Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Australian Public Assessment Report for Brinzolamide/ Timolol Maleate

Proprietary Product Name: Azarga

Submission No: PM-2008-3124-5

Sponsor: Alcon Laboratories (Australia) Pty Ltd

February 2010

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	New Fixed Combination
Decision:	Approved
Date of Decision	23 December 2009
Active ingredient(s):	Brinzolamide/ Timolol Maleate
Product Name(s):	Azarga
Sponsor's Name and Address	Alcon Laboratories (Australia) Pty Ltd Locked Bag 1019 Frenchs Forest NSW 2086
Dose form(s):	Eye Drops
Strength(s):	10.0 mg/mL of brinzolamide and 5.0 mg/mL timolol (as the maleate)
Container(s):	8 mL LDPE Bottle
Pack size(s):	5 mL
Approved Therapeutic use:	Decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension for whom monotherapy with either component provides insufficient IOP reduction.
Route(s) of administration:	Topical (eye drops)
Dosage:	One drop twice daily

Product Background

Brinzolamide (Azopt) is a carbonic anhydrase (CA) inhibitor selective for the isoenzyme, CA-II. An application was considered by the Australian Drug Evaluation Committee (ADEC) at its 210th meeting and it was recommended for approval as second line treatment. It was referred back for advice to ADEC as the sponsor did not agree with the recommendation that it should be used as second line treatment. Based on the justification of the sponsor, the Committee waived its recommendation that it should not be used as first-line treatment. It is now registered for the following indication:

to decrease intraocular pressure in ocular hypertension or open angle glaucoma.

Brinzolamide is structurally similar to dorzolamide which was considered at the 178th ADEC meeting and was recommended for registration for the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open angle glaucoma. A fixed dose combination product (Cosopt) containing dorzolamide hydrochloride (2.0%) and timolol maleate (0.5%) was considered by ADEC at its 203rd meeting and approved for treatment of elevated IOP in patients with ocular hypertension or open angle glaucoma when concomitant therapy is appropriate.

The current letter of application states that the rationale for developing this fixed dose combination product is that majority of patients with open angle glaucoma or ocular hypertension eventually require adjunctive therapy to control their IOP; the combination therapy would fare better than one component alone. It would also result in better compliance. The latter claim, however, has not been verified with data.

This submission is to register a fixed combination eye drop in LDPE bottles under the brand name Azarga with an indication:

for the decrease of intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction

The eye drops contain 10.0 mg/mL (1.0% w/v) of brinzolamide and 5.0 mg/mL (0.5% w/v) of timolol as the maleate salt (6.8 mg/mL of timolol maleate).

Regulatory Status at the Time of Submission

Azarga eye drops suspension has received marketing approval in the European Union (26 November 2008). The indication is as follows: to decrease intraocular pressure in adult patients with open angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction. This is identical to the indication proposed in Australia. The product has also been approved in Canada (13 August 2009) and Switzerland (25 March 2009) as well as in Armenia, Bahrain, Belarus, Colombia, Georgia, Korea, Kuwait and Uruguay.

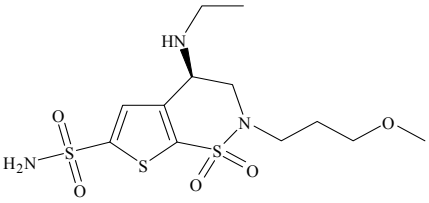
Product Information

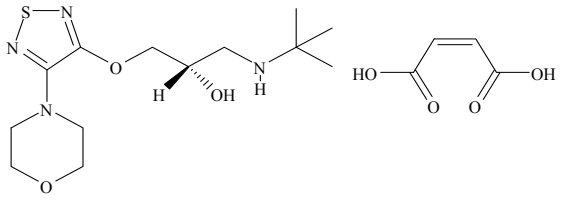
The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

The eye drops contain a suspension of 10.0 mg/mL (1% w/v) of brinzolamide and 5.0 mg/mL (0.5% w/v) of timolol as the maleate salt (6.8 mg/mL of timolol maleate).





brinzolamide: $C_{12}H_{21}N_3O_5S_3$
MW = 383.51 *CAS# [138890-62-7]*
aqueous solubility = 0.43 mg/mL (0.043%)
to give pH ~4.5: *pKa = 5.9 and 8.5*
optical rotation = -26.7°

timolol maleate: $C_{13}H_{24}N_4O_3S.C_4H_4O_4$
MW = 432.50 *CAS# [26921-17-5]*
aqueous solubility = 33-100 mg/mL (3.3-10%)
to give pH ~4 *pKa = 9.2*
optical rotation = -5.7 to - 6.2°

Alcon currently supply an eye drop containing 10.0 mg/mL of brinzolamide under the brand names Azopt and Brinzoquin (AUST R 72750 and 99179). These are the only eye drops containing brinzolamide currently registered in Australia.

Alcon does not supply a timolol monotherapy eye drop, but it does supply a fixed-dose combination eye drop containing travoprost and timolol (as maleate), Duotrav (AUST R 125607). There are also a large number of other timolol eye drops registered in Australia either as a monotherapy or in combination with pilocarpine hydrochloride, dorzolamide hydrochloride or latanoprost. In all these eye drops timolol is present as the maleate and the concentration of timolol free base is 2.5 or 5.0 mg/mL.

According to the PI the maximum daily dose is 1 drop per eye twice a day. Therefore assuming a drop size of 50 μL (actual drops are 30-39 μL), the maximum daily dose of brinzolamide is 2 mg/day and the maximum daily dose of timolol is 0.1 mg/day.

Brinzolamide is a single (*R*) enantiomer. It is very slightly soluble in water and is in suspension in the finished product. The drug substance is milled during the manufacture of the finished product. The brinzolamide is manufactured and controlled as that used in the registered Azopt eye drops.

Timolol (as maleate) is soluble in water and used in many eye drop solutions. However its degradation is pH dependent: the stability being greatest at pH 4. The timolol maleate used in the product meets the requirements of the British Pharmacopoeia (BP)/European Pharmacopoeia (EP) monograph.

Drug Product

The product contains no unusual excipients and none are of animal origin. Benzalkonium chloride is used as the preservative at the same concentration in Alcon's brinzolamide monotherapy and disodium edetate is used as a preservative aid. Carbomer 974P is used to increase the viscosity of the drop to ensure that the brinzolamide remains in suspension. Tyloxapol is used to wet the brinzolamide during milling. Sodium chloride and mannitol are used as tonicity agents and sodium hydroxide and hydrochloride acid are used to adjust pH. During manufacture the pH is adjusted to 7.2 and it is preserved with 0.10 mg/mL (0.010 %w/v) benzalkonium chloride. The suspension is isotonic. It is sterilised by a combination of moist heat and filtration. It is packed in a pre-sterilised white low density polyethylene (LDPE) bottle with pre-sterilised natural low density (LD) PE dropper tip and pre-sterilised white polypropylene cap. Microbiology and container safety issues were all resolved. It was checked that brinzolamide and timolol are compatible with each other and with the proposed excipients.

Specifications for the eye drops ensure BP/EP general requirements for eye drops are met and include requirements for: the potency of each active; limits for degradants related to each active; pH; osmolality; particle size analysis; sterility; and preservative efficacy. Appropriate release limits were set to allow for any changes that occurred on storage and the specifications were acceptable.

Data were provided that supported an un-opened shelf life of 2 years when stored below 25°C (with no other conditions) and an opened shelf life of 4 weeks.

Bioavailability

This product is for ocular use and is intended to act without systemic absorption. As a consequence no bioavailability data were required to be submitted to the quality evaluator. However, the presence of both active pharmaceutical ingredients in combination may lead to different absorption profiles compared to the monotherapies. The Delegate was informed of these facts.

Consideration by PSC

Details relating to this submission were presented at the 128th meeting of the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee. The PSC had no objections to registration provided the issues raised by the quality evaluator were resolved to the satisfaction of the TGA. The PSC particularly noted four issues, which were all resolved:

- A limit for drop size was added to the finished product expiry specifications;
- Appropriate additional stability data were provided;
- Under normal in-use conditions light did not affect the product and it was accepted that the storage condition 'protect from light' was not required; and
- The Office of Laboratories and Scientific Services evaluator was satisfied that appropriate in-use data had been provided to support the in-use shelf life.

The PSC also noted the comments on bioavailability. It was noted that clinical study C-05-27 was relevant to the pharmacokinetics and recommended that the clinical evaluator undertake a detailed evaluation of this study and that the findings of this should be reported in the Product Information.

Quality Summary and Conclusions

There were no objections on pharmaceutical chemistry grounds to the registration of the proposed fixed-dose combination eye drop.

III. Nonclinical Findings

Introduction

Azarga represents a new fixed-dose combination of brinzolamide and timolol. The nonclinical submission contained new data on primary pharmacology, safety pharmacology, pharmacokinetics, repeat-dose toxicity and skin sensitisation potential. Most of the submitted studies involved the use of brinzolamide or timolol alone; one primary pharmacology study and three (of eight) repeat-dose toxicity studies utilised brinzolamide and timolol in combination. Most of the safety-related studies —and, specifically, all of the repeat-dose toxicity studies—were GLP compliant. The submission also contained extensive references to data previously evaluated for single-agent brinzolamide. There were no major deficiencies in the nonclinical package.

Pharmacology

Primary pharmacology

Brinzolamide is a carbonic anhydrase inhibitor and timolol is a non-selective β-blocker. The efficacy of single-agent brinzolamide and single-agent timolol to lower intraocular pressure (IOP) in laboratory animal species has been demonstrated in previously evaluated studies. The sponsor submitted a number of additional nonclinical efficacy studies with brinzolamide and timolol alone (in rabbits and/or monkeys). These were primarily exploratory studies conducted to examine the effect of various changes in formulation. While activity to reduce IOP was shown, they are of limited relevance to the current application.

In the only nonclinical efficacy study with the proposed combination, the IOP-lowering effect of brinzolamide and timolol in combination (2:1 ratio, as in Azarga) was no greater than that of brinzolamide alone following single topical ocular instillation in the rabbit. No significant increase in efficacy could be shown for brinzolamide when combined with levo-betaxolol, another β-blocking agent, in other single-dose studies in rabbits. The applicant's Clinical Overview, though, reports that greater mean IOP reductions were obtained in patients treated with brinzolamide and timolol in combination compared with groups receiving monotherapy with either agent.

Safety pharmacology

Newly submitted safety pharmacology studies focused on potential cardiovascular effects (of brinzolamide) and potential local anaesthetic effects (of brinzolamide and timolol alone).

Brinzolamide (≤1.0 μg/mL) did not inhibit the hERG K^+ channel in transfected mammalian cells; the highest concentration tested is ≥100-times the clinical C_{max} for brinzolamide in plasma after topical ocular dosing. Intravenous (IV) infusion of brinzolamide or its desethyl metabolite[1] to dogs (≤10 mg/kg; over 15 min) did not induce QTc prolongation, and had no or only a minimal effect on blood pressure and heart rate up to 30 minutes post-dose. Increased heart rate (by up to 40% at 3 mg/kg and 46% at 10 mg/kg) was noted from about 12–21 hours after subcutaneous (SC) dosing

[1] N-desethyl brinzolamide is the sole major circulating metabolite of brinzolamide in humans.

with brinzolamide in another *in vivo* study in dogs; a diuretic effect was also evident at these doses. There were no significant effects at 1 mg/kg SC, a dose >21-times greater than the maximum human dose of brinzolamide from Azarga on a body surface-area basis (in a 50 kg subject). Single topical ocular instillation of brinzolamide (500 µg) or timolol (150 µg) did not affect the corneal blink reflex of rabbits; treatment also had no significant effect on pupil diameter.

Pharmacokinetics

The effect of co-administration on the pharmacokinetics of brinzolamide and timolol was assessed in rabbits after single and repeat (daily for up to 14 days) topical ocular dosing. $AUC_{0-6\,h}$ and C_{max} values for brinzolamide in aqueous humour (single and repeat dose), cornea, iris-ciliary body and whole blood (repeat dose) were comparable for the 1%/0.5% brinzolamide/timolol combination and the single-agent product. For timolol, increases in plasma $AUC_{0-6\,h}$ and C_{max} of almost 2-fold and increases in AUC and C_{max} in aqueous humour, cornea and iris-ciliary body of about 3–4-fold were seen with the combination compared with the single agent. In humans, no significant difference in levels of brinzolamide in red blood cells occurred when brinzolamide and timolol were given together; plasma AUC and C_{max} values for timolol were about 30% lower with Azarga compared with 0.5% timolol alone.

Brinzolamide and timolol remained detectable in rabbit aqueous humour for up to 48 hours after topical ocular administration of the combination. Other new data submitted by the sponsor identified CYP3A4 as the P450 isoform chiefly responsible for the metabolism of brinzolamide; CYPs 2A6, 2B6, 2C8 and 2C9 are also involved. Neither brinzolamide nor its desethyl metabolite significantly inhibited the activities of human CYPs 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4 (IC_{50} values > 1 µg/mL).

Only very limited pharmaco-/toxicokinetic data are available to enable cross-species exposure comparisons. Relative exposure achieved in the newly submitted studies (Table 1) has been calculated based on animal:human doses adjusted for body surface area (for consideration of systemic effects) and aqueous humour volume (for consideration of local effects); relative exposure has also been calculated based on animal:human plasma AUC values for timolol (for the 9-month rabbit study only). The maximum recommended human dose is based on one 35 µL drop to both eyes twice daily (in a 50 kg subject). Exposure ratios for timolol in rabbits based on body surface area- and aqueous humour volume-adjusted doses have not been modified to account for the about 2–4-fold increase in ocular absorption/systemic exposure associated with co-administration with brinzolamide. Considering this, greater exposure to timolol is expected to have been achieved in the combination studies in rabbits compared with those studies with timolol alone.

Table 1: Relative exposure

Species; Study		Brinzolamide						Timolol							
		Dose (/day)				Exposure ratio		Dose (/day)				plasma AUC	Exposure ratio		
		mg	mg/kg	mg/m^2	mg/mL aq.h.	based on: BSA	based on: aq.h.	mg	mg/kg	mg/m^2	mg/mL aq.h.	ng·h/mL	based on: BSA	based on: aq.h.	based on: AUC
Rat (SD); 2-week PO [N-00-299]		–	20	120	–	130	–	–	–	–	–	–	–	–	–
		–	60	360	–	390	–	–	–	–	–	–	–	–	–
		–	180	1080	–	1169	–	–	–	–	–	–	–	–	–
Rabbit (NZW)	5-week [N-00-300]	2.4	0.87	10.9	8	12	1.7	–	–	–	–	–	–	–	–
		4.8	1.7	21.8	16	24	3.4	–	–	–	–	–	–	–	–
	5-week [N-94-173]	–	–	–	–	–	–	0.6	0.24	3.0	2.0	–	6.5	0.9	–
		–	–	–	–	–	–	1.2	0.48	6.0	4.0	–	13	1.7	–
		–	–	–	–	–	–	2.4	0.96	12	8.0	–	26	3.4	–
	3-month [N-96-226]	–	–	–	–	–	–	1.6	0.5	6.3	5.3	–	13.5	2.3	–
	2-week [N-96-157]	3.2	1.1	13.3	11	14	2.3	0.8	0.27	3.3	2.7	–	7	1.1	–
	6-month [N-97-075]	2.4	1.0	12.5	8	14	1.7	1.2	0.5	6.3	4.0	–	13.5	1.7	–
		4.8	2.0	25	16	27	3.4	1.2	0.5	6.3	4.0	–	13.5	1.7	–
Rabbit (NZF_1)	9-month [N-05-096]	1.6	0.53	6.7	5	7	1.1	0.8	0.27	3.3	2.7	10.2	7	1.1	2.2
		2.4	0.8	10	8	11	1.7	1.2	0.4	5.0	4.0	11.3	11	1.7	2.4
		4.8	1.6	20	16	22	3.4	1.2	0.4	5.0	4.0	11.2	11	1.7	2.4
Monkey (Cynomolgus); 12-month [N-97-020]		–	–	–	–	–	–	0.4	0.12	1.5	2.7	–	3.3	1.1	–
Human; Maximum recommended dose [C-05-27]		1.4	0.028	0.924	4.7	–	–	0.7	0.014	0.462	2.3	4.71	–	–	–

All studies utilised topical ocular administration except for Study N-00-299 (rat; oral). Bodyweights of 2.75, 2.5, 3.2, 3.0, 2.4 & 3.0 (respective rabbit studies), 3.3 (monkey) and 50 kg (human) were assumed. Factors of 6, 12.5, 12 & 33 were used to convert mg/kg doses to mg/m^2 body surface area (BSA) in the rat, rabbit, monkey & human, respectively.
"aq.h." = aqueous humour (assumed volume: 300 µL in the rabbit and in humans, 150 µL in the cynomolgus monkey).

Toxicology

Repeat-dose toxicity

Studies with brinzolamide and timolol in combination were conducted in rabbits for up to 9 months; administration was by the clinical route. The maximum study duration and use of a single species is consistent with the EU guideline on the *Nonclinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005).* The studies did not include parallel groups treated with the individual components as the guideline recommends, but this is not considered a significant deficiency. Other newly submitted repeat-dose toxicity studies involved oral dosing with brinzolamide alone in rats (for 2 weeks), topical ocular dosing with brinzolamide alone in rabbits (5 weeks), and topical ocular dosing with timolol alone in rabbits (5 weeks and 3 months) and cynomolgus monkeys (6–12 months).

The doses and strengths of brinzolamide and timolol for Azarga match those approved for the single agent products.

Brinzolamide and timolol, alone or together, showed no or only a low degree of ocular irritation in the studies. Notable treatment-related findings in the combination studies were limited to increases in corneal thickness and corneal epithelial cell density (with a corresponding decrease in cell area). Based on previously evaluated studies, these changes are attributable to brinzolamide, and there was no evidence of exacerbation by timolol. Moreover, these findings are not considered adverse, and appear to be rabbit-specific as well — that is, they were not observed in monkeys treated with brinzolamide at higher doses in a 1-year study (≤9.6 mg/day by topical ocular administration; ~14-fold greater than the human dose adjusted for aqueous humour volume.

Treatment with brinzolamide at doses ≥60 mg/kg/day orally for 2 weeks had effects on the kidney (with associated changes in clinical chemistry) and stomach in rats, in line with findings in a previously evaluated 2-week oral rat study, submitted in the original application to register single-agent brinzolamide. No adverse systemic effects were evident at 20 mg/kg/day orally, a dose 130-times larger (on a body surface-area basis) than the clinical dose of brinzolamide provided by therapy with Azarga.

Genotoxicity and carcinogenicity

The genotoxic and carcinogenic potential of brinzolamide and timolol has been assessed previously in single-agent studies. No studies with brinzolamide and timolol in combination were submitted, and these are not required under the relevant EU guideline.

Reproductive toxicity

No new reproductive toxicity studies were submitted. The absence of studies with the combination is considered acceptable as the individual components have been adequately characterised in existing studies. Brinzolamide has been assigned pregnancy category B3, and timolol, category C. A pregnancy category of C, as nominated by the sponsor, is therefore appropriate for Azarga.

Sensitisation potential

Timolol maleate did not produce skin sensitisation in a newly submitted, and adequately conducted, study in guinea pigs. Brinzolamide also showed negative results in the guinea pig skin sensitisation test, evaluated previously.

Nonclinical Summary and Conclusions

A single nonclinical efficacy study with the combination was submitted. It showed no additional lowering of IOP in rabbits given a single topical ocular dose of brinzolamide and timolol in combination compared with that with brinzolamide alone. Additive effects are apparently seen in humans, however. Safety pharmacology studies revealed no inhibition of the hERG K^+ channel and no QT prolongation (in dogs) for brinzolamide and no anaesthetic effect on the cornea for either agent (in rabbits).

The ocular and systemic absorption of brinzolamide were not significantly affected by co-administration with timolol in either rabbits or humans. For timolol, there was an almost 2-fold increase in systemic absorption and about a 3–4 fold increase in ocular absorption associated with co-administration with brinzolamide in the rabbit. In contrast, in humans, plasma AUC and C_{max} values for timolol were seen to be about 30% lower with Azarga compared with single-agent timolol.

Brinzolamide and timolol remained detectable in rabbit aqueous humour for up to 48 hours after topical ocular administration of the combination. CYP3A4 was identified as the P450 isoform chiefly responsible for the metabolism of brinzolamide.

Repeat-dose toxicity studies with brinzolamide and timolol in combination were conducted in rabbits for up to 9 months. No novel or exacerbated toxic effects were observed with the

combination compared with the single agents. Notable treatment-related findings in studies with the combination were limited to increased corneal thickness and increased corneal epithelial cell density. These effects are attributable to brinzolamide, not considered adverse, and not seen in monkeys at higher doses (relative exposure, ~14). The drugs, alone or together, produced no or only a low degree of ocular irritation.

Timolol maleate was negative in the guinea-pig skin sensitisation test (as had been shown for brinzolamide in previously evaluated studies).

There were no nonclinical objections to the registration of Azarga for the proposed indication.

IV. Clinical Findings

Introduction

The application comprised a data package which included clinical study reports (CSRs) in various levels of detail.

For the main pharmacokinetic studies (C-98-62 and C-05-27), individual values of drug concentration measurements were provided graphically. Listings of individual adverse effects (AEs) were included. For the studies of efficacy and safety (C-97-22, C-05-24 and C-05-10), individual efficacy measurements and AEs were provided in tabulated form but detailed efficacy data linking treatment outcomes to individual patient characteristics were not given.

Studies C-00-17 (comparing brinzolamide drops to levobetaxolol drops in paediatric patients), and C-01-01 (comparing betaxolol drops and two strengths of timolol gel forming solution in paediatric patients), included in the dossier, do not appear relevant to the present application. The application explains that these studies were included in the European dossier in compliance with a specific EU requirement.

Justification for Fixed Dose Combination

The relevant guideline (European Union 1998a) (*pp 175-180 of Rules 1998 (3c) – 3CC10a*) states (at section 2):

The applicant should clearly state if the claimed indication is first line, second line therapy or other uses and the clinical development should be performed accordingly.

The indications chosen relate to second line therapy.

The evaluator noted that Australian regulatory requirements include submission of a justification for any fixed-dose combination for which approval is sought. The evaluator could not find any such specific justification document, although the *Clinical overview* makes the following relevant points:

- The rationale for the development of a topical ocular product that combines a CAI and a β-blocker in a single formulation was based on the consideration that the majority of patients with OAG or OH eventually require adjunctive therapy to control their IOP.
- Azarga has IOP-lowering efficacy that is greater than either component product alone, and the combination product promotes better compliance.
- The preservatives contained within topical eye drop preparations may cause inflammatory conjunctival side effects and cytotoxic effects on the ocular surface. Increasing the number of preparations instilled (as in the case with adjunctive therapies) would also increase this risk. Fixed combinations like Azarga offer the benefit of multiple actives without increasing exposure to preservatives.

- The active components of Azarga have each received marketing authorisation as therapeutic agents for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.
- Several clinical studies demonstrating the safety and efficacy of Azopt as an adjunctive therapy to timolol 0.5% eye drops were included in the application for registration of Azopt.

Study C-05-24 provides evidence in support of the second point. The evaluator accepted the third, fourth and fifth points. No reference was cited in support of the first point. Certainly there are many patients under treatment with combination products. However, it is not clear whether this is necessitated by (a) the emergence of specific medication resistance; (b) advancing disease; (c) compliance problems; or (d) something else. Regarding (a), diminishing effectiveness of timolol drops over time has been reported, but is controversial (see Bengtsson and Heijl, 2001). Clineschmidt et al. (1998) touches upon (c).

The deficiency in the justification of this fixed-combination product relates to the concentration of timolol. Evidence supporting the choice of timolol concentration (0.5%) has not been submitted. Hypothetically, the product may have been no less efficacious with timolol concentration 0.25%, and may have been associated with a lower rate of AEs related to timolol. As a relevant guideline (European Union 1998a, at section 3.1) states:

Frequently, the addition or the potentiation of the pharmacodynamic effects of the various substances may constitute the rationale of the fixed combination.

In this case several dose combinations for each substance might have to be tested and the concentration-response information can help to select the fixed combination leading to a satisfactory response.

Pharmacokinetics

Study C-98-62

This was a phase 4 pharmacokinetic study, which compared the steady-state pharmacokinetics of timolol maleate ophthalmic gel-forming solution (TGFS) 0.5% once daily to those of Timoptic 0.5% bd and Timoptic-XE 0.5% once daily. The relevance of this study to the present application was not clear.

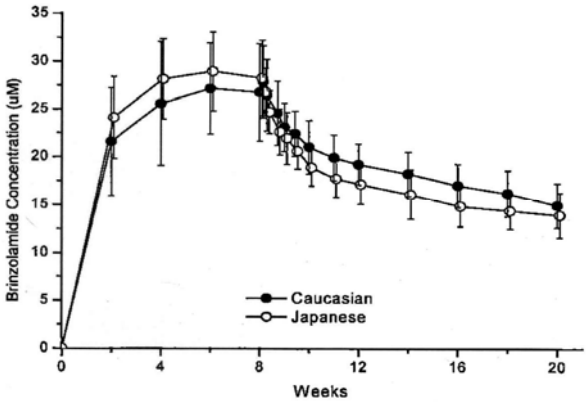
Study C-99-88

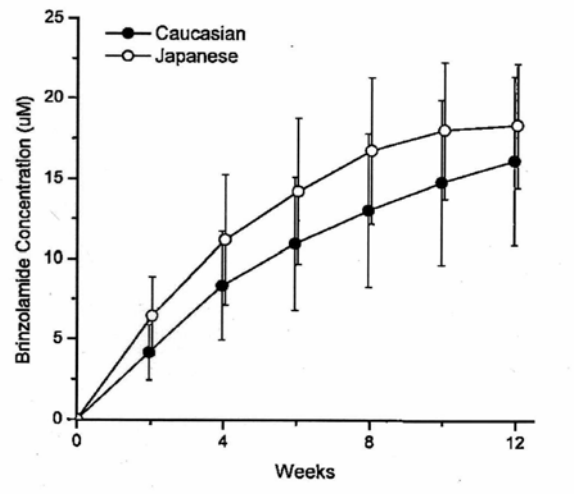
This was a phase 1 study of the pharmacokinetics of brinzolamide and its main metabolite N-desethyl brinzolamide, following oral or ocular dosing with brinzolamide. The study was done in support of an application made to the drug regulatory agency of Japan for approval of brinzolamide 1% ophthalmic suspension. It was designed to demonstrate that the pharmacokinetics of the drug are similar in Japanese and "Caucasian" people. The precise definition of "Caucasian" used in the trial was not clear. Like many studies of this kind, it was done in Hawaii, where there is apparently a group of people with documented Japanese ancestry. The study design was open-label, stratified, parallel, multiple-dose. Inclusion criteria included: healthy non-smoker, age 40-80, Japanese or Caucasian ancestry. The trial included 2 cohorts. Cohort A received oral brinzolamide. Cohort B received brinzolamide 1% ophthalmic suspension.

Results

The results may be of interest for their contribution to pharmacokinetic, pharmacodynamic and safety data on brinzolamide 1% ophthalmic suspension. Details are shown in Table 2.

Table 2: Details of Study C-99-88

Design	Treatments	Subjects entered	Brinzolamide RBC concentration (µM)	Adverse events
Open-label, parallel group.	Cohort A Brinzolamide 1 mg capsule bd, 8 weeks.	45 healthy subjects were enrolled and commenced treatment. (22 Japanese, 22 Caucasian, 1 other). Of these, 2 were excluded for non-compliance, leaving the following PP population: 22 Japanese: 11M, 11F; 14 < age 65, 8 others. 21 Caucasian: 11M, 10F; 13 < age 65, 8 others.		4 withdrawals for AE. The AEs classified as drug related were: • dry irritated eye; • pruritus eye with tearing; • paraesthesia, taste perversion, headache, hypaesthesia; • paraesthesia, dyspnoea, abdo pain, vomit, dry mouth.

	Cohort B Brinzolamide 1% ophthalmic suspension, 1 drop (say, 35 µL[†] or 0.35 mg) each eye bd, 12 weeks. [†]Estimated volume of 1 drop, given in Module 1, section 1.11.	38 healthy subjects were enrolled and formed the ITT population (19 Japanese, 19 Caucasian). Of these, 2 were excluded for non-compliance, leaving the following PP population: 18 Japanese: 8M, 10F; 15 < age 65, 3 others. 18 Caucasian: 10M, 8F; 14 < age 65, 2 others.		2 withdrawals for AE. The AEs classified as drug related were: • discomfort eye; • taste perversion, nausea, diarrhoea.

Study C-05-27

This was a study of the pharmacokinetics of brinzolamide and its main metabolite N-desethyl brinzolamide, following ocular dosing with either a combination product or the separate drugs. To shorten the time to reach steady-state levels of brinzolamide, a 2-week oral phase was incorporated into the design, followed by 13 weeks of topical ocular treatment. The main features of the study are shown in Table 3.

The only explanation for the selection of dosages used in the study was that they "were consistent with those approved for Azopt and Timolol 5 mg/mL solution". However, Timoptol (timolol) is marketed in Australia in two strengths (0.25% and 0.5%), each recommended in the approved PI for use at 1 drop each eye bd. Alcon does not explain the choice of timolol concentration in its combination product.

Table 3: Details of Study C-05-27

Design	Treatments	Subjects entered	C_{max} Mean (sd) (ng/mL) Timolol	T_{max} $t_{½}$ Mean (sd) (h) Timolol	AUC_{0-12h} Mean (sd) (h·ng/mL) Timolol	Adverse events
Multiple dose, double-blind, randomised.	(1) Brinzolamide capsule 1 mg bd, 2 w, then test combination 1 drop OU bd, 13 w.	87 healthy subjects randomised and treated ≥ 1 time. Exclusion of 6 left the ITT population: 25: 9M, 16F; mean age 51.1 (sd 9.2); weights not given; iris colours 17, 4, 1, 3.	0.82 (0.45) N=23	0.79 (0.45) *4.8 (1.8)* N=23	4.71 (2.49) N=23	4 subjects withdrawn due to AEs, 3 with AEs considered related to drug treatment: 3 on the combination product, all with decreased intraocular pressure.
	(2) Brinzolamide capsule 1 mg bd, 2 w, then Azopt 1 drop OU bd, 13 w.	28: 9M, 19F; mean age 53.8 (sd 10.3); weights not given; iris colours 15, 3, 3, 7.				
	(3) Placebo capsule bd, 2 w, then timolol 1 drop OU bd, 13 w.	28 : 5M, 23F; mean age 53.6 (sd 9.3); weights not given; iris colours 19, 3, 1, 5.	1.13 (0.49) N=26	1.11 (0.72) *3.9 (1.1)* N=26	6.58 (3.18) N=26	

sd = standard deviation

Plasma concentrations of brinzolamide were not accessible, being generally below the limit of quantitation. The following pharmacokinetic measurements were made for each subject:

From the brinzolamide and the N-desethyl brinzolamide whole blood concentration time data, using model independent methods:

- The observed drug concentration (C_{107day}) on Day 107;
- The area under the plasma drug concentration time curve from Day 15 (1st day of topical ocular dosing) to Day 107 (last day of topical ocular dosing) ($AUC_{15-107day}$).

From the timolol plasma concentration time data, using model independent methods:

- The observed maximum drug concentration (C_{max}) on Day 107;
- The time to the maximum drug concentration (T_{max}) on Day 107;

- The area under the plasma drug concentration time curve over the dosing interval following the final dose ($AUC_{0\text{-}12h}$);
- The elimination half-life ($t_{½}$).

These measurements for timolol are given in Table 3. Those for brinzolamide and N-desethyl brinzolamide are given in Table 4.

Table 4. Pharmacokinetic Parameters based on RBC concentrations of brinzolamide and N-desethyl brinzolamide. Study C-05-27.

		Brinzolamide		**N-desethyl brinzolamide**	
		C_{107} (µM)	**$AUC_{15\text{-}107}$ (µM·day)**	**C_{107} (µM)**	**$AUC_{15\text{-}107}$ (µM·day)**
Brinzolamide/Timolol	N	23	23	23	23
	Mean	18.4	1681	1.57	118
	sd	3.01	225	1.13	61.8
	Min	10.3	1260	0.631	42.6
	Max	22.7	2110	6.06	312
Azopt	N	26	26	26	26
	Mean	17.2	1633	1.63	124
	sd	3.86	263	0.98	65.9
	Min	8.92	1090	0.58	51.7
	Max	23.6	2080	3.59	255

In the opinion of the clinical evaluator, the parameters derived from whole blood measurements are of no value in assessing bioequivalence. There is no evidence that erythrocyte concentrations of brinzolamide accurately reflect systemic absorption. There may be an active transport mechanism or saturable process which governs erythrocyte concentration of drug. Steady-state concentrations of brinzolamide in erythrocytes may well reflect erythrocytic carbonic anhydrase concentrations, and may not bear a simple relationship to plasma concentrations of drug.

Comments on the pharmacokinetic studies

The evaluator considered that it was odd that the size of patients was not taken into account in presenting the pharmacokinetic data. For example, in the material relating to Study C-05-27 in the dossier, the only place data could be found on subjects' weights was in the listing of individual AEs. In that listing, the weight unit was not given, but was presumably pounds (the weight of the first patient listed being given as "222.5"). No useful data on brinzolamide bioequivalence were submitted.

Bioequivalence of the combination product and the active constituents

The relevant guideline on bioequivalence studies (*CPMP/EWP/QWP/1401/98*) states at 5.1.8:

For products for local use (after oral, nasal, inhalation, ocular, dermal, rectal, vaginal etc. administration) intended to act without systemic absorption the approach to determine bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are in principle required.

The product now under consideration would appear to be covered by the above quotation. However, the sponsor has included a document entitled *Justification for not submitting biopharmaceutical data.*.

The *Justification* document

Arguments against the need to submit biopharmaceutical data normally address one or more of the following propositions for the product in question:

- there is no need for systemic bioequivalence between the combination product and the active constituents; or
- it is impossible to generate data which would demonstrate bioequivalence; or
- there is reason to believe bioequivalence can be assumed.

As the *Justification* document specifically states: "... Alcon makes no claim that Azarga is bioequivalent to the concomitant administration of its individual constituents …", it appears that the third dot point above is not applicable. The issues which (if applicable) the sponsor was required to address are listed below, together with comments on relevant parts of the sponsor's *Justification*.

The nature of the dosage form

The sponsor offers no particular argument on this, but states: "Azarga is sterile, preserved, multi-dose, buffered (approximately pH 7.2), isotonic solution".

Elsewhere, Azarga is described as a suspension. In the opinion of the evaluator the fact that the product is a suspension rather than a solution would militate in favour of requiring biopharmaceutical data.

The solubility of the active ingredients

The sponsor notes that brinzolamide is "very slightly soluble in water at neutral pH", but offers no argument.

The low solubility would militate in favour of requiring biopharmaceutical data.

The comparative dissolution profiles across the physiological pH range (1-7.5) of the products being considered.

The evaluator considered that this was probably not applicable.

The pharmacokinetic characteristics of the active ingredient(s), such as permeability (or absolute bioavailability), linearity or otherwise, first pass effect (if any) and its significance.

The sponsor summarised some of the results of Study C-05-27, observing that there were no clinically relevant differences noted amongst the Azarga, brinzolamide 1% and timolol 0.5% treatment groups. The evaluator noted that such an observation would not eliminate the need for bioequivalence data.

The clinical consequences of any potential differences in bioavailabilities of the products under consideration (for example, increased dose leading to toxicity or decreased dose leading to lack of efficacy).

This point is discussed above, and below.

The width of the margin between the minimum effective and minimum toxic plasma concentration.

The sponsor states that "The safety margin determined in safety pharmacology studies conducted and those reported in the literature are considered sufficiently wide for Azarga administered by the topical ocular route to preclude any concerns of significant adverse events occurring in humans.

The individual active components of Azarga, brinzolamide and timolol, have been characterised thoroughly in terms of the acute toxicity, chronic toxicity, genotoxicity, carcinogenicity, sensitisation and reproduction and developmental effects. The individual agents have adequate

safety margins based on expected systemic exposure from topical ocular dosing as in the case of the chronic and reproductive toxicity or have no potential for effects as in the case of carcinogenicity and sensitisation."

The evaluator noted that if it is argued that the degree of systemic absorption of brinzolamide is unimportant, why does the current PI recommend (under *Instructions to patients*) an administration technique directed at minimising systemic absorption?

The similarities of, or differences between, the formulations being considered.

The sponsor compared the concentrations of excipients in Azarga and Azopt, pointing out that the formulations were similar.

The evaluator noted that this argument has no force. As well as the excipients, Azarga contains timolol. The questions to be settled are (a) whether brinzolamide is absorbed at the same rate and extent from Azarga as from Azopt, and (b) whether timolol is absorbed at the same rate and extent from Azarga as from other timolol eye drop products on the Australian market.

Discussion

In the opinion of the evaluator, most of the *Justification* document seems to be irrelevant. The evaluator made the points (a) that the relevant guideline does not stipulate a regulatory requirement for biopharmaceutical data showing bioequivalence between the combination product and the individual actives administered separately, and (b) that it is doubtful whether it would be feasible to produce such pharmaceutical data which are meaningful (in terms of efficacy).

Consequences of this are:

- It cannot be assumed the combination product will have the same clinical effect as the individual active drugs administered separately (except to the extent shown by the submitted efficacy and safety data); and
- It will not be possible to prove using pharmaceutical data that any future combination of the same active drugs is equivalent to Azarga.

However, if a strict regulatory approach were to be adopted, the evaluator believed the result may be that no combination product with these active constituents could be marketed, despite the advantages in terms of enhanced compliance and reduced exposure to preservative.

Pharmacodynamics

Some pharmacodynamic data were provided in Study C-99-88.

Efficacy

Study C-97-22

This was a study of the efficacy and safety of the combination product, compared to timolol 0.5% eye drops (Table 5).

Table 5: Details of Study C-97-22

Design Purpose	Subjects Demographics Treatments	Parameters studied	Results LS means (mmHg)	Safety	Comments
Randomised, double-blind, active-comparator, parallel. Described as a "pilot study".	66 patients randomised and treated: Combination product: 33 (11M, 22F); mean age 60.5 (sd 14.7); weights not given; iris colours 20, 6, 1, 6. Timolol: 33 (8M, 25F); mean age 61.1 (sd 12.5); weights not given; iris colours 15, 10, 1, 7.	Primary efficacy parameters: change from baseline in IOP at 8am and 10am time points.	Day 1, 8am -2.9 Day 7, 8am -2.8 Day 7, 10am -3.4 Day 14, 8am -3.3 Day 14, 10am -3.3 Day 1, 8am -1.7 Day 7, 8am -1.3 Day 7, 10am -2.2 Day 14, 8am -1.6 Day 14, 10am -2.2	See text, section 9.3.1.	The "Day 1, 8am" IOP measurement was the last one taken before double blind treatment commenced, but was not defined as "baseline". See text.

The trial protocol did not make clear whether this was a superiority or non-inferiority trial. Based on the form of the analysis, the evaluator assumed it was the former. The protocol did not stipulate the primary efficacy variable, but it was given in the applicant's Clinical Study Report (*CSR*), somewhat ambiguously, as "... mean IOP at the 8 am and 8 pm time points. Study visits were planned at Day 1, Day 7, Day 13, and Day 14. Only comfort evaluation was done on Day 13." The text "8 pm" must have been an error, as no IOP measurements were done at 8 pm. Tables in the *CSR* show measurements at 8 am and 10 am, so it is assumed the *CSR* intended to refer to these time points.

Inclusion criteria included:

- Patients aged at least 21, diagnosed with primary open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension.
- Mean IOP measurements (that is, the mean of 2 measurements in the same eye) of 22 to 36 mmHg, in at least one eye (the same eye) at each of the 8 am and 10 am IOP measurements while using timolol 5 mg/ml eye drops, at both visits 1 and 2 of the Eligibility Phase. Mean IOP in both eyes ≤ 36 at all times.

Exclusion criteria included:

- Only one sighted eye.
- History of inflammatory eye disease or retinal disease.
- Uncontrolled cardiovascular disease.

The Eligibility Phase commenced with timolol 0.5% eye drops bd for at least 3 weeks, followed by 2 eligibility visits, separated by 1 week, at which IOPs were measured at 8 am (just before morning dose) and 10 am. Eligible patients then entered a double-blind treatment phase, in which they were randomised to either the combination product or timolol 0.5% eye drops, bd for 14 days. The protocol did not stipulate any maximum interval between the second eligibility visit and the commencement of the double-blind treatment phase.

Assessments related to the worst eye at "baseline", which was not defined in the protocol, but defined in the *CSR* as "the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used."

In Table 5, the "mean IOP change from baseline" at the time points when measurements were taken is presented. These results were derived using an ANOVA model together with values relating to differences between treatment groups. The complete table is shown below.

Table 6: C-97-22: Mean IOP Change from Baseline

	Baseline		**Day 1**	**Day 7**		**Day 14**	
	8am	**10am**	**8am**	**8am**	**10am**	**8am**	**10am**
Brinzolamide/Timolol							
Mean	24.7	23.7	-2.9	-2.8	-3.4	-3.3	-3.3
N	33	33	33	33	33	33	33
Timolol							
Mean	24.0	23.5	-1.7	-1.3	-2.2	-1.6	-2.2
N	33	33	33	33	33	33	33
Difference	0.7	0.3	-1.3	-1.5	-1.2	-1.7	-1.1
P-value	0.1916	0.6011	0.0163	0.0042	0.0206	0.0017	0.0425
Upper 95% CI	1.71	1.30	-0.23	-0.48	-0.19	-0.63	-0.04
Lower 95% CI	-0.34	-0.75	-2.28	-2.52	-2.24	-2.68	-2.09

The evaluator found the efficacy outcome unconvincing, particularly as it seems the analysis was not pre-specified in the protocol. Possibly by chance, the test group was associated with an IOP advantage over the reference group at Day 1, before the double-blind treatment started. In these circumstances, the P-values are specious.

Similar results were obtained for the *per* protocol population, which comprised the ITT population, less 3 patients who had committed major protocol breaches. These 3 included the non-completer, the only patient who was withdrawn without completing the study, for the reason "poor reliability".

Study C-05-24

This was a pivotal superiority study of the efficacy and safety of the combination product, compared to Azopt and timolol 0.5% eye drops (Table 7).

Table 7: Details of Study C-05-24

Design **Purpose**	**Subjects** **Demographics** **Treatments**	**Parameters studied**	**Results** **Mean change from baseline (mmHg)**	**Comments**
Randomised, double-blind, active-comparator, parallel. Demonstrate superiority.	523 patients randomised and treated. 517 evaluable (the ITT population): (1) Combination product: 171 (80M, 91F); mean age 62.3 (sd 12.9); weights not given; iris colours 90, 28, 8, 44, 1. (2) Azopt: 173 (74M, 99F); mean age 63.1 (sd 12.1); weights not given; iris colours 99, 26, 10, 35, 3. (3) Timolol: 173 (67M, 106F); mean age 62.9 (sd 10.4); weights not given; iris colours 98, 28, 1, 42, 4.	Primary efficacy parameters: change from baseline in IOP at 8am and 10am time points.	Week 2, 8am -8.4 (N=170) Week 2, 10am -8.7 (N=170) Month 3, 8am -8.3 (N=171) Month 3, 10am -8.7 (N=171) Month 6, 8am -8.1 (N=171) Month 6, 10am -8.0 (N=171) Week 2, 8am -5.1 (N=172) Week 2, 10am -5.2 (N=172) Month 3, 8am -5.6 (N=173) Month 3, 10am -5.3 (N=173) Month 6, 8am -5.2 (N=173) Month 6, 10am -5.1 (N=173) Week 2, 8am -6.9 (N=173) Week 2, 10am -6.6 (N=173) Month 3, 8am -6.9 (N=173) Month 3, 10am -6.4 (N=173) Month 6, 8am -6.6 (N=173) Month 6, 10am -5.7 (N=173)	At each time point, differences between (a) groups (1) and (2), and (b) groups (1) and (3), were statistically significant at the < 0.01 level, using repeated measures ANOVA.

Inclusion criteria for the Treatment Phase included:

- Patients aged at least 18, diagnosed with primary open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension.

- Mean IOP measurements (*ie*, the mean of 2 measurements) in at least one eye (the same eye) of 24 to 36 mmHg at 8 am, and 21 to 36 mmHg at 10 am, at both visits 1 and 2 of the Eligibility Phase. The first of these eligibility visits took place after a variable washout period (aimed at washing out all glaucoma medications), and the second 1 week later. Mean IOP in both eyes ≤ 36 at all times.

Exclusion criteria were similar to those for study C-97-22.

The Treatment Phase commenced the day after the second eligibility visit. Patients were randomised to receive 1 drop at 8am and 8pm for 6 months of (1) the combination product, (2) Azopt, or (3) timolol 0.5%. Assessments related to the worst eye at "baseline", which was defined as "the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used."

Outcomes for the primary efficacy parameters are shown in Table 7. They appear to demonstrate adequately the superiority of the test product in the population studied.

Secondary efficacy parameters were percentages of patients who achieved target IOP < 18 mmHg at post-dosing time points. These data are shown in Table 8, for the ITT population. The difference between the combination and Azopt treatment groups was formally statistically significant ($p \leq 0.0001$) at each time point. The difference between the combination and timolol treatment groups was not statistically significant after week 2.

Table 8: Patients achieving target IOP (< 18 mmHg), ITT population. Study C-05-24.

	Week 2		**Month 3**		**Month 6**	
	8am	**10am**	**8am**	**10am**	**8am**	**10am**
Brinzolamide/ Timolol						
Total	170	170	171	171	171	171
N	64	53	34	32	26	23
%	37.6	31.2	19.9	18.7	15.2	13.5
Azopt						
Total	172	172	173	173	173	173
N	14	12	7	6	4	4
%	8.1	7.0	4.0	3.5	2.3	2.3
Timolol						
Total	173	173	173	173	173	173
N	39	34	24	22	19	17
%	22.5	19.7	13.9	12.7	11.0	9.8

Of the 523 patients randomised and treated, 477 completed the study and 46 (13 on the combination product, 20 on Azopt, 13 on timolol) did not.

Study C-05-10

This was a pivotal non-inferiority study of the efficacy and safety of the test combination product (brinzolamide 1% and timolol 0.5% eye drops), compared to the reference combination product Cosopt (dorzolamide 2% and timolol 0.5% eye drops). (Table 9).

Inclusion and exclusion criteria were similar to those for study C-05-24, except that the first dot point above was extended to read:

- Patients aged at least 18, diagnosed with primary open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension who were currently on an IOP-lowering medication and, in the opinion of the investigator, would benefit from a combination therapy.

Table 9: Details of Study C-05-10

Design **Purpose** **Location**	**Subjects** **Demographics** **Treatments**	**Parameters studied**	**Results** **Mean IOP at time point (mmHg)**	**Comments**
Randomised, double-blind, active-comparator, parallel. Demonstrate non-inferiority. 45 sites in Australia, Belgium, France, Italy, Latvia, Lithuania, Singapore, Sweden, Taiwan, UK and USA.	437 patients randomised and treated. 419 evaluable *per* protocol (the PP population): (1) Test combination product: 218 (95M, 123F); weights not given; iris colours 94, 22, 17, 70, 15. (2) Cosopt 201 (79M, 122F); weights not given; iris colours 101, 19, 7, 60, 14.	Primary efficacy parameters: change from baseline in IOP at 8am, 10 am and 4 pm time points at 6 Month visit.	Baseline 27.3 (N=218) Month 6, 8am 18.5 (N=205) Month 6, 10am 17.1 (N=204) Month 6, 4pm 17.3 (N=200) Baseline 27.3 (N=201) Month 6, 8am 18.9 (N=181) Month 6, 10am 17.2 (N=181) Month 6, 4pm 17.2 (N=180)	Differences (95% CI) between groups at each time point: Baseline 0.0 (-0.7, 0.6) Month 6, 8am -0.5 (-1.2, 0.3) Month 6, 10am -0.1 (-0.8, 0.6) Month 6, 4pm 0.1 (-0.6, 0.9)

The Treatment Phase commenced on the evening of the second eligibility visit. Patients were randomised to receive 1 drop at 8am and 8pm for 12 months of (1) the test combination product, (2) the reference combination product. Assessments related to the worst eye at "baseline", which was defined as "the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used."

The protocol stipulated a non-inferiority margin of 1.5 mmHg, to be satisfied at all 3 time points (8am, 10am and 4pm) at the Month 6 visit. The value of 1.5 was chosen on the basis that it was "the margin of clinical relevance" and "can be considered an overall class difference from placebo and is

a common criterion used in clinical studies". The evaluator noted that this is broadly consistent with the relevant EU Guideline (EMEA 2005, section 4).

Sample size calculation was based upon the assumption of IOP sd 3.5 mmHg (from previous experience); specification of Type 1 error 0.05, power 90%, and non-inferiority margin 1.5 mmHg; and taking account of multiple time points in the efficacy analysis. This yielded the number 166 per group, and 210 were planned.

Outcomes for the primary efficacy parameters are shown in Table 9. They demonstrate adequately the non-inferiority of the test product.

Secondary efficacy parameters were percentages of patients who achieved target IOP < 18 mmHg at post-dosing time points. These data are shown in Table 10 for the ITT population. The test and comparator treatment groups were comparable.

Table 10: Patients achieving target IOP (< 18 mmHg), ITT population. Study C-05-10.

	Week 2		Month 3		Month 6			Month 9		Month 12		
	8am	10am	8am	10am	8am	10am	4pm	8am	10am	8am	10am	4pm
Brinzolamide/ Timolol												
Total	219	218	219	218	219	218	209	219	218	219	218	211
N	78	132	88	132	86	120	114	86	117	86	119	108
%	35.6	60.6	40.2	60.6	39.3	55.0	54.5	39.3	53.7	39.3	54.6	51.2
COSOPT												
Total	212	212	212	212	212	212	194	212	212	212	212	196
N	64	104	82	119	73	112	111	70	100	78	104	112
%	30.2	49.1	38.7	56.1	34.4	52.8	57.2	33.0	47.2	36.8	49.1	57.1

Of the 437 patients randomised and treated, 393 completed the study and 44 (16 on the test product, 28 on Cosopt) did not.

Efficacy summary

In Study C-05-24, superiority of the test product over the individual components has been demonstrated in the population studied. Note however, that while this population included patients who had been previously treated with a range of products, there was no requirement for previous treatment failure. In Study C-05-10, the test product was shown non-inferior to the combination product Cosopt, in a population of patients who, "in the opinion of the investigator, would benefit from a combination therapy".

For the pivotal efficacy studies (C-05-24 and C-05-10), the evaluator could not find in the CSRs any presentation of the treatment patients had been receiving before enrolment in the study, or any analysis relating efficacy to success or otherwise of previous treatment. However, some summary data was available which indicated that in the pivotal studies combined, 65.1% of patients had used one pre-study IOP-lowering medication, 17.2% had used two, 4.2% had used 3 or 4 and 13.5% had used none. Of those who used monotherapy, 39.6% used a prostaglandin while 17.6% used a beta-blocker with less than 5% for each of carbonic anhydrase inhibitors and alpha agonists.

The evaluator noted that it was unsatisfactory that the data on pre-study medication appear only in a summary document. Although the data provided give an idea of the previous treatment in the populations studied, they do not permit any analysis (for example) of treatment success in patients not adequately responding to monotherapy.

A small iris colour effect was observed in studies C-97-22, C-05-24 and C-05-10, the mean IOP (pooled across visits and time points) for patients with brown irises being slightly higher than that for other iris colours.

Safety

The pharmacokinetic studies

Safety-related information relating to these is summarised in Tables 2 and 3.

Study C-05-27

AEs tabulated by preferred term are shown in Table 11.

Table 11: AEs by preferred term. Study C-05-27.

	Brinz/Tim N=26		Azopt N=28		Timolol N=28		Brinz cap N=59		Pbo cap N=28	
	n	%	n	%	n	%	n	%	n	%
System Organ Class Preferred term										
Considered at least possibly related										
Eye Disorders										
Eye irritation	1	3.8	3	10.7					1	3.6
Vision blurred	1	3.8	1	3.6	1	3.6				
Eye pain	1	3.8								
Scleral hyperaemia	1	3.8								
Photophobia			1	3.6	1	3.6				
Eye discharge			1	3.6						
Abnormal sensation in eye					1	3.6	1	1.7		
Gastrointestinal Disorders										
Stomach discomfort							1	1.7		
Investigations										
Intraocular pressure decreased	3	11.5								
Nervous System Disorders										
Dysgeusia			2	7.1						
Dizziness							1	1.7		
Psychiatric Disorders										
Euphoric mood							1	1.7		
Respiratory, Thoracic and Mediastinal Disorders										
Sinus congestion			1	3.6						

Study C-05-49

This was a phase 2 tolerability study of brinzolamide 1% and timolol 0.5% eye drops bd versus Cosopt eye drops bd. The stated objective was to evaluate ocular discomfort, based on burning and stinging, of a combination product compared with Cosopt. The protocol made clear that the superiority, rather than non-inferiority, was to be demonstrated. The measure chosen was "Ocular discomfort score", in which burning and stinging was assessed using the scale: 0 (none), 1 (mild), 2 (moderate), 3 (severe), 4 (very severe). The main details are given in Table 12.

On the basis of previous studies using ocular discomfort scores, a common sd of 1.0 was assumed. It was calculated that with 44 subjects per group, there would be 90% power to detect a difference of 0.7 in mean ocular discomfort score using $\alpha = 0.05$.

Inclusion criteria included: age at least 18, diagnosed with open-angle glaucoma, using a single IOP-lowering medication in a stable regimen for at least 1 month. Exclusion criteria included: unable to discontinue contact lens use during the study; inflammatory eye disease; ocular infection in past 3 months; history of severe dry eye; use of any ocular carbonic anhydrase inhibitors in the past 6 months.

The evaluator agreed that these results demonstrate superiority of the test product in terms of the pre-specified comfort criterion

Table 12. Details of Study C-05-49

Design **Purpose** **Location**	**Subjects** **Demographics** **Treatments**	**Parameters studied**	**Results**	**Adverse Events**
Multi-centre, randomised, double-blind, active-controlled, parallel. Assess ocular comfort of product.	Patients with open-angle glaucoma or ocular hypertension, currently controlled on a single drug. Number randomised and treated (1 drop each eye bd) for 1 week: 4 US sites (1) Test product (brinzolamide 1% + timolol 0.5%): 48 (20M, 28F); mean age 67.2 (sd 11.3); ocular hypertension 17, open-angle glaucoma 29, open-angle glaucoma with pigment dispersion 2. (2) Cosopt (dorzolamide 2% + timolol 0.5%): 47 (13M, 34F); mean age 67.9 (sd 11.8); ocular hypertension 14, open-angle glaucoma 33, open-angle glaucoma with pigment dispersion 0.	Ocular discomfort score: change from baseline to end of week.	**Change** **Number** -1 4 0 27 +1 9 +2 4 +3 2 +4 1 missing 1 Mean change 0.49 (sd 1.06) **Change** **Number** -1 0 0 12 +1 16 +2 12 +3 6	Numbers of patients in whom AEs at least possibly related to treatment: (1) 5 eye pain; 4 eye irritation; 9 vision blurred; 2 dry eye; 1 photophobia. The 9 cases of blurred vision were all non-serious. Intensity was mild in 7 and moderate in 2. Onset was Day 2 in every case. Time of onset in relation to treatment was not given; duration of event was < 5 min in 6/9. (2) 11 eye pain; 8 eye irritation; 1 vision blurred; 2 lacrimation; 1 ocular hyperaemia

	All completed.		+4 1 missing 0 Mean change 1.32 (sd 1.07)	

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Study C-97-22

AEs tabulated by preferred term are shown in Table 13.

Table 13. AEs by preferred term in study C-97-22.

	Brinz/Tim N=33		Timolol N=33	
	n	%	n	%
System Organ Class Preferred term				
Considered at least possibly related				
Eye Disorders				
Vision blurred	7	21.2	1	3.0
Eye irritation	3	9.1	1	3.0
Foreign body sensation	1	3.0		
Lacrimation increased	1	3.0		
Ocular hyperaemia	1	3.0		
Eye pain			1	3.0
Nervous System Disorders				
Dysgeusia	3	9.1		
Considered unrelated				
Eye Disorders				
Foreign body sensation			1	3.0
Surgical and Medical Procedures				
Dental treatment			1	3.0

9.3.2 Study C-05-24

AEs tabulated by Preferred Term are shown in Table 14 There was only 1 report of a serious AE classified as related to treatment: treatment in hospital of an elderly patient with chronic obstructive pulmonary disease.

Specific assessments were made at baseline and Month 6 of

- dilated fundus parameters,
- cup/disk ratio, and
- corneal thickness; and

cardiovascular parameters (pulse and BP) were measured at baseline and all subsequent visits. Analysis of parameter changes revealed no untoward safety issues for any of the treatment groups.

Table 14: AEs by preferred term in study C-05-24.

	Brinz/Tim N=174		Azopt N=174		Timolol N=175	
	n	%	n	%	n	%
System Organ Class Preferred term						
Eye Disorders						
Blurred vision	6		5		1	
Eye irritation	5		2		6	
Punctate keratitis	3		1		3	
Conjunctival hyperaemia	2		2		1	
Eye pain	2		1		2	
Eye pruritus	2		1			
Foreign body sensation in eyes	1		1		1	
Ocular hyperaemia	1		1			
Corneal epithelium disorder	1					
Dry eye			1		1	
Eyelid oedema			1		1	
Photophobia			1		1	
Eye discharge			1			
Lacrimation increased					2	
Conjunctival oedema					1	
Reduced visual acuity					1	
Cardiac Disorders						
Bradycardia					2	
Gastrointestinal Disorders						
Nausea			2			
Vomiting			1			
Investigations						
Blood pressure decreased	2					
Heart rate decreased					1	
Nervous System Disorders						
Dysgeusia	2		8		1	
Headache			1			
Sinus headache					1	
Respiratory, Thoracic and Mediastinal Disorders						
Pharyngolaryngeal pain	1		1			
COPD	1					
Dyspnoea					1	
Wheezing					1	
Skin and Subcutaneous Tissue Disorders						
Periorbital oedema			1			

9.3.3 Study C-05-10

AEs tabulated by Preferred Term are shown in Table 15.

Table 15: AEs by preferred term in study C-05-10.

	Brinz/Tim N=220		Cosopt N=217	
	n	%	n	%
System Organ Class Preferred term				
Eye Disorders				
Blurred vision	8	3.6	1	0.5
Eye irritation	6	2.7	23	10.6
Eye pain	6	2.7	14	6.5
Foreign body sensation in eyes	3	1.4	1	0.5
Eye discharge	2	0.9		
Ocular hyperaemia	1	0.5	3	1.4
Blepharitis	1	0.5	1	0.5
Blepharitis allergic	1	0.5	1	0.5
Eye pruritus	1	0.5	1	0.5
Eyelid margin crusting	1	0.5	1	0.5
Abnormal sensation in eye	1	0.5		
Anterior chamber flare	1	0.5		
Asthenopia	1	0.5		
Conjunctival hyperaemia	1	0.5		
Conjunctivitis allergic	1	0.5		
Corneal erosion	1	0.5		
Dry eye	1	0.5		
Erythema of eyelid	1	0.5		
Eyelids pruritus	1	0.5		
Conjunctival follicles			1	0.5
Lacrimation increased			1	0.5
Photophobia			1	0.5
Cardiac Disorders				
Bradycardia			1	0.5
Immune System Disorders				
Hypersensitivity			2	0.9
Investigations				
Heart rate decreased			2	0.9
Blood pressure decreased			1	0.5
Corneal staining			1	0.5
Nervous System Disorders				
Dysgeusia	7	3.2	6	2.8
Headache			2	0.9
Psychiatric Disorders				
Insomnia	1	0.5		

Respiratory, Thoracic and Mediastinal Disorders				
Cough	1	0.5		
Rhinorrhoea	1	0.5		
Orthopnoea			1	0.5
Skin and Subcutaneous Tissue Disorders				
Hair disorder	1	0.5		
Lichen planus	1	0.5		

Specific assessments were made as for study C-05-24, above, at baseline, Month 6, and exit (Month 12). Analyses of cup/disk ratio, corneal thickness, and cardiovascular parameters were unremarkable. Maximum (for either eye) dilated fundus parameter changes from baseline to any visit are tabulated below in Table 16.

Table 16: Maximum Dilated Fundus Parameter Changes from Baseline to Any Visit for C-05-10

	Total	**Optic Nerve**		**Retina/Macula/Choroid**		**Vitreous**	
Treatment	**N**	**N**	**%**	**N**	**%**	**N**	**%**
Total	**427**	**2**	**0.5**	**5**	**1.2**	**8**	**1.9**
Brinzolamide/timolol	**215**[a]	**2**	**0.9**	**4**	**1.9**	**1**	**0.5**
Age 18-64	90	0	0	0	0	1	1.1
Age ≥ 65	125	2	1.6	4	3.2	0	0
Cosopt	**212**[a]	**0**	**0**	**1**	**0.5**	**7**	**3.3**
Age 18-64	105	0	0	0	0	4	3.8
Age ≥ 65	107	0	0	1	0.9	3	2.8

[a]5 patients had missing baseline or follow-up fundus parameter data.

Periodic Safety Update Reports

For brinzolamide, no specific areas of concern were identified in the PSUR, while for timolol, no evidence of previously unidentified toxicity was ascertained.

Safety summary

No safety issues are raised by the data presented, other than those already recognised as associated with the individual components of the combination. In Study C-05-49, the test product was found better tolerated than Cosopt.

Clinical Summary and Conclusions

Proof of efficacy in the proposed indication is incomplete, in that no detailed information has been submitted relating to efficacy in patients "for whom monotherapy provides insufficient IOP reduction". In view of this deficiency, the evaluator recommended against approval.

The evaluator also recommended that the sponsor be invited to respond to the two paragraphs below.

The justification for the fixed-combination is incomplete, in that no explanation has been offered for the chosen concentration of timolol. An argument may be available based on the apparent reduced bioavailability of timolol in the combination product, but no such argument was explicitly put forward.

Bioequivalence of the combination product to the components separately administered is neither proven nor claimed. However, a strict approach to this matter may not be feasible, as explained above.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

The evaluator states that the chemistry and quality control issues have been resolved and recommends approval.

The closed shelf life recommended is 2 years when stored below 25^0C and an opened shelf life is 4 weeks.

No bioavailability studies were submitted. The evaluator states that the combination product may have different absorption profiles to that of the individual components when administered separately.

This concern was also noted by the PSC which mentioned that study C-05-27, a pharmacokinetic study, needed review in relation to these issues, by the clinical evaluator.

Nonclinical

A single efficacy study using the fixed dose combination product on rabbits was submitted. There was no additive efficacy seen with the combination product. Safety pharmacology did not reveal any significant changes in rabbits or dogs.

The ocular and systemic absorption of brinzolamide was not significantly affected by co-administration of timolol (rabbits and humans). When administered concomitantly, there was a two fold increase in timolol in relation to systemic absorption and a greater ocular absorption (3-4 fold) in rabbits.

Repeat dose toxicity studies (9 month duration) were conducted in rabbits. No significant toxicity was seen.

Overall, there were no objections to registration from a nonclinical point of view.

Clinical

The formulation of Azarga used in the clinical studies has been that which is proposed for marketing. Formulation details of the comparator eye drops used in the studies are given in the sponsor's response to the clinical evaluation report.

Fixed Dose Combination

The issue of the justification of the fixed dose combination was discussed by the evaluator. It is stated that there is better efficacy and safety than the individual components when given alone; both

components are registered separately for the indication sought as a fixed dose combination. The evaluator notes two deficiencies in the sponsor's rationale for this justification.

Firstly, the sponsor states that disease progression/tolerance to one medication requires adjunctive therapy; however, no supporting information has been provided for this assertion. Secondly, lower dose strengths of timolol have not been tried as recommended in the justification for fixed dose combination (FDC) guidelines to ascertain the minimum effective dose.

The sponsor has responded that it is generally recommended that if treatment is started with timolol 0.25%, it is increased in strength to 0.5% before adding the second agent; this is seen in a range of agents used in glaucoma treatment such as Duotrav (travoprost 0.04 mg/mL plus timolol 5mg/mL), Xalacom (latanoprost 0.05mg/mL plus timolol 5mg/mL), Ganfort (bimatoprost 0.3mg/mL plus timolol 5mg/mL) and Cosopt (dorzolamide 2mg/mL plus timolol 5mg/mL). Thus, the use of a lower strength of timolol in combination with brinzolamide is not necessary to ascertain adequate efficacy and safety of a fixed dose combination product. This justification appears acceptable.

Pharmacokinetics:

The evaluator mentions that the three pharmacokinetic studies do not provide information on whether there is interaction between the two components in the FDC and are of limited relevance to this application.

The first study, C-98-62, discussed the pharmacokinetics of various gel formulations of timolol 0.5% and has been considered irrelevant to the application. C-99-88 has been previously submitted and is an open label, parallel group multiple dose pharmacokinetic study of brinzolamide following oral or topical ocular administration in 83 middle aged and elderly Japanese and Caucasian subjects. The whole blood concentrations of brinzolamide and N-desethyl brinzolamide increased in a similar manner after topical ocular administration of brinzolamide in both racial groups. Similarly, Study C-05-27 did not provide information on the pharmacokinetics of the FDC. In this study, the plasma concentrations of brinzolamide were "not accessible, being generally below the limit of quantification". In addition, pharmacokinetic parameters derived from whole blood measurements are submitted; the evaluator comments that these results are of no value in assessing bioequivalence.

The sponsor has provided a justification for not submitting bioavailability data which was reviewed by the evaluator. The Delegate agreed with the evaluator that most of the arguments put forward are irrelevant to this application. The sponsor makes no claim that Azarga is bioequivalent to its individual components when administered concomitantly. The submission needs to rely on demonstrating efficacy and safety of the FDC as recommended in the EU Guideline CPMP/EWP/240/95.

Efficacy

Study C-97-22, described as a pilot study, was a randomised double blind active comparator (0.5% timolol eye drop) parallel group study on 66 patients with primary open angle glaucoma or ocular hypertension. IOP measure at baseline was to be 22 to 36 mm Hg in at least one eye. Azarga versus timolol 0.5% was administered bd for 14 days. The evaluator noted that the drop in IOP with the FDC was unconvincing; also the margin of difference was not pre-specified in the protocol. The sponsor has stated (in its response) that this was an exploratory study.

Study C-05-24 was a pivotal superiority study that was randomised, double blind and compared Azarga with timolol 0.5% and Azopt (brinzolamide 1.0 %) bd for 6 months. Of the total of 523 recruits, 171 were randomised to Azarga, 173 to Azopt and 173 to timolol. Those who were over 18 years with open angle glaucoma or ocular hypertension were eligible to participate. IOP was to be 24 -36 mm Hg at 8 am and 21- 36 mm Hg at 10 am at both screening visits.

The evaluator noted that statistically significant difference favouring Azarga was displayed at each time point (week 2, month 3 and month 6). The secondary efficacy endpoint (the percentage of patients achieving a target ≤ 18mm Hg) is shown below:

	Week 2		Month 3		Month 6	
	8am	10am	8am	10am	8am	10am
Brinzolamide/ Timolol	37.6	31.2	19.9	18.7	15.2	13.5
Azopt	8.1	7.0	4.0	3.5	2.3	2.3
Timolol	22.5	19.7	13.9	12.7	11.0	9.8

Based on this endpoint there appears to be a waning of effect over time in relation to the secondary efficacy endpoint. The sponsor should tabulate the results at each time point in relation to the primary efficacy endpoint, in the PI.

Study C-05-10 was a pivotal non-inferiority study comparing Azarga with Cosopt (dorzolamide 2% and timolol 0.5%). The inclusion criteria were similar to the previous study; however subjects were already to be on IOP lowering medications and would benefit from combination therapy. Patients were to receive one drop twice daily for 12 months. The non-inferiority margin was 1.5 mmHg and the evaluator states that this was acceptable. The primary efficacy endpoint was the change from baseline in IOP at 8 am, 10 am and 4 pm time points to 6 months. The secondary endpoint (the percentage achieving less than 18 mm Hg at the same time points) was comparable in the two treatment groups.

The evaluator noted that previous treatment failure was not a requisite for inclusion in study C-05-24. Study C-05-10, however, states that those who would benefit from a combination product were eligible to participate. The evaluator also noted that details of the pre-study medications were not specified. The sponsor subsequently provided analyses on the pre-study IOP lowering medications used in the pivotal studies, the percentage of subjects using one, two or more medications, the extent of IOP drop with these medications.

Safety

The overall safety population included a total of 1203 patients with open angle glaucoma or ocular hypertension, of whom 501 patients were exposed to Azarga (bd). The number of patients exposed in the pivotal studies is as follows:

Treatment	Patients with 6 months of exposure			Patients with one year exposure
	Total	C-05-24	C-05-10	C-05-10
Total	830	422	408	385
Azarga	354	140	214	200
Cosopt	194	-	1194	185
Azopt	135	135	-	-
Timolol	147	147	-	-

Two serious adverse events were reported: one was an elderly patient on Azarga who was hospitalised due to decompensation of previously undiagnosed COPD; another elderly patient on Cosopt who was hospitalised due to a hypersensitivity reaction. 24 patients discontinued due to AEs, 9 were on Azarga, 9 on Cosopt and 2 on Azopt and 4 on timolol. The reasons for discontinuation in Azarga treated group included allergic conjunctivitis, anterior chamber flare, blurred vision, pruritus, hyperaemia, redness etc.

The adverse events reported in the two pivotal studies displayed no unusual trends. In study C-05-49 (which was pharmacokinetic study) the test product was better tolerated than Cosopt.

Overall conclusions of the evaluator

The evaluator recommended rejection as information in those "for whom monotherapy provides insufficient IOP reduction" (the requested indication) is lacking.

Sponsor's response to the clinical evaluation report: The sponsor has provided an extensive response to the report. These responses are addressed in the relevant sections of the Delegate's summary.

Risk-Benefit Analysis

Fixed dose combination

The evaluator's concern was that the minimum effective dose of timolol was not tried in relation to the optimum concentration. However the Delegate accepted the sponsor's argument that 0.5% timolol is used in other registered fixed dose combinations; also, clinical guidelines and the treatment paradigm adopted and used in Australia provide for the use of 0.5% timolol rather than 0.25% in the fixed dose combination product.

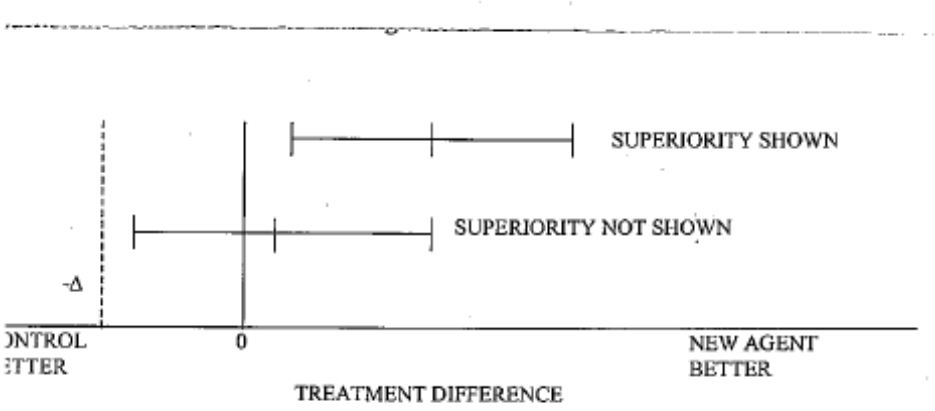
The sponsor has addressed the evaluator's concern regarding lack of data on the proposed indication, that is, for whom monotherapy provided insufficient IOP reduction. The Delegate agreed with the sponsor that there is adequate information for the population for whom the indication is sought. However, this indication should be expanded to:

for whom monotherapy (with either component alone) provided insufficient IOP reduction.

This is in keeping with the adopted Fixed Dose Combination Guidelines.

Other Issues

The Delegate agreed with the evaluator that the pivotal study which compares Azarga with Cosopt, designed as a non-inferiority trial should be presented as such in the draft PI and not as a study showing superior efficacy. This is because the adopted EU Guidelines (CPMP/EWP/482/99) that addresses the interpretation of a non-inferiority study as a superiority trial states that "if the 95% confidence interval for the treatment effect not only lies above – delta but **also above zero**, then there is evidence of superiority in terms of statistical significance at the 5% level ($p < 0.05$): see the figure included in the EU Guideline, below. As evidenced in the company response, this is not the case in the treatment difference depicted in this study.



gure 4: Non-inferiority to superiority

Thus, the criteria for superiority were not met and the sponsor should amend the draft PI to state that the results showed non-inferiority at all time points.

The Delegate proposed to register Azarga for the following indication:

decrease of intraocular pressure in patients with open angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction.

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and suggested the following wording:

decrease of intraocular pressure (IOP) in patients 18 years and over with open angle glaucoma or ocular hypertension for whom monotherapy with each component provides insufficient IOP reduction.

In making this recommendation, the Committee noted that the pre-ADEC response adequately addresses all the concerns raised by clinical evaluator. The ADEC reflected that there were no clinical data provided for children, therefore the indication should be limited to patients 18 years and over.

ADEC also recommended that the addition of a statement in the product information to the effect of the pivotal study which compares Azarga and Cosopt demonstrating non inferiority at all time points should be made prior to approval.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Azarga eye drops containing brinzolamide 1% and timolol maleate 0.5% for the following indication:

Decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension for whom monotherapy with either component provides insufficient IOP reduction.

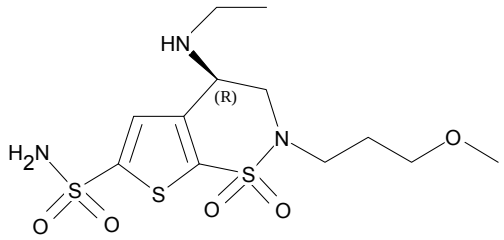
Attachment 1. Product Information

PRODUCT INFORMATION

AZARGA® (brinzolamide 1% & timolol 0.5%) Eye Drops

NAME OF THE DRUG

AZARGA® Eye Drops is a suspension containing a combination of brinzolamide (10 mg/mL) and timolol (5 mg/mL; as timolol maleate). The chemical structure of each active ingredient is represented below:



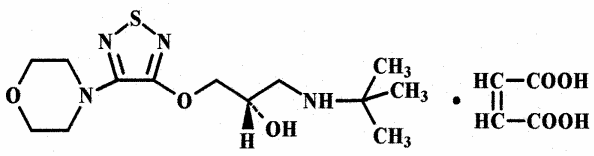
Brinzolamide

Empirical formula: $C_{12}H_{21}N_3O_5S_3$

Molecular weight: 383.51

Chemical name: (R)-4-(Ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide

CAS Number: 138890-62-7



Timolol maleate

Empirical formula: $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$

Molecular weight: 432.50

Chemical name: (S)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2 propanol maleate (1:1) (salt)

CAS Number: 26921-17-5

DESCRIPTION

Brinzolamide is a white to off-white, crystalline powder which is very slightly soluble in water at neutral pH.

Timolol maleate is a white to off-white, crystalline powder which is soluble in water, alcohol and practically insoluble in ether.

AZARGA is a white to off-white uniform suspension for multiple-dose topical ophthalmic use. The pH of AZARGA is approximately 7.2.

AZARGA also contains mannitol, carbomer 974P, tyloxapol, disodium edetate, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), purified water and benzalkonium chloride (0.1 mg/mL) as preservative.

PHARMACOLOGY

Mechanism of Action

AZARGA contains two active substances: brinzolamide and timolol maleate. These two components decrease elevated intraocular pressure (IOP) primarily by reducing aqueous humour secretion, but do so by different mechanisms of action. Clinical data demonstrates that the combined effect of these two active substances results in additional IOP reduction compared to either compound alone.

Brinzolamide exhibits a high affinity for and is a potent inhibitor of human carbonic anhydrase II (CA-II). Carbonic anhydrase exists as a number of isoenzymes and is found in many tissues in the body; CA-II is the predominant iso-enzyme in the eye. Inhibition of CA-II in the ciliary processes of the eye decreases aqueous humour secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Brinzolamide exhibited minimal cardiovascular effects, including no inducement of QTc prolongation and no or minimal effect on blood pressure and heart rate, and had no significant local anaesthetic (membrane stabilising) activity on the cornea.

Timolol is a non-selective beta-adrenergic receptor blocking agent that has no significant intrinsic sympathomimetic, direct myocardial depressant or local anaesthetic (membrane-stabilising) activity. The precise mechanism of action of timolol in lowering IOP is not clearly established at this time, although tonography and fluorophotometry studies suggest that its predominant action is related to reduced aqueous humour formation; a slight increase in outflow facility was also observed in some studies.

Pharmacokinetics

Absorption

Following topical ocular administration, brinzolamide and timolol are absorbed through the cornea and into the systemic circulation. In a pharmacokinetic study, healthy subjects received oral brinzolamide (1 mg) twice daily for 2 weeks to shorten the time to reach steady-state prior to starting AZARGA administration. Following twice daily dosing of AZARGA for 13 weeks, the concentrations of brinzolamide in erythrocytes at weeks 4, 10 and 15, averaged 18.8 $\pm$ 3.29 µM, 18.1 $\pm$ 2.68 µM and 18.4 $\pm$ 3.01 µM respectively. Steady state concentrations of brinzolamide in erythrocytes may not bear a simple relationship to plasma concentrations of the drug, which have been observed to be low and generally below assay quantitiation limits (<10 ng/mL) following topical ocular administration in other studies.

At steady state, following administration of AZARGA, the mean plasma C_{max} and $AUC_{0\text{-}12h}$ of timolol were 27% and 28% lower (C_{max}: 0.824 $\pm$ 0.453 ng/mL; $AUC_{0\text{-}12h}$: 4.71 $\pm$ 4.29 ng h/mL), respectively in comparison to the administration of timolol 5 mg/mL (C_{max}: 1.13 $\pm$ 0.494 ng/mL; $AUC_{0\text{-}12h}$: 6.58 $\pm$ 3.18 ng h/mL). The lower systemic exposure to timolol following AZARGA administration is not clinically relevant. Following administration of AZARGA, mean C_{max} of timolol was reached at 0.79 $\pm$ 0.45 hours.

Distribution

Plasma protein binding of brinzolamide is moderate (about 60%). Brinzolamide is sequestered in red blood cells (RBCs) due to its high affinity binding to CA-II and to a lesser extent to CA-I. Its active N-desethyl metabolite also accumulates in RBCs where it binds primarily to CA-I. The affinity of brinzolamide and metabolite to RBCs and tissue carbonic

anhydrase results in low plasma concentrations.

Ocular tissue distribution data in rabbits showed that timolol can be measured in aqueous humour up to 48 hours after administration of AZARGA. At steady-state, timolol is detected in human plasma for up to 12 hours after administration of AZARGA.

Metabolism

The metabolic pathways for brinzolamide involve N-dealkylation, O-dealkylations and oxidation of its N-propyl side chain. N-desethyl brinzolamide is a major metabolite of brinzolamide formed in humans, which also binds to CA-I in the presence of brinzolamide and accumulates in RBCs. *In vitro* studies show that the metabolism of brinzolamide mainly involves CYP3A4 as well as at least four other isozymes (CYP2A6, CYP2B6, CYP2C8 and CYP2C9).

Timolol is metabolised by two pathways. One route yields an ethanolamine side chain on the thiadiazole ring and the other gives an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. Timolol metabolism is mediated primarily by CYP2D6.

Excretion

Brinzolamide is eliminated primarily by renal excretion (approximately 60%). About 20% of the dose has been accounted for in urine as metabolite. Brinzolamide and N-desethyl-brinzolamide are the predominant components found in the urine along with trace levels (<1%) of the N-desmethoxypropyl and O-desmethyl metabolites.

Timolol and its metabolites are primarily excreted by the kidneys. Approximately 20% of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites. The plasma $t_{1/2}$ of timolol is 4.8 hours after administration of AZARGA.

CLINICAL STUDIES

In a twelve-month, double-masked, randomised clinical trial in patients (n=437) with open-angle glaucoma or ocular hypertension who, in the investigator's opinion, could benefit from combination therapy and who had baseline mean IOP of 25 to 27 mm Hg, the mean IOP-lowering effect of AZARGA was 7 to 9 mm Hg and for dorzolamide 20 mg/mL + timolol 5mg/mL it was 7 to 9 mm Hg, when dosed twice daily. The non-inferiority of AZARGA as compared to dorzolamide 20 mg/mL + timolol 5 mg/mL in the mean IOP reduction was demonstrated across all on-therapy time-points at all visits. When evaluated at each visit, up to 60% of patients in the AZARGA group and up to 59% of patients in the dorzolamide 20 mg/mL group had IOP of less than 18 mm Hg.

In a six-month, double-masked, randomised clinical study in patients (n=523) with open-angle glaucoma or ocular hypertension and baseline mean IOP of 25 to 27 mm Hg, the mean IOP-lowering effect of AZARGA dosed twice daily was 8 to 9 mm Hg, and was up to 3 mm Hg greater than that of brinzolamide 10 mg/mL dosed twice daily and up to 2 mm Hg greater than that of timolol 5 mg/mL dosed twice daily. A statistically superior reduction ($p < 0.05$) in mean IOP was observed compared to both brinzolamide and timolol at all on-therapy time-points and visits throughout the study. IOP measurements conducted at 8 am, 10 am, 12 pm, 4 pm and 8 pm confirm that diurnal IOP control is superior ($p < 0.05$) and clinically relevant for AZARGA compared to either brinzolamide 10 mg/mL or timolol 5 mg/mL. The primary efficacy endpoint of mean IOP at 8 am and 10 am post dose for this study can be seen in Table 1 below.

Table 1: Mean IOP (mm/Hg)

	Mean IOP (mmHg)							
Visit	**Baseline**		**Week 2**		**Month 3**		**Month 6**	
Time point	**8am**	**10am**	**8am**	**10am**	**8am**	**10am**	**8am**	**10am**
Azarga*	27.1	25.8	18.6	17.1	18.8	17.2	19.0	17.8
Brinzolamide	27.1	25.6	22.0	20.4	21.5	20.4	21.9	20.5
Timolol	27.0	25.4	20.1	18.8	20.1	19.0	20.4	19.6

* $p<0.05$ compared to brinzolamide and timolol at all on therapy time points

In a 7-day double masked, randomised clinical trial (n=96), the ocular comfort, based on burning and stinging, of AZARGA was superior (p=0.0003) to that of dorzolamide 20 mg/mL + timolol 5 mg/mL. A comparison of the frequency distribution of the severity of ocular discomfort demonstrated a significant difference (p=0.0001) between the two treatment groups, with AZARGA having a lesser percentage of patients experiencing mild, moderate and severe ocular discomfort compared to dorzolamide 20 mg/mL + timolol 5 mg/mL. A significantly higher percentage of patients randomized to AZARGA experienced no ocular discomfort after 1 week of dosing (p=0.0004) compared to patients who received dorzolamide 20 mg/mL + timolol 5 mg/mL.

INDICATIONS

Decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension for whom monotherapy with either component provides insufficient IOP reduction.

CONTRAINDICATIONS

A history of hypersensitivity to brinzolamide and other sulphonamides, timolol, or any other component of the medication.

The following conditions may also contraindicate the use of AZARGA:

- bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease.
- sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock.
- severe allergic rhinitis and bronchial hyperreactivity; hypersensitivity to other beta-blockers.
- hyperchloraemic acidosis.
- severe renal impairment (see Hepatic / Renal Impairment).

AZARGA is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

PRECAUTIONS

FOR TOPICAL USE ONLY - NOT FOR INJECTION OR ORAL INGESTION

AZARGA should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Systemic effects

Like other topically applied ophthalmic agents, brinzolamide and timolol are absorbed systemically.

Brinzolamide

AZARGA contains brinzolamide, a sulphonamide. The same types of undesirable effects that are attributable to sulphonamides may occur with topical administration. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. If signs of serious reactions or hypersensitivity occur, discontinue use of this medicine.

There is potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and AZARGA. The concomitant administration of AZARGA and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

Timolol

Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta-adrenergic blocking agents may occur. Cardiac failure should be adequately controlled before beginning therapy with timolol. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked. Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of timolol maleate. Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile insulin-dependent diabetes, as beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycaemia. They may also mask the signs of hyperthyroidism and cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension.

Anaphylactic reactions

While taking beta-adrenergic blocking agents, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Ocular effects

AZARGA has not been studied in patients with narrow-angle glaucoma and its use is not recommended in these patients.

There is limited experience with AZARGA in the treatment of patients with pseudoexfoliative glaucoma or pigmentary glaucoma. Caution should be utilized in treating these patients and close monitoring of IOP is recommended.

The possible role of brinzolamide on corneal endothelial function has not been investigated in patients with compromised corneas (particularly in patients with low endothelial cell count). Specifically, patients wearing contact lenses have not been studied and careful monitoring of these patients when using brinzolamide is recommended, since carbonic anhydrase inhibitors may affect corneal hydration and wearing contact lenses might increase

the risk for the cornea. Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.

Use with contact lenses

AZARGA contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses is to be avoided. Patients must be instructed to remove contact lenses prior to the application of AZARGA and wait 15 minutes after instillation of the dose before reinsertion.

Interactions with other medicines

No drug interaction studies have been performed with AZARGA.

Brinzolamide

AZARGA contains brinzolamide, a carbonic anhydrase inhibitor and, although administered topically, is absorbed systemically. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. The potential for interactions must be considered in patients receiving AZARGA.

The cytochrome P-450 isozymes responsible for metabolism of brinzolamide include CYP3A4 (main), CYP2A6, CYP2B6, CYP2C8 and CYP2C9. It is expected that inhibitors of CYP3A4 such as ketoconazole, itraconazole, clotrimazole and ritonavir will inhibit the metabolism of brinzolamide by CYP3A4. Caution is advised if CYP3A4 inhibitors are given concomitantly. However, accumulation of brinzolamide is unlikely as renal elimination is the major route. Brinzolamide is not an inhibitor of cytochrome P-450 isozymes.

Timolol

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when eye drops with timolol are administered concomitantly with oral calcium channel blockers or beta-adrenergic blocking agents, antiarrhythmics, digitalis glycosides or parasympathomimetics. The use of two local beta-adrenergic blocking agents or two local carbonic anhydrase inhibitors is not recommended.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-adrenergic blocking agents.

Potential systemic beta-blockade (eg. decreased heart rate) has been reported during combined treatment with CYP2D6 inhibitors (eg. quinidine, cimetidine) and timolol.

Beta-adrenergic blocking agents may increase the hypoglycaemic effect of antidiabetic agents. Beta-adrenergic blocking agents can mask the signs and symptoms of hypoglycaemia.

Effects on fertility

There are no human data on the effects of AZARGA on male or female fertility. Studies in rats, in which animals were treated orally with brinzolamide up to 18 mg/kg/day or with timolol up to 100 mg/kg/day, showed no adverse effects on male or female fertility.

Use In Pregnancy - Category C

No studies have been conducted with AZARGA in pregnant women, and no animal studies have been conducted with the combined components to evaluate effects on reproduction. AZARGA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Brinzolamide

Developmental toxicity studies with brinzolamide in rabbits at oral doses up to 6 mg/kg/day produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, e.g. accessory skull bones; at 1 and 6 mg/kg/day, the incidence was only slightly higher than seen historically. In rats, statistically significant decreased bodyweights of fetuses from dams receiving oral doses of 18 mg/kg/day during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. No treatment-related malformations were seen. Exposure levels are much lower following topical administration of brinzolamide. There are no adequate data from the use of brinzolamide in pregnant women. The potential risk for humans is unknown.

Timolol

Timolol maleate was not teratogenic in mice, rats and rabbits. Embryofetal development studies with timolol maleate in mice and rabbits showed no evidence of embryofetal toxicity at oral doses up to 50 mg/kg/day. At higher doses, increases in resorptions and fetal variations (14 ribs and hypoplastic sternebrae) in mice (1000 mg/kg/day) and increased resorption in rabbits (≥90 mg/kg/day) were observed. In rats, delayed ossification was seen at oral doses ≥50 mg/kg/day, and decreased number of caudal vertebral bodies and arches, and an increase in hypoplastic sternebrae were noted at 500 mg/kg/day. In humans, well-controlled epidemiological studies with systemic use of beta-adrenergic blocking agents did not indicate malformative effects, but some pharmacological effects such as bradycardia have been observed in fetuses or neonates. Data on a limited number of exposed pregnancies indicate no adverse effects of timolol in eye drops on pregnancy or on the health of the fetus/newborn child but bradycardia and arrhythmia have been reported in one case in the fetus of a woman treated with timolol eye drops. To date, no other relevant epidemiological data are available.

Use in Lactation

It is not known whether brinzolamide is excreted in human milk following topical ocular administration. Timolol is detectable in human milk following topical ocular administration.

Following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma. Decreases in pup bodyweights were observed at 15 mg/kg/day in a prenatal and postnatal study in which rats were given brinzolamide by oral gavage at doses up to 15 mg/kg/day.

Because of the potential for serious adverse reactions in breastfed infants from brinzolamide and timolol, a decision should be made whether to discontinue breastfeeding or to discontinue AZARGA, taking into account the importance of the drug to the mother.

Use in Children

AZARGA is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Use in Elderly

There are no modifications to the recommended dosing regimen for elderly patients.

Hepatic / Renal Impairment

No studies have been conducted with AZARGA in patients with hepatic or renal impairment. No dosage adjustment is necessary in patients with hepatic impairment or in patients with mild to moderate renal impairment.

AZARGA has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min) or in patients with hyperchloraemic acidosis. Since brinzolamide and its main metabolite are excreted predominantly by the kidney, AZARGA is therefore contraindicated in patients with severe renal impairment.

Carcinogenicity

No carcinogenicity studies have been conducted with the combined components of AZARGA.

Brinzolamide

A 2-year bioassay, in which rats were treated with brinzolamide by oral gavage at doses up to 8 mg/kg/day, revealed no evidence of a carcinogenic effect. A similar study conducted in mice, involving oral dosing at 0, 1, 3 or 10 mg/kg/day for 2 years, revealed a statistically significant increase in urinary bladder tumours in females at 10 mg/kg/day, and dose-related proliferative changes in the urinary bladder in females at all dose levels and among males at 10 mg/kg/day. The elevated bladder tumour incidence was primarily due to the increased incidence of a tumour and was considered to be unique to mice.

Timolol

No evidence of carcinogenicity was observed with timolol maleate at oral doses up to 100 mg/kg/day in rats and up to 50 mg/kg/day in mice. However, there was a statistically significant increase in the incidence of adrenal pheochomocytomas in male rats administered 300 mg/kg/day. In female mice, statistically significant increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinomas were found at 500 mg/kg/day. The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin, which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin.

Genotoxicity

Brinzolamide did not display mutagenic potential in bacteria (Ames test) or produce chromosomal damage *in vivo* (mouse micronucleus test). Brinzolamide did induce forward mutations in the mouse lymphoma assay *in vitro* in the presence, but not in the absence, of metabolic activation. Brinzolamide was negative in a sister chromatid exchange assay in mice. Timolol was not genotoxic in assays for mutagenicity (Ames test) and clastogenicity (mouse micronucleus and cytogenic assays).

Effects on ability to drive and use machines

As with any eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

ADVERSE REACTIONS

In two clinical trials of 6 and 12 months duration involving 394 patients treated with AZARGA, the most frequently reported adverse reaction was transient blurred vision upon instillation (3.6%), lasting from a few seconds to a few minutes.

The following adverse reactions were assessed to be treatment-related. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Eye disorders:

Common (≥1% to <10%): blurred vision, eye pain, eye irritation, foreign body sensation in eyes

Uncommon (≥0.1% to <1%): corneal erosion, punctate keratitis, dry eye, eye discharge, eye pruritus, ocular hyperaemia, blepharitis, allergic conjunctivitis, corneal disorder, anterior chamber flare, conjunctival hyperaemia, eyelid margin crusting, asthenopia, abnormal sensation in eye, eyelids pruritus, allergic blepharitis, erythema of eyelid.

Nervous system disorders:

Common (≥1% to <10%): dysgeusia

Dysgeusia (bitter or unusual taste in the mouth following instillation) was a frequently reported systemic undesirable effect associated with the use of AZARGA during clinical studies. It is probably caused by passage of the eye drops in the nasopharynx via the nasolacrimal canal. Nasolacrimal occlusion and gently closing the eyelid after instillation may help reduce the incidence of this effect.

Respiratory, thoracic and mediastinal disorders:

Uncommon (≥0.1% to <1%): chronic obstructive pulmonary disease, pharyngolaryngeal pain, rhinorrhoea, cough

Skin and subcutaneous tissue disorders:

Uncommon (≥0.1% to <1%): hair disorder, lichen planus

Vascular disorders:

Uncommon (≥0.1% to <1%): decreased blood pressure

Psychiatric disorders:

Uncommon (≥0.1% to <1%): insomnia

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop of AZARGA in the conjunctival sac of the affected eye(s) twice daily. Shake the bottle well before use.

Nasolacrimal occlusion and gently closing the eyelid after instillation are recommended. This may reduce the systemic absorption of eye drops and result in a decrease in systemic adverse reactions.

If more than one topical ophthalmic medicine is being used, the medicines must be administered at least 5 minutes apart.

If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye(s) twice daily.

When substituting another ophthalmic antiglaucoma agent with AZARGA, the other agent should be discontinued and AZARGA should be started the following day.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Instruct patients to keep the bottle tightly closed when not in use.

OVERDOSAGE

No case of overdose has been reported.

A topical overdose of AZARGA may be flushed from the eye(s) with warm tap water.

If an overdose with AZARGA occurs, treatment should be symptomatic and supportive. Electrolyte imbalance, development of an acidotic state, and possibly central nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol does not dialyse readily.

POISON SCHEDULE OF THE DRUG

Prescription Only Medicine.

PRESENTATION

AZARGA is presented in an 8 mL round opaque low density polyethylene DROP-TAINER® dispenser containing 5 mL suspension.

Consumer Medicine Information is supplied with this product.

STORAGE

AZARGA should be stored below 25°C. It can be stored in the fridge. Do not freeze.

Discard container 4 weeks after opening.

NAME AND ADDRESS OF SPONSOR

In Australia this product is supplied by:

Alcon Laboratories (Australia) Pty Ltd
25 Frenchs Forest Road East
Frenchs Forest NSW 2086

In New Zealand this product is distributed by:

Alcon New Zealand Limited
c/o Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt Wellington, Auckland
New Zealand

DATE OF APPROVAL

Approved by TGA on XXXXXXXX

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