PRODUCT INFORMATION

This module reflects the initial scientific discussion for the approval of Azopt. This scientific discussion has been updated until 1 November 2002. For information on changes after this date please refer to module 8B.

SCIENTIFIC DISCUSSION

1. Introduction

Azopt contains the new active ingredient brinzolamide, which was developed for ophthalmic use and is a topically effective inhibitor of CA-II. It is intended to decrease elevated IOP in ocular hypertension and open-angle glaucoma, as monotherapy in patients unresponsive to beta-blockers or in patients in whom beta-blockers are contra-indicated, or as adjunctive therapy to beta-blockers.

When used as monotherapy or adjunctive therapy, the dose is one drop of Azopt in the conjunctival sac of the affected eye(s) BID.

Glaucoma is the leading cause of irreversible blindness worldwide. It is a frequent disease and it has been estimated that by the year 2000, 66.8 million people will be affected by it. Glaucoma is an optic neuropathy that leads to loss of optic-nerve tissue with an excavation of the ophthalmoscopically visible optic nerve head and consequently, to a progressive loss of vision. Elevated IOP is a risk factor for its development and reduction of IOP has been demonstrated to protect against further damage to the optic nerve.

Up to 10% of people over the age of 40 years have an IOP above 21 mmHg (normal range 10 to 21 mmHg); those who have such high pressures but no optic-nerve damage are considered to have ocular hypertension. In medical practice, those patients who have ocular hypertension should be periodically examined (optic nerve, visual field) to determine whether there is evidence of progressive damage which would indicate the need to start with treatment. However, in some cases (e.g., additional risk factors for glaucoma) a high IOP may be treated even in the absence of optic nerve damage.

The current therapeutic approach is focused on lowering IOP. Pharmacological treatments are based on the decrease of production of aqueous humor produced by the ciliary body but there is also the possibility to increase its outflow by means of surgery or laser. The target pressure is that which is thought to be safe to the optic nerve, taking into account the current amount of optic damage and the pressure at which the damage occurred, but in principle, it should stay below 21 mmHg.

The medical treatment of glaucoma usually starts with a topical beta-blocker that permits a sufficient decline in IOP in most cases. If necessary (patients poorly controlled on beta-blockers or when beta-blockers are contra-indicated), either other topical drugs can be used or other topical or systemic drugs have to be added to the patient's regimen. Laser procedures or filtering surgery are usually performed after failure of medical treatment.

Beta-blockers, and particularly timolol, which is the most popular product, have a high pressure-lowering efficacy, long duration of action and a few ocular undesirable effects. However, the systemic side effects of topical beta-blockers (bronchospasm and cardiac side effects) may limit their use in special populations (e.g., patients suffering from asthma, chronic obstructive pulmonary disease, bradycardia).

Carbonic anhydrase (CA) inhibitors decrease the aqueous humor production by means of inhibiting the conversion of carbon dioxide to bicarbonate at the ciliary body. In order to decrease IOP through that mechanism, more than 98% of the activity of the enzyme must be inhibited. Oral CAIs such as oral acetazolamide have been a classical treatment for glaucoma but are very poorly tolerated because of systemic side effects. The first topical CA-II inhibitor, dorzolamide, was approved for the treatment of glaucoma or ocular hypertension when beta-blockers are contraindicated or as adjunctive therapy to beta-blockers. Side effects of dorzolamide are mainly local. Most of the systemic side effects of oral carbonic anhydrase inhibitors (CAIs) are not present with topical therapy because they are related to the systemic inhibition of the CA present in many tissues. However, some of the severe side effects, such as blood dyscrasias were not dose-related and therefore, attention should be paid to the occurrence of such side effects.

Brinzolamide is a new CA inhibitor, also selective for CA-II, which is the predominant ocular isoenzyme. It has been developed only for topical use, and shows an efficacy and safety profile, which is similar to that of dorzolamide.

Also recently, two other products have received an approval in one or more EU Member States for the treatment of glaucoma, also as a second line therapy:

1) latanoprost, a prostaglandin analogue with the indication of reduction of elevated ocular pressure in patients with open angle glaucoma and ocular hypertension intolerant or with insufficient response to any other therapy.

2) Brimonidine, a new alpha$_2$ agonist, in monotherapy in patients with open-angle glaucoma or ocular hypertension, who do not tolerate therapy with beta-blockers topically and/or patients in which beta-blockers are contraindicated. In adjunctive therapy, it is used topically in addition to a beta-blocker agent, when IOP can not be controlled properly.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

The product is formulated as a suspension in a purified water based vehicle. It contains benzalkonium chloride as a preservative, edetate disodium as a preservative and chelating agent , sodium chloride and mannitol as tonicity agents, tyloxapol as a wetting agent and carbomer 974P as a suspending agent. Sodium hydroxide or hydrochloric acid are used for pH adjustment. Azopt does not contain any materials of animal or human origin or derivatives of such materials. Such materials or derivatives are not used in the manufacturing process either. The container is a natural low-density polyethylene (LDPE) bottle. The container is equipped with a natural LDPE dispensing plug and a white polypropylene closure.

Active substance

Brinzolamide is a new active substance, white to off-white crystals, and is not described in a pharmacopoeia. The compound has a single chiral centre that has been established as having the R configuration. It is produced by two manufacturers using a validated stereoselective process, which proceeds in eight steps, including final purification, from commercially available starting materials.

The two manufacturers are Amcis AG (Bubendorf, Switzerland) and Sylachim, Finorga division (Chasse sur Rhône, France). During process development, the synthetic route for the active substance was optimised by Amcis. Therefore, not all of the batches of brinzolamide described in this dossier were prepared using the current commercial process. However, these modifications do not affect the quality and the specifications of the active substance, and have no impact on safety and efficacy.

Batches manufactured according to old procedures contained 9 impurities (A, B, C, D, F, G, H, S-isomer and PS4999) at more than 0.1%. Also three non-identified impurities have been detected in some of the batches at more than 0.1%. These impurities have not been detected in current batches at more than 0.1%.

The number and percentage of impurities detected in batches manufactured according to the optimised procedure has been reduced. Only impurities A, G, F, H, S-isomer and PS 4999 have been detected.

None of the specified impurities have been detected as degradants in the finished product, except for the (S)-isomer.

A second degradation product, the des-ethyl compound, is observed as an impurity in drug substance, but only at concentrations less than 0.1%. This impurity will be controlled as an unspecified impurity (<0.1%) in the drug substance specification.

The routine controls and established specifications include description, identification (IR and chiral HPLC) and solution colour and clarity.

Impurities are determined by HPLC. The impurity limits in the specification are justified by toxicology studies.

Chiral purity is also determined by HPLC (S-isomer ≤ 0.5%). The S-isomer is observed both as an impurity and a degradation product, and an additional toxicology study, N96-99, was done which included the S-isomer at 20%. This study supports the proposed specification.

The solvent isopropyl alcohol has been detected in brinzolamide, which is used for the final recrystallisation phase. The results obtained from the batches manufactured using the optimised process support that there is no need to perform routine control of class 2 solvents used during the manufacturing process. Isopropyl alcohol, which is a class 3 solvent and relatively non-toxic, is tested by the general method of loss on drying.

No metal catalysts are used in the procedure. However, the catalyst used contains boron, and several of the reactants contain lithium. Boron was detected in two batches (2 ppm), calcium was detected in one batch (12 ppm), and lithium was not detected in any of the tested batches. The specifications for heavy metals (20 ppm) and residue on ignition (≤ 0.1%) are consistent with the quality produced and are acceptable considering the low dose of the product.

The assay is performed by HPLC (98.0-101.0%, dried base), and a test for microbiologic quality (≤ 100 CFU/g) is included.

Only one crystal form has been formed; however, this is not specifically controlled as brinzolamide dissolves during the product manufacturing process (see further).

Results of 19 batches have been presented (7 batches manufactured by AMCIS following the previous procedure, 4 batches manufactured by AMCIS and 8 batches manufactured by Finorga following the optimised procedure). All batches manufactured according to the optimised procedure meet the specifications. Batches obtained following the previous procedure, present a higher level of impurities, and do not meet specifications.

The results presented support the quality level established and confirm the consistency and uniformity of the manufacturing process.

The active substance is stored in polyethylene bags in well-closed container. The analytical methods used in the stability studies were similar to those used for the routine control of the raw material. Three-year long-term stability date and 6 months of accelerated stability data are available for active substance synthesised by the previous AMCIS process. One batch from each of the two suppliers using the optimised process was placed on an accelerated stability study to demonstrate equivalence to the initial lots tested. Additional studies according to ICH conditions on three batches from each of the suppliers have also been started to confirm the retest period.

A photostability study was performed prior to issuance of ICH Guideline and no significant degradation products were observed.

On the basis of these data it can be concluded that brinzolamide is a stable drug substance and is not photosensitive or hygroscopic. A retest period of two years is acceptable.

Other ingredients

All the excipients used in the manufacture of the drug products are of European Pharmacopoeia (Ph.Eur.) quality, except tyloxapol, which is of US Pharmacopoeia (USP) quality. Certificates of analysis of all excipients are presented, which are in accordance with the proposed specifications.

Product development and finished product

The objective of the pharmaceutical development was to develop a stable, well-preserved 1% sterile suspension dosage form.

The enantiomeric form used in Azopt is the R-isomer. A small amount of the S-isomer is formed during autoclaving. The amount is dependent on the time/temperature exposure of the solution. This is controlled in the finished product at not more than 1.5% of the total brinzolamide, which is toxicologically qualified.

The clinical trial formulations contained different percentages of the active ingredient ranging from 0% to 3%. A 5% excess of brinzolamide was added to all but one of the development batches in anticipation of losses during manufacturing. This excess was found to be unnecessary for manufacturing scale-up.

All clinical trial formulations contain an overage of 5% benzalkonium chloride, which has been removed from the proposed formulation intended for marketing. There were also differences with regard to the carbomer (934 P vs. 974P) and the surfactant (polysorbate 80 vs. tyloxapol).

Results showed that brinzolamide was soluble only to about 0.04 at physiologic pH and room temperature. Therefore a suspension dosage form was designed. However, at elevated temperatures brinzolamide dissolves, but is recrystallised into large needle-like crystals (~ 200 µm) during cooling and therefore it is not possible to terminally sterilise the product in the final container.

The main feature of the manufacturing process is the aseptic ball milling of a sterile (autoclaved) slurry of brinzolamide. This is effected by zirconium alloy beads. Only one polymorphic form of brinzolamide has been observed and there are no polymorphic changes during manufacturing.

The manufacturing process is composed of five major steps:

1) Preparation of the milling slurry. Transfer of the tyloxapol solution to milling bottles, addition of beads and active ingredient, and steam sterilisation followed by aseptic milling;

2) Preparation of the vehicle concentrate (containing soluble ingredients) and carbomer slurry. Adjustment of the pH and sterilisation in a reactor;

3) Aseptic addition of milling slurry to the previous reactor. Rinsing of the beads with sterilised water;

4) Sterile filling (class A) into sterilised packaging (gamma irradiation or EtO);

5) Secondary packaging.

The product is being manufactured in a facility that holds the necessary Manufacturing Authorisation (see Annex II of the Opinion).

The finished product specifications include tests for appearance, identification (HPLC, chiral HPLC (R)), brinzolamide assay (HPLC; 95-105%), benzalkonium chloride identity and assay (HPLC, 90-110%), disodium edetate dihydrate identity and assay (HPLC, 90-110%), pH (7.1-7.9), osmolality (270-320 mOsm/kg), resuspendability (NMT 15 seconds), viscosity (20-150 mPa.s), sterility (EP), and fill volume.

Particle size distribution is important. A validated method, HIAC, for measuring the suspension particle size has been developed, since the Ph.Eur. method (microscope) is difficult to use for products containing carbomer, as these products contain small gel-globules with a similar appearance to that of the particles. Specifications concerning particle size are in accordance with Ph.Eur. for this type of compound.

Degradation products are measured by HPLC (total NMT 1% (except S-isomer); des-ethyl brinzolamide NMT 0.2% ; any single unspecified NMT 0.3%; S-isomer by chiral HPLC NMT 1.5%), The methods used for monitoring of des-ethyl brinzolamide and other potential degradation products (HPLC) and for monitoring the S-isomer have been validated. The impurity limits in the are justified by toxicology studies.

Batch analysis results of 7 batches (using active substance supplied by AMCIS and Finorga and packaged in both EtO and gamma sterilised packaging) comply with the specifications.

Stability of the product

Stability data for six sublots (originating from 3 manufactured batches) of finished product are presented. The longest duration of study for these lots is 2 years at room temperature (25 °C). In addition to the stability study, data of five batches of finished product manufactured at Alcon, Puerto Rico, has been presented. For those batches sterilisation by gamma irradiation is used.

The stability data show that Azopt is chemically, physically, and microbiologically stable for 2 years in packaging sterilised with ethylene oxide. The efficacy of the antimicrobial preservative has been shown in this period. This is reflected in the SPC. Updated stability data will be submitted when available.

Once opened, a 28-day in-use period is justified on microbiological grounds. In addition an in-use study of chemical parameters was conducted on two batches, which have been stored at the long-term storage condition (25°C/35% RH) for 2 years. After 28 days, the product samples were tested for chemical as well as physical parameters**.** The proposed 28 days in-use shelf life is justified and acceptable, and is reflected in the SPC.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

Inhibition of CA

The potency and selectivity of brinzolamide for inhibition of CA-II has been studied *in vitro*. Brinzolamide has a K_i for binding to CA-II of 0.13 nM, and an enzyme inhibition IC_{50} of 3.2 nM. It is 240 to 400 times more selective for CA-II than CA-I. Brinzolamide and dorzolamide present a similar selectivity for CA-II, although dorzolamide might be more selective for CA-II than for CA-I. The primary metabolite of brinzolamide, desethyl-brinzolamide, was also tested in the binding and functional activity assays, and was demonstrated to have a similar profile as the parent drug

In *in vitro* assays brinzolamide selectively inhibited CA-II with a potency similar to that of dorzolamide: Ki for brinzolamide = 0.13nM compared to 0,31 nM for dorzolamide: IC 50 for brinzolamide = 3.19 nM compared to 3.74 nM for dorzolamide. The selectivity of brinzolamide for CA was demonstrated by a lack of affinity in 34 other types of receptor and enzyme-based ligand binding assay systems. Desethyl-brinzolamide shows the same pharmacological profile (IC 50 = 2.9 nM).

Topical ocular IOP reducing activity

The CA inhibitory activity of brinzolamide is supported by *in vitro* binding affinity and functional activity studies with purified human CA enzyme. IOP reducing efficacy has been assessed *in vivo* in rabbits and monkeys and its ability to increase optic nerve head blood flow was studied also in rabbits and cats.

The IOP lowering efficacy of brinzolamide was tested in normal Dutch-belted (Db) rabbits and in ocular hypertensive Cynomolgus monkeys. Suspension formulations of both the hydrochloride salt and the free base effectively lowered IOP in both species. Dose dependent reductions of IOP were demonstrated in rabbits, while both 0.3 mg and 0.6 mg doses reduced IOP by about 32% in the monkey. In multi-dose studies with BID treatment up to 9 days in rabbits and 2 days in monkeys, a relatively constant IOP reduction was evident. IOP was reduced in monkeys by 29-38% peak and 15-25% trough .

Ocular blood flow enhancement

Optic nerve head (ONH) microvascular blood flow of the cat and total, ONH and regional intraocular blood flows in the rabbit were evaluated using coloured microsphere (CM) or laser Doppler flowmetry (LDF) techniques. ONH (LDF method) blood flow was increased in both rabbits and cats by intravenous administration of 5 mg/kg brinzolamide (46 ± 17% increase in cats, $p < 0.05$). In rabbits, brinzolamide at 0.5, 2.5 and 5 mg/kg cumulative intravenous doses produced significant, dose related increases in blood flow (CM methods) of iris, ciliary body, choroid as well as the total ocular blood flow. After one week of BID topical ocular administration of brinzolamide to Db rabbits blood flow to the optic nerve head was significantly increased (11% increase, $p < 0.05$), as measured by the LDF.

General and safety pharmacology studies

Effects of brinzolamide on the Central Nervous System

Brinzolamide and the desethyl-brinzolamide with doses up to 30 mg/kg did not have any effects on behaviour; locomotor activity; phenylquinone induced writhing; rotarod performance; or barbiturate induced sleep time. There was also no effect on sensitivity to electroshock-induced convulsion or on yeast-induced pyresis.

Effects of brinzolamide on the cardiovascular system

At a dose of 1 mg/kg neither brinzolamide nor desethyl-brinzolamide modified any cardiovascular parameter in dogs. At a dose of 10 mg/kg, brinzolamide, but not the desethyl-brinzolamide, induced small increases in cardiac output and contractility. Neither compounds at a dose of 10 mg/kg significantly modified the blood pressure response to epinephrine, norepinephrine, acetylcholine, histamine and isoproterenol.

Effects of brinzolamide on the respiratory system

Pulmonary mechanics of Guinea pigs were not altered by 1 or 30 mg/kg doses of brinzolamide or desethyl brinzolamide.

Blood gases in rats were not altered by 0.3 mg/kg or 1.0 mg/kg doses of either compound, but at 3 mg/kg, minor changes were noted with both compounds. These effects are consistent with inhibition of CA, as evidenced by similar changes with the reference standard acetazolamide.

Effects of brinzolamide on the gastrointestinal system

In the gastrointestinal propulsion test, no changes were observed with oral doses of 1 or 10 mg/kg of brinzolamide or 1 mg/kg of desethyl-brinzolamide. A small reduction of charcoal propulsion was noted with 30 mg/kg brinzolamide and with 10 and 30 mg/kg of desethyl-brinzolamide. This effect is consistent with local inhibition of CA, altering volume in the intestinal tract, and secondarily peristaltic activity. Neither compound at a 10 mg/ml concentration altered contraction of isolated Guinea pig ileum induced *in vitro* by acetylcholine, histamine or barium chloride.

Effects of brinzolamide on the renal system

Minor dose-related increases in urine pH and in excretion of Na^+ and K^+ were observed in rats following intravenous administration of 1 and 3 mg/kg brinzolamide and desethyl-brinzolamide.

The doses employed in these studies exceeded those achievable following topical ocular administration of brinzolamide. If completely absorbed, ocular administration of BID 350 µg (one drop of 1%) brinzolamide per eye would result in a systemic load of only 28 µg/kg/day in a 50 kg individual. Therefore, an ocular dose of 350 µg brinzolamide per eye per dose is not expected to cause significant adverse side effects in man.

Pharmacodynamic interaction studies

No studies with regard to pharmacodynamic interactions with beta-blockers have been performed, in view of the fact that beta-blockers such as timolol and metoprolol are metabolised by different isozymes and those beta-blockers do not inhibit the metabolism of brinzolamide and vice versa. Furthermore, brinzolamide does not strongly bind to plasma proteins and general pharmacology studies with brinzolamide did not reveal any pharmacodynamic action that indicates a potential for exacerbation of a beta-blocker effect.

Pharmacokinetics

The pharmacokinetics of brinzolamide are specific and typical of sulfonamide anhydrase inhibitors which are essentially influenced by a tight binding to CA. Brinzolamide is mainly distributed to tissues containing high levels of CA and particularly in red blood cells (RBCs). As brinzolamide binding to RBCs is tight and saturable, low plasma levels and non linear kinetics were observed. The pharmacokinetics of brinzolamide were studied in rats, rabbits and monkeys.

Absorption

Brinzolamide is absorbed into the eye following topical ocular administration. Maximum drug concentrations in aqueous humor and iris-ciliary body (ICB) of 1.04 ± 0.38 µg/ml and 1.36 ± 0.34 µg/mg, respectively, were achieved 1 hour following a single topical ocular administration of a 1% aqueous suspension to New Zealand White (NZW) rabbits.

Absorption into the systemic circulation from the topical ocular route also occurs. Following a single 30 µl dose of a 4% suspension to NZW rabbits, maximum whole blood concentrations were observed between 3 and 24 hours. In the rabbit, plasma brinzolamide concentrations were approximately 4 and 30 µg/ml 5 minutes after i.v. doses of 5 and 30 mg/kg, respectively.

Brinzolamide was readily absorbed following oral dosing to rats. Due to the saturable binding to CA in erythrocytes, non-linear kinetics and a lack of dose-proportionality were observed in whole blood, which are characteristic features of this drug class. Maximum plasma drug concentrations were achieved within 15-30 minutes and exhibited dose dependence. Based on areas under the plasma concentration versus time curves (AUC) for oral and intravenous doses, oral bioavailability ranged from about 70% at 20 mg/kg to about 45% at 180 mg/kg.

Distribution

Tissue distribution of ^{14}C-brinzolamide was investigated in rats and rabbits.

In male Fisher rats, after single oral dose the highest levels were observed in tissues containing high CA activities, i.e. kidneys, liver, stomach, small intestine, spleen, lungs and salivary glands. After repeated dose administration, the maximum tissue concentrations were 2 fold higher than after simple dosing, showing a limited accumulation ratio (about 2). Autoradiography studies showed a slight penetration of brinzolamide through the blood brain barrier. The compound was found to cross the placenta and was distributed in foetal tissues and in milk without accumulation (the milk/plasma ratio ranging from 0.03 to 0.6). See also section 4.6 of the SPC.

In the rabbit, brinzolamide was recovered in iris-ciliary body (ICB), choroid, retina, lens and aqueous humor after topical ocular administration. The shortest half-life (3 hours) was observed in aqueous humor, followed by ICB. Lens and retina exhibited very prolonged exposure in both strains ($t_{1/2}$ =294 days and $t_{1/2}$ = 95.9 days respectively). A systemic redistribution has been demonstrated.

In vitro plasma protein binding studies showed that brinzolamide binds moderately to plasma proteins from various species (unbound fractions being 75%, 41% and 25% in rats, humans and monkeys, respectively).

Due to its high affinity for CA-II, brinzolamide distributes extensively into the RBCs and exhibits a long half-life in whole blood (mean of approximately 24 weeks).

Metabolism

From biotransformation studies of brinzolamide in rats and monkeys models, six different metabolites were identified in blood and faeces. Significant concentrations of the main metabolite observed in man (N-desethyl-brinzolamide) were also observed in these two species.

Excretion

Excretion of brinzolamide was investigated in rats after I.V. injection of a 1 mg/kg dose. Approximately equal amounts of radioactivity were excreted in urine (32%) and in the faeces (29%). Mass balance of radioactivity showed that 61% of the total radioactivity was recovered in the excreta within 48 hours post dosing and the remaining was recovered in the carcass and blood.

Conclusion

No adverse findings for lens or retina were demonstrated in preclinical safety studies of brinzolamide by either topical ocular or oral administration. The systemic exposure in animals and humans is summarised in table 1.

Table 1: Systemic exposure in animals and humans

Species	Study	Regimen (Highest Dose)	Brinzolamide		N-Desethyl Brinzolamide	
			µg/ml Whole Blood	µM RBC	µg/ml Whole Blood	µM RBC
Human	C-92-34	3% topical TID, 2 weeks	2.17 ± 0.85 (males)	12.3 ± 4.8	NM	
	C-95-76	1 mg p.o. BID, 32 weeks	3.95 ± 0.58 (males) 4.10 ±0.26 (females)	22.7 ± 2.4 27.1 ± 1.3	1.17 ± 0.29 2.54 ± 1.02	7.31 ± 1.82 18.2 ± 7.5
	C-96-59	1mg p.o. BID, 32 weeks	Range: 4.25 – 5.11 (males & females)	22.0 – 46.1	Range: 3.06 – 10.6	17.1 – 88.6
	C-95-47	1% topical TID, 18 months	2.70 ± 1.19 (males & females)	17.1 ± 7.2	1.08 ± 1.11	5.85 ± 7.57
Monkey	N-94-57	4% topical TID, 1 year	11.51 ± 1.27 (males & females)	83.4 ± 9.2	7.04 ± 1.22	55.0 ± 9.5
Rat	N-91-177	180 mg/kg p.o., 2 weeks	10.70 ± 0.71 (males) 6.89 ±1.01 (females)	66.4 ± 6.8 42.8 ± 6.3	NM	
	N-95-77	8 mg/kg p.o., 6 months	10.63 ± 0.71 (males & females)	66.0 ± 4.4	0.52 ± 0.08	3.21 ± 0.46
Rabbit	N-91-176	4% topical QID, 3 months	7.17 ± 0.39 (males & females)	44.5 ± 2.4	NM	
	N-92-172	4% topical QID, 6 months	5.20 ± 0.45 (males & females)	32.3 ± 2.8	NM	

NM= Not Measured

Toxicology

Single-dose toxicity

Single dose toxicity studies included a 1-day topical ocular irritation evaluation in rabbits and acute oral toxicity studies in rats and mice. The 1-day topical ocular study employed a 2% brinzolamide ophthalmic suspension administered as two drops to one eye of each of three rabbits, every 30 minutes over five hours, for a total of 10 doses. Over the period of administration, animals were exposed to 20 drops (40 µl/drop) of a 2% suspension (20 µg/µl), resulting in an overall exposure of 800 µl x 20 µg/µl, or 16 mg total exposure per day (approximately 5 mg/kg). Ocular comfort and irritation were evaluated. Irritation and comfort scores were consistent with those normally observed with ophthalmic suspensions, and no significant clinical findings were noted. These are considered screening studies, are non-GLP, and extensive systemic evaluations and histopathology were not conducted.

Administration of single high oral doses of brinzolamide induced lethargy and reduced activity. The proposed dosage form, 5 ml or 10 ml bottles (containing a total of 50 or 100 mg of drug, respectively), precludes comparable accidental systemic exposure, the maximum possible accidental exposure being approximately 5 mg/kg, assuming the complete contents were ingested by a 10 kg child. No significant effects are likely to occur at this exposure. The total daily dose for clinical ophthalmic exposure (1 drop, BID, both eyes) is approximately 1.6 mg/day, or about 0.032 mg/kg/day.

Repeated-dose toxicity

A series of repeated-dose studies was conducted by the clinical route of administration, topical ocular, and by oral administration for increased systemic exposure and toxicological assessment.

Ocular studies

Five repeated-dose topical ocular studies were conducted in albino rabbits, ranging in duration from one to six months, and a one year study was conducted in pigmented Cynomolgus primates (Table 2).

Table 2: Repeated dose topical ocular studies

Duration/Species	Concentration	Regimen	Number
1 Mo/Rabbit	0, 2%, 4%	2 drops, OD[a], QID[b]	020:38520:0392
1 Mo/Rabbit	0, 1%, 3%	2 drops, OD[a], TID[c]	093:38520:1293
3 Mo/Rabbit	0, 2%, 4%	2 drops, OD[a], QID[b]	076:38520:0792
3 Mo/Rabbit	0, 2%, 4%	1 drop, OU[d], TID[c]	051:38520:0396
6 Mo/Rabbit	0, 2%, 4%	2 drops, OD[a], QID[b]	031:38520:0594
1 Yr/Monkey	0, 1%, 2%, 4%	2 drops, OD[a], TID[c]	095:38520:0795

[a]OD = right eye; [b]QID = four times a day; [c]TID = three times a day; [d]OU = both eyes

Concentrations as high as 4% brinzolamide ophthalmic suspension were administered up to QID in rabbits and TID in monkeys, thus significantly exceeding the proposed clinical concentration and dosing frequency of 1%, BID.

In the topical ocular studies the following was carried out: slit-lamp biomicroscopic ophthalmic examinations, indirect ophthalmic examinations, corneal pachymetry as well as body weight, serum chemistry and haematology evaluations, organ weights, macroscopic and microscopic pathologic evaluations. The primate study also included specular microscopic evaluation of the corneal endothelium.

Analysis of whole blood samples from the six-months rabbit study obtained at study weeks 1 and 2, and months one, three and six, demonstrated that a steady state whole blood concentration of approximately 5-7 µg/ml was reached at about one week of dosing for both the 2% and 4% concentrations, while plasma levels were below the limits of quantitation.

These studies show that there was no significant ocular toxicity or irritation when the drug was administered topically in either the rabbit or the monkey eye. Irritation scores, as evaluated by slit-lamp scoring of conjunctivitis, iritis and aqueous flare, were unremarkable compared with controls. In addition, there were no significant findings from indirect ophthalmic examinations of ocular tissues of the anterior or posterior segments of the fundus.

Statistically significant increases in corneal thickness were observed in rabbits following 1, 3 and 6 months of treatment with brinzolamide eye drops. This information has been included in section 5.3 of the SPC. Increases in corneal thickness up to approximately 16% were not accompanied by changes in slit-lamp biomicroscopic appearance or histologic morphology. No significant change in corneal thickness was observed in the 1-year topical ocular study in monkeys, and specular microscopy of the corneal endothelium revealed no changes in cell density or morphology.

A slight change in the product formulation (0.05% polysorbate 80 replaced with 0.025% tyloxapol) was made after the completion of the six month rabbit study, and a three-month topical ocular study in rabbits was conducted to confirm the safety of the modified formulation. In addition, a change in the raw material sterilisation process (from gamma irradiation to EtO) was made during development. This change was addressed by re-supplying of dosing materials for the 1-year topical ocular study in monkeys at approximately the six-month interval. Thus, approximately six months of dosing was completed before and after the minor product change.

Systemic studies

Repeated-dose systemic toxicity was evaluated by oral administration to rats and mice. An early two-week study by oral gavage administration in rats employed brinzolamide at relatively high concentrations in a low pH aqueous vehicle (in order to provide a dosing solution). Administration of this solution, containing high concentrations of the CA inhibitor at low pH, resulted in significant gastric lesions, including ulcerative and proliferative changes in the forestomach. Gastric ulceration has been reported with administration of acetazolamide to rats, and may be related to inhibition of CA activity and mucus secretion. A change of dosing preparations to a suspension at a more neutral pH essentially eliminated the occurrence of gastric lesions. Lethargy, dehydrated appearance and unkemptness, and reduced body weight gain were apparent, particularly at the high dose of 180 mg/kg/day.

A four-week oral study in rats with the dosing suspension demonstrated reduced body weight gain at 100 mg/kg/day, with slight reductions in erythrocyte count, haematocrit and haemoglobin, increased serum sodium, chloride and cholesterol and reduced serum potassium. The subsequent three-month study in rats employed dose levels of up to 10 mg/kg/day without biologically significant effects on haematology and serum chemistry parameters. Urinary volume was significantly increased, while urine specific gravity, sodium and potassium were significantly decreased. Similar findings were seen in a four-week study in mice.

Three-month oral toxicity studies in rats with 0, 1, 3 and 8 mg/kg/day revealed nephrotoxicity and urinary bladder hyperplasia. Similar urinary tract findings were observed in the three-month oral study in mice.

A six-month oral toxicity study in rats, with dose levels of 0, 1, 3 and 8 mg/kg/day, yielded results similar to those observed in the three-month study. There were no significant effects in any of these studies aside from urinary-renal findings. Slight but statistically significant increases were observed in serum chloride concentrations, particularly at the high dose. Serum sodium and potassium levels appeared to be minimally affected. Urine volumes were generally modestly increased with the higher doses, with concomitant reductions in specific gravity. Urinary sodium and potassium concentrations were significantly reduced. A slight increase in relative kidney weight was also apparent at the highest dose, with females affected more than males. These findings are consistent with those observed with other CAIs such as acetazolamide and dorzolamide. Urothelial hyperplasia has been found among rodents receiving other CAIs.

Genotoxicity

Two *in vitro* and two *in vivo* mutation assays as well as an *in vivo/in vitro* unscheduled DNA synthesis assay were conducted with brinzolamide in order to evaluate the genotoxicity potential of the drug substance. In a bacterial reverse mutation (Ames) assay brinzolamide did not induce increases in the numbers of revertants per plate for any tester strain in the presence or absence of metabolic activation.

A mouse lymphoma forward mutation assay was conducted at concentrations of up to 3000 µg/ml without activation and up to 2000 µg/ml with metabolic activation. Brinzolamide demonstrated no mutagenic activity without hepatic microsomal enzyme activation. In the presence of activation, dose related increases in mutant frequencies, approximately two- to four-fold above background, were observed. However, mutagenicity was always accompanied by high cytotoxicity (relative growth generally reduced by 85% or more). Hence, cytotoxicity may have contributed to mutagenicity.

A mouse micronucleus assay employing oral doses of up to 1000 mg/kg revealed no genotoxic effects on bone marrow cells harvested 24, 28 and 72 hours after dosing.

Furthermore an *in vivo* sister chromatid exchange assay in hamsters was conducted. Treatment with brinzolamide did not induce an increase in sister chromatid exchange in bone marrow cells and an *in vivo/in vitro* unscheduled DNA synthesis assay was also negative. CAIs, as a class, are not mutagenic and although brinzolamide showed some mutagenicity in one of the five tests performed, the overall weight of evidence suggests that brinzolamide is consistent with the class.

Carcinogenicity

The applicant has sought scientific advice with regard to the need of the requirement for carcinogenicity studies in January 1996. Although the CPMP accepted at that time not to perform carcinogenicity studies, carcinogenicity studies in rats and mice have been performed.

The study in rats, which employed oral gavage administration of 0,1,3 and 8 mg/kg/day brinzolamide, demonstrated non-neoplastic lesions consistent with those observed in previous studies in this species. One male of the high dose had an epithelial adenocarcinoma of the urinary bladder, and one male of the high dose had a papilloma of the urinary bladder. There was no other indication of carcinogenic effect following two years of oral administration of brinzolamide to rats.

An increase in urinary bladder tumors (leiomyosarcomas) was observed in female mice given brinzolamide 10 mg/kg/day, orally, for 24 months. Dose-related proliferative changes in the urinary bladder were observed among female mice at 1, 3 and 10 mg/kg/day, and among males at 3 and 10 mg/kg/day.

The elevated bladder tumor incidence, which was statistically significant, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. This information is included in section 5.3 of the SPC.

In conclusion it can be considered that brinzolamide pose little risk regarding carcinogenic potential.

Reproduction toxicity

Studies investigating fertility and early embryonic development, embryo-foetal development and prenatal and postnatal development have been performed.

Repeated dose toxicity studies in rats and mice incorporated careful histopathologic evaluation of the testes to encompass complete spermatogenic cycles (approximately 10 weeks).

Fertility and early embryonic development

In the fertility and general reproduction study in rats, 40 F0 males were treated for 99 days (more than one spermatogenic cycle) and females were treated for 2 weeks prior to the mating period. Brinzolamide did not affect male or female fertility or general reproductive performance. Slight, statistically significant differences in body weight (up to approximately 10% at the high dose) were seen in F0 males during the treatment phase and in females during the treatment phase and through gestation. F1 foetal weights were lower in a dose-related manner, though no other maternal or foetal parameters were affected. F1 pup weights were comparable between control and treated groups at lactation Day 1 but F1 pups weights were slightly to moderately decreased (approximately 13%), in the high dose group at lactation Days 14 and 21. There were no effects on F1 fertility and reproductive performance, or on F2 offspring. The no-effect level for fertility and reproduction was considered to be 18 mg/kg/day.

Embryo-foetal development

Doses of 0, 2, 6 and 18 mg/kg/day, were given orally by gavage, to 40 pregnant dams on gestation days 6 through 17, with 20 employed for caesarean section and 20 delivering F1 pups. Results were generally similar to those obtained in the fertility study, with a slightly lower body weight for F0 dams and a lower mean foetal weight for the high dose group compared with controls. Increases in the incidence of unossified sternebrae or hyoid and reduced ossification of the skull were observed at the high dose only. This was hinted at in the fertility study, where only an apparent increase in unossified sternebrae was noted. Day 1 mean weights of delivered pups were comparable between the control and treated groups.

A developmental toxicity study in rabbits employed oral gavage administration of brinzolamide at dose levels of 0, 1, 3 and 6 mg/kg/day on gestation Days 6 through 18. Substantial maternal toxicity was evidenced at the high dose by one fatality, absence of faeces and emaciation, and two instances of abortion. No malformations were observed and ossification appeared to be unaffected. Thus, brinzolamide appeared to have no adverse effects on foetal development even in the presence of extreme maternal toxicity.

Classic CAIs are recognised as possessing developmental toxicity potential. Acetazolamide, dichlorphenamide, ethoxzolamide and benzolamide, at high dose levels, have been associated with forelimb skeletal malformations in rats and mice. It has been suggested that the characteristic forelimb reduction deformities observed in rats, mice and rabbits receiving acetazolamide does not occur in monkeys due to lack of embryonic CA activity during the sensitive period of causal development. Further investigations suggested a reduction in embryonic intracellular pH to be the mechanism. In the present studies with brinzolamide, only slight reductions in ossification have been observed in rats, with no limb malformations apparent.

Prenatal and postnatal development

A peri- and postnatal study in rats employed oral gavage administration of 0, 1, 5 and 15 mg/kg/day brinzolamide from gestation Day 16 through lactation Day 20. Sporadic instances of differences in F1 pup viability at or before Day 4 and at the low and mid dose levels may have been due to cannibalisation.

Pup weights during lactation were comparable with controls for all treatment groups, until Day 21, when the mean pup weight for the high dose group was slightly lower (8%) than controls. There was no indication of impairment of late foetal or pup morphological, behavioural or functional development.

Other toxicity studies:

Immunostimulation study

An immunostimulation study in the guinea pig, consisting of an induction phase by intradermal injection and a challenge phase with patch applications showed no response. It can be concluded that brinzolamide is a non-sensitiser substance.

Cell proliferation study in rats

Oral administration of 20, 60, 180 mg/kg/day to rats did not induce cell proliferation in the liver.

Phototoxicity study

In a preliminary phototoxicity study New Zealand White rabbits were exposed to Azopt by dermal application, followed by exposure to 5 joules/cm^2 UVA for 37 minutes. No phototoxic response was observed at 24, 48 and 72 hours post-exposure.

Ecotoxicity/Environmental risk assessment:

Exposure assessment estimates for the different environmental compartments have shown that, based on the methods and calculations presented in the guideline for environmental risk assessment, the concentration of brinzolamide is below the established threshold values (0.001 µg/l for water and 10 ppb for soil) for concern. There are no factors regarding the toxicity of brinzolamide that would require consideration of stricter criteria, and further investigations are not considered necessary.

4. Part IV: Clinical aspects

Introduction

The most common type of glaucoma encountered in Europe is primary open-angle glaucoma (POAG) which is strongly related to elevated IOP (i.e., IOP $\geq$ 21 mm Hg).

Topical CAIs constitute a new class, in which the single representative is 2% dorzolamide (Trusopt), eye drops marketed since 1996 in Europe and indicated as second-line therapy (after a topical beta-blocker, e.g. timolol) with a TID regimen in monotherapy and BID regimen as adjunctive therapy.

Both pilocarpine, the most commonly used miotic, and dorzolamide have similar additive hypotensive effects when combined with a beta-blocker.

A total of 12 clinical trials are included in the efficacy submission of 1% brinzolamide eye drops with a total of 1390 patients or healthy volunteers involved. The studies were conducted in the USA, Europe, Japan and Australia.

Studies were performed in accordance with GCP requirements (CPMP/ICH/135/95 and the declaration of Helsinki).

Clinical pharmacology

Pharmacodynamics

In Table 3 an overview of the studies performed is presented.

Table 3: Tabular summary of pharmacodynamic studies

Study number	Study Design	Treatment duration	Patient Population	Dosing Regimen	No. of Sites	No. Patients (Intent-to-Treat)
C-97-61	Double-blind, cross-over	1 day	Healthy volunteers	Brinzolamide 1%: 2 drops study eye Placebo: 2 drops fellow eye	1 (US)	16 total 16 brinzolamide 15 placebo
C-92-34	Open-label	15 days	Healthy volunteers	Brinzolamide 3%: 1 drop TID	1 (US)	15 brinzolamide
C-92-38	Single-blind, cross-over	4 days	Healthy volunteers	Brinzolamide 3%: 1 drop BETOPTIC S: 1 drop	1 (US)	20 brinzolamide
C-92-25	Double-blind, randomised, placebo-controlled	15 days	Primary open-angle glaucoma or ocular hypertension	Brinzolamide 0.3, 1, 2, 3%: 1 drop BID Placebo: 1 drop BID	20 (US)	157 total 126 brinzolamide 31 placebo
C-94-49	Double-blind, randomised, active-controlled	28 days	Primary open-angle glaucoma or ocular hypertension	Brinzolamide 1%: 1 drop BID Brinzolamide 1%: 1 drop TID	6 (US)	105 total 51 brinzolamide BID 54 brinzolamide TID
C-94-71	Double-blind, randomised, placebo-controlled	28 days	Primary open-angle glaucoma or ocular hypertension	Brinzolamide 1%: 2 drops QID + NLO Placebo: 2 drops QID + NLO	1 (US)	28 total 23 brinzolamide 5 placebo
C-94-05	Double-blind, randomised, placebo-controlled	14 days	Primary open-angle glaucoma or ocular hypertension	Brinzolamide 2%: 1 drop BID (GDS) Placebo: 1 drop BID (GDS)	2 (US)	55 total 41 brinzolamide 14 placebo
C-93-86	Double-blind, randomised, placebo-controlled	14 days	Primary open-angle glaucoma or ocular hypertension	Brinzolamide 1%: 1 drop BID Placebo: 1 drop BID (dosing adjunctive to Timoptic 0.5%)	5 (US)	30 total 23 brinzolamide 7 placebo

Abbreviations and drug names used include the following: BID (twice-daily), TID (three times daily), QID (four times daily), PO (oral administration), NLO (nasal lacrimal occlusion), US (United States), EU (Europe), AUS (Australia), Brinzolamide 1% (brinzolamide 1% eye drops), Betoptic S (betaxolol suspension 0.25% eye drops), Timoptic 0.5% (timolol 0.5% ophthalmic solution), and Trusopt (dorzolamide 2% ophthalmic solution

In preclinical studies, brinzolamide was demonstrated to be a potent inhibitor of CA-II. The mechanism of action of CA inhibitors on IOP is described in literature as an inhibition of CA in the ciliary processes of the eye decreasing aqueous humour secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. No clinical pharmacodynamic studies to further determine the mechanism of action on IOP in humans were performed.

Recent studies suggested that glaucoma might have a vascular component on which drugs may act directly contributing to improve ocular blood flow and visual contrast sensitivity. Thus, in study C-97-61 brinzolamide (1%) was tested against placebo in healthy volunteers in a specific double-blind, cross-over, single dose study to evaluate the effects of brinzolamide on ocular blood flow and visual function. Results showed that topical brinzolamide had no acute effects on retrobulbar and retinal and superficial optic nerve head blood flows as well as on contrast sensitivity.

CA-II and IV isoenzymes are present in corneal endothelial cells and play an important role in the maintenance of corneal transparency. Due to the important local concentrations given by eye drops, topical CA inhibitors may modify electrolytes and water transport within the cornea, leading to a corneal oedema and to an increase in corneal thickness.

In study C- 95-47 (see also under "Pharmacokinetics") corneal pachymetry and endothelial cell density were assessed in most patients at baseline and at months 6, 12 and 18. Although there was no placebo group in that study, the results showed that brinzolamide (BID or TID) had no obvious effect on corneal function or endothelial cellularity.

No corneal oedema was observed in the phase III studies.

Pharmacokinetics

Table 4 presents an overview of the studies performed.

Table 4: Tabular summary of pharmacokinetic studies

Study number	Study Design	Treatment Duration	Patient Population	Dosing Regimen	No. of Sites	No. Patients (Intent-to-Treat)
C-92-34	Open-label	15 days	Healthy volunteers	Brinzolamide 3%: 1 drop TID	1 (US)	15 brinzolamide
C-95-47	Double-blind, randomised, active-controlled	18 months	Primary open-angle glaucoma or ocular hypertension	Brinzolamide 1%: 1 drop BID Brinzolamide 1%: 1 drop TID Timoptic 0.5%: 1 drop BID	3 (US)	56 total (kinetic evaluation) 29 brinzolamide BID 27 brinzolamide TID
C-95-76	Double-blind, randomised, placebo-controlled	32 weeks + 12 week wash-out	Healthy volunteers	Brinzolamide: 1 mg PO BID Placebo: PO BID	1 (US)	24 total 20 brinzolamide 4 placebo
C-96-59	Double-blind, randomised, placebo-controlled	60 weeks + 12 week washout	Renally impaired volunteers	Brinzolamide: 1 mg PO BID Placebo: PO BID	6 (US)	38 total 28 brinzolamide 10 placebo
C-96-74	Double-blind, randomised, placebo-controlled	1 week	Healthy Japanese volunteers	Brinzolamide 1%: 1 drop BID study eye Brinzolamide 2%: 1 drop BID study eye Placebo: 1 drop BID fellow eye	1 (JPN)	16 total 8 brinzolamide 1% 8 brinzolamide 2% 16 placebo

Abbreviations: see Table 3.

Topical ocular administration

None of the three topical studies (C-92-34, C-96-74, and C-95-47) was designed as a pharmacokinetic study. Some blood samples were obtained during safety or efficacy studies that only show that brinzolamide is absorbed to some extent after topical ocular administration. The absorption of brinzolamide after topical ocular administration cannot be estimated from these studies.

Main pharmacokinetic properties

The data on pharmacokinetic parameters are limited. The bioavailability and volume of distribution have not been determined as this would require intravenous administration of brinzolamide and this could introduce a risk for patients or healthy volunteers.

Following topical ocular administration, brinzolamide is absorbed into the systemic circulation. Due to its high affinity for CA-II, brinzolamide distributes extensively into the RBCs and exhibits a long half-life in whole blood (mean of approximately 24 weeks). The major isozyme involved in the metabolism of brinzolamide is CYP3A4, but at least 4 other isozymes are involved including CYP2A6, CYP2B6, CYP2C8 and CYP2C9. In humans, the metabolite N-desethyl brinzolamide is formed, which also binds to CA and accumulates in RBCs. This metabolite binds mainly to CA-I in the presence of brinzolamide. In plasma, both brinzolamide and N-desethyl brinzolamide concentrations are low and generally below assay quantitation limits (<7.5 ng/ml). Binding to plasma proteins is not extensive (about 60%). 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 in the urine along with trace levels of the N-desmethoxypropyl and O-desmethyl metabolites.

Oral administration

Healthy volunteers

In study C-95-76 (1 mg) parent drug steady-state was achieved at approximately 12 weeks. N-desethyl metabolite steady-state was achieved within 20 to 28 weeks. The other metabolites were not detected in whole blood. The levels of the parent drug and even more of N -desethyl metabolite were higher in females than in males, but this was not considered to be clinically relevant.

Renally impaired volunteers (CrCl ≥ 30ml/min)

In study C-96-59 (1 mg) steady-state levels were obtained later than that in normal healthy volunteers. At steady-state, the parent drug levels were about twice that measured in healthy normal volunteers. The same phenomenon occurred for the N -desethyl metabolite, but was more pronounced. However, safety studies did not show an increase in the frequency of systemic adverse events due to accumulation and consequently a higher degree of CA inhibition.

No studies have been performed in patients with severe renal impairment (CrCl<30ml/min) as CAIs can produce acidosis and this population is susceptible to this adverse reaction. CA inhibitors are contra-indicated in patients with severe renal impairment and patients with hyperchloraemic acidosis (see section 4.3 of the SPC).

Hepatic impairment

Brinzolamide has not been studied in hepatic impaired subjects because brinzolamide does not have a narrow therapeutic index and renal excretion is the main route of elimination, and therefore studies in such a population were not considered necessary. However, brinzolamide should be used with caution, as reflected in sections 4.2 of the SPC.

Elderly patients (>65 years of age)

A representative number of patients from 66 to 75 years (n=670) and from 76 to 85 years (n=222) have been included in the clinical studies. No dosage alteration in elderly patients is necessary, as reflected in section 4.2 of the SPC.

Interactions

No specific drug interaction studies were performed, in view of the fact that beta-blockers such as timolol and metoprolol are metabolised by different isozymes and those beta-blockers do not inhibit the metabolism of brinzolamide and vice versa. Furthermore, brinzolamide does not strongly bind to plasma proteins. The lack of interaction studies is justified on the basis of available clinical data with regard to the co-administration with timolol, which is currently by far the most used beta-blocker in glaucoma. Based on theoretical grounds no differences are expected with the behaviour of other beta-blockers.

No specific interaction studies were performed. This was considered acceptable as efficacy is related to local rather than systemic concentrations.

It is recognised that brinzolamide and its main metabolite (N-desethyl-brinzolamide) bind to CA and are sequestered into RCBs. Based on this fact, brinzolamide is unlikely to be involved in interactions with other medicinal products. The reasons that indicate that brinzolamide is unlikely to interact with other drugs are:

1 Brinzolamide has multiple elimination pathways and metabolism by multiple isozymes of cytochrome P-450. CYP-3A4 is a major contributor to metabolic elimination but 4 other isozymes are also available for clearance of the drug. Hence, if CYP-3A4 was inhibited, renal clearance and liver metabolism by the remaining isozymes could eliminate the drug.

2 Changes in brinzolamide availability due to inhibition of CYP-3A4 will not significantly alter concentrations of drugs in plasma or RBCs because at steady state brinzolamide binding to CA is saturated and unbound brinzolamide is rapidly cleared by renal excretion and liver metabolism.

3 Brinzolamide is not an inhibitor of cytochrome P-450 isozyme even at concentrations that are more than 100-fold higher than those found in plasma at steady state in humans.

4 Brinzolamide is approximately 60% plasma protein bound.

Clinical efficacy

The clinical trials were performed according to GCP standards and agreed international ethical principles.

Dose-response studies and main clinical studies

Dose-response and dosing regimen studies

To establish the appropriate concentration of brinzolamide one study was performed (Study C-92-25; see Table 3). This was a multicentre, randomised, double blind, placebo controlled study in patients with open angle glaucoma or ocular hypertensive patients for whom ocular hypotensive therapy is indicated. Patients were administered Azopt 0.3% (n=29), 1% (n=34), 2% (n=30) and 3% (n=33). All treatment dosed one drop/eye BID, topically during 15 days. Placebo was used in the same dose-regimen (n=31).

The efficacy endpoint was the mean per cent change from diurnally adjusted baseline IOP. The dose response curve represented by a graph of least square means of percent reduction in IOP, reached a plateau at 1%, indicating that the optimal effective brinzolamide concentration is 1%. This concentration showed similar tolerance as lower concentrations.

Two studies were designed with the purpose of finding the proper dosing regimen (study C-94-49 and study C-94-71, see table 3).

Study C-94-49

This was a double-blind, randomised, active-controlled study, in patients with primary open angle glaucoma or ocular hypertension. Patients were administered brinzolamide 1% ophthalmic suspension, one drop/eye BID (n=51) or TID (n=54), topically. Patients in the BID group also received one drop/eye vehicle to preserve the study blinding. Duration of treatment was 4 weeks.

The efficacy endpoint was IOP changes in mmHg from diurnal baselines. Clinically and statistically significant IOP decrease was noted when BID or TID regimens were administered. BID and TID treatments were equivalent.

Study C-94-71

This was a single centre, double-blind, placebo-controlled randomised, parallel group study in patients with primary open angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension. Patients were administered brinzolamide 1% ophthalmic suspension, two drops in each eye QID (n=23) employing nasal lacrimal occlusion after each dose during four weeks. The placebo consisted of brinzolamide vehicle, two drops in each eye QID (n=5), during four weeks.

The efficacy endpoint was IOP changes from diurnal baseline. Brinzolamide 1% ophthalmic suspension dosed QID followed by two minutes of nasal lacrimal occlusion resulted in clinically significant IOP reduction from baseline. Compared to the previous results, in this reduced sample size the IOP lowering efficacy of brinzolamide 1% ophthalmic suspension was not significantly enhanced by increasing the dosing frequency to QID. In addition, brinzolamide ophthalmic suspension was well tolerated when administered QID.

Main studies

Table 5 shows an overview of the studies performed.

Table 5: Efficacy and comfort studies

Study number	Study Design	Treatment Duration	Patient Population	Dosing Regimen	No. of Sites	No. Patients (Intent-to-Treat)
EFFICACY STUDIES						
C-95-46	Double-blind, randomised, placebo-controlled	3 months	Primary open-angle glaucoma or ocular hypertension	Brinzolamide 1%: 1 drop BID Brinzolamide 1%: 1 drop TID Trusopt: 1 drop TID Placebo: 1 drop TID	29 (US)	463 total 134 brinzolamide BID 133 brinzolamide BID 131 Trusopt 65 placebo
C-95-48	Double-blind, randomised, active-controlled	3 months	Primary open-angle glaucoma or ocular hypertension	Brinzolamide 1%: 1 drop BID Brinzolamide 1%: 1 drop TID Trusopt: 1 drop TID Timoptic 0.5%: 1 drop BID	46 21 (US) 25 (EU)	572 total 165 brinzolamide BID 169 brinzolamide TID 165 Trusopt 73 Timoptic 0.5%
C-95-39	Double-blind, randomised, active-controlled	13 weeks	Primary open-angle glaucoma or ocular hypertension	Brinzolamide 1%: 1 drop BID Trusopt: 1 drop BID (dosing adjunctive to Timoptic 0.5%)	32 28 (EU) 4 (AUS)	238 total 116 brinzolamide 122 Trusopt
C-95-38	Double-blind, randomised, placebo-controlled	3 months	Primary open-angle glaucoma or ocular hypertension	Brinzolamide 1%: 1 drop TID Placebo: 1 drop TID (dosing adjunctive to Timoptic 0.5%)	23 (US)	132 total 65 brinzolamide 67 placebo
C-95-47	Double-blind, randomised, active-controlled	18 months	Primary open-angle glaucoma or ocular hypertension	Brinzolamide 1%: 1 drop BID Brinzolamide 1%: 1 drop TID Timoptic 0.5%: 1 drop BID	18 (US)	378 total 150 brinzolamide BID 153 brinzolamide TID 75 Timoptic 0.5%
COMFORT STUDIES						
C-92-38	Single-blind, crossover	4 days	Healthy volunteers	Brinzolamide 3%: 1 drop BETOPTIC S: 1 drop	1 (US)	20 total 20 brinzolamide 20 BETOPTIC S
C-96-29	Double-blind, randomised, active-controlled	1 week	Primary open-angle glaucoma or ocular hypertension	Brinzolamide 1%: 1 drop TID Trusopt: 1 drop TID	3 (US)	109 total 55 brinzolamide 54 Trusopt
C-96-40	Double-blind, randomised, active-controlled	1 week	Primary open-angle glaucoma or ocular hypertension	Brinzolamide 1%: 1 drop TID Trusopt: 1 drop TID	3 (US)	104 total 52 brinzolamide 52 Trusopt

Abbreviations: see Table 3.

IOP, measured by Goldmann applanation tonometry was the efficacy parameter in all clinical efficacy studies and the chosen primary endpoint was the change of IOP from the diurnal baseline. However, results are also expressed as the mean decrease of IOP and percentage of responders, who were defined as patients reaching an IOP ≤ 21 mmHg or with a decrease of at least 5 mmHg. To accept equivalence between treatments, the minimum relevant difference to be detected was fixed at 1.5 mmHg.

The endpoint was evaluated at three months in all clinical trials except in one trial where the double blind period was extended up to 18 months.

Assessment of visual loss and optic nerve damage has been performed only from the safety point of view, and studies were neither long nor large enough to detect differences in these relevant parameters. However, the demonstration of efficacy based only on decreases in IOP is an acceptable approach.

The demographic characteristics of patients receiving brinzolamide 1%, Trusopt and Timoptic 0.5% in the controlled trials were similar regarding age distribution, sex, ethnic origin and iris colour. The number of patients ≥ 65 years of age included in the studies with brinzolamide was 683, of which 579 received brinzolamide monotherapy and 104 brinzolamide added to timolol.

Treatment in monotherapy

Versus beta-blocker

Two comparative monotherapy studies versus timolol (with BID and TID-dosing over 3 months and 18 months) have been presented (study C-95-47 and C-95-48). The difference in IOP reduction between timolol and brinzolamide was up to 2 mm Hg at trough, favouring timolol (study C-95-47). At peak, pooled data demonstrated that timolol was also more effective than brinzolamide with a statistically significant difference in mean IOP changes between timolol (BID) and brinzolamide (TID). The magnitude of the decrease across studies ranged from -2.7 to -5.7 mmHg with brinzolamide BID, from -2.8 to -5.6 mmHg with brinzolamide TID and from -5.2 to -6.0 mmHg with timolol 0.5% BID.

Versus CAIs

The IOP-lowering effect of brinzolamide 1% (BID or TID) was comparable to that of dorzolamide 2% (TID) when given as first-line monotherapy in two studies (C-95-46 and C-95-48). However, in the EU, topical dorzolamide is considered to be a second-line drug in the treatment of glaucoma. The magnitude of the decrease across studies ranged from -3.4 to -5.7 mmHg with brinzolamide BID, from -4.1 to -5.6 mmHg with brinzolamide TID and from -4.3 to -4.9 mmHg with dorzolamide TID.

The long-term effect of brinzolamide on the diurnal rhythm of IOP has not been extensively investigated in long-term studies (study C-95-47).

Statistical Analysis

Both intent-to-treat and per-protocol analyses were presented in the clinical study reports of the superiority trials versus placebo and versus timolol. For studies C-95-38, C-95-48, C-95-46 and C-95-47 results of the ITT analyses and per protocol analyses are similar.

There were four confirmatory studies where statistical tests relative to timolol or placebo were performed. The applicant has extracted the intent-to-treat and the per-protocol results for the superiority results for these studies. The results have been pooled across visits and by visit.

Treatment in adjunctive therapy

In addition to timolol

Two studies as an add-on to timolol have been performed, the first versus placebo (Study C-95-38), the second versus dorzolamide (study C-95-39). The length of the two adjunctive studies is relatively short (3 months)

Versus placebo

TID dosing with brinzolamide 1% ophthalmic suspension when used adjunctively with timolol 0.5% ophthalmic solution produced clinically and statistically significant IOP reductions from baseline. Mean IOP changes from baseline of brinzolamide as add-on to timolol were significantly greater ($p=0.0329$) compared to placebo + timolol. The magnitude of the decrease with brinzolamide ranged from -3.2 to -4.1 mmHg and the decrease with placebo ranged from -1.0 mmHg to -2.6 mmHg

Versus dorzolamide

BID dosing with brinzolamide 1% ophthalmic suspension when used adjunctively to timolol 0.5% ophthalmic solution produced clinically and statistically significant IOP reductions from baseline at each treatment visit. The results were equivalent for brinzolamide 1% ophthalmic suspension and dorzolamide 2% ophthalmic solution. None of the upper limits of the 95% confidence interval of the differences was above the a priori established value of 1.5 mmHg and most of them were inferior to 1 mmHg. The magnitude of the decrease ranged from –3.6 to –5.3 mmHg with brinzolamide BID and from –3.6 to –5.1 mmHg with dorzolamide BID.

In addition to other agents

The efficacy of brinzolamide 1% in adjunction with other drugs used in ocular hypertension treatment (prostaglandins, adrenergic agonists, and miotics) was not studied. The only recommended association is with beta-blockers.

Long term effects

There was no tachyphylaxis during the study period (18 months). A duration of 3 months is generally sufficient to show adequate efficacy of a topical ocular hypotensive medication, since it allows IOP to stabilise. In adjunctive therapy, long term data (up to 6 months) are available on 75 patients. Additionally, up to 9 months data are available on 38 of these 75 patients.

Rebound effect

A possible rebound increase in IOP after withdrawal of brinzolamide eye drops has not been investigated. This is reflected in section 4.4. of the SPC.

Clinical studies in special populations

The experience with brinzolamide in the treatment of pseudoexfoliative glaucoma or pigmentary glaucoma is limited and no specific clinical data were obtained in patients wearing contact lenses. This has been reflected in section 4.4. of the SPC.

Dose regimen

With regards to the possible superiority of the TID regimen versus the proposed BID regimen, the following information is available.

One clinical pharmacology study (C-94-49) compared BID and TID dosing regimens measuring IOP at 5 different time points during the day, without finding differences between both regimens (magnitude of differences at all time points less than 1 mmHg).

Both regimens were tested in the three pivotal clinical trials. In them, brinzolamide BID showed superiority versus placebo and similar efficacy as dorzolamide. In one of these trials (C-95-46), equivalence between BID and TID could not be demonstrated and the BID regiment appeared to be inferior to TID. Confidence intervals of the difference were above the prespecified delta of 1.5 mmHg at different time points. Regarding the percentage of responders there is about a 10% less responders to BID brinzolamide than with the other two regimens.

The other two studies failed to show differences between both regimens, one of them showing also equivalence to dorzolamide (C-95-48) and the third one inferiority versus timolol (C-95-47). In both trials IOP was measured at different time points including the worst possible case for the BID regimen which is 12 hours post dose coinciding with the peak of the circadian rhythm of the IOP. If equivalence is tested, the upper limit of the confidence interval of the difference is below 1.1 mmHg at all time points during the 3 months trial and below 1.4 mmHg at all time points during the 18 months trial.

The Applicant states that the BID regimen is the preferred regimen. The superior efficacy of the TID regimen, if it exists, would be about 1 mmHg, which has no clinical significance. The long-term trial does not find differences in IOP between both regimens and only one of the two 3-month trials suggests a difference of the above-mentioned magnitude.

According to the Applicant it is obvious that most patients controlled with brinzolamide do not need more than BID and also facilitation of compliance and commodity should be taken into account as well as minimising the exposure to benzalkonium. Moreover, it is mandatory that patients with high IOP are closely monitored allowing to detect easily an insufficient control.

However, it could be argued that the TID regimen should be the preferred one. The arguments in favour of a TID regimen are the following: with regard to the compliance, the statement made by the applicant is weak as compliance was never assessed in the file. Although the IOP differences are inferior to 1 mmHg and thus, without clinical significance the overall number of controlled patients is always higher with the TID regimen rather than the BID regimen.

This is of clinical significance and demonstrated in the file. Moreover in the 18-month study IOP was not measured at the late afternoon point, and thus due to the inter-individual variation in nycthemeral IOP, there is no confirmation of the nycthemeral control beyond a 3-month duration.

Therefore the following wording has been included in section 4.2 of the SPC:

"When used as monotherapy or adjunctive therapy, the usual dose is one drop of Azopt eye drops in the conjunctival sac of the affected eye(s) twice daily. Some patients may have a better response with one drop three times a day."

Clinical safety

Patient exposure

A total of 2530 patients or healthy volunteers were included in the clinical trials (excluding the on-going study C-96-60). Of them, 1227 patients received brinzolamide eye drops 1% alone. As primary therapy, 542 were treated at the recommended daily dosage of brinzolamide 1% BID and 616 and 23 patients were treated with brinzolamide 1% TID or QID respectively. As adjunctive therapy to timolol 0.5% 139 and 65 patients received brinzolamide 1% BID or TID respectively. In addition, 48 volunteers received brinzolamide orally and 176 patients received concentrations of topical brinzolamide other than 1%.

Two studies in specific populations were added as required by the CPMP for safety evaluation (Scientific Advice; 1996):

- Study C-97-46, a clinical safety study to demonstrate the absence of acute effects of a single drop administration of brinzolamide on pulmonary function.
- Study C-96-60, a clinical safety study to demonstrate the reversibility of timolol- induced airway obstruction and the safety advantage of brinzolamide as first-line therapy.

Furthermore, a multicentre, open label, adjunctive-therapy study (C-97-27) was performed to study the long-term safety of BID-dosed brinzolamide 1.0% ophthalmic suspension.

An overview of the studies performed is presented in Table 6.

Table 6: Safety studies

Study number	Study Design	Treatment Duration	Patient Population	Dosing Regimen	No. of Sites	No. Patients (Intent-to-Treat)
C-97-46	Double-blind, randomised, crossover	Single administration	Volunteers with asthma or COPD	Brinzolamide 1%: 1 drop / eye Timoptic 0.5%: 1 drop / eye	1 (EU)	30 total 30 brinzolamide 30 Timoptic 0.5%
C-96-60 (ongoing)	Double-blind, randomised, active-controlled	3 months	Primary open-angle glaucoma or ocular hypertension in patients ≥ 60 years of age	Brinzolamide 1%: 1 drop TID Timoptic 0.5%: 1 drop BID	22 (EU)	148 expected 74 brinzolamide 74 Timoptic 0.5%
C-97-27	Open-label	6 months	Primary open angle glaucoma or ocular hypertension	Brinzolamide 1%: 1 drop BID (dosing adjunctive to Timoptic 0.5%)	17 15 (EU) 2 (AUS)	75 total 75 brinzolamide

Abbreviations: see Table 3.

601 Patients were exposed to brinzolamide 1% BID, TID or QID up to 3 months, and another 303 were exposed for 18 months. 181 Patients received brinzolamide 1% + Timoptic 0.5% for 3 months.

No clinically relevant differences between the patient demographics of the subgroups for each treatment group with or without adverse events were observed

Adverse events and serious adverse events

One hundred and fifty-seven (157) of the 1227 patients (12.8%) experienced 227 ocular events and 106 (8.6%) patients experienced 140 non-ocular events related with brinzolamide 1%.

The reported adverse events were generally mild to moderate, usually resolved with or without therapy and generally did not requested discontinuation in the study.

The most frequent ocular adverse events related or unrelated to brinzolamide 1%, taking into account the overall frequency and incidence of adverse events for all treatment groups, were blurred vision (temporary blurring upon instillation lasting from a few seconds to a few minutes) 5.8%, ocular discomfort (transient burning or stinging upon instillation) 3.1%, ocular hyperaemia (2.5%), foreign body sensation (2.4%), ocular pain (1.8%), blepharitis (1.5%), dry eye (1.5%), cataract (1.5%), optic nerve disorder (1.5%), ocular discharge (1.3%), ocular pruritus (1.3%), and keratitis (1.1%). Other ocular events at an incidence rate between 0.9 and 0.6 percent were conjunctivitis, tearing, abnormal vision, subconjunctival haemorrhage, and lid margin crusting.

Non-ocular events at an incidence higher than 1% included taste perversion (bitter or unusual taste) 5.5%, headache (2.2%), infection (2.1%), surgical/medical procedures (2%), cold syndrome (1.9%), pain (1.9%), hypertension (1.1%), diarrhoea (1%), rhinitis (1.5%), sinusitis (1.4%), pharyngitis (1.5%), bronchitis (1.4%), and dermatitis (1.1%).

The profile of ocular adverse events of brinzolamide in association to timolol 0.5 % was similar to brinzolamide alone. The most frequent events was blurred vision (4.9%) taste perversion (4.4%) ocular discomfort (1.5%) and foreign body sensation (1%). However some specific adverse events of beta-blockers, as asthma appeared with an incidence of 1%.

No serious related adverse events were reported for brinzolamide 1%, but 20 patients (6 in regimen TID and 14 in BID) were discontinued from the study due to related ocular events (blurred vision, ocular pain, keratitis and ocular discomfort were the most frequent reasons) and 14 patients (7 in regimen TID and 7 in BID) were discontinued due to related non-ocular events (taste perversion, dizziness, headache, diarrhoea, asthenia, depersonalisation, nervousness, dermatitis, pruritus were some of the reasons).

In 4 patients the reason of discontinuation was taste perversion, which appeared in 3 of the 4 cases in TID regimen. The 2 cases of dizziness that conducted to discontinuation of treatment appeared in TID regimen.

Five patients treated with the association of brinzolamide and timolol 0.5% discontinued the study due to 4 related non-ocular events (2 cases of asthma, cough, pharyngitis).

Adverse events of brinzolamide 1% (BID, TID) in comparisons of 2% and 3%.

Four dose-ranging studies were conducted (C-95-25, C-95-46, C-95-47 and C-95-48); two of them were conducted including placebo (C-95-46 and C92-25).

Blurred vision (1.7%, 5.0 %, 5.3 % and 7.4 % with placebo, brinzolamide 1%, 2% and 3% respectively) ocular discomfort (2.6%, 2.5 %, 2.6 % and 2.9 % with placebo, brinzolamide 1%, 2% and 3%, respectively) and taste perversion (5.5% with brinzolamide 1% but 13.2 % and 38.2 % with brinzolamide 2% and 3% respectively) were the most frequent events related to brinzolamide. Other events related were hyperaemia, dry eye, pain, discharge, ocular pruritus, keratitis, lid margin crusting and ocular precipitate (active substances residue; only with brinzolamide 3%).

In general it seems that there is correlation between adverse events and dose, especially for blurred vision and taste perversion. The greatest percentage of patients experiencing treatment related adverse events was described with brinzolamide 3% and the least with brinzolamide 0.3%, with no clinically significant difference between brinzolamide 1% and 2%.

Adverse events in comparisons to the same therapeutic class (dorzolamide)

Four studies (C-95-46, C-95-48, C-96-29 and C-96-40) were conducted with dorzolamide as active control treatment.

In study C-95-46, ocular discomfort (3.0 % and 3.0%) and blurred vision (3.0% and 2.3%) were the most frequent ocular events related to brinzolamide 1% BID and TID respectively. Ocular discomfort was the most frequent ocular event (10.7%) related to dorzolamide 2%.

The percentage of patients with ocular discomfort was higher (10.7%) in the dorzolamide group than in any of the brinzolamide groups (3.0%), but the percentage of other ocular events was slightly higher in the brinzolamide group. As a consequence, the global percentage of adverse events was similar in both groups. The ocular discomfort was not related to a higher number of withdrawals since only one patient withdrew in the dorzolamide group (accident injury) whereas 4 patients receiving brinzolamide 1% BID were discontinued from the study due to 9 adverse events (most of which ocular events) and 2 patients from placebo group (corneal abrasion and pneumonia). One patient receiving brinzolamide 1% TID was discontinued due to dermatitis and urticaria and one due to treatment unrelated myocardial infarction. In contrast the percentage of patients experiencing ocular discomfort in the placebo group was very low (1.5%).

In study C-95-48 the adverse events profile with brinzolamide and dorzolamide was similar to that observed in the previous study: blurred vision (3% and 0.6%) and ocular discomfort (1.8% and 16.4%) were the most frequent adverse events with brinzolamide 1% BID and dorzolamide 2% TID, respectively.

In studies C-96-29 and C-96-40, brinzolamide 1% ophthalmic suspension TID resulted in statistically lower ocular discomfort score (0.2 and 0.4 units) than dorzolamide 2% ophthalmic solution TID (1.3 and 1.7). There was a greater percentage of patients experiencing no discomfort with brinzolamide (71.2 and 81.3% respectively) compared to dorzolamide (19.6 and 17.0% respectively), that is 28.8 and 18.7.7% respectively of the patients in the group of brinzolamide and 80.4-83.0 % in the group of Trusopt presented discomfort. Because of the design of the studies, the percentage patients showing some extent of discomfort is greater than the incidence of ocular discomfort reported spontaneously in the remaining studies.

Other ocular events were observed in the brinzolamide and in the Trusopt group with a similar percentage as in phase III studies.

No statistically or clinically significant worsening in visual acuity was observed between treatment groups.

Adverse events in comparisons to the reference therapeutic class (beta-blockers)

Two studies (C-95-47 and C-95-48) were conducted with timolol 0.5% as active control treatment.

The incidence of ocular adverse events in the brinzolamide 1% group and timolol group seems similar, however, a higher percentage of patients with blurred vision (5.0% and 2.8 % in brinzolamide 1% and Timoptic 0.5 % respectively) was observed in the brinzolamide group.

The only non-ocular adverse events described in timolol group with an incidence higher than 1 % was dyspnea (2%). Headache was described in the timolol group with an incidence of 0.8% (1.3% with brinzolamide 1%), asthenia with 0.4% (0.1% in brinzolamide group), dry mouth with 0.4% (0.7% in brinzolamide group), bronchitis or asthma 1.2% compared to 0.2 % asthma in brinzolamide 0.1%.

Endothelial cell density (cells/mm3) and corneal thickness (pachymetry) was measured in the study C-95-47 at baseline, month 6, month 12 and month 18. No effects have been observed.

Laboratory findings

Blood chemistry, haematology and urinalysis values were measured at baseline and post dosing in nine studies on study weeks 1 to 32 for 1668 patients. No relevant changes were detected from baseline or between active drugs.

Haematological effects

No bone marrow effect was observed in the clinical trials with 1% brinzolamide, but anaemia was reported in one patient.

Renal and metabolic effects

Acid-base and electrolyte disturbances were observed with brinzolamide. For brinzolamide 1% used as monotherapy 4 ADRs were reported (1 case of kidney calculus, 1 case of gout, 1 case of hypokalemia, and 1 case of hyperchloremia). 1 case of dysuria has been reported for brinzolamide 1% used as adjunctive therapy

Respiratory tolerance of topical brinzolamide

This was assessed in patients with asthma or chronic obstructive pulmonary disease (Study C-97-46).

In contrast to timolol 0.5%, brinzolamide 1% TID-dosed did not reduce forced expiratory volume in one second (FEV1) in volunteers with asthma or chronic obstructive pulmonary disease.

Cardiovascular evaluation

No clinically relevant differences were shown in the mean pulse, systolic or diastolic blood pressure between patients receiving ocular brinzolamide, dorzolamide or timolol.

Safety in special populations

A separate analysis of ADRs in risk groups has been presented.

Diabetics

Elevated blood glucose and glycosuria have been reported in diabetics and prediabetics receiving systemic CA inhibitors. These drugs may interfere with the hypoglycaemic response to insulin or oral antidiabetic agents.

In clinical studies, 174 diabetic patients received brinzolamide. None of the adverse events associated with discontinuation from the studies were associated with a worsening of the diabetic condition. No serious events related to brinzolamide were reported in diabetics and no specific adverse events were documented in such patients receiving brinzolamide.

Asthmatics

CA inhibitors may increase carbon dioxide tension in tissues and may decrease carbon dioxide tension in alveoli. Respiratory and metabolic acidosis caused by CA inhibitors may increase oxygenation during hypoxia by increasing ventilation, cerebral blood flow and/or dissociation of oxygen from oxyhemoglobin.

Respiratory difficulties may be increased by systemic CA inhibitors in patients with chronic obstructive lung disease. Forty-nine asthmatics were administered brinzolamide in clinical studies. No serious events related to brinzolamide were reported in asthmatics and no specific adverse events were documented in such patients receiving brinzolamide.

Patients on antihypertensive medications

Systemic CA inhibitors may augment the effects of other diuretics. Diuretics may cause increased excretion of potassium and patients receiving diuretics plus a CAIs may experience severe hypokaliemia. CA inhibitors can compete with chlorthalidone and alter the response to it. Four hundred and thirty nine patients receiving antihypertensive medications participated in brinzolamide studies in monotherapy (386) or added to timolol (53). No serious events related to brinzolamide were reported in patients on antihypertensive medications and no specific adverse events were documented in such population while receiving brinzolamide.

Patients with hepatic insufficiency

Patients with hepatic cirrhosis and hypokaliemia and/or elevations in blood ammonia concentrations caused by systemic CA inhibitor may develop hepatic coma or precoma, as well as disorientation.

No patients with hepatic insufficiency participated in clinical studies with brinzolamide. This has been reflected in section 4.2. of the SPC

Elderly patients

The number of patients ≥ 65 years of age included in the studies with brinzolamide was 683, of which 579 received brinzolamide monotherapy and 104 added to timolol. The adverse events associated with brinzolamide 1% are similar to those in patients other ages. No serious events related to brinzolamide were reported for elderly patients. For CA inhibitors there is a general recommendation to warn that the ability to perform tasks requiring mental alertness and/or physical coordination could be impaired. This warning has been included in section 4.4 of the SPC.

Females on hormone replacement therapy

One hundred sixty female patients on hormone replacement therapy participated in clinical studies with brinzolamide (150 in monotherapy and 10 added to timolol). No serious events or discontinuations related to brinzolamide were reported for females on hormone replacement therapy.

5. Overall conclusion and benefit/risk assessment

Quality

In summary, the documentation of substances, materials, methods of production as well as the quality controls is sufficient to ensure a sterile product of consistent quality, suitable for ophthalmic use when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

A number of follow-up measures have been agreed (see section II.3)

Preclinical pharmacology and toxicology

Brinzolamide has shown to be toxico-pharmacologically comparable to the other drug of its class.

Overall, the primary pharmacodynamic studies provided adequate evidence that the properties of brinzolamide, both general and ocular, are consistent with inhibition of CA, with affinity for the CA isoform II.

The pharmacokinetics of brinzolamide are specific and typical of sulphonamide anhydrase inhibitors which are essentially influenced by a tight binding to CA.

Overall, the toxicology programme revealed no major findings. Based on the results of the carcinogenicity studies it can be considered that brinzolamide poses little risk regarding carcinogenic potential and that the benefit-risk ratio is not affected.

Relevant information on the toxicity profile has been included in the SPC.

Efficacy

The clinical development program of brinzolamide 1% BID ophthalmic suspension is considered adequate. Brinzolamide 1% BID or TID is considered to be comparable to dorzolamide 2% TID in monotherapy, the TID administration of brinzolamide being closer to TID administration of dorzolamide.

Assessment of visual loss and optic nerve damage has been performed only from the safety point of view, and studies were not long or large enough to detect differences in these relevant parameters. However, the demonstration of efficacy based only on decreases in IOP is an acceptable approach.

Evidence of efficacy is not sufficient to recommend the use of brinzolamide 1% in the treatment of glaucoma or ocular hypertension as first line monotherapy. Brinzolamide 1% BID used in monotherapy showed a consistently lower efficacy than timolol 0.5% BID in both clinical trials where this comparison was performed. The percentage of responders was greater with timolol and that difference was more evident in the first measure in the morning, the peak measure of IOP.

Brinzolamide 1% BID or TID is considered to be comparable to dorzolamide 2% TID in monotherapy. Therefore the use as monotherapy in patients unresponsive to beta-blockers or in patients in patients in whom beta-blockers are contraindicated is acceptable.

Although the clinical trials did not focus on showing efficacy in those patients, they were included in clinical trials and there is no reason to suspect that underlying diseases such as asthma or other contraindications to beta-blockers could be associated with a different response of this drug in glaucoma patients. In addition, brinzolamide (although used TID in this trial) is superior to placebo when used in addition to timolol.

There are no clinical trials carried out in patients unresponsive to beta blockers. Therefore, there is no knowledge on the expected rate of response in such population. However, in line with the accepted indication for other CA inhibitors the wording of the indication is acceptable.

The doses and dose regimens have been properly defined. The amount of long-term data is limited, but is considered to be sufficient. No studies have been performed in patients with renal and hepatic impairment, and this has been reflected in the SPC. No dosage adjustments are necessary in the elderly. The lack of studies with regard to pharmacodynamic interactions with beta-blockers has been justified.

Safety

No major safety concerns were identified in the pre-clinical studies and clinical trials. The reported adverse events were generally mild to moderate, usually resolved with or without therapy, and generally did not request the discontinuation of trial therapy.

The profile of ocular adverse events of brinzolamide 1% was similar to that of dorzolamide 2%. The percentage of patients with ocular discomfort was higher in the dorzolamide group than in the brinzolamide group, but the percentage of other ocular events was lightly superior in the brinzolamide group. As a consequence, the overall incidence of adverse events was similar in both groups.

The profiles of ocular adverse events of brinzolamide 1% BID and TID were similar.

Timolol produced less ocular adverse events than brinzolamide 1%, but some non-ocular adverse events related to specific effects of beta-blockers occurred. However, adverse event related to digestive tract (dry mouth, nausea, dyspepsia, diarrhoea), nervous system (paresthesia, depression, dizziness, dream abnormality) and special senses (taste perversion) that were described in the brinzolamide group, were not described in the timolol group.

The profile of ocular adverse events of brinzolamide in association to timolol 0.5 % was similar to that of brinzolamide alone. However, some specific adverse events of beta-blockers occurred.

No serious drug related adverse events were reported for brinzolamide 1%. The amount of long-term safety data, although limited, is acceptable.

Benefit/risk assessment

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk ratio of Azopt was favourable in the indication to decrease elevated intraocular pressure in ocular hypertension and open-angle glaucoma as monotherapy in patients unresponsive to beta-blockers or in patients in whom beta-blockers are contra-indicated, or as adjunctive therapy to beta-blockers.