proposed dose (0.15%) was not used in these two studies.
- One pharmacokinetic/ tolerability study (190342-006 [Study 006]; n=39 healthy subjects), using single and multiple doses, to 28 days, measuring plasma levels of brimonidine.

Pharmacokinetics

The introduction to Study 008 mentions non-clinical findings that Brimonidine-Purite 0.2% produced approximately twice the aqueous humour and plasma concentrations of brimonidine as Alphagan (Studies PK-97-030; PK-97-P009). Altered systemic bioavailability of a Purite-containing formulation (even one containing less brimonidine, for example, 0.15%) would therefore be important to investigate, as there may be safety implications.

According to the introduction to Study 006, kinetics of Alphagan were investigated in healthy volunteers after single ocular administration in Study PK-1991-035 and A342-120-8042 and in a dose-proportionality study, A342-119-7831 [none of these was in the Clinical data module of this Dossier]. Maximum plasma concentrations were <0.3 ng/mL; C_{max} in plasma occurred 1-4 hrs after ocular administration. In a steady-state study, PK-95-042, after one week of BID dosing of Alphagan to healthy volunteers, mean plasma concentrations of brimonidine peaked at 0.05-0.06 ng/mL after about 2.2 hrs.

Study 190342-006

This study of systemic brimonidine PK was conducted from March to May 1998 at one US site. It did not examine the proposed dose of 0.15% brimonidine, but examined lower (0.10%) and higher (0.20%) doses with a vehicle arm as comparator. It did not examine twice daily dosing, but rather examined three times daily dosing. It did not compare Alphagan P with Alphagan, so only cross-study (historical) comparison is available to allow comparison of bioavailability for the two formulations.

In addition to examining systemic brimonidine PK, the study aimed to assess pharmacodynamic effects of brimonidine on glucose metabolism. Non-clinical studies suggested a hyperglycaemic effect of brimonidine, mediated by interaction of brimonidine with α_{2A} receptors causing inhibition of insulin secretion from pancreatic β cells.

The study was double-masked (double-blinded).

Thirty-nine healthy subjects were enrolled. Inclusion criteria included: age ≥18 years (yrs); general good health; weight within 15% of normal; normal screening for fasting glucose/ glucose challenge/ C-peptide/ glycosylated haemoglobin (HbA_1C); non-smoker; IOP 12-21 mmHg with ≤5 mmHg asymmetry; best corrected ETDRS (Early Treatment Diabetic Retinopathy Study) visual acuity equal to or better than 20/80 in each eye. Exclusion criteria included: females who were pregnant or nursing or Women of Childbearing Potential (WOCBP) without contraception; active ocular or systemic disease; history of diabetes or glucose intolerance in subject or immediate family. The sponsor justified use of subjects as young as 18 yrs by reference to Study PK-1993-074, which "showed that the kinetics are not significantly influenced by age".

There were 21 males and 18 females. Mean age was 33.4 yrs (range, 18-63) – about half the average age of subjects in the efficacy studies. (By contrast, in the pivotal PK study for Alphagan, an 'elderly' cohort of ages 65-73 yrs was examined in addition to a younger cohort of ages 23-39 yrs.) Mean age in the lower strength active treatment group was 36.9 yrs, the higher strength 32.8 yrs and the vehicle 30.5 yrs.

Subjects were randomised to one of three groups:

(1) brimonidine-Purite 0.2% ophthalmic solution (Allergan formulation 9115X)
(2) brimonidine-Purite 0.1% ophthalmic solution (Allergan formulation 9118X)
(3) brimonidine-Purite vehicle ophthalmic solution (Allergan formulation 9117X)

Treatments were given to both eyes, TID, for 27⅓ days.

There were 4 study visits (some involving staying at the clinic overnight): screening; Days 0-1; Days 6-8 and Days 27-28. PK blood sampling was performed following doses given on Days 1, 7, 8 and 28. For Days 1 and 7, there were 12 samples over 8 hours (including pre-dose). For Days 8 and 28, there were single samples at 1 hour post-dose. The gas chromatography-mass spectroscopy (GC-MS) assay used had a lower limit of quantitation of 2 pg/mL, and an upper limit of 1000 pg/mL.

Glucose metabolism was assessed at screening with a glucose tolerance test / total HbA_1C/ C-peptide. Glucose levels were measured pre- and 1 and 3 hours after drug on Days 8 and 28; an oral glucose tolerance test was conducted on Day 8 and 28; total HbA_1C was measured on Day 28.

Table 5 summarises PK results from analysis of plasma concentrations of brimonidine over time at Days 1 and 7. Plasma concentrations of brimonidine did not exceed 0.15 ng/mL in any individual. There was evidence of modest accumulation from Day 1 to Day 7, in that AUC_{0-t} rose from Day 1 to Day 7 in both active treatment groups (for 0.1%, from 79.3 pg.hr/mL to 127 pg.hr/mL; for 0.2%, from 211 pg.hr/mL to 245 pg.hr/mL), although differences from Day 1 to Day 7 were only statistically significant for the 0.1% group. Changes from the lower to the upper dose strength were broadly dose proportional, supporting extrapolation of data to the 0.15% dose strength.

Comparison of 1 hour post-dose concentration results at Days 1, 7, 8 and 28 was used to show that steady-state had been reached by Day 7.

Table 5 – Study 006 – Summary of selected PK parameters

Collection Day		C_{max} (pg/mL)	t_{max} (Hour)	AUC_{0-t} (pg•hr/mL)	AUC_{0-8} (pg•hr/mL)	$t_{1/2}$ (Hour)
		Brimonidine-Purite™ 0.1%				
1	Mean	23.3	1.54	79.3	NA	NA
	SD	14.07	0.660	47.78	NA	NA
	n	13	13	12	NA	NA
7	Mean	30.0	1.50	127	136	1.88
	SD	17.78	0.677	86.8	84.8	0.809
	n	13	13	13	12	12
		Brimonidine-Purite™ 0.2%				
1	Mean	48.4	1.77	211	NA	NA
	SD	35.10	0.599	147.0	NA	NA
	n	13	13	13	NA	NA
7	Mean	64.7	1.35	245	245	1.95
	SD	37.76	0.944	124.1	123.8	0.628
	n	13	13	13	13	13

AUC_{0-t} Area under the plasma concentration-time curve to the last measurable plasma concentration.
AUC_{0-8} Area under the plasma concentration time curve from Hours 0 to 8 on Day 7.
C_{max} Maximum plasma concentration.
n Number of points used in the mean calculation of each parameter.
$t_{1/2}$ Apparent terminal half-life.
t_{max} Time to maximum plasma concentration.

Comparison of PK between brimonidine 0.2% Purite and Alphagan was made in the sponsor's Clinical Overview. No submitted clinical study directly compared the ocular or systemic bioavailability of the two products. Alphagan data were from Study PK-95-042. It was appreciated that "conclusions drawn from such comparisons are not ideal". The sponsor presented the following table:

Table 6

Formulation	**Day**	**Number**	**T_{max} (hr)**	**C_{max} (pg/mL)**	**$AUC_{interval}$ (pg.hr/mL)[1]**	**AUC_{0-24} (pg.hr/mL)[2]**
Brimonidine Purite 0.2% TID	7	13 (7M+6F)	1.35 +/- 0.94	64.7 +/- 37.8	245 +/- 124	735
Alphagan 0.2% BID	10	7 (3M+4F)	2.21 +/- 0.57	58.5 +/- 29.9	309 +/- 142	618

[1] calculated during one interval of 8 hrs for TID dosing or 12 hrs for BID dosing. [2] calculated as mean AUC_{0-8} x 3 or as mean AUC_{0-12} x 2. T_{max}= time to maximum concentration of drug in serum

In the sponsor's Clinical Overview, results of modelling (using the technique of "nonparametric superposition") were presented that gave predicted PK results for single dose and steady state 0.15% brimonidine Purite BID. Predicted C_{max} and AUC_{0-12} values following 0.15% brimonidine Purite BID for 7 days to both eyes of healthy subjects were 32.3 pg/mL and 147 pg.hr/mL respectively. These results were identical to those predicted after a single dose. *Actual data showed higher C_{max} and higher AUC at Day 7 than at Day 1 for both 0.1% and 0.2% products used TID, so modelling that indicates no change from Day 1 to Day 7 for an intermediate strength product is difficult to interpret. While twice daily dosing would seemingly make accumulation less likely, modelling does not provide strong grounds to accept absence of accumulation. Indeed, for Alphagan, BID dosing for 10 days in healthy subjects resulted in slight accumulation (AUC_{0-12hr} after first dose = 228 pg.hr/mL; AUC_{0-12hr} after last dose = 309 pg.hr/mL), as noted in the Summary of Clinical Pharmacology.*

The Sponsor's Clinical Overview briefly addressed the issue of PK in elderly versus younger populations, seemingly in response to the use of a young population in the PK study provided. The only argument provided was that single dose Alphagan data revealed similar C_{max}, AUC and half-life in "adults and the elderly (healthy volunteers)". The sponsor's Summary of Clinical Pharmacology (SCR) notes that in Alphagan Study PK-95-042 there was "slightly greater systemic exposure to brimonidine" in the elderly relative to the young (AUC_{0-12hr} 337 pg.hr/mL versus 309 pg.hr/mL; $p>0.05$). Considerable inter-subject variation in systemic exposure was noted (AUC_{0-12hr} range, 48-672 pg.hr/mL after one dose).

There were no important changes in glucose metabolism. While HbA1C (the dominate fraction of HbA_1C) was not assayed, total HbA_1C includes changes in HbA1C. Change in this parameter over 28 days is not very informative.

Intraocular pressure (IOP) monitoring was included as part of the safety evaluation in this study of healthy subjects. Mean change in IOP in active treatment groups was about -2.5 to -3.4 mmHg on all study visits after baseline, which the sponsor claimed did not put any subjects at risk. Consistent with this claim, there were no clinically significant findings with respect to ocular examination and clinical laboratory tests.

Along with Adverse Event (AE) monitoring, there was monitoring of blood pressure, heart rate, ocular findings and standard laboratory testing of blood samples for clinical chemistry / haematology, and urinalysis. Given the small size of the study population, only markedly abnormal safety findings will be commented upon.

One subject (in the vehicle group) was discontinued due to supraventicular extrasystoles after the 3rd dose on Day 7. PK findings in this subject were not commented upon. Another subject withdrew due to difficulty with venipuncture.

In the vehicle group there was only one ocular AE reported; in the active groups 6-8 ocular AEs were reported.

There was a consistent decrease in heart rate in the higher dose active treatment arm (that is, the decrease was seen at Day 7 and Day 28; the average decrease was by 8-10 beats per minute, bpm). The average decrease at different post-baseline time points for the lower dose active arm ranged from 2-7 bpm; and for the vehicle arm the average decrease ranged from 2-5 bpm. Thus, there was some evidence of a systemic effect of higher dose brimonidine on heart rate. There was no evidence of any consistent effect on blood pressure.

Drug Interactions

No clinical drug interaction studies were submitted.

Pharmacodynamics

No clinical pharmacodynamic studies were submitted.

Efficacy

Individual efficacy studies

Study 190342-017 (pivotal)

Design and aims

This study was conducted from October 2000 to July 2001 at 23 sites in USA. It examined maintenance of effect in subjects whose IOP was already controlled on Alphagan.

Study population and subject disposition

Inclusion criteria were as follows: age≥18 yrs; ocular hypertension or chronic glaucoma (including chronic primary open angle, pseudoexfoliative, pigmentary, chronic angle closure with a patent peripheral iridectomy / iridotomy for at least 3 months) which required medical therapy in each eye; IOP controlled on Alphagan BID monotherapy for at least 6 weeks prior to study entry; IOP likely to be controlled on monotherapy *[it was not specified how investigators determined this]*; at baseline (Day 0, hour 0, 12 hrs after last instillation of Alphagan), IOP≤21 mmHg in each eye (that is , *IOP relatively controlled by previous maintenance Alphagan therapy)*, and asymmetry≤5 mmHg; best -corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity, score equivalent to a Snellen score of 20/100 or better in each eye; written informed consent; ability to follow study instructions and likely to complete required visits; negative urinary pregnancy test for WOCBP (Women of childbearing potential).

The proposed indication is chronic open angle glaucoma or ocular hypertension; in this study and others, patients with types of glaucoma in addition to open angle glaucoma were allowed. The clinical study report (CSR) did not discuss the frequency of glaucoma sub-types per arm.

Exclusion criteria were as follows: uncontrolled systemic disease; pregnant or nursing females, or WOCBP without reliable contraception; abnormally low or high blood pressure or heart rate *[values were not supplied]*; known allergy or sensitivity to study medications or diagnostic agents; contraindications to brimonidine use, for example, use of Monoamine Oxidase Inhibitor drugs (MAOIs); anticipated initiation or alteration of existing chronic therapy with agents that could substantially effect IOP, for example, systemic adrenergic agents such as β-blockers (but continuation of such medications at a constant dose was permitted); anticipated treatment with adrenergic-augmenting psychotropic drugs (for example, desipramine, amitriptyline); intermittent use of oral, injectable or topical ophthalmic steroids within 21 days prior to study entry, or anticipated use within 21 days prior to a follow-up study visit; current signs or a history of chronic blepharitis; any other active ocular disease (for example, uveitis; ocular infection; severe dry eye) (but patients with cataracts, age-related macular degeneration (ARMD) or background diabetic retinopathy could be enrolled); normal tension glaucoma; corneal abnormalities precluding accurate use of applanation tonometer; required chronic use of other ocular medications (intermittent use of artificial tears was allowed); any ocular surgery (including laser, refractive, intraocular filtering surgery, and so on) within 3 months prior to study entry; visual field loss which was functionally significant, or evidence of progressive field loss over the last year; contraindications to pupil dilation; current or recent (30 days) involvement in another study; any condition which "might put the patient at a significant risk, might confound study results, or might interfere significantly with patient's participation in the study".

Overall, exclusion criteria were not always rigorously defined; inclusion criteria were adequately defined.

Subject disposition. Four hundred and seven (407) patients entered the study. Two hundred and three (203) were randomised to the brimonidine Purite group, and 204 to the Alphagan group. These subjects constituted the intent-to-treat (ITT) dataset. Overall, 95.6% of subjects (389/407) completed the 3 month treatment period.

Nine subjects in each group discontinued the study. One of these 18 patients, in the Alphagan group, discontinued due to lack of efficacy. Two patients in each group discontinued due to allergic conjunctivitis. One patient in the brimonidine Purite group died of a cerebrovascular accident. The low rate of discontinuation in this study relative to Studies 007 and 008 should be seen in the context of previous use of Alphagan in this study.

Six patients (1.5%) were excluded from Per-protocol (PP) analysis due to major protocol deviations (such deviations were specified prior to database lock). It was stated that deviations from protocol were similarly distributed between treatment groups, although no tables were supplied to describe actual deviations. The PP dataset comprised 401 patients (199 in the brimonidine Purite arm, 202 in the Alphagan arm).

Subject demographics. Mean age was 63-64 yrs across arms (overall range, 26-91 yrs). About 8% of subjects were <45 yrs of age; 50.7% of Brimonidine Purite subjects were >65 yrs, while 45.1% of Alphagan subjects were >65 yrs of age. 57% of subjects in each arm were female; 72-76% were Caucasian. Average weight was 81-82 kg. There were no major disparities in other variables (for example, eye colour; visual fields).

Subject baseline characteristics – ocular. The diagnosis for patients was: glaucoma (66.6%); ocular hypertension (31.7%) and mixed (1 eye with glaucoma, the other eye with ocular hypertension) in 1.7%. There were no major disparities in these variables across arms.

Other common ophthalmic disorders were cataract (about 73% across arms), vitreal disease (28-30%), lid disorders (28-30%), conjunctival disorders (26-27%), corneal disease (15-19%), vision abnormalities (13%), retinal abnormalities (12-14%), anterior chamber abnormalities (11-14%) and dry eye (9.9% in the Purite arm, 16.2% in the Alphagan arm; p=0.058). Incidence of choroidal abnormalities was 3.4% for brimonidine Purite and 0.5% for Alphagan (p=0.037). Incidence of neuro-ophthalmologic disorders was 3.0% (Purite) versus 6.4% (Alphagan) (p=0.102); incidence of eye pruritus was 3.4% versus 1.5% respectively (p=0.220).

Pre-study exposure to Alphagan was typically 5 weeks to 3 months (in 51-55%), although about 13% had exposure for 3-6 months, 13% for 6-12 months, 11% for 12-24 months, 7% for 24-36 months and 3% for >36 months.

Subject baseline characteristics – other. There was a tendency towards a higher incidence of prior gastrointestinal disorders in the Purite arm (50.2% versus 41.7%), a higher incidence of systemic hypertension in the Alphagan arm (48.3% versus 57.4%), a higher incidence of endocrine disorders in the Purite arm (14.3% versus 8.8%), and a higher incidence of renal disorders in the Alphagan arm (4.4% versus 8.3%).

Concomitant medications were used by about 90% of subjects; these were commonly lipid lowering drugs, antithrombotic agents, blood pressure lowering agents, Non-steroidal Anti-inflammatory Drugs (NSAIDs)/anti-rheumatic agents, blood glucose lowering agents, anti-peptic ulcer agents, beta-blockers (systemic: 14.3% of subjects), oestrogen replacement therapies, analgesics, anti-depressants and anti-histamines. Use was similar across arms,

although thyroid preparations were used in 12.8% (Purite) versus 5.9% (Alphagan) and the category 'other analgesics and anti-pyretics' was used in 16.7% and 8.8% respectively.

Interventions

Patients with chronic glaucoma or ocular hypertension whose IOP was controlled on Alphagan BID for at least 6 weeks were randomly assigned to one of two treatment groups:

(1) brimonidine Purite™ 0.15% (that is, brimonidine tartrate 0.15% with Purite 0.005%, carboxymethylcellulose sodium 0.5%, purified water / boric acid / sodium borate decahydrate / electrolytes (unspecified amounts), and HCl / NaOH to adjust pH; Allergan formulation number 9174X), or
(2) brimonidine tartrate 0.20% ophthalmic solution (with benzalkonium chloride 0.005%, purified water / polyvinyl alcohol / sodium chloride / sodium citrate / citric acid, and HCl / NaOH to adjust pH) (Alphagan; Allergen formulation number 7831X)

Brimonidine Purite corresponds to Alphagan P in active ingredient and excipients, with the caveat that a full quantitative description of excipients was not included in the relevant section (identity of investigational products) of the sponsor's CSR. It was stated in the sponsor's Clinical Overview that "the 0.15% formulation used during development is identical to that proposed in this application". Likewise, Alphagan as described above corresponds to the registered Alphagan product, although a full quantitative description of excipients was not included.

The two treatment groups were double-masked (double-blinded).

Patients instilled one drop of study medication into each eye twice daily (that is, at 12 hr intervals; once in the morning [07:30-09:30] and once in the evening [19:30-21:30]).

Treatment with randomised medication was for 3 months.

Efficacy methodology

There were 5 scheduled visits: pre-study/ Day 0 (baseline) / Week 2/ Week 6/Month 3.

The primary efficacy variable was IOP. This was measured using a Goldmann applanation tonometer, affixed to a slit lamp, with the patient sitting. During data analysis, the average of 2 measurements was used per eye (or the median of 3 measurements if the first two measures differed by >2 mmHg); for analyses, average IOP from both eyes was used. For mean change from baseline, change from baseline was calculated for each eye then the average was taken. At follow-up visits (Weeks 2, 6 and Month 3), IOP was measured at trough (hour 0, before the morning dose) and at peak effect (hour 2, 2 hrs after the morning dose). It is not clear whether trough or peak IOP control (or some other parameter, for example, area under the curve for IOP) correlates better with protection from progressive disease.

Secondary variables were:

- IOP mean change from baseline at various time-points; mean percentage change from baseline in IOP.
- Analysis of IOP in the PP dataset.
- pharmacoeconomic evaluation at Month 3 (the investigator was asked whether he/ she would continue using the study medication if possible).
- patient satisfaction at some visits (patients rated their satisfaction on a 7-point scale: very dissatisfied/ dissatisfied/ slightly dissatisfied/ neither satisfied nor dissatisfied/ slightly satisfied/ satisfied /very satisfied).
- patient comfort (patients rated their overall comfort using a 6-point scale: soothing / very comfortable / comfortable / uncomfortable / very uncomfortable / intolerable).

Statistical methodology

Three populations were analysed: safety (all randomised patients who received at least one dose)/ ITT (all randomised subjects; used for efficacy analyses) / PP (randomised subjects, excluding those with a major protocol deviation; this dataset was analysed for the primary efficacy variable, but since results were similar between PP and ITT, only ITT results were detailed).

Last Observation Carried Forward (LOCF) methodology was used to impute missing data in the analysis of IOP, but observed values methodology was used for other variables.

A strategy of combined tests of superiority and non-inferiority suggested by Morikawa and Yoshida (1995)[15] was employed in analysis of IOP.

The non-inferiority test's alternative hypothesis was that mean IOP of the brimonidine Purite group is less than 1.5 mmHg greater than that of the Alphagan group. A 2-sided 95% confidence interval around the difference in mean IOP was constructed. If the upper limit of this CI for the difference between brimonidine Purite and Alphagan groups was <1.5 mmHg, the null hypothesis was rejected. This choice of delta was not well justified.

The superiority test's alternative hypothesis was that there was a difference between treatment groups in mean IOP.

All statistical tests were 2-sided. Level of significance for IOP differences was adjusted due to an interim analysis (interim level: $\alpha = 0.005$; final analysis, $\alpha = 0.048$); otherwise, a significance level of $\alpha=0.05$ was used.

The planned interim analysis included 169 patients, and only IOP was studied. To maintain masking, results were not shared with personnel actively involved in clinical monitoring or study site personnel.

Efficacy results

Trough (Hour 0) IOP. Mean Hour 0 IOP values at baseline were 18.88 mmHg for Purite and 19.14 mmHg for Alphagan. *These values are quite close to the stated exclusion threshold of 21 mmHg.* Mean hour 0 IOP at follow-up visits was 19.28-19.51 mmHg for Purite and 19.54-19.71 mmHg for Alphagan. The upper limit of the 95.2% confidence interval around the difference in mean IOP between Purite and Alphagan was <0.37 mmHg at all follow-up time points (see Table 7). The nominated delta was 1.5 mmHg. There was a slight increase in IOP over the 3 months, but this was seen in both arms.

[15]Morikawa T, Yoshida M. A useful testing strategy in Phase III trials: combined test of superiority and test of
equivalence. Journal of Biopharmaceutical Statistics 1995; 5(3):297–306.

Table 7 – Study 017 – Hour 0 IOP with LOCF mean values at each visit (ITT)

Hour 0 Intraocular Pressure (mm Hg) with Last Observation Carried Forward
Mean Values at Each Scheduled Visit
(Intent-to-Treat Population)

Visit		Brimonidine-Purite 0.15% (N=203)	Alphagan (N=204)	P-value[a] Difference[b] 95.2% CI[c]
Baseline	N	203	204	0.130
	Mean	18.88	19.14	-0.28
	SD	1.815	2.020	(-0.65, 0.09)
	Median	19.50	19.75	
	Min	11.0	11.5	
	Max	21.5	31.0	
Week 2	N	203	204	0.307
	Mean	19.28	19.54	-0.26
	SD	2.402	2.931	(-0.78, 0.25)
	Median	19.50	19.50	
	Min	12.5	11.5	
	Max	25.5	29.0	
Week 6	N	203	203	0.499
	Mean	19.51	19.68	-0.19
	SD	2.664	3.255	(-0.76, 0.37)
	Median	19.25	20.00	
	Min	11.5	11.3	
	Max	27.0	32.8	
Month 3	N	203	204	0.415
	Mean	19.49	19.71	-0.23
	SD	2.812	3.019	(-0.79, 0.33)
	Median	19.50	20.00	
	Min	12.5	11.3	
	Max	34.5	29.0	

[a] P-value for between-group comparison at each visit based on the 2-way analysis of variance with treatment and site as model terms.
[b] Estimated difference was based on the least-squares means from the analysis of variance model. The difference was calculated by Brimonidine-Purite 0.15% group minus Alphagan group.
[c] 95.2% confidence interval of the estimated difference.

Peak effect (Hour 2) IOP. Mean Hour 2 IOP values at baseline (that is, pre-commencement of randomised study medication, but after usual Alphagan) were 16.11 mmHg for Purite and 16.30 mmHg for Alphagan. Values at this hour at follow-up were 16.45-16.59 mmHg for Purite and 16.39-16.70 for Alphagan. The upper limit of the 95.2% CI around the difference in mean IOP between Purite and Alphagan was≤0.64 mmHg at all time po ints (see Table 8).

Table 8 – Study 017 – Hour 2 IOP with LOCF mean values at each visit (ITT)

Hour 2 Intraocular Pressure (mm Hg) with Last Observation Carried Forward
Mean Values at Each Scheduled Visit
(Intent-to-Treat Population)

Visit		Brimonidine-Purite 0.15% (N=203)	Alphagan (N=204)	P-value[a] Difference[b] 95.2% CI[c]
Baseline	N	203	204	0.378
	Mean	16.11	16.30	-0.22
	SD	2.507	2.675	(-0.73, 0.28)
	Median	16.50	16.50	
	Min	8.0	10.0	
	Max	21.8	22.3	
Week 2	N	203	204	0.777
	Mean	16.45	16.49	-0.07
	SD	2.560	2.890	(-0.59, 0.44)
	Median	16.75	16.50	
	Min	9.0	9.8	
	Max	23.5	26.0	
Week 6	N	202	203	0.714
	Mean	16.55	16.39	0.10
	SD	2.603	3.000	(-0.44, 0.64)
	Median	16.50	16.00	
	Min	9.5	7.5	
	Max	25.0	28.0	
Month 3	N	203	204	0.640
	Mean	16.59	16.70	-0.13
	SD	2.884	2.910	(-0.69, 0.43)
	Median	16.50	16.75	
	Min	9.0	10.0	
	Max	28.5	28.0	

[a] P-value for between-group comparison at each visit based on the 2-way analysis of variance with treatment and site as model terms.
[b] Estimated difference was based on the least-squares means from the analysis of variance model. The difference was calculated by Brimonidine-Purite 0.15% group minus Alphagan group.
[c] 95.2% confidence interval of the estimated difference.

Change from baseline. For trough (Hour 0) results, the upper limit of the 95% CI around the difference in mean IOP change from baseline between Purite and Alphagan was ≤0.60 mmHg at all time points. For peak effect (Hour 2) results, the upper limit was ≤0.79 mmHg at all time points; the greatest disparity was at Week 6 where the change (that is, increase in or worsening of IOP) from baseline was 0.43 mmHg for Purite but only 0.08 mmHg for Alphagan; in the PP dataset this difference in favour of Alphagan was 0.50 mmHg and reached statistical significance (p=0.032), but even here non-inferiority of Purite was technically established (upper limit of 95% CI around difference between arms for this parameter was 0.96 mmHg). There was no such disparity either at Week 2 or at Month 3.

Clinical success as defined by the investigator, using the question 'Would you continue the patient on this medication?' Clinical success was achieved in 87.4% of the Purite arm and 83.7% of the Alphagan arm (p=0.283).

Patient comfort and patient satisfaction. At the pre-study visit, about 96% of subjects were finding Alphagan comfortable; 3.4% (Purite) and 4.4% (Alphagan) were 'less than comfortable'. At two Weeks 1% and 5.9% were 'less than comfortable', and at 3 months

0.5% and 2.1% were 'less than comfortable'. These results corresponded to results for patient satisfaction.

Evaluator comments

Trough IOP indicates 'worst case' decrease in IOP with treatment over a day, whereas peak effect IOP indicates the best case scenario. The sponsor did not comment on which surrogate endpoint was more relevant for protection of the optic nerve from damage.

This study selected patients who were on maintenance Alphagan, that is, that had not discontinued Alphagan, for example, due to lack of efficacy or problems with AEs. Thus, results will show exaggerated efficacy and safety relative to a naïve population. In the population studied, there was evidence of the non-inferiority of Purite relative to Alphagan. There is no evidence that Purite and Alphagan will produce a similar level of treatment discontinuation in a naïve population.

The magnitude of effect was apparently not great, but subjects' IOP was already ostensibly controlled by Alphagan at the time of study medication commencement. At the time of peak effect, the mean change in IOP was around 2 mmHg. The fraction of subjects with more substantial falls (for example, >3 mmHg) was not reported.

The study does not provide long-term data. Patients were studied for only 3 months. Long-term changes in IOP are of relevance for preserving vision in glaucoma.

The sponsor stated: "the comparable efficacy, despite lower concentrations [in the formulation] of brimonidine, is believed to be due to the higher bioavailability of brimonidine in the new formulation". This claim was supported by reference to rabbit studies. The sponsor asserted without further evidence that: "factors that contributed to this finding are likely the presence of the stabilised oxychloro complex preservative, Purite and the higher pH of Brimonidine Purite 0.15% compared to Alphagan (~7.2 versus ~6.5)".

Study 190342-007 (supportive)

Design and aims

This study was conducted from October 1998 to June 2000 at 23 US sites. The study was randomised and double-masked. The study examined subjects with uncontrolled elevated IOP.

Study population and subject disposition

Inclusion criteria differed from Study 017 in that subjects required baseline IOP ≥22 mmHg and ≤34 mmHg in each eye (and asymmetry of IOP of ≤5 mmHg), and also required visual field results within 6 months of the study start.

Exclusion criteria were broadly similar to those of Study 017, although use of contact lenses during the study and corneal grafts / refractive surgery (for sites performing endothelial cell counts) were also exclusions, while recent use of corticosteroids and presence of chronic mild blepharitis were not exclusions in this study. Patients on anti-glaucoma medications were required to have adequate wash-out periods (4-28 days depending on drug), and use of concomitant medications for ocular indications (other than artificial tears) was not allowed.

Subject disposition. 593 patients were enrolled: 197 were randomised to a "0.15% / Purite" arm (1/197 received no study drug), 197 to a "0.20% / Purite" arm and 199 to an Alphagan arm.

67.1% of patients completed the 12 month study; 31.5-33.7% of subjects across arms discontinued early. Most commonly, discontinuation was due to AEs (21.8% of all subjects),

and most such AEs were ocular. For a drug meant for long-term use, this is a relatively high percentage. Discontinuation due to ocular AEs occurred in 16.2% of "0.15%/ Purite" subjects, 17.3% of "0.20%/ Purite" subjects and 25.1% of Alphagan subjects. Inefficacy was the cause of discontinuation in 5.4% of subjects (specifically, in 7.6% of "0.15%/ Purite" subjects, 5.1% of "0.20%/ Purite" subjects and 3.5% of Alphagan subjects).

The PP dataset comprised 193 patients in the "0.15%/ Purite" group, 193 patients in the "0.20%/ Purite" group and 197 patients in the Alphagan group.

Subject demographics. Groups were balanced with respect to age (mean age 61.4 yrs), sex (56.2% female), race (74% Caucasian), iris colour, weight (mean 82.9 kg) and height.

Subject baseline characteristics – ocular. There was no statistically significant difference across groups with regard to history of ophthalmic disorders. Diagnosis for study inclusion was glaucoma in 57.7%, ocular hypertension in 42.2% and mixed in 0.17%. Baseline IOP was measured at hours 0, 2, 7 and 9 (to assess diurnal fluctuation and allow comparison at subsequent visits with the matching baseline 'hour' IOP), and mean values ranged from 21.7-24.9 mmHg for "0.15% / Purite", 21.8-24.8 mmHg for "0.20% / Purite" and 21.6-24.7 mmHg for Alphagan.

Washout of ophthalmic medication was required in 52-61% of patients, implying that the remaining subjects were treatment-naïve or at least not recently treated. Non-selective β-blockers were most commonly used.

Subject baseline characteristics – other. There was no statistically significant difference across groups with regard to medical history.

Interventions

Subjects with glaucoma or ocular hypertension were randomly assigned (2:2:2, block size 6) to one of three treatment groups:

(1) Brimonidine Purite 0.15% (Allergan formulation number 9174X)
(2) Brimonidine Purite 0.20% (Allergan formulation number 9115X)
(3) Alphagan (brimonidine tartrate 0.20% with BAK preservative) (Allergan formulation number 7831X)

Subjects instilled one drop of study medication into each eye three times daily (TID; 07:30-08:30, 14:30-15:30 and 21:30-22:30) for 12 months.

Efficacy methodology

Effectiveness in this study was considered as lowering of IOP by≥3 mmHg from baseline.

IOP was the primary efficacy variable, measured with a Goldmann applanation tonometer. IOP was measured at trough (hour 0) and at Hours 2, 7 and 9 at baseline, Week 6, Month 3, Month 6 and Month 12. (NB, Hours 7 and 9 presumably correspond to Hours 0 and 2 for the 2nd dose of the day.) IOP was also measured at Hour 0 and Hour 2 at Week 2 and Month 9. Thus, after baseline, there were a total of 20 planned IOP measurements per subject.

Secondary efficacy variables were similar to those in Study 017.

Statistical methodology

Each of the Purite arms was compared for non-inferiority to the Alphagan arm. Comparison of the two Purite arms was secondary. For non-inferiority testing relative to Alphagan, methodology was as per Study 017 (that is, for non-inferiority, upper limit of 95% CI around difference was not to exceed 1.5 mmHg).

Co-primary analyses were an ITT LOCF analysis, and a PP Observed Values analysis. Results in both datasets were stated to be similar (despite the significant fraction of subjects who discontinued) so only ITT LOCF analyses were detailed.

Between group differences were calculated by subtracting the value for Alphagan from the value for a Purite group (so a negative between-group difference favours Purite); likewise, a negative difference in the comparison of Purite arms favours the 0.15% Purite arm.

Efficacy results

Results were presented by visit. Although the CSR does not specify this, the final visit results are taken to be primary in this evaluation, since these results will best indicate durability of effect (an important consideration for a chronic treatment). At each visit, non-inferiority was assessed for each discrete IOP measurement time-point (by comparing the upper limit of the 95% CI around the difference between study arms with the pre-specified threshold of 1.5 mmHg). IOP and change in IOP from baseline were studied separately. ITT and PP datasets were analysed separately.

- At Week 2, ITT IOP results at trough and at 2 hours supported non-inferiority of Purite products relative to Alphagan.
- At Week 6, ITT IOP results at trough and at 2, 7 and 9 hours supported non-inferiority of Purite products relative to Alphagan.
- At Month 3, all ITT IOP results supported non-inferiority of Purite products relative to Alphagan, except for the 9 hour comparison of "0.15% / Purite" versus Alphagan, where the upper limit of the 95% CI was 1.68 mmHg (that is, above the pre-specified threshold of 1.5 mmHg).
- At Month 6, all ITT IOP results supported non-inferiority of Purite products relative to Alphagan, except for the 9 hour comparison of "0.15% / Purite" versus Alphagan where the upper limit of the 95% CI was 1.51 mmHg, and for the 0 hour comparison of "0.20% / Purite" versus Alphagan, where the upper limit was 1.73 mmHg.
- At Month 9, all ITT IOP results supported non-inferiority of Purite products relative to Alphagan, except for the 0 hour comparison of "0.15% / Purite" versus Alphagan, where the upper limit of the 95% CI was 1.62 mmHg. In the PP dataset, at hour 0, non-inferiority was not supported for Purite products.
- At Month 12, all ITT IOP results supported non-inferiority of Purite products relative to Alphagan. Raw ITT LOCF IOP values are shown in Table 9. In the PP dataset, at hours 0 and 2, non-inferiority was not supported for "0.15% / Purite". Raw PP Observed Values IOP values are shown in Table 10.

Table 9. – Study 007 – Diurnal IOP (mmHg) at month 12; ITT dataset; mean values at each time point

Diurnal Intraocular Pressure (mm Hg) at Month 12
Mean Values at Each Timepoint

(Intent-to-Treat LOCF Analysis)

Timepoint		Brimonidine-Purite^ 0.15% (N=197)	Brimonidine-Purite^ 0.2% (N=197)	ALPHAGAN-P (N=199)
Hour 0	N	197	197	199
	Mean	21.6	21.8	21.3
	SD	4.1	4.2	4.1
	Min	10.5	12.5	13.5
	Max	34.0	40.0	51.0
Hour 2	N	197	197	199
	Mean	18.6	18.1	18.1
	SD	3.8	3.7	3.7
	Min	9.0	8.5	10.5
	Max	29.0	34.5	34.0
Hour 7	N	197	197	199
	Mean	19.9	19.7	19.6
	SD	3.9	3.7	3.7
	Min	11.5	8.0	11.0
	Max	30.0	35.0	35.0
Hour 9	N	197	197	199
	Mean	17.9	17.3	17.4
	SD	3.8	3.6	3.6
	Min	9.5	9.0	9.5
	Max	28.0	30.5	31.0

Table 10. Study 007. Diurnal IOP (mmHg) at month 12/PP dataset/mean values at each time point

Diurnal Intraocular Pressure (mm Hg) at Month 12
Mean Values at Each Timepoint

(Per Protocol Analysis)

Timepoint		Brimonidine-Purite^ 0.15% (N=193)	Brimonidine-Purite^ 0.2% (N=193)	ALPHAGAN-P (N=197)
Hour 0	N	119	130	114
	Mean	21.7	21.0	21.0
	SD	3.6	3.5	3.4
	Min	11.0	12.5	13.5
	Max	34.0	33.5	34.0
Hour 2	N	121	130	115
	Mean	18.4	17.4	17.7
	SD	3.6	3.3	3.1
	Min	9.0	9.0	10.5
	Max	29.0	27.5	28.5
Hour 7	N	120	130	114
	Mean	19.7	19.1	19.4
	SD	3.8	3.5	3.3
	Min	12.5	8.0	11.0
	Max	30.0	30.0	29.0
Hour 9	N	120	128	115
	Mean	17.4	16.8	17.2
	SD	3.5	3.3	3.3
	Min	9.5	9.0	9.5
	Max	28.0	27.5	27.0

Table 11 – Study 007 – Change from baseline in diurnal IOP (mmHg) at month 12; ITT dataset; mean values at each time point

Diurnal Intraocular Pressure (mm Hg) at Month 12
Mean Changes from Baseline at Each Timepoint

(Intent-to-Treat LOCF Analysis)

Timepoint		Brimonidine-Purite^ 0.15% (N=197)	Brimonidine-Purite^ 0.2% (N=197)	ALPHAGAN~ (N=199)
Hour 0	N	197	197	199
	Mean	-3.3	-3.0	-3.4
	SD	3.8	3.9	3.9
	Min	-17.5	-13.5	-13.5
	Max	9.5	14.0	17.0
	P-value[a]	<0.001	<0.001	<0.001
Hour 2	N	197	197	199
	Mean	-4.5	-4.8	-4.9
	SD	4.1	3.8	3.5
	Min	-14.0	-16.5	-13.5
	Max	7.0	9.0	7.5
	P-value[a]	<0.001	<0.001	<0.001
Hour 7	N	197	197	199
	Mean	-1.9	-2.1	-2.3
	SD	3.9	3.3	3.8
	Min	-16.0	-12.0	-14.0
	Max	8.0	8.5	14.0
	P-value[a]	<0.001	<0.001	<0.001
Hour 9	N	197	197	199
	Mean	-3.8	-4.5	-4.3
	SD	3.9	3.6	4.1
	Min	-13.0	-12.5	-18.0
	Max	7.5	4.5	8.0
	P-value[a]	<0.001	<0.001	<0.001

[a] Within-group analysis of changes from baseline using paired t-test.

Analysis of change in IOP from baseline was broadly consistent with the above findings. For month 12, ITT results are shown in Table 11, and PP results are shown in Table 12. Overall, there is a trend for modestly less control of IOP in the "0.15% / Purite" arm than in the other two arms.

Table 12. – Study 007 – Change from baseline in diurnal IOP (mmHg) at month 12; PP dataset; mean values at each time point

Diurnal Intraocular Pressure (mm Hg) at Month 12
Mean Changes from Baseline at Each Timepoint

(Per Protocol Analysis)

Timepoint		Brimonidine-Purite^ 0.15% (N=193)	Brimonidine-Purite^ 0.2% (N=193)	ALPHAGAN-P (N=197)
Hour 0	N	128	135	127
	Mean	-3.4	-3.4	-3.8
	SD	3.5	3.6	3.4
	Min	-13.0	-13.5	-12.0
	Max	9.5	10.0	6.0
	P-value[a]	<0.001	<0.001	<0.001
Hour 2	N	119	126	121
	Mean	-5.3	-5.4	-5.7
	SD	3.8	3.8	3.2
	Min	-14.0	-16.5	-13.5
	Max	5.0	9.0	7.5
	P-value[a]	<0.001	<0.001	<0.001
Hour 7	N	118	126	120
	Mean	-2.4	-2.5	-2.7
	SD	4.0	3.5	4.0
	Min	-16.0	-12.0	-14.0
	Max	8.0	8.5	9.0
	P-value[a]	<0.001	<0.001	<0.001
Hour 9	N	118	123	121
	Mean	-4.6	-5.1	-5.1
	SD	3.5	3.4	4.0
	Min	-13.0	-12.0	-18.0
	Max	6.0	2.5	8.0
	P-value[a]	<0.001	<0.001	<0.001

[a] Within-group analysis of changes from baseline using paired t-test.

Treatment was considered a success by the investigator (based on the question, 'Would you continue the patient on this medication?') in 65-69% of cases across arms – not an extraordinarily high percentage, and generally aligning with the proportion of subjects who completed the study.

Patient satisfaction tended to be highest in the "0.15% / Purite" arm, for example at Month 12 only 0.8% of subjects in that arm were dissatisfied versus 4-5% in other arms. This was also reflected in the patient comfort questionnaire results. This endpoint would not reflect efficacy so much as safety. Efficacy was not analysed according to prior treatment status.

Study 190342-008 (supportive)

This study was conducted from September 1998 to June 2000 at 21 US sites. Design (including treatment) and methodology (including thresholds used to define non-inferiority) replicated Study 007.

Subject disposition. 554 subjects were enrolled: 184 were randomised to the "0.15% / Purite" group, 186 to the "0.2% / Purite" group and 184 to the Alphagan group. Overall, 62.1% of patients completed the 12 month treatment period. Discontinuation was generally due to AEs (27.8%, a high rate for a drug aimed for long-term use) and lack of efficacy (5.2% overall; specifically, 7.6% in the "0.15% / Purite" arm, 4.3% in the "0.20% / Purite" arm and 3.8% in the Alphagan arm). Discontinuations due to ocular AEs were seen in 21.7%, 27.4% and 26.1% respectively. These patterns were also seen in Study 007. Overall, 97.5% of patients were included in the PP dataset.

Subject demographics. Mean age was 65.3 yrs (range, 22.4-90.4). 57% of subjects were female; 84.3% were Caucasian. Mean weight was 80.8 kg.

Subject baseline characteristics – ocular. Diagnosis for study inclusion was glaucoma for 62.5%, ocular hypertension for 34.8% and mixed diagnosis for 2.7%. Baseline IOP was measured at hours 0, 2, 7 and 9, and mean values ranged from 22.4-24.9 mmHg for "0.15% / Purite", 22.3-24.8 mmHg for "0.20% / Purite" and 23.0-25.3 mmHg for Alphagan.

Washout of ophthalmic medications was required for 55-67% of subjects; about half of subjects had taken anti-glaucoma medications within the preceding 5 yrs, most commonly non-selective β blockers.

A higher percentage of Alphagan subjects had a history of ocular pruritus than subjects in other groups. Also, a history of ocular allergy was reported by 5.4% of Alphagan patients but 2.7% of subjects in both Purite groups.

Subject baseline characteristics – other. Generally, medical histories were balanced across groups. Endocrine disorders were less frequent in the "0.2% / Purite" arm than in other arms, and gynaecological disorders were less frequent in that arm than in the Alphagan arm.

Efficacy results.

- At Week 2, ITT IOP results at trough and at 2 hours supported non-inferiority of Purite products relative to Alphagan.
- At Week 6, month 3, Month 6, Month 9 and Month 12, ITT IOP results at trough and at 2, 7 and 9 hours supported non-inferiority of Purite products relative to Alphagan.
- Analysis of differences from baseline partially corresponded to the above results, but at Week 6, hour 2, the upper limit of the 95% CI for the comparison between "0.15% / Purite" and Alphagan was 1.53 mmHg; at month 3, the upper limit was 1.70 mmHg at hour 2 and 1.61 mmHg at Hour 9 for the same comparison; at month 6, the upper limit was 1.72 mmHg at hour 2 and 1.77 mmHg at hour 9 for the same comparison; and at month 12, the upper limit was 1.64 mmHg at Hour 2 and 1.64 mmHg at Hour 9 for the same comparison. Thus, there was difficultly establishing non-inferiority based on pre-specified criteria when the 'change from baseline' variable was considered, at least for the "0.15% / Purite" versus Alphagan comparison, most notably at the time of peak effect.
- In general, the PP analysis supported the above ITT analysis for the 'mean IOP' analysis, but at 6 discrete time-points where ITT analysis suggested inferiority the PP analysis suggested non-inferiority.
- Treatment was considered a clinical success in 66.5% for "0.15% / Purite", 63.7% for "0.20% / Purite" and 61.3% for Alphagan. By month 6 (but not before), slightly fewer

"0.15% / Purite" subjects than Alphagan subjects were dissatisfied with treatment (for example, Month 12: 5.0% versus 6.7%). Results for patient comfort were generally in favour of Purite products over Alphagan, by small margins (for example, Month 12: 3.3% less than comfortable for "0.15% / Purite", 3.6% for "0.20% / Purite" and 5.0% for Alphagan).

Additional data from pooling of Studies 007 and 008

The sponsor presented pooled data from Studies 007 and 008, which is reasonable given their shared design and methodologies. Table 13 shows patient disposition and demography for the pooled datasets. This table highlights the higher rate of discontinuation due to lack of efficacy in the brimonidine Purite 0.15% pooled arm than in other pooled arms (7.6% versus 3.7-4.7%), and the lower rate of discontinuation in the 0.15% arm due to ocular AEs (18.9% versus 22.2-25.6%).

Table 13. – Summary of Clinical Efficacy – Patient disposition and selected demographic information for pooled supportive studies 007 and 008

	Brimonidine Purite 0.15%	Brimonidine Purite 0.2%	ALPHAGAN®	OVERALL
Exit Status				
Enrolled	381[a]	383	383	1147
Completed	248 (65.1%)	245 (64.0%)	249 (65/0%)	742 (64.7%)
Discontinued	133 (34.9%)	138 (36.0%)	134 (35.0%)	405 (35.3%)
Lack of Efficacy	29 (7.6%)	18 (4.7%)	14 (3.7%)	61 (5.3%)
Pregnancy	1 (0.3%)	1 (0.3%)	0 0.0%)	2 (0.2%)
AEs	83 (21.8%)	95 (24.8%)	105 (27.4%)	283 (24.7%)
Ocular	72 (18.9%)	85 (22.2%)	98 (25.6%)	255 (22.2%)
Systemic	16 (4.2%	13 (3.4%)	13 (3.4%)	42 (3.7%)
Protocol Violations	6 (1.6%)	11 (2.9%)	2 (0.8%)	20 (1.7%)
Administrative	11 (2.9%)	9 (2.3%)	9 (2.3%)	29 (2.5%)
Other	3 (0.8%)	4 (1.0%)	3 (0.8%)	10 (0.9%)
Age (years)				
Mean	63.4	63.8	62.7	63.3
SD	12.8	12.1	12.6	12.5
Range	22.4 – 88.8	25.4 – 90.4	25.2 – 93.4	22.4 – 93.4
Sex				
Male	169 (44.4%)	162 (42.3%)	167 (43.6%)	498 (43.4%)
Female	212 (55.6%)	221 (57.5%)	216 (56.4%)	649 (56.6%)
Race and Iris Colour				
Black	48 (12.6%)	59 (15.4%)	47 (12.3%)	154 (13.4%)
Non-black	333 (87.4%)	324 (84.6%)	336 (87.7%)	993 (86.6%)
Light[b]	202 (53.0%)	187 (48.8%)	200 (52.2%)	589 (51.4%)
Dark[c]	179 (47.0%)	196 (51.2%)	183 (47.8%)	558 (48.6%)

Note: N= number of patients; SD = standard deviation

a Includes 1 patient who was enrolled but did not receive study medication

b Light: blue, green, hazel and other

c Dark: brown

Data Source: Clinical documentation, vol. 28. 5.3.5.3. Phase 3 Pooled 12-Month Efficacy Tables 1.1. 2.1, pp. 39.41

For pooled data, the sponsor presented sub-group analyses by age, gender, race and iris colour. In subjects <65 yrs of age, brimonidine Purite 0.15% was inferior to Alphagan at 3 time-points out of 20, with upper limits of 95% CIs for differences in mean IOP exceeding 1.5 mmHg on these occasions (Week 2, Hour 2; Month 3, Hour 9; and Month 6, Hour 9; however at two of these three points, the upper limit was 1.50 mmHg, that is, borderline non-inferior according to the sponsor's delta). For subjects≥65 yrs of age, no such non -inferiority was seen. In females, brimonidine Purite 0.15% was inferior to Alphagan at 1 time-point out of 20 (Month 3, Hour 9), by only 0.03 mmHg, whereas for males no non-inferiority was seen. In subjects classified as black for racial group (13.4% of the pooled dataset), brimonidine Purite 0.15% was inferior to Alphagan at 7 time-points out of 20, however the number of subjects examined was fairly small, resulting in wide confidence intervals. In subjects with light irides (all colours except brown; 51.4% of the pooled dataset), brimonidine Purite 0.15% was inferior to Alphagan at 2 time-points out of 20.

Study 190342-004 (dose-ranging; Alphagan as comparator)

Design and aims

This study was conducted from January to April 1998 at 6 US sites. The study was not double-blinded; only investigators were masked to treatment allocation.

Study population and subject disposition

Inclusion and exclusion criteria were similar to those used in studies 007 and 008. The washout period was again 4-28 days depending on drug.

Subject disposition. 103 subjects were enrolled. 25 were in the "0.10% / Purite" arm, 26 in the "0.20% / Purite" arm, 26 in the Alphagan arm and 26 in the vehicle arm. There were 0, 1, 1 and 2 discontinuations respectively. No subjects were excluded from PP analysis.

Subject demographics. Mean age was 66.8 yrs (65.7-65.8 for Purite arms and 67.8-67.9 for other arms); range was 39-86 yrs. 54.4% of subjects were male. 80.6% were Caucasian.

Subject baseline characteristics – ocular. 76.7% of subjects had a diagnosis of glaucoma and 23.3% had ocular hypertension. 56-64% of subjects in each arm had been on topical β-blocker therapy immediately prior to study entry

Interventions

Subjects were randomised to receive:

(1) brimonidine-Purite 0.2% ophthalmic solution (Allergan formulation number 9115X)
(2) brimonidine-Purite 0.1% ophthalmic solution (Allergan formulation number 9118X)
(3) brimonidine-Purite vehicle ophthalmic solution (Allergan formulation number 9117X) (this had Purite 0.005%, carboxymethylcellulose sodium 0.5% and the other excipients found in Alphagan P; for these other excipients, amounts were not described)
(4) Alphagan (Allergan formulation number 7831X)

Study medication was given as one drop in each eye three times daily for 1 month.

Efficacy

There were 6 visits: pre-study; baseline (Day 0); Day 1; Day 7; Day 21; and Day 28. IOP was measured at all visits. At baseline, mean trough (hour 0) IOP was similar across groups (26.0-26.3 mmHg; range 23.0-32.5). A distinct treatment effect was apparent by the Day 7 visit, at the trough time-point (mean change in IOP, -3.7 to -4.2 mmHg in active treatment arms; +0.1 mmHg in vehicle arm). At Day 28, at the trough time-point, mean change was -2.8 mmHg ("0.10% / Purite"), -3.10 mmHg ("0.20% / Purite"), -3.20 mmHg (Alphagan) and -0.8 mmHg (vehicle).

IOP results were shown for hours 0, 1, 2, 3, 5, 7, 9 and 12 at baseline (that is, pre-treatment, to show normal diurnal variation) and Days 21 and 28, and results focused on hours 0, 1 and 2 at Days 1 and 7. Results at Days 1 and 7 were relatively balanced across active treatment arms, and showed efficacy relative to the vehicle arm (for example, Day 7, hour 2: mean change from baseline -5.7 to -6.2 mmHg, versus +0.4 mmHg). At Day 21, there was a suggestion of improved efficacy in the Alphagan arm relative to the Purite arms (especially the "0.10% / Purite" arm). For example, at hour 2, mean change from baseline was -5.0 mmHg ("0.10% / Purite"), -4.9 mmHg ("0.20% / Purite"), -6.2 mmHg (Alphagan) and -0.90 (vehicle). At Hour 12, corresponding results were -2.4, -4.9, -5.4 and -0.6 mmHg (and the difference in efficacy between the lower strength Purite arm and the vehicle arm is seen to be reduced). This pattern was broadly similar at Day 28. (Note: study medication was given after the trough (Hour 0) and Hour 7 measurements.)

Study 190342-005 (dose-ranging; Timoptic as comparator)

Design and aims

This study matched Study 004 in design, except that Timoptic replaced Alphagan as a study treatment, and treatment was BID rather than TID. It was conducted from January to April 1998 at 5 US sites.

Study population and subject disposition

Exclusion criteria were adjusted to incorporate contraindications to β-blocker therapy (for example, obstructive pulmonary disease; asthma; heart block more severe than first degree; uncontrolled congestive heart failure).

122 patients were enrolled. 30 were randomised to the "0.1% / Purite" arm, 30 to the "0.2% / Purite" arm, 31 to the Timoptic arm and 31 to the vehicle arm. 2 subjects discontinued from the lower dose Purite arm; otherwise, all subjects completed the study. No patients were excluded from PP analysis.

There were no significant differences amongst treatment groups with respect to demographics. Mean age was 61 yrs (range 22-90). 48.4% of subjects were male. Over 74% of subjects per arm were Caucasian.

About half of subjects were diagnosed with glaucoma and half with ocular hypertension. About 27-36% of subjects per arm had been on topical β-blocker therapy immediately prior to study entry.

Interventions

Subjects were randomised to receive:

(1) brimonidine-Purite 0.2% ophthalmic solution (Allergan formulation number 9115X)
(2) brimonidine-Purite 0.1% ophthalmic solution (Allergan formulation number 9118X)
(3) brimonidine-Purite vehicle ophthalmic solution (Allergan formulation number 9117X) (this had Purite 0.005%, carboxymethylcellulose sodium 0.5% and the other excipients found in Alphagan P; for these other excipients, amounts were not described)
(4) Timoptic (timolol maleate 0.5% ophthalmic solution; Allergan formulation number 6151X; contains benzalkonium chloride 0.01% as a preservative)

Study medication was given as one drop in each eye twice daily for 1 month.

Efficacy

At baseline, mean IOP was 25.0-25.5 mmHg across arms (at Hour 0), and diurnal fluctuation in mean IOP of around 5 mmHg (to a lowest point (nadir) of 19.9-21.3 mmHg) was shown by recording IOP at 8 points over 12 hours at baseline.

It was shown that brimonidine Purite was not as effective as Timoptic in maintaining IOP lowering over 12 hours after dosing. For example, at Day 21, the lower dose Purite arm did not achieve a mean lowering of IOP of≥3 mmHg from hours 5 -12, while the higher dose arm did not achieve this from hours 7-12. Similar results were obtained at Day 28. At hours 1, 2 and 3 on these days, active treatments were similar in their IOP-lowering efficacy.

Discussion of efficacy

Studies 007 and 008 cannot be used to support efficacy of Alphagan P when given twice daily, because of the TID dosing used in those studies. The sponsor identifies Study 017 as pivotal (the other BID dosing study, Study 005, was a small dose-finding study). Even Study 017 is limited in providing evidence of efficacy: given its study population, it can only show efficacy in maintenance of IOP control in subjects previously controlled on Alphagan.

Evidence of efficacy of Alphagan P relative to the currently registered Alphagan is therefore direct in the case of subjects already on Alphagan therapy, and indirect for other subjects (for example, treatment-naïve subjects and subjects on other anti-glaucoma medications). Indirect evidence is limited to generalisation from Studies 007 and 008 (using the reasoning that if non-inferiority is seen between Alphagan P and Alphagan for TID dosing, there is also non-inferiority for BID dosing), and – less convincingly – generalisation from Study 017 (using the reasoning that if non-inferiority between the two treatments is seen in subjects already successfully controlled with Alphagan, non-inferiority will also be seen in other patient populations). Studies 004 and 005 do not convincingly add to evidence of efficacy, because of their relatively small sample sizes, their non-selection of the proposed dose strength, and – in the case of Study 004 – the use of TID dosing.

Even accepting these caveats due to study design, evidence of actual non-inferiority between Alphagan P and Alphagan was only moderately strong. For example, in the 12 month studies, the picture emerged of an increased frequency of discontinuation due to inefficacy in the Alphagan P arms relative to other active arms. Also, in considering detailed IOP results, the general trend based on point estimates of IOP averages for treatment arms was for better performance in the Alphagan arms, even if formal non-inferiority testing (using a sponsor-defined delta of 1.5 mmHg, which was not strongly justified) generally supported non-inferiority.

Efficacy was assessed at estimated peak and trough times of brimonidine's pharmacological effect on IOP. There is some evidence in the literature that brimonidine's effect on IOP, relative to other pharmacotherapies, is more pronounced at peak than at trough[16]; results of Study 005 are consistent with this position. For the comparison of the proposed formulation and Alphagan, there was no clear-cut difference between trough and peak.

There was no analysis of efficacy according to previous treatment status (for example, analysis of results for treatment-naïve subjects).

There was no analysis of efficacy according to percent reduction from baseline IOP at each time-point. Analysis by absolute magnitude may disguise a relatively small percentage change in subjects with a high baseline value. In Phase 3 studies, upper limits of baseline IOP were incorporated as exclusion criteria.

There was no analysis by percentage of subjects above (or below) threshold of IOP or change from baseline in IOP. Analysis relied on comparison of group means, which even with standard deviations supplied may hide heterogeneity of study drug effects (especially if sub-

[16] van der Valk R *et al.* A network meta-analysis combined direct and indirect comparisons between glaucoma drugs to rank effectiveness in lowering intraocular pressure. J Clinical Epidemiology. Article in press. 2009

group analysis is not thorough). This analysis by group means may also hide 'loss of effect' in some patients, a phenomenon mentioned in the current Alphagan PI. This is particularly the case given that actual mean decreases in IOP were often not spectacularly large.

Overall, the impression is that Alphagan P is on average slightly less efficacious in treating elevated intra-ocular pressure than Alphagan. There is evidence from the rate of discontinuations due to inefficacy (in 12 month studies using TID dosing) that this slightly lower average efficacy translates to more frequent cases of clinically significant inefficacy (in controlling IOP) with Alphagan P than with Alphagan.

These conclusions regarding efficacy should be seen in the context of safety conclusions.

Safety

General issues / methodology

In Study 017, AEs were elicited with open-ended questions followed by directed questions as appropriate. Serious AEs had a standard definition. Severity was graded as mild (awareness; easily tolerated)/moderate (discomfort, interfering with usual activity)/severe (incapacitating)/not applicable. Relationship to study medication was graded as unrelated/ possible/ probable/ definite.

Visual acuity was measured as best-corrected acuity using a standard ETDRS chart and recorded in Snellen equivalent units. Biomicroscopy was performed without dilatation using slit-lamp examination and fluoroscopy; the lid, conjunctiva, cornea, anterior chamber and lens were assessed; a 5-point scale was used to grade observations (0 = none; 0.5 = trace; 1 = mild; 2 = moderate; 3 = severe). Ophthalmoscopy was used to assess the vitreous and optic nerve head, through a dilated pupil. The cup-disc ratio was measured using direct and indirect ophthalmoscopy, and the Allergan Armaly chart, on a scale from 0.0 to 0.9. Visual field exam (undilated) was performed using automated perimetry testing.

Heart rate and blood pressure were monitored. WOCBP had urine pregnancy tests. Otherwise, no blood or urine samples were collected for testing.

In other studies, safety monitoring methodology was similar to that in Study 017. In addition, at selected sites, an endothelial cell count was made by using a non-contact specular microscope. In Study 006, additional safety monitoring was conducted (for example, blood tests).

Individual safety studies

Study 190342-017 (pivotal)

Exposure

Mean duration of exposure was 87.8 days for Purite arms and 86.6 days for Alphagan. About 97% of subjects were treated for≥42 days. Compliance was not noted to be an issue; it was monitored by drug reconciliation.

Deaths

There was one death, in the Purite group: a man died from a CVA (cerebrovascular accident or stroke).

Other serious AEs

7/203 (3.4%) (Purite) and 8/204 (3.9%) (Alphagan) reported serious AEs, none of which was considered treatment-related.

AEs leading to discontinuation of study drug

These occurred in 2.5% in each group. In the Purite group the AEs were: conjunctival hyperaemia (n=2, in one case combined with eyelid oedema); allergic conjunctivitis (n=2) and CVA/ death (n=1). In the Alphagan group the AEs were: Cerebrovascular accident (CVA); allergic conjunctivitis (n=2); conjunctival folliculosis / eyelid oedema (n=1); and oral dryness / pharyngitis / asthenopia combined (n=1). Overall, this was a much lower rate of discontinuation than seen in supportive studies, a finding consistent with the enrolment of subjects who had previously received Alphagan.

Treatment-emergent AEs

One or more AEs were reported in 35% of the Purite group and 43.1% of the Alphagan group (p=0.092). Table 14 shows AEs reported for 4 or more patients in any treatment group. Ophthalmic AEs with notable differences across arms included: conjunctival hyperaemia (mostly mild but in one Purite case severe), reported in 7.9% (Purite) versus 4.4% (Alphagan); conjunctival haemorrhage, in 0.5% versus 0%; excessive tear production, in 0% versus 2.0%; blepharitis in 0.5% versus 2.0%; and eye dryness in 0.5% versus 2.0%. Oral dryness was reported in 0.5% versus 3.4%; tachycardia in 2/203 versus 0/204.

Brimonidine-related allergic responses typically present after 3-9 months (and development of late allergic conjunctivitis is a key reason for discontinuation). A 3-month study in a group that has already been exposed to Alphagan (and who is therefore presumably free of individuals in whom Alphagan allergic responses have been problematic in the past) will not reveal useful data in this regard.

Table 14 – Study 017 – AEs reported for 4 or more patients in any treatment group

Preferred Term[a]	Brimonidine Purite™ N=203 Number (%)		ALPHAGAN® N=204 Number (%)		Between-Group P-value[b]
Overall	71	(35.0%)	88	(43.1%)	0.092
Body as a Whole					
Infection	5	(2.5%)	7	(3.4%)	0.564
Accidental Injury	5	(2.5%)	1	(0.5%)	>0.122
Cardiovascular System					
Hypertension	5	(2.5%)	4	(2.0%)	0.751
Digestive System					
Oral Dryness	1	(0.5%)	7	(3.4%)	0.068
Respiratory					
Infection Sinus	4	(2.0%)	3	(1.5%)	0.724
Special Senses					
Conjunctival hyperemia	16	(7.9%)	9	(4.4%)	0.145
Allergic Conjunctivitis	8	(3.9%)	9	(4.4%)	0.812
Conjunctival Folliculosis	4	(2.0%)	4	(2.0%)	>0.999
Corneal Erosion	4	(2.0%)	4	(2.0%)	>0.999
Burning Sensation in Eye	3	(1.5%)	4	(2.0%)	>0.999
Blepharitis	1	(0.5%)	4	(2.0%)	0.372
Eye Dryness	1	(0.5%)	4	(2.0%)	0.372
Epiphora	0	(0.0%)	4	(2.0%)	0.123

a Adverse events presented in decreasing frequency of reports in the Brimonidine Purite™ group.
b Fisher's exact test or Pearson's chi-square test was used.

Treatment-related AEs

These were reported in 16.7% (Purite) versus 22.1% (Alphagan). Most notably, oral dryness (0.5% versus 3.4% [including one severe case]), conjunctival hyperaemia (7.9% [including one severe case] versus 3.9%), allergic conjunctivitis (3.9% versus 4.4%), conjunctival folliculosis (2.0% versus 2.0%), corneal erosion (2.0% versus 1.5%) and burning eye sensation (1.0% versus 2.0%) were considered treatment-related.

Ophthalmic and other findings of note

There were no differences at study exit in the proportion of subjects from each arm falling into each category for visual acuity. However, worsening of visual acuity ≥2 lines was seen in 7.4% (Purite) versus 3.9% (Alphagan).

There were no differences across arms in biomicroscopy / ophthalmoscopy findings. A finding of conjunctival erythema / hyperaemia was made in 5.9% (Purite) versus 6.4% (Alphagan), somewhat inconsistent with reported AE results. Corneal staining / erosion was seen in 2.0% versus 0.5%. No change in cup-disc ratio was seen in 94.9% (Purite) versus 93.0% (Alphagan).

There were no changes of statistical significance between groups in heart rate or blood pressure. At 3 months, mean heart rate had fallen by 0.8 beats per minute (bpm) in the Purite arm, and risen by 0.4 bpm in the Alphagan arm. These findings were in stark contrast to those in Study 006, where healthy and younger subjects experienced larger falls in heart rate (although, given that this applied to some degree to the vehicle arm of that study, the difference could be related to disparities between studies in sample size). It would have been relevant to present heart rate changes in efficacy studies by age group. It would also have been relevant to present the proportion of subjects with clinically significant changes in blood pressure (for example, using 10 mmHg bins).

Study 190342-007 (supportive)

Exposure

Mean duration of exposure was 291-293 days across arms. 91% of subjects were treated for ≥69 days, 72% for ≥242 days and 68% for ≥332 days.

Deaths

One death was reported in the "0.15%/Purite" arm, due to a "lymphoma-like reaction" considered unrelated to study drug.

Other serious AEs

Overall, SAEs were reported by 9.2% of "0.15% / Purite" subjects *(abdominal aortic aneurysm; recurrent prostate adenoma; renal failure secondary to diabetic nephropathy; acute bronchospasm and pneumonia; pain secondary to rotator cuff repair; congestive heart failure possibly due to hypertension; myocardial infarction; large cell lymphoma of the lungs and subsequent death; kidney stones; prostatic hypertrophy; leg fracture and electrolyte imbalance; leg ischaemia; neurogenic claudication; sepsis with arrhythmias and confusion; shoulder and arm pain; prophylactic hysterectomy prior to tamoxifen; unstable angina; and alcohol detoxification)*, 3.6% of "0.20% / Purite" subjects *(congestive heart failure; anal prolapse; exacerbation of* chronic obstructive pulmonary disease *(COPD); breast carcinoma; hip osteoarthritis; SVT; benign uterine tumour)* and 5.0% of Alphagan subjects *(failed arthroplasty; myocardial infarction; loss of consciousness; septic bursitis; aortic stenosis; congestive heart failure; gallstones; lower GI bleed; viral pneumonia; vasculitis in right leg; congestive heart failure)*. No SAE was considered related to study drug. SAEs were listed above since there was some imbalance in frequency across groups; there was no particular pattern although it would have been informative to have a vehicle control group for comparison.

AEs leading to discontinuation of study drug

AEs resulted in discontinuation for 19.4% ("0.15% / Purite"), 20.3% ("0.20% / Purite") and 25.6% (Alphagan).

Treatment-emergent AEs

AEs were reported by 78-81% of patients across arms. Commonly, reported AEs were ocular in nature. There was no imbalance across arms in overall incidence of systemic AEs.

Allergic conjunctivitis was reported in 7.1% ("0.15%/ Purite"), 14.7% ("0.20%/ Purite") and 17.1% (Alphagan) ($p \leq 0.016$). Various other differences in AE rates between groups attained statistical significance (for example, dizziness, flu, sinus disorder, prostatic disorder), but there was no consistent pattern, dose-response or signal raised by these findings.

Conjunctival hyperaemia was reported in 22.4% of "0.15% / Purite" patients, 22.3% of "0.20% / Purite" patients and 28.6% of Alphagan patients. Severe conjunctival hyperaemia

was reported in 3/196 "0.15% / Purite" patients, 7/197 "0.20% / Purite" patients and 2/199 Alphagan patients. Eye pruritus was reported in 7.7%, 12.2% and 11.6% respectively. Severe allergic conjunctivitis was reported in 3 "0.15% / Purite" patients, 6 "0.20% / Purite" patients and 1 Alphagan patient. Other ocular AEs tended to be less frequent in the "0.15% / Purite" arm, over the 12 months, as were the AEs of oral dryness and somnolence. All AEs reported by ≥2% in any one group are shown in Table 15.

Treatment-related AEs

Treatment-related AEs were reported by 49% ("0.15%/ Purite"), 54.3% ("0.20%/Purite") and 54.3% (Alphagan). Treatment-related allergic conjunctivitis was reported in 6.6% versus 12.7% versus 17.1% ($p \leq 0.042$).

Ophthalmic and other findings of note

Worsening of visual acuity by≥2 lines was seen in 13.3% ("0.15%/ Purite"), 15.2% ("0.20%/ Purite") and 11.1% (Alphagan). Worsening in the optic cup/disc ratio by≥0.2 units was seen in <1% of patients across arms.

Endothelial cell counts were made in 242 people across 9 sites. At baseline, there were no statistically significant differences across arms. At 12 months, there was no statistically significant change within groups and no statistically significant differences across arms.

Improvement in visual fields by >5 dB were seen in 2.0% ("0.15%/ Purite"), 3.6% ("0.20%/ Purite") and 5.1% (Alphagan), however worsening by≥5 dB was seen in 0%, 1 .0% and 0.5% respectively.

No safety signals emerged from analysis of heart rate and blood pressure.

Table 15 – Study 007 – Number (%) of patients with AEs reported by≥2% of patients in any one treatment group (12 month report)

Preferred Term[a]	Brimonidine-Purite™ 0.15% N=196		Brimonidine-Purite™ 0.2% N=197		ALPHAGAN® N=199		Among-group p-value[b]
Conjunctival Hyperemia	44	(22.4%)	44	(22.3%)	57	(28.6%)	0.248
Eye pruritus	15	(7.7%)	24	(12.2%)	23	(11.6%)	0.283
Allergic Conjunctivitis	14	(7.1%)	29	(14.7%)	34	(17.1%)	0.009
Infection	14	(7.1%)	8	(4.1%)	13	(6.5%)	0.390
Visual Disturbance	13	(6.6%)	21	(10.7%)	14	(7.0%)	0.272
Burning Sensation in Eye	11	(5.6%)	10	(5.1%)	15	(7.5%)	0.559
Conjunctival Folliculosis	11	(5.6%)	15	(7.6%)	16	(8.0%)	0.605
Oral Dryness	10	(5.1%)	15	(7.6%)	14	(7.0%)	0.576
Eye Dryness	9	(4.6%)	15	(7.6%)	15	(7.5%)	0.387
Hypertension	9	(4.6%)	10	(5.1%)	10	(5.0%)	0.971
Infection Sinus	8	(4.1%)	1	(0.5%)	3	(1.5%)	0.036
Arthritis	7	(3.6%)	5	(2.5%)	4	(2.0%)	0.623
Blepharitis	7	(3.6%)	2	(1.0%)	5	(2.5%)	0.241
Flu Syndrome	7	(3.6%)	2	(1.0%)	11	(5.5%)	0.045
Asthenia	6	(3.1%)	5	(2.5%)	10	(5.0%)	0.369
Bronchitis	6	(3.1%)	1	(0.5%)	1	(0.5%)	0.040
Epiphora	6	(3.1%)	7	(3.6%)	12	(6.0%)	0.290
Eye Discharge	6	(3.1%)	3	(1.5%)	8	(4.0%)	0.324
Headache	6	(3.1%)	6	(3.0%)	5	(2.5%)	0.933
Pharyngitis	6	(3.1%)	4	(2.0%)	2	(1.0%)	0.285
Superficial Punctate Keratitis	6	(3.1%)	2	(1.0%)	2	(1.0%)	0.194
Visual Acuity Worsened	6	(3.1%)	6	(3.0%)	5	(2.5%)	0.933
Accidental Injury	5	(2.6%)	8	(4.1%)	6	(3.0%)	0.685
Eyelid Edema	5	(2.6%)	8	(4.1%)	5	(2.5%)	0.594
Prostatic Disorder	5	(2.6%)	1	(0.5%)	0	(0.0%)	0.012
Allergic Reaction	4	(2.0%)	2	(1.0%)	3	(1.5%)	0.717
Asthma	4	(2.0%)	1	(0.5%)	0	(0.0%)	0.032
Back Pain	4	(2.0%)	3	(1.5%)	3	(1.5%)	0.855
Conjunctival Edema	4	(2.0%)	4	(2.0%)	4	(2.0%)	>0.999
Eye Pain	4	(2.0%)	9	(4.6%)	7	(3.5%)	0.379
Foreign Body Sensation	4	(2.0%)	6	(3.0%)	12	(6.0%)	0.092
Photophobia	4	(2.0%)	0	(0.0%)	4	(2.0%)	0.128
Stinging Sensation in Eye	4	(2.0%)	0	(0.0%)	4	(2.0%)	0.128
Tenosynovitis	4	(2.0%)	0	(0.0%)	3	(1.5%)	0.123
Visual Field Defect	4	(2.0%)	5	(2.5%)	1	(0.5%)	0.235
Arm Pain	3	(1.5%)	1	(0.5%)	4	(2.0%)	0.504
Cataract	3	(1.5%)	3	(1.5%)	5	(2.5%)	0.801
Dyspepsia	3	(1.5%)	4	(2.0%)	1	(0.5%)	0.375
Erythema Eyelid	2	(1.0%)	3	(1.5%)	4	(2.0%)	0.913
Nausea	2	(1.0%)	1	(0.5%)	4	(2.0%)	0.467
Rhinitis	2	(1.0%)	4	(2.0%)	5	(2.5%)	0.643
Asthenopia	1	(0.5%)	3	(1.5%)	4	(2.0%)	0.548
Dizziness	1	(0.5%)	8	(4.1%)	3	(1.5%)	0.043
Hypercholesterolemia	1	(0.5%)	3	(1.5%)	4	(2.0%)	0.548
Papillary Hypertrophy	1	(0.5%)	4	(2.0%)	3	(1.5%)	0.504
Rash	1	(0.5%)	5	(2.5%)	2	(1.0%)	0.239
Somnolence	1	(0.5%)	6	(3.0%)	5	(2.5%)	0.161
Urinary Tract Infection	1	(0.5%)	2	(1.0%)	5	(2.5%)	0.291
Arthralgia	0	(0.0%)	4	(2.0%)	0	(0.0%)	0.024
Irritation Eye	0	(0.0%)	1	(0.5%)	5	(2.5%)	0.052

[a] Adverse events presented in decreasing frequency of reports in the Brimonidine-Purite™ 0.15% group.

[b] Among-group p-value based on the Fisher's exact test or the Pearson's chi-square test.

Study 190342-008 (supportive)

Exposure

Mean duration of exposure was 288 days for "0.15% / Purite", 283 days for "0.20% / Purite" and 286 days for Alphagan patients. 90.6% of patients were treated for≥69 days; 68.2% were treated for ≥242 days; and 63.7% were treated for ≥332 days.

Deaths

There were 3 deaths: a subject in the "0.15% / Purite" group died after a myocardial infarction; a subject in the "0.20%/Purite" group died after a stroke or cerebrovascular accident (CVA); and a subject in the Alphagan group died due to cardiac arrest. No death was considered treatment-related.

Other serious AEs

Serious AEs were reported for 8.7% of "0.15% / Purite" patients, 7.5% of "0.20% / Purite" patients and 9.2% of Alphagan patients. No SAE was considered treatment-related. One subject in the "0.20% / Purite" arm experienced bradycardia requiring hospitalisation; the subject was also being treated with clonidine as an anti-hypertensive. The Allergan medical monitor could not rule out a contributory effect of brimonidine.

AEs leading to discontinuation of study drug

AEs resulted in discontinuation in 24.5% of "0.15%/ Purite" patients, 29.6% of "0.20%/Purite" patients and 29.3% of Alphagan patients

Treatment-emergent AEs

AEs were reported for 77.7% of "0.15%/ Purite" subjects, 80.6% of "0.20%/ Purite" subjects and 87.5% of Alphagan subjects. Subjects in the "0.15% / Purite" arm tended to report fewer 'special senses' AEs (these were primarily ocular) and fewer neurological AEs (for example, somnolence, dizziness, insomnia) than subjects in other groups. Severe AEs were generally uncommon, but were reported more frequently in the Alphagan than in other groups (for example, severe allergic conjunctivitis in 5 Alphagan subjects and 3 subjects in each other group; severe conjunctival hyperaemia in 5 Alphagan subjects, 3 "0.20% / Purite" subjects and 1 "0.15% / Purite" subject). Table 16 shows the number and percentage of patients with AEs reported by ≥2% of patients in any one treatment group over the 12 months of study.

Table 16 – Study 008 – Number (%) of patients with AEs reported by≥2% of patients in any one treatment group (12 month report)

Preferred Term[a]	Brimonidine-Purite™ 0.15% N=184		Brimonidine-Purite™ 0.2% N=186		ALPHAGAN® N=184		Among-group p-value[b]
Conjunctival hyperemia	36	(19.6%)	42	(22.6%)	48	(26.1%)	0.328
Allergic Conjunctivitis	22	(12.0%)	32	(17.2%)	28	(15.2%)	0.357
Eye pruritus	20	(10.9%)	25	(13.4%)	28	(15.2%)	0.464
Visual Disturbance	17	(9.2%)	19	(10.2%)	20	(10.9%)	0.873
Infection	16	(8.7%)	7	(3.8%)	14	(7.6%)	0.136
Burning Sensation in Eye	12	(6.5%)	20	(10.8%)	23	(12.5%)	0.143
Conjunctival Folliculosis	12	(6.5%)	15	(8.1%)	15	(8.2%)	0.802
Foreign Body Sensation	11	(6.0%)	10	(5.4%)	11	(6.0%)	0.960
Epiphora	10	(5.4%)	14	(7.5%)	11	(6.0%)	0.692
Hypertension	10	(5.4%)	9	(4.8%)	8	(4.3%)	0.889
Oral Dryness	10	(5.4%)	22	(11.8%)	27	(14.7%)	0.013[c]
Blepharitis	7	(3.8%)	3	(1.6%)	6	(3.3%)	0.423
Dyspepsia	7	(3.8%)	4	(2.2%)	4	(2.2%)	0.644
Headache	7	(3.8%)	9	(4.8%)	5	(2.7%)	0.565
Irritation Eye	7	(3.8%)	4	(2.2%)	9	(4.9%)	0.363
Rhinitis	7	(3.8%)	2	(1.1%)	5	(2.7%)	0.226
Eye Dryness	6	(3.3%)	8	(4.3%)	6	(3.3%)	0.825
Eye Pain	6	(3.3%)	8	(4.3%)	13	(7.1%)	0.215
Visual Acuity Worsened	6	(3.3%)	3	(1.6%)	4	(2.2%)	0.536
Conjunctival Hemorrhage	5	(2.7%)	0	(0.0%)	2	(1.1%)	0.038[d]
Accidental Injury	4	(2.2%)	4	(2.2%)	4	(2.2%)	>0.999
Arthritis	4	(2.2%)	5	(2.7%)	4	(2.2%)	>0.999
Bronchitis	4	(2.2%)	4	(2.2%)	4	(2.2%)	>0.999
Cough Increased	4	(2.2%)	2	(1.1%)	3	(1.6%)	0.653
Diabetes Mellitus	4	(2.2%)	2	(1.1%)	2	(1.1%)	0.675
Erythema Eyelid	4	(2.2%)	7	(3.8%)	8	(4.3%)	0.495

Table 16 continued.

Flu Syndrome	4	(2.2%)	4	(2.2%)	7	(3.8%)	0.644
Infection Sinus	4	(2.2%)	4	(2.2%)	1	(0.5%)	0.410
Periodontal Abscess	4	(2.2%)	2	(1.1%)	2	(1.1%)	0.675
Pharyngitis	4	(2.2%)	3	(1.6%)	1	(0.5%)	0.461
Vitreous Floaters	4	(2.2%)	4	(2.2%)	4	(2.2%)	>0.999
Dermatitis	3	(1.6%)	3	(1.6%)	6	(3.3%)	0.580
Dizziness	3	(1.6%)	3	(1.6%)	8	(4.3%)	0.184
Eye Discharge	3	(1.6%)	5	(2.7%)	11	(6.0%)	0.057
Eyelid (NOS)	3	(1.6%)	2	(1.1%)	5	(2.7%)	0.449
Eyelid Edema	3	(1.6%)	7	(3.8%)	6	(3.3%)	0.441
Asthenia	2	(1.1%)	4	(2.2%)	9	(4.9%)	0.087
Back Pain	2	(1.1%)	8	(4.3%)	3	(1.6%)	0.165
Cataract (NOS)	2	(1.1%)	5	(2.7%)	0	(0.0%)	0.076
Chalazion	2	(1.1%)	4	(2.2%)	0	(0.0%)	0.174
Depression	2	(1.1%)	2	(1.1%)	4	(2.2%)	0.675
Intraocular Pressure	2	(1.1%)	2	(1.1%)	6	(3.3%)	0.256
Papillary Hypertrophy	2	(1.1%)	4	(2.2%)	2	(1.1%)	0.741
Somnolence	2	(1.1%)	7	(3.8%)	6	(3.3%)	0.248
Allergic Reaction	1	(0.5%)	2	(1.1%)	4	(2.2%)	0.418
Insomnia	1	(0.5%)	5	(2.7%)	2	(1.1%)	0.291
Irritant Contact Dermatitis	1	(0.5%)	0	(0.0%)	4	(2.2%)	0.052
Abnormal Vision	0	(0.0%)	0	(0.0%)	4	(2.2%)	0.024[c]
Visual Field Defect	0	(0.0%)	4	(2.2%)	1	(0.5%)	0.134

[a] Adverse events presented in decreasing frequency of reports in the 0.15% group.

[b] Among-group p-value based on the Fisher's exact test or the Pearson's chi-square test

[c] Statistically significant differences between Brimonidine-Purite™ 0.15% vs ALPHAGAN® (p = 0.003) and 0.15% Brimonidine-Purite vs 0.2% (p = 0.029) for oral dryness;

[d] Statistically significant difference between Brimonidine-Purite 0.15% vs 0.2% (p = 0.030 (b) for conjunctival hemorrhage;

[e] Pairwise comparison revealed no statistically significant difference

Oral dryness was reported for 5.4% versus 11.8% versus 14.7% respectively (p ≤ 0.029 for "0.15% / Purite" versus other groups).

Treatment-related AEs

Treatment-related AEs were reported for 50.5% of "0.15%/ Purite" patients, 58.6% of "0.20%/ Purite" patients and 65.8% of Alphagan patients (Table 17).

Table 17 – Study 008 – Number (%) of patients with treatment-related AEs reported by ≥2% of patients in any one treatment group (12 month report)

Preferred Term[a]	Brimonidine-Purite™ 0.15% N=184		Brimonidine-Purite™ 0.2% N=186		ALPHAGAN® N=184		Among-group p-value[b]
Conjunctival hyperemia	32	(17.4%)	39	(21.0%)	45	(24.5%)	0.250
Allergic Conjunctivitis	22	(12.0%)	31	(16.7%)	26	(14.1%)	0.431
Eye pruritus	17	(9.2%)	22	(11.8%)	24	(13.0%)	0.502
Visual Disturbance	12	(6.5%)	11	(5.9%)	17	(9.2%)	0.422
Conjunctival Folliculosis	11	(6.0%)	14	(7.5%)	15	(8.2%)	0.709
Burning Sensation in Eye	10	(5.4%)	18	(9.7%)	19	(10.3%)	0.187
Oral Dryness	10	(5.4%)	21	(11.3%)	26	(14.1%)	0.020
Foreign Body Sensation	8	(4.3%)	7	(3.8%)	11	(6.0%)	0.581
Epiphora	6	(3.3%)	8	(4.3%)	8	(4.3%)	0.833
Irritation Eye	6	(3.3%)	4	(2.2%)	8	(4.3%)	0.492
Eye Dryness	5	(2.7%)	6	(3.2%)	4	(2.2%)	0.946
Headache	5	(2.7%)	4	(2.2%)	4	(2.2%)	0.942
Erythema Eyelid	4	(2.2%)	6	(3.2%)	7	(3.8%)	0.655
Eye Pain	4	(2.2%)	5	(2.7%)	5	(2.7%)	>0.999
Rhinitis	4	(2.2%)	0	(0.0%)	0	(0.0%)	0.024
Eyelid Edema	3	(1.6%)	5	(2.7%)	6	(3.3%)	0.632
Asthenia	2	(1.1%)	4	(2.2%)	7	(3.8%)	0.228
Somnolence	2	(1.1%)	6	(3.2%)	5	(2.7%)	0.461
Eye discharge	1	(0.5%)	4	(2.2%)	8	(4.3%)	0.050
Intraocular Pressure spike	0	(0.0%)	2	(1.1%)	4	(2.2%)	0.133

[a] Adverse events presented in decreasing frequency of reports in the 0.15% group.

[b] Among-group p-value Based on the Fisher's Exact Test or Pearson's Chi-squareTest. Number (%) of Patients with Treatment-Related Adverse Events Reported by ≥ 2% of Patients in Any One Treatment Group (12 Month Report)

rms.

Worsening of optic disc cupping by≥0.2 units was seen in 1.1% of "0.15%/ Purite" patients, 0.6% of "0.20%/ Purite" patients and 2.8% of Alphagan patients. Examination findings of conjunctival erythema reflected reports of conjunctival hyperaemia being more common in the Alphagan arm than in the "0.15%/ Purite" arm. There were no statistically significant changes in endothelial cell counts at Month 12 relative to baseline within groups, nor were there differences across groups. Worsening of visual fields by≥5 dB was reported in 1.1% of patients in each group.

In the "0.15% / Purite" group there were statistically significant mean decreases in diastolic blood pressure at Week 2, Week 6, Month 9 and Month 12, relative to baseline (range: -1.3 to -2.4 mmHg). The proportion of subjects with clinically meaningful decreases was not described. Having a fall in mean blood pressure of this magnitude in a group makes it more likely that a reasonable proportion of subjects do indeed have a clinically meaningful decrease in blood pressure. This pattern had not been seen in Study 007.

Additional data from pooling of Studies 007 and 008

The sponsor pooled data from Studies 007 and 008 and presented safety results at the 3 month and 12 month interval, to show change in AE profile over time. This approach allowed comparison with 3 month results for Study 017. The number of AEs reported in Study 017 was overall lower than in pooled studies 007 and 008, at 3 months. This is shown in Table 19. This is consistent with BID dosing in Study 017 and with the selection of patients in Study 017 already using Alphagan for IOP control.

For some important AEs this pattern was not shown. Thus, for conjunctival hyperaemia, incidence in Study 017 ("0.15% / Purite" arm) was 7.9%, while in pooled studies 007 and 008 incidence was also 7.9%. Likewise, for allergic conjunctivitis, incidences were 3.9% and 2.1% respectively. This may reflect variation in study populations or inconsistency across studies in diagnosis or recording of AEs. It seems less likely that BID dosing itself would increase the risk of allergic conjunctivitis, relative to TID dosing. An unexplored but plausible alternative is that prior use of Alphagan may increase this risk. In a comparison of Alphagan arms across studies, allergic conjunctivitis was seen in 4.4% (Study 017: BID but prior use) versus 5.0% (pooled studies: TID but not necessarily prior use).

In the comparison of 3-month and 12-month results in pooled studies 007 and 008, the incidence of most AEs was broadly similar, but allergic reactions became more apparent by the 12 month mark. This is shown in Table 18. For example, allergic conjunctivitis was seen in 2.1% of the pooled "0.15% / Purite" arm at 3 months, but in 9.5% at one year. In addition, hypertension was seen in 1.1% and 5.0% respectively.

AEs were reviewed by sub-groups (age <65 or ≥65 yrs; gender; race; iris colour) for subjects pooled from studies 007 and 008. No findings of major interest emerged that were not already revealed by analysis of the whole dataset.

Table 18 – Summary of Clinical Safety – AEs regardless of causality in Studies 017, pooled 007 and 008 (3 months) and pooled 007 and 008 (12 months), if occurring in ≥2% of patients in any group

n (%)	017 3-month data		Pooled 007 + 008 3-month data			Pooled 007 + 008 1-year data		
AE – by COSTART term	Brimonidine-Purite 0.15% (N = 203)	ALPHAGAN® 0.2% (N = 204)	Brimonidine-Purite 0.15% (N = 380)	Brimonidine-Purite 0.2% (N = 383)	ALPHAGAN® 0.2% (N = 383)	Brimonidine-Purite 0.15% (N = 380)	Brimonidine-Purite 0.2% (N = 383)	ALPHAGAN® 0.2% (N = 383)
Overall	71 (35.0)	88 (43.1)	198 (52.1)*	209 (54.6)*	233 (60.8)*	297 (78.2)	305 (79.6)	322 (84.1)
Special Senses								
Conjunctival Hyperaemia	16 (7.9)	9 (4.4)	30 (7.9)	37 (9.7)	45 (11.7)	80 (21.1)	86 (22.5)	105 (27.4)
Allergic Conjunctivitis	8 (3.9)	9 (4.4)	8 (2.1)	19 (5.0)	19 (5.0)	36 (9.5)*	61 (15.9)*	62 (16.2)*
Eye Pruritus	3 (1.5)	2 (1.0)	17 (4.5)	26 (6.8)	22 (5.7)	35 (9.2)	49 (12.8)	51 (13.3)
Visual Disturbance	0	3 (1.5)	26 (6.8)	31 (8.1)	25 (6.5)	30 (7.9)	40 (10.4)	34 (8.9)
Conjunctival Folliculosis	4 (2.0)	4 (2.0)	6 (1.6)	12 (3.1)	15 (3.9)	23 (6.1)	30 (7.8)	31 (8.1)
Corneal erosion	4 (2.0)	4 (2.0)	2 (0.5)	0	0	1 (0.3)	0	1 (0.3)
Burning sensation in eye	3 (1.5)	4 (2.0)	15 (3.9)	19 (5.0)	24 (6.3)	23 (6.1)	30 (7.8)	38 (9.9)
Foreign Body Sensation	2 (1.0)	3 (1.5)	8 (2.1)	11 (2.9)	16 (4.2)	15 (3.9)	16 (4.2)	23 (6.0)
Eye Dryness	1 (0.5)	4 (2.0)	9 (2.4)	15 (3.9)	11 (2.9)	15 (3.9)	23 (6.0)	21 (5.5)
Epiphora	0	4 (2.0)	5 (1.3)	11 (2.9)	12 (3.1)	16 (4.2)	21 (5.5)	23 (6.0)
Blepharitis	1 (0.5)	4 (2.0)	6 (1.6)	1 (0.3)	6 (1.6)	14 (3.7)	5 (1.3)	11 (2.9)
Visual Acuity Worsened	0	1 (0.5)	4 (1.1)	4 (1.0)	4 (1.0)	12 (3.2)	9 (2.3)	9 (2.3)
Eye Pain	0	1 (0.5)	3 (0.8)*	9 (2.3)*	13 (3.4)*	10 (2.6)	17 (4.4)	20 (5.2)
Eyelid Oedema	1 (0.5)	3 (1.5)	2 (0.5)	6 (1.6)	5 (1.3)	8 (2.1)	15 (3.9)	11 (2.9)

continued next page.

Table 18 continued.

n (%)	017 3-month data		Pooled 007 + 008 3-month data			Pooled 007 + 008 1-year data		
AE – by COSTART term	Brimonidine-Purite 0.15% (N = 203)	ALPHAGAN® 0.2% (N = 204)	Brimonidine-Purite 0.15% (N = 380)	Brimonidine-Purite 0.2% (N = 383)	ALPHAGAN® 0.2% (N = 383)	Brimonidine-Purite 0.15% (N = 380)	Brimonidine-Purite 0.2% (N = 383)	ALPHAGAN® 0.2% (N = 383)
Eye Discharge	1 (0.5)	1 (0.5)	3 (0.8)*	5 (1.3)*	12 (3.1)*	9 (2.4)*	8 (2.1)*	19 (5.0)*
Erythema Eyelid	1 (0.5)	0	3 (0.8)	2 (0.5)	4 (1.0)	6 (1.6)	10 (2.6)	12 (3.1)
Irritation Eye	0	2 (1.0)	5 (1.3)	3 (0.8)	6 (1.6)	7 (1.8)	5 (1.3)	14 (3.7)
Papillary hypertrophy	0	0	3 (0.8)	2 (0.5)	3 (0.8)	3 (0.8)	8 (2.1)	5 (1.3)
Intraocular pressure	0	0	0	0	3 (0.8)	2 (0.5)	4 (1.0)	8 (2.1)
Cataract (NOS)	0	0	1 (0.3)	0	0	5 (1.3)	8 (2.1)	5 (1.3)
Visual Field Defect	0	0	1 (0.3)*	5 (1.3)*	0*	4 (1.1)	9 (2.3)	2 (0.5)
Body as a whole								
Infection	5 (2.5)	7 (3.4)	19 (5.0)*	7 (1.8)*	18 (4.7)*	30 (7.9)	15 (3.9)	27 (7.0)
Accidental Injury	5 (2.5)	1 (0.5)	3 (0.8)	4 (1.0)	2 (0.5)	9 (2.4)	12 (3.1)	10 (2.6)
Headache	0	0	10 (2.6)	12 (3.1)	9 (2.3)	13 (3.4)	15 (3.9)	10 (2.6)
Flu Syndrome	2 (1.0)	0	5 (1.3)	3 (0.8)	8 (2.1)	11 (2.9)*	6 (1.6)*	18 (4.7)*
Asthenia	0	3 (1.5)	7 (1.8)	7 (1.8)	15 (3.9)	8 (2.1)*	9 (2.3)*	19 (5.0)*
Back Pain	2 (1.0)	2 (1.0)	3 (0.8)	5 (1.3)	4 (1.0)	6 (1.6)	11 (2.9)	6 (1.6)
Cardiovascular								
Hypertension	5 (2.5)	4 (2.0)	4 (1.1)	6 (1.6)	11 (2.9)	19 (5.0)	19 (5.0)	18 (4.7)
Digestive								
Oral Dryness	1 (0.5)	7 (3.4)	16 (4.2)*	32 (8.4)*	35 (9.1)*	20 (5.3)*	37 (9.7)*	41 (10.7)*
Dyspepsia	0	0	2 (0.5)	2 (0.5)	1 (0.3)	10 (2.6)	8 (2.1)	5 (1.3)
Musculoskeletal								
Arthritis	1 (0.5)	1 (0.5)	5 (1.3)	4 (1.0)	4 (1.0)	11 (2.9)	10 (2.6)	8 (2.1)
Nervous								
Somnolence	0	1 (0.5)	3 (0.8)	11 (2.9)	10 (2.6)	3 (0.8)*	13 (3.4)*	11 (2.9)*

Table 18 continued.

n (%)	017 3-month data		Pooled 007 + 008 3-month data			Pooled 007 + 008 1-year data		
AE – by COSTART term	Brimonidine-Purite 0.15% (N = 203)	ALPHAGAN® 0.2% (N = 204)	Brimonidine-Purite 0.15% (N = 380)	Brimonidine-Purite 0.2% (N = 383)	ALPHAGAN® 0.2% (N = 383)	Brimonidine-Purite 0.15% (N = 380)	Brimonidine-Purite 0.2% (N = 383)	ALPHAGAN® 0.2% (N = 383)
Dizziness	1 (0.5)	1 (0.5)	1 (0.3)	8 (2.1)	6 (1.6)	4 (1.1)	11 (2.9)	11 (2.9)
Respiratory								
Infection Sinus	4 (2.0)	3 (1.5)	9 (2.4)*	1 (0.3)*	3 (0.8)*	12 (3.2)	5 (1.3)	4 (1.0)
Rhinitis	1 (0.5)	0	3 (0.8)	5 (1.3)	3 (0.8)	9 (2.4)	6 (1.6)	10 (2.6)
Bronchitis	0	0	2 (0.5)	2 (0.5)	4 (1.0)	10 (2.6)	5 (1.3)	5 (1.3)
Pharyngitis	0	2 (1.0)	8 (2.1)	7 (1.8)	1 (0.3)	10 (2.6)	7 (1.8)	3 (0.8)
Urogenital								
Urinary tract infection	0	2 (1.0)	0	2 (0.5)	1 (0.3)	3 (0.8)	5 (1.3)	8 (2.1)

* Statistical significance between treatment groups ($p<0.05$)

Study 190342-004 (dose-ranging; Alphagan as comparator)

This was a one month study, so only key results will be described. AEs were reported in 24% ("0.1% / Purite" arm), 31% ("0.2% / Purite" arm), 31% (Alphagan arm) and 23% (vehicle arm). Treatment-related AEs were reported in 20%, 23%, 19% and 8% respectively. There was one SAE in the Alphagan arm (ovarian cancer diagnosis; unrelated to treatment).

More common AEs were: oral dryness; systemic hypotension (in 5/51 Purite arm subjects and 0/52 remaining subjects); and headache.

Heart rate did not change significantly from baseline in any group, but there were statistically significant decreases in blood pressure at most follow-up visits in Purite arms.

For systolic blood pressure (BP), the decreases were seen only in the "0.10% / Purite" arm. For example, at Day 28, at trough (that is, pre-first dose on that day), mean change in BP was -7.3 mmHg ("0.1% / Purite" arm), +3.2 mmHg ("0.2% / Purite" arm), -0.7 mmHg (Alphagan arm) and -0.2 mmHg (vehicle arm). Over the course of 12 hours after first dosing on Day 28, mean change in systolic BP ranged from -1.4 to -8.9 mmHg in the lower dose Purite arm, and from +1.0 to -5.9 mmHg in the higher dose Purite arm. The range was -1.7 to -9.2 mmHg for Alphagan, and +0.1 to +4.6 mmHg for vehicle.

For diastolic BP, the decreases were seen in both Purite arms – but also in the Alphagan arm. By Day 28, over the course of 12 hours after first dosing, mean change in diastolic BP ranged from -0.9 to -5.1 mmHg in the lower dose Purite arm, and from -0.8 to -3.3 mmHg in the higher dose Purite arm. The range was -1.9 to -6.3 mmHg for Alphagan, and +1.7 to -1.0 mmHg for vehicle. Given that baseline diastolic BP averaged about 80 mmHg, these mean changes are clinically significant, if only because they indicate that many patients will have falls in blood pressure greater than indicated by the mean value. This is consistent with the reports, in Purite arms at least, of hypotension as an AE. However, fewer subjects were enrolled in this study than in the Phase 3 studies, where vital signs were monitored and no safety signals emerged.

Study 190342-005 (dose-ranging; Timolol as comparator)

This was a one month study, so only key results will be described. AEs were reported in 43% ("0.1%/ Purite" arm), 43% ("0.2%/Purite" arm), 45% (Timolol arm) and 32% (vehicle arm). Treatment-related AEs were reported in 30%, 33%, 23% and 10% respectively. There were no SAEs.

Mean heart rate at baseline varied from 71.6 bpm ("0.2% / Purite") to 78.1 bpm (Timolol). In the Timolol arm, significant decreases in mean heart rate were seen at various time-points, ranging up to 8.4 bpm (Day 7, hour 2). At some time-points there were also lesser decreases in mean heart rate in Purite arms.

Lowering of mean blood pressure was also observed at some time-points (for example, for systolic and for diastolic BP, hours 1-3 after administration of brimonidine-Purite 0.2% and to a lesser extent Timolol), but there were no reports of hypotension as AEs.

AEs of special interest

Deaths. Three deaths were reported in any "0.15% Purite" group, due to lymphoma-like reaction, myocardial infarction (MI) and CVA. One death due to CVA was reported in a "0.2%/ Purite" subject; and one death due to cardiac arrest was reported in an Alphagan subject. No death was considered treatment-related. There is no reason to suppose this disparity is due to anything but chance.

Visual acuity. Worsening of visual acuity by≥2 lines was reported, in Study 017, in 7.4% of "0.15% / Purite" subjects and 3.9% of Alphagan subjects. This pattern recurred in Study 007 (13.3% and 11.1% respectively) and in Study 008 (12.0% and 10.3% respectively), though the difference between arms was lesser in these supportive studies. There was no safety signal generated from monitoring of visual fields or the optic disc/ cup.

Topical allergy. Brimonidine may cause ocular allergic reactions, for example, follicular conjunctivitis, resolving after discontinuation. The Purite formulation is described in recent literature as causing less topical allergy[17]. In Study 007, allergic conjunctivitis was reported in 7.1% ("0.15% / Purite"), 14.7% ("0.20% / Purite") and 17.1% (Alphagan) (p≤0.016). This suggests an important effect of lowering the concentration of brimonidine, rather than replacement of BAK with Purite preservative. Results from Study 008 support this view. One caveat is that severe allergic conjunctivitis was more common in the Purite subjects (3, 6 and 1 subjects respectively) in Study 007; but this pattern was not repeated in Study 008. Overall, it is reasonable to conclude that there is a lower rate of topical allergic symptoms with the "0.15%/ Purite" formulation than with Alphagan, but the extent of this decrease depends on which endpoint is chosen for analysis. Allergic conjunctivitis at 12 months, for example, decreased by about 40% from the Alphagan group (62/383; pooled studies 007 and 008) to the "0.15% Purite" group (36/380)– but conjunctival folliculosis decreased by about 25% (31/383 versus 23/380). There was no difference in the frequency of severe allergic conjunctivitis. These statistics were from subjects treated with a TID regimen, so their applicability to the Australian setting with BID dosing is less than ideal.

Systemic AEs. There is some evidence (again, from the supportive studies that used TID dosing; see Tables 16 and 17) of a reduced incidence with the proposed formulation of important systemic AEs such as somnolence, asthenia and oral dryness (but there was more pharyngitis).

Discussion of safety

The studies provided a safety database of 1817 patients, however only 583 of these received brimonidine Purite 0.15%, and only 203 received this twice daily.

The sponsor's Clinical Overview states that "the number of patients exposed to BID dosing with Brimonidine Purite was insufficient to make an accurate evaluation of safety and the study design makes interpretation difficult. Therefore the safety profile described in the labelling can be considered a 'worst case' scenario and is likely to be worse than would be expected when the product is administered in clinical practice".

It is logical that TID dosing with Alphagan P would reveal an AE profile no better than BID dosing. Despite this, it is not ideal to rely on safety profiling from studies that used anything other than the proposed dose and dosing frequency. For example, the apparent difference between Alphagan and Alphagan P in frequency of some AEs could be narrowed with BID dosing, with resultant changes to the risk-benefit analysis for Alphagan P.

The sponsor noted that the following AEs were reported less frequently in the "0.15%/Purite" group: allergic conjunctivitis; oral dryness; asthenia; and somnolence. The sponsor claimed that "this is a key safety advantage for Brimonidine Purite 0.15% over Alphagan as these are

[17] Galanopolous A and Goldberg I. Clinical efficacy and neuroprotective effects of brimonidine in the management of glaucoma and ocular hypertension. Clinical Ophthalmology 2009: 3; 117–122.

key adverse events consistent with the pharmacology of brimonidine". Also, numerically fewer subjects in the "0.15%/Purite" group reported conjunctival hyperaemia, eye pruritus, burning eye, eye dryness and foreign body sensation. It is reasonable to accept that the "0.15% / Purite" group had fewer ocular AEs, and this is consistent with the decreased frequency in this group of study discontinuation due to ocular AEs.

Smaller studies revealed some changes in heart rate and/or blood pressure that were (a) difficult to interpret because only mean (+ standard deviation, S.D) and/or median changes from baseline were presented, and (b) not reproduced in larger studies. Combined study results did not rule out clinically significant systemic effects on heart rate or blood pressure in a small, indeterminate fraction of subjects, but the overall pattern of mean changes in these cardiovascular parameters suggests any clinically significant effects would not be widespread.

To expand on this point, Study 005 is used as an example. Assessment of heart rate at trough (Hour 0) using mean values showed changes from baseline at Days 7, 21 and 28 of:

- -0.23 bpm, -1.41 bpm and -4.21 bpm respectively for the "0.1% / Purite" group
- -3.66 bpm, -1.59 bpm and -1.34 bpm for the "0.2% / Purite" arm
- -2.90 bpm, -3.97 bpm and -3.35 bpm for the Timoptic arm, and
- -1.74 bpm, +0.87 bpm and +1.45 bpm for the vehicle arm

A brief, exploratory analysis at the trough time (0 hrs) used the arbitrary threshold of a change ≥10 bpm relative to baseline. In this analysis, in the "0.1% / Purite" arm, 6/30 subjects had a fall in heart rate of ≥10 bpm relative to baseline at ≥2 visits, and 3/30 had an increase in heart rate of ≥10 bpm. In the "0.2% / Purite" arm, 8/30 had a fall and 4/30 had an increase. In the Timoptic arm, 8/31 had a fall and 2/31 had an increase. In the vehicle arm, 4/31 had a fall and 5/31 had an increase.

Similarly, at the time of peak pharmacological effect (2 hrs, at least for brimonidine), in the "0.1%/ Purite" arm again 6/30 subjects had a fall in heart rate of ≥10 bpm relative to baseline at ≥2 visits, and 3/30 had an increase. In the "0.2%/ Purite" arm, 6/30 had a fall and 4/30 had an increase. In the Timoptic arm, 11/31 had a fall and 2/31 had an increase. In the vehicle arm, 2/31 had a fall and 4/31 had an increase. Analysis of group means at Hour 2 at each visit also revealed a generally greater fall in heart rate with Timoptic than with other treatments.

This analysis is not definitive (for example, it may be more useful to assess percentage change, as a fall of 10 bpm may be clinically more important for baseline bradycardic subjects than baseline tachycardic subjects; also, the time of peak effect may be closer to hour 1 or hour 3 for different people [and different for Timoptic]). The analysis would be better performed using the company's electronic database than by hand using individual patient data; ideally, it would be refined and applied to all studies in the Dossier.

The cardiovascular disease status of studied subjects was not well characterised; while 'abnormally high or low blood pressure or heart rate' were exclusion criteria, no specific values were nominated as thresholds for exclusion.

Post-marketing experience

The clinical data included a single report comprising Periodic Safety Update Report (PSUR) 13 for Alphagan, PSUR 5 for Alphagan and Alphagan P 0.15% and PSUR 3 for Alphagan P 0.1%. The report summarised safety information from worldwide sources for these products from 1st October 2007 to 30th September 2008. Over the 12 month period, global patient exposure was estimated at 598 884 patient years for Alphagan, 431 854 patient-years for Alphagan P 0.15% and 158 444 patient-years for Alphagan P 0.1%.

For Alphagan, there were 104 cases reported and 20 of these were serious and unlisted[18]. For Alphagan P 0.15% there were 57 cases and 1 of these was serious and unlisted. For Alphagan P 0.1% there were 32 cases and 3 of these were serious and unlisted. Serious and unlisted events included 'apnoeic attack' and 'hypoventilation' occurring in both children and adults. There were 3 serious and unlisted reports of mental state changes in children.

In the EU, changes were made to the Alphagan Summary of Product Characteristics (SPC) regarding paediatric patients, in response to the 'Final Assessment Report (FAR) of the Mutual Recognition Procedure n°UK/H/199/001/R/002 (Day 90, 11 February 2007)'. Of most importance, the contraindication for neonates was extended to infants <2 yrs of age.

It should also be noted that the current SPC for Alphagan includes the following contraindications, based on information last updated 28/03/2008[19]

- Hypersensitivity to the active substance or to any of the excipients.
- Neonates and infants.
- Patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenergic transmission (for example, tricyclic antidepressants and mianserin).

The sponsor should comment on the additional contraindication for antidepressants affecting noradrenergic transmission. Specifically, (a) this information should be confirmed by the sponsor; and (b) the evidence and arguments used to add this contraindication should be supplied to TGA for evaluation. The sponsor should comment on whether paragraph four of the PRECAUTIONS – Drug interactions section of the proposed PI is still valid, that is, whether any relevant new information regarding interactions with antidepressants has been published or otherwise come to light.

The PSUR refers to a Company Core Data Sheet (CCDS) update "that involves cumulative review of various AEs (for example, myocardial infarction and angina pectoris; iritis / uveitis; corneal events; allergic reactions including ocular, dermal and systemic reactions; mental status changes in children; dizziness; erectile dysfunction; respiratory events; hypertension) reported in the post-marketing phase. *The sponsor should be asked to provide this CCDS update to TGA when it is finalised, along with any proposed changes to the PI and evidence in support of such changes.*

Clinical Summary and Conclusions

The sponsor (Allergan Australia Pty Ltd) is proposing to register Alphagan P (and an identical additional trade-name product, Enidin P). Alphagan P is brimonidine tartrate 0.15% with Purite as the preservative, and a new composition of excipients resulting in a higher pH. The currently registered Alphagan is brimonidine tartrate 0.20% with benzalkonium chloride as the preservative.

As pivotal evidence of efficacy, the sponsor provided a Phase 3 study of Alphagan P versus Alphagan, using BID dosing. This study demonstrated non-inferiority of Alphagan P relative to Alphagan in maintenance of already controlled IOP in subjects previously treated for at

[18] That is, they were not listed in the Core Company Safety Information.

[19] http://emc.medicines.org.uk/medicine/109/SPC/Alphagan/#CONTRAINDICATIONS; accessed 11/09/2009.

least 6 weeks with Alphagan. This study population does not strictly allow generalisation of study results to a wider population. Other aspects of the approach chosen to analyse study data also diminish the study's relevance.

As supportive evidence of efficacy, the sponsor provided two Phase 3 studies of Alphagan P (0.15%) versus Alphagan P (0.20%) versus Alphagan, using TID dosing. Evidently, TID dosing results in a 50% increase in exposure to the active ingredient, so it is difficult to use efficacy results from these studies as direct evidence of the non-inferiority of Alphagan P versus Alphagan using BID dosing. Any actual inferiority of Alphagan P relative to Alphagan may be unapparent with TID dosing but revealed with BID dosing, and quite plausibly this could only be an issue in treatment-naïve subjects, or subjects intrinsically less likely (for whatever reason) to have treatment success with brimonidine, etc. The pivotal study (Study 017) may not be able to detect actual non-inferiority in these subjects.

No study had the length of follow-up or power to demonstrate efficacy in preventing progression of glaucoma-related damage; all studies used IOP as the primary endpoint. The sensitivity of the IOP endpoints examined (for example, trough, peak) for detection of clinically relevant differences in risk of glaucoma progression was not well characterised.

There was evidence that Alphagan P has a better safety profile than Alphagan, but caveats include the choice of the study population for the pivotal study (subjects sensitive to effects of brimonidine or excipients are less likely to have enrolled) and the use of TID dosing in supportive studies. A strength of the safety profiling was the length of follow-up (12 months), although it must be remembered that the product could be used for many years.

The 13th PSUR brought into focus the issue of brimonidine's safety in the paediatric population. It was revealed in this PSUR that in the EU, a contraindication has been extended to infants as well as neonates. In the absence of argument otherwise, the Australian PI should be aligned with this position as it is clear that children older than neonates have had serious AEs after exposure to brimonidine.

It would be of some importance to establish whether the dropper bottles are child-resistant, as significant adverse events have occurred with accidental ingestion of brimonidine by infants/ toddlers.

It is not clear whether the sponsor proposes to replace the currently registered product with Alphagan P, however the proposed PI makes detailed reference to both products.

Currently, Alphagan (0.20% brimonidine tartrate; BAK preservative) is registered for use with BID dosing in Australia. In both USA and Canada (but not in NZ), Alphagan P (0.15% brimonidine tartrate; Purite preservative) is registered for use with TID dosing; of some relevance, in USA there is also a 0.10% strength product, used TID. It was not stated on what basis the 0.1% formulation was approved in USA.

Given the approval of Alphagan P 0.15% with TID dosing in USA and Canada, evidence for efficacy of BID dosing would ideally be compelling. No clinical study directly compared BID and TID dosing.

Overall, the apparently minor decrease in efficacy of Alphagan P relative to Alphagan seems offset by increased tolerability and safety of the product.

Recommendations.

The evaluator recommended approval of registration for Alphagan P and Enidin P, for the indication proposed by the sponsor, subject to changes to the PI as outlined above.

V. Pharmacovigilance Findings

A Risk Management Plan was not included in the application, on the grounds that Alphagan P is lower strength than the currently registered Alphagan; this argument is rather selective in that no mention is made of the new formulation / preservative.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

All chemistry and quality control issues have been resolved. Sterility data support the currently amended shelf life of 18 months when stored below 25^0C. An open shelf life of 4 weeks is also recommended.

No bioavailability data were evaluated as this was considered a locally acting product, by the quality evaluator.

The evaluator concludes that all outstanding issues have been resolved and recommended approval from a chemistry point of view.

Nonclinical

The evaluator noted that the proposed formulation has a lower strength of the active ingredient, brimonidine, a new preservative Purite (a replacement for benzalkonium chloride) and also contains carboxymethyl cellulose (CMC). The nonclinical data focussed primarily on the safety of the preservative Purite. Purite consists of chlorite (approximately 99.5%), chlorate (0.5%) and chlorine dioxide (trace) and is converted to natural tear products after topical ocular administration.

The toxicity was assessed in repeat dose topical ocular studies in rabbits. No ocular toxicity was seen with Purite (+ CMC) at 3 times the clinical local daily dose (that is, in the one day multiple dose study). Ocular discomfort was only seen at much higher doses. There was no evidence of corneal or conjunctival damage after 7 daily treatments (60 times the clinical dose).

Greater ocular damage was observed with 100 ppm BAK than 1000 ppm Purite/CMC.

No systemic toxicity was observed with ocularly applied Purite greater than 480 times the clinical dose, based on body surface area.

In two previously submitted studies with eye drop formulations containing brimonidine and Purite/CMC in combination, there was no evidence of ocular toxicity in rabbits that received 1.3 and 2 times the clinical local dose of brimonidine and PURITE respectively for 6 months.

Purite was not genotoxic; published studies indicate that it is not carcinogenic.

Reduced fertility was observed in female mice at high chlorite exposures and is not of particular concern with the proposed dose and administration route.

Several PI amendments were recommended.

There were no objections on nonclinical grounds to the registration of Alphagan P.

Clinical

Pharmacokinetics:

There was one pharmacokinetic study (190342-006) that examined the systemic brimonidine pharmacokinetics (pages 9-11, CER). This study however examined two strengths (0.10%

and 0.20%) other than proposed for marketing in Australia; the study regimen was a TID regimen and not a BID regimen. There was no comparator Alphagan arm. Thus this study is of limited relevance to this application, possibly supporting a "worst case" extent of absorption.

The findings show that the plasma concentrations did not exceed 0.15 ng/mL in any individual. There was dose proportionality seen with the two concentrations. In relation to pharmacokinetics, the evaluator noted a cross study comparison extracted from the clinical overview; the C_{max} and AUC were generally similar in the Alphagan (0.2%) and Alphagan P (0.2%) treated groups. These were in small number of subjects.

Efficacy:

The evaluator noted that the formulation used is that which is proposed for marketing.

The pivotal study **(190342-017)** was a double blind randomised study assessing the maintenance of effect in subjects whose IOP was already controlled on Alphagan. Those with ocular hypertension or chronic glaucoma over the age of 18 were eligible to participate. Patient who had glaucoma controlled on Alphagan BID for at least 6 were randomly assigned to brimonidine Purite 0.15% or Alphagan (brimonidine 0.2%) to be administered twice daily.

Duration of treatment was three months.

The evaluator stated that combined statistical tests of superiority and non-inferiority were employed. The delta was 1.5 mm Hg between treatment groups.

A total of 407 patients entered the study. 203 were randomised to the brimonidine Purite group, 204 to the Alphagan group. 95.6% completed the three month period.

The trough, peak values at end of treatment and change from baseline levels in IOP between the treatment groups satisfied the non-inferiority criterion. The evaluator points out that the subjects were not treatment naïve.

Study **190342-007** was considered a supportive study. This was a double blind randomised study comparing brimonidine purite 0.15%, 0.20% with Alphagan 0.2% (with benzalkonium chloride). This study included subjects with uncontrolled elevated IOP. Patients with IOP≥ 22 mm Hg and ≤ 34 mmHg were eligible to enrol. This was a 12 month study; however the dosing regimen used was TID and thus different to that proposed here in Australia.

Mean change in IOP was the primary variable. Non inferiority was to be established for each Purite arm versus the Alphagan arm. This was conducted on the intention to treat (ITT) and per protocol (PP) arms of the study.

593 were enrolled; 197 were randomised to the 0.15% arm; 197 to the 0.20% arm and 199 to the Alphagan arm. These subject groups were balanced in relation to relevant demographics including baseline IOP. The evaluator mentions that the efficacy measurements at the various time stations (Week 2, Week 6, Month 3, Month 6, Month 9 and Month 12) supported non-inferiority of the Purite products relative to Alphagan.

Study **190342-008** was similar in design to the previous study. 554 patients were enrolled and the study conducted over 12 months. The results were broadly similar to that observed in the previous study. The studies have been pooled – the evaluator noted several subgroup analyses; it is not stated whether these were post hoc analyses. The sponsor should clarify these in its pre-Advisory Committee for Prescription Medicines (ACPM) response.

The evaluator observed a higher discontinuation rates in brimonidine Purite 0.15% (7.6% versus 3.7%-4.7%) due to lack of efficacy and a lower rate of discontinuation due to ocular adverse events (18.9% versus 22.2 -25.6%).

There are two dose ranging studies (004 and 005) that compared brimonidine Purite (0.10% and 0.15%) versus Alphagan (Study 004) and Timoptic (005) as comparator. These studies were of 1 month duration and the treatment groups included small number of patients. This did not add further information relating to efficacy.

Efficacy conclusions:

Overall, the evaluator concluded the following:

- Study 017 being the pivotal study shows non-inferiority of Alphagan P with Alphagan in maintenance of IOP control.
- Studies 007 and 008 only provide supportive evidence of efficacy as the dosing regimen was different (TID instead of the proposed BID).
- Though statistical non-inferiority was seen between the two treatment regimens, in the 12 month studies (studies 007 and 008) there was an increased frequency of discontinuation due to inefficacy in the Alphagan P arms. There was also a general trend showing better efficacy with Alphagan.
- The evaluator mentions that these conclusions on efficacy should be seen in the context of its safety profile.

Safety:

The evaluator noted that the studies provide a safety database of 1817 patients; however only 583 of these received brimonidine Purite (0.15%) and only 203 received this twice daily.

Clearly, the safety profile elicited from Study 017 is the most relevant to this application. Treatment related adverse events were observed in a smaller percentage in the brimonidine P 0.15% group (16.7% versus 22.1%). Worsening of visual acuity≥ 2 lines was greater in the brimonidine P groups versus Alphagan group (7.4% versus 3.9%). The evaluator noted that the pooled safety analysis from Studies 007 and 008 where a TID regimen was used showed higher incidence of adverse events than in Study 017. This was consistent with TID than BID regimen. Conjunctival hyperaemia, however, appeared to be similar in Study 017 and in the pooled analysis (7.9%).

Incidence of allergic conjunctivitis, in study 007 was 7.1% (0.15 Purite), 14.7 (2.0% Purite) and 17.1% (Alphagan) groups. Study 008 showed similar results. The evaluator concluded that there was a lower rate of topical allergic symptoms with 0.15% Purite that is, Alphagan P; the extent of the difference depended on the endpoint chosen.

Overall the evaluator concluded that the "apparently minor decrease in efficacy of Alphagan P relative to Alphagan" appears to be offset by increased tolerability and safety of the product.

The evaluator recommended registration of Alphagan P.

Sponsor's response to the clinical evaluation report:

The sponsor responded in detail to the clinical evaluation report. An important outstanding issue was that the proposed indication is different to the registered indication of Alphagan. It is different in that it does not include the statement (as in the Alphagan indication), that it could be used in the treatment of glaucoma either as monotherapy or in combination with topical beta blockers.

The sponsor's rationale for this is that the current treatment practice has changed significantly since Alphagan was registered in 1999. Currently, prostanoids are selected as first line therapy followed by adding timolol as adjunctive therapy. The role of brimonidine (in the sponsor's opinion) is as "add on" to prostanoids or combination of prostanoid/ timolol.

Thus, this proposal would widen the registered indication.

Another issue was a concern identified by the evaluator regarding the lack of child resistant packaging. The sponsor responds that the packing is in accordance with the guidelines for "Child resistant packaging for therapeutic goods". All other eye drop products conform to this guideline. This is an acceptable response.

Risk-Benefit Analysis

1. The sponsor has submitted a "non-inferiority" study examining the effect of Alphagan P versus Alphagan in those whose IOP was maintained with Alphagan. The other supportive studies of some relevance have used a dosing regimen not proposed in Australia. Thus, efficacy data are not robust as this submission lacks information on the effect of this new formulation in treatment naïve patients using the proposed dosing regimen. The Delegate agreed with the evaluator that safety profile of this product appears better than the registered Alphagan product. Thus, the overall, risk benefit profile appears to be acceptable.
2. The lack of bioavailability/ bioequivalence data appears to be of limited significance as the pivotal study shows some evidence of therapeutic equivalence.
3. It is noted that the trade name of the proposed formulation was changed during the evaluation process to Alphagan P 0.15. This would imply that Alphagan would remain on the market. The company should confirm that this is the case in its pre-ACPM response and the reason why the old formulation is to remain registered.
4. The indication is not consistent with that which is registered as mentioned by all the evaluators. The proposed indication is: "Alphagan P Eye Drops are effective for lowering elevated intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension.". The sponsor has stated that this is to ensure that brimonidine could be used as adjunctive therapy with prostanoids or prostanoid/ timolol products. Clearly, no data on the proposed combination (especially in relation to efficacy, safety, drug interactions) have been submitted. Thus, it was recommended that Alphagan P be registered for the same indication as that for Alphagan.

Advisory Committee for Prescription Medicines (ACPM, formerly called the Australian Drug Evaluation Committee or ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission from Allergan Australia Pty Limited to register the new strength and formulation for brimonidine tartrate (Enidin P/Alphagan P) eye drops 1.5 mg / mL for the indication:

> *Alphagan P/ Enidin P eye drops are effective in lowering elevated intraocular (IOP) in patients with chronic open angle glaucoma or ocular hypertension. Alphagan P/ Enidin P eye drops can be used in the treatment of glaucoma either as a monotherapy or in combination with topical beta-blockers.*

In making this recommendation the ACPM considered that the evidence of safety and efficacy of the formulation and the dosage regimen for the proposed indications has been sufficiently demonstrated. The ACPM considered the change in preservative and noted that while specific data were not available the preservative is less toxic to the cornea and is consistent with previous ADEC recommendations and the overall industry trends.

The ACPM noted that the studies were based on a TID dosage regimen and the proposed indication is for a BID regimen. While noting the possible increased compliance with a BID regimen the ACPM advised the delegate to consider the comparative dosage efficacy in the approval of the Product and Consumer Information.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Alphagan P/Enidin P, as 0.15% brimonidine tartrate, 5 ml in a 10 mL container, with the indication:

> *'Alphagan P/Enidin P eye drops are effective in lowering elevated intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension. Alphagan P/Enidin P eye drops can be used in the treatment of glaucoma either as a monotherapy or in combination with topical beta-blockers.'*

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

ALPHAGAN® P 1.5 Eye Drops

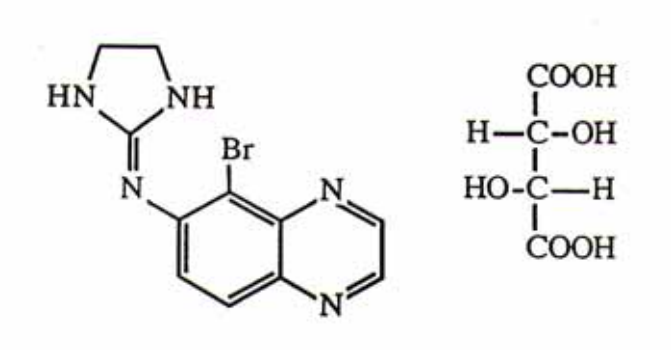
(brimonidine tartrate 1.5 mg per 1 mL)

Date of TGA Approval – 25 May 2010

ALPHAGAN® P 1.5 Eye Drops

NAME OF THE DRUG

The active constituent of ALPHAGAN® P 1.5 eye drops is brimonidine tartrate.



(structure of brimonidine tartrate)

CAS Registry No.: 79570-19-7

DESCRIPTION

Brimonidine tartrate is an off-white, pale yellow to pale pink powder and is soluble in water (34 mg/mL). In solution, brimonidine tartrate has a clear, greenish-yellow colour.
Chemical name: 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate.
Molecular weight: 442.24 as the tartrate salt.
Empirical formula: $C_{11}H_{10}BrN_5$, $C_4H_6O_6$

ALPHAGAN® P 1.5 0.15% is a sterile ophthalmic solution. Each mL of ALPHAGAN® P 1.5 solution contains:
ACTIVE: brimonidine tartrate 1.5 mg (equivalent to 0.99 mg as brimonidine free base)
PRESERVATIVE: Sodium chlorite (as PURITE)® 1.8µg
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)

PHARMACOLOGY

Mechanism of action
Brimonidine tartrate is an alpha-2 adrenergic agonist that is 1000-fold more selective for the alpha-2 adrenoreceptor than the alpha-1 adrenergic receptor. Affinities at human alpha-1 and alpha-2 adrenoreceptors 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 solution decreases intraocular pressure (IOP) in humans. When used as directed, brimonidine eye drops have 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 12 hours or greater.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action. ALPHAGAN® 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 ALPHAGAN® P 1.5 eye drops three times daily for 7 days, plasma concentrations were low (mean C_{max} was 0.03 ng/mL and 0.06 ng/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_{0-8h}) 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_{max}) is predicted to be 0.03 ng/mL when ALPHAGAN® P 1.5 is administered twice daily for 7 days.
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 ALPHAGAN® 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).

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

Studies with ALPHAGAN® eye drops

MONOTHERAPY
The efficacy of ALPHAGAN® eye drops was demonstrated in two multicentre studies comparative with timolol 0.5% lasting up to one year in subjects with glaucoma or ocular hypertension. A total of 513 subjects received ALPHAGAN® eye drops in the two studies.

The overall mean decrease (± SD) in IOP from baseline at 12 months, as measured at peak response, was 6.20 ± 4.08 mmHg for brimonidine monotherapy and 5.56 ± 3.65 mmHg for timolol monotherapy. At trough response, these figures were 3.74 ± 3.83 mmHg for brimonidine and 5.80 ± 3.35 mmHg for timolol.

These results represent approximately 16% - 26% mean reduction from baseline measurements. IOP decreases were maintained for up to one year; no tachyphylaxis was observed. 9.4% of subjects treated with ALPHAGAN® eye drops and 5.1% of subjects treated with timolol 0.5% were discontinued because of inadequately controlled intraocular pressure. 30% of these patients withdrew during the first month of therapy.

ADJUNCTIVE THERAPY

The ability of ALPHAGAN® eye drops to lower IOP when used in combination with other anti-glaucoma agents has been evaluated in two large scale multicentre, randomised studies, involving 321 patients, 150 of which received brimonidine.

In the first study, brimonidine 0.2% twice daily as an adjunct to β-blocker therapy was compared with pilocarpine 2% administered three times daily, as an adjunct to β-blocker therapy. The overall mean decrease (± SD) in IOP from baseline at 3 months, as measured at peak response, was 4.92 ± 3.02 mmHg for brimonidine adjunctive therapy and 5.52 ± 3.08 mmHg for pilocarpine adjunctive therapy. At trough response, these figures were 3.95 ± 2.67 mmHg for brimonidine adjunctive therapy and 3.81 ± 2.75 mmHg for pilocarpine adjunctive therapy. These results represent a mean additional decrease in IOP for ALPHAGAN® adjunctive therapy of 17% - 22%.

The second study was an 8 month comparison of the additive IOP lowering effect to an already established β-blocker eye drop regimen, of ALPHAGAN® 0.2% eye drops or dipivefrine 0.1% eye drops. Adjunctive ALPHAGAN® eye drops was shown to be superior to adjunctive dipivefrine 0.1% at peak effect and equivalent in efficacy to adjunctive dipivefrine at trough at most time points.

The overall mean decrease (± SD) in IOP from baseline at 3 months, as measured at peak response, was 3.26 ± 3.16 mmHg for ALPHAGAN® adjunctive therapy and 2.33 ± 3.13 mmHg for dipivefrine adjunctive therapy. At trough response, these figures were 2.89 ± 3.14mmHg for ALPHAGAN® adjunctive therapy and 3.31 ± 3.69 mmHg for dipivefrine adjunctive therapy. These results represent a mean additional decrease in IOP for brimonidine adjunctive therapy of 12% - 15%.

Studies with ALPHAGAN® P 1.5 *eye drops*

The efficacy and safety of ALPHAGAN® P 1.5 eye drops was demonstrated by comparison with that of ALPHAGAN® eye drops in a 3 month multicentre study involving 407 patients with glaucoma or ocular hypertension already controlled with ALPHAGAN® eye drops (study 017). ALPHAGAN® P eye drops used twice daily were found to provide non-inferior efficacy compared to ALPHAGAN® eye drops used twice daily, with the upper limit of the 95% confidence interval around the difference in mean IOP change from baseline between ALPHAGAN® P 1.5 and ALPHAGAN® being no more than 0.79 mm at any timepoint (NS). ALPHAGAN® 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 most frequently reported adverse reaction was conjunctival hyperaemia (7.9% vs 3.9%).

The long-term safety of ALPHAGAN® 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 randomised to brimonidine 0.15% (ALPHAGAN® P 1.5) 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 ALPHAGAN® 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, ALPHAGAN® P 1.5 eye drops were associated with significantly less adverse reactions than brimonidine-Purite® 0.2% for allergic conjunctivitis (9.2% vs 14.6%) and oral dryness (5.3% vs 9.4%). Brimonidine-Purite® 0.2% eye drops were also associated with less adverse reactions than ALPHAGAN® eye drops for allergic conjunctivitis (14.6% vs 15.7%) and oral dryness (9.4% vs 10.4%) suggesting a safety benefit from PURITE® substitution, even when brimonidine concentration was unchanged. These safety data

support those of study 017, and demonstrate that ALPHAGAN® P 1.5 eye drops provide the most favourable safety profile with the lowest effective dose of brimonidine.

INDICATIONS AND USE

ALPHAGAN® P 1.5 eye drops are effective in lowering elevated intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension. ALPHAGAN® P 1.5 eye drops can be used in the treatment of glaucoma as either monotherapy or in combination with topical beta-blockers.

CONTRAINDICATIONS

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

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

PRECAUTIONS

General

Although ALPHAGAN® 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.

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

ALPHAGAN® 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.

Information for Patients: As with other alpha-agonists, brimonidine 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.

Drug Interactions:

Although specific drug interaction studies have not been conducted with ALPHAGAN® 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 ALPHAGAN® 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 ALPHAGAN® 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 ALPHAGAN® 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

Genotoxicity
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.

Carcinogenicity
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.

Effects on Fertility
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).

Use in 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.

Use in Lactation
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.

Paediatric Use:
Safety and effectiveness of ALPHAGAN® 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.

ADVERSE REACTIONS

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 ALPHAGAN® 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, blepharitis, eye pain), eye dryness, epiphora, photophobia, superficial punctate keratitis, visual disturbance, worsening of visual acuity
Uncommon	Eye oedema, eyelid pruritus, conjunctivitis, papillary hypertrophy, iritis

Systemic effects:

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

In another 3-month clinical study in patients whose IOP was already controlled with ALPHAGAN® eye drops, ALPHAGAN® 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® 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

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of ALPHAGAN® 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 ALPHAGAN® P 1.5 eye drops.
In order to minimise systemic absorption of ALPHAGAN® P 1.5 eye drops, apply pressure to the tear duct immediately following administration.

To avoid contamination of the solution, keep container tightly closed. Do not touch dropper tip to any surface. Discard contents 4 weeks after opening the bottle. Contents are sterile if seal is intact.

OVERDOSAGE

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® as part of medical treatment of congenital glaucoma or by accidental oral ingestion.

Oral overdoses of other α_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.
In the event of a topical overdosage, flush eye with a topical ocular irrigant.

PRESENTATION:

ALPHAGAN® P 1.5 (brimonidine tartrate ophthalmic solution) 0.15% sterile solution is supplied in plastic dropper bottles.

Eye drops: 5 mL
Storage: Store below 25°C.
Shelf life: 18 months

AUST R 158888
Allergan Australia Pty Ltd
810 Pacific Highway
Gordon NSW 2072
A.C.N.: 000 612 831

Poisons schedule: S4

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Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au