1. NAME OF THE MEDICINAL PRODUCT

Simbrinza 10 mg/ml + / 2 mg/ml eye drops, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of the eye drop suspension contains 10 mg of brinzolamide, and 2 mg brimonidine tartrate corresponding to 1.3 mg of brimonidine.

Excipient(s) with known effect

1 ml of the eye drop suspension contains 0.03 mg of benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, suspension

White-to-off-white uniform suspension, pH 6.5 (approximately).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Simbrinza eye drops, suspension is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension.

4.2 Posology and method of administration

Posology

General target population
Adults
For regions/countries with twice daily dose:
The recommended dose for adults is 1 drop in the affected eye(s) up to 2 times daily.

Missed dose
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.

For regions/countries with three times daily dose:
The recommended dose for adults is 1 drop in the affected eye(s) up to 3 times daily.

Missed dose
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) three times daily. When substituting another ophthalmic

antiglaucoma agent with Simbrinza, the other agent should be discontinued and Simbrinza should be started the following day.

Simbrinza may be used concomitantly with other topical ophthalmic medicinal products to lower intraocular pressure. If more than 1 topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye Ointments should be administered last.

Special populations
Paediatric patients (below 18 years)
Simbrinza is contraindicated in children less than 2 years of age.

Simbrinza is not recommended in children or adolescents aged 2 to 17 years.

Geriatric patients (65 years of age or above)
There are no special precautions to be followed in prescribing Simbrinza for the elderly.

Method of administration

For ocular use.

Patients should be instructed to shake the bottle well before use.

To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye. Patients should be instructed to keep the bottle tightly closed when not in use.

Nasolacrimal occlusion and closing the eyelid for 2 minutes after instillation is recommended. This may result in a decrease in systemic side effects and an increase in local activity.

Patients must be instructed to remove soft contact lenses prior to application of Simbrinza and to wait 15 minutes after instillation of the dose before reinsertion.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients or to sulphonamides.
- Patients receiving monoamine oxidase (MAO) inhibitor therapy.
- Severe renal impairment.
- Hyperchloremic acidosis.
- Neonates and infants younger than 2 years old (see section 4.4).

4.4 Special warnings and precautions for use

Ocular effects
Simbrinza contains brimonidine tartrate which may cause ocular allergic reactions. If allergic reactions are observed, treatment should be discontinued.

Delayed ocular hypersensitivity reactions have been reported with brimonidine tartrate, with some reported to be associated with an increase in IOP.

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). Carbonic anhydrase inhibitors may affect corneal hydration, which may lead to a corneal decompensation and oedema. Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.

Systemic effects

Like other topically applied ophthalmic agents, brinzolamide and brimonidine tartrate are absorbed systemically. Systemic absorption can be minimized by nasolacrimal occlusion (see section 4 Dosage regimen and administration).

Simbrinza contains brinzolamide, a sulphonamide. Hypersensitivity reactions reported with sulphonamide derivatives, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can occur in patients receiving Simbrinza as it is absorbed systemically. At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs of serious reactions or hypersensitivity occur, use of this product should be discontinued immediately.

Cardiac disorders

Simbrinza has a minimal effect on blood pressure of patients in clinical studies, caution should be taken in treating patients with severe cardiovascular disorders due to the brimonidine tartrate component.

Simbrinza should be used with caution in patients with depression, cerebrovascular or coronary insufficiency, Raynaud's disease, orthostatic hypotension or thromboangiitis obliterans due to the brimonidine tartrate component.

Acid/base disturbances

Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. Simbrinza should be used with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis.

Hepatic impairment

Simbrinza has not been studied in patients with hepatic impairment; caution should be exercised in treating such patients.

Paediatric population

Simbrinza is not recommended in children or adolescents aged 2 to 17 years because of the potential for CNS depression due to the brimonidine tartrate component (see section 10 Overdosage).
Simbrinza is contraindicated in children under 2 years of age (see section 4.3 Contraindications).

Contact lenses

Benzalkonium chloride may cause eye irritation and is known to discolour soft contact lenses. Patients must be instructed to remove contact lenses prior to application of Simbrinza and to wait at least 15 minutes before reinsertion.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions are expected with Simbrinza due to potential drug interactions with the mono-components: Simbrinza is contraindicated in patients receiving monoamine oxidase inhibitors (see section 4.3 Contraindications).

Brinzolamide is 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 (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates) must be considered in patients receiving Simbrinza.

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and topical brinzolamide. The concomitant administration of Simbrinza and oral carbonic anhydrase inhibitors is not recommended.

Alpha agonists, as a class, may reduce pulse and blood pressure. Caution is advised with concomitant use of drugs such as antihypertensive and/or cardiac glycosides with similar cardiovascular effects (drugs that cause hypotension).

Caution is advised in patients taking tricyclic antidepressants as these agents may blunt the hypotensive response. No data on the level of circulating catecholamines after Simbrinza administration are available. Caution, however, is advised in patients taking medicinal products which can affect the metabolism and uptake of circulating amines (e.g. chlorpromazine, methylphenidate, reserpine).

The possibility of an additive or potentiating effect with CNS depressants (e.g., alcohol, barbiturates, opiates, sedatives or anaesthetics) should be considered.

Caution is advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of pharmaceutical form) which may interact with α-adrenergic agonists or interfere with their activity i.e. agonists or antagonists of the adrenergic receptor (e.g. isoprenaline, prazosin).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well controlled studies in pregnant women regarding the ocular use of Simbrinza. Brinzolamide and brimonidine were not teratogenic in rats and rabbits following systemic administration.

In reproductive toxicity studies, brinzolamide administered orally to rats during organogenesis induced foetal toxicity at 375 times the maximum recommended ophthalmic human dose (MROHD) based on body weight (BW). In rabbits, no foetal toxicity was observed following oral brinzolamide administration during organogenesis at 125 times the MROHD based on BW (see Animal data). Oral administration of brimonidine to rats and rabbits during organogenesis showed no evidence of teratogenicity and embryo toxicity at 107- and 27- times, respectively, the MRHOD based on plasma concentrations (see Animal data).

Simbrinza, should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the foetus.

Animal data
Brinzolamide
Embryofoetal development studies were conducted in pregnant rats administered 0, 2, 6 or 18 mg/kg/day of brinzolamide by oral gavage on gestation days 6 to 17 to target the period of organogenesis. Decreased maternal weight gain was observed at 6 and 18 mg/kg/day. Decreased

foetal body weight and reduced skeletal ossification were observed at 18 mg/kg/day (375 times the MROHD based on BW and 60 times the MROHD based on Body Surface Area (BSA)). The No-Observed effect level (NOEL) was 2 mg/kg/day (42 times the MROHD based on BW and 7 times the MROHD based on BSA).

Embryofoetal development studies were conducted in pregnant rabbits administered 0, 1, 3, or 6 mg/kg/day of brinzolamide by oral gavage on gestation days 6 to 18 to target the period of organogenesis. Maternal weight loss during pregnancy was observed at ≥ 3 mg/kg/day (63 times the MROHD based on BW and 20 times the MROHD based on BSA). At 6 mg/kg/day, mortality, emaciation, lack of faeces and abortions were noted in does. The NOEL for maternal toxicity was 1 mg/kg/day (21 times the MROHD based on BW and 7 times the MROHD based on BSA). No treatment-related foetal effects were observed up to the maximum tested dose of 6 mg/kg/day (125 times the MROHD based on BW and 41 times the MROHD based on BSA).

In a rat peri and postnatal development study, brinzolamide was orally administered at doses of 1, 5 and 15 mg/kg/day from gestation day 16 through lactation day 20. Decreases in food consumption and mean body weight gain was seen in the dams during gestation and lactation at 15 mg/kg/day. Decreased pup body weight was observed at 15 mg/kg/day (313 times the MROHD based on BW and 51 times the MROHD based on BSA). No indications of impaired behaviour, fertility or reproductive capabilities were observed in the F1 generation. F2 growth and development appeared normal throughout lactation. The NOEL for maternal and developmental toxicity was 5 mg/kg/day (104 times the MROHD based on BW and 17 times the MROHD based on BSA).

Following oral administration of 1 mg/kg 14C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and the levels of radioactivity in foetal tissues were 3- to 10 fold less than those measured in the dams.

Brimonidine
In embryofoetal development studies, pregnant rats were orally administered brimonidine at doses of 0.066, 0.66 or 1.650 mg base/kg/day on gestation days 6 to 15 to target the period of organogenesis. No evidence of teratogenicity or embryo lethality were observed. Reduction in body weight of dams at 0.66 and 1.65 mg base/kg/day and of pups (F1) at 1.65 mg base/kg/day were observed. Oral doses of 0.66 mg base/kg/day revealed no evidence of harm to the foetus corresponding to 107-times the maximal plasma concentrations (Cmax) in humans treated with one drop of Simbrinza in both eyes three times daily.

In embryofoetal development studies, pregnant rabbits were orally administered brimonidine at doses of 0.165, 0.660 and 3.330 mg base/kg/day on gestation days 6 to 18 to targeting the period of organogenesis. No evidence of treatment-related embryotoxicity, foetal toxicity, or teratogenicity were observed up to the highest tested dose of 3.3 mg base/kg/day, corresponding to 27-times the Cmax in humans treated with one drop of Simbrinza in both eyes three times daily.

In a peri- and postnatal development study, brimonidine was administered orally to pregnant rats from gestation day 16 through lactation day 20. Reproductive capabilities (survival, development, and behaviour) of F1 and F2 generations were not affected. The dose of brimonidine (0.66 mg/kg/day) was estimated to achieve area under the curve (AUC) values that correspond to 60-fold the estimated AUC in humans treated with one drop of brimonidine in both eyes three times daily.

After a single oral dose of 0.25 mg/kg 14C-brimonidine in pregnant rats, radioactivity was found to cross the placenta and entered into the foetal circulation to a limited extent, producing 14C-brimonidine concentrations in foetal blood that were 10-27% of that in maternal blood.

Breast-feeding

There are no data regarding the effects of brinzolamide or brimonidine tartrate on milk production of breast-feeding women or on the breastfed infant.

It is not known whether brinzolamide or brimonidine is transferred into human milk following topical ocular administration of Simbrinza. Brinzolamide and brimonidine have been detected in the milk of lactating rats following oral administration of brinzolamide and brimonidine respectively in two different studies (see Animal data).

A risk to the breastfed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Animal data
Brinzolamide
Following oral administration of 1 mg/kg 14C-brinzolamide (21 times the MROHD) to lactating rats, radioactivity was found in milk at concentrations below those found in the rat blood and plasma.

Brimonidine
Following oral administration of 0.25 mg/kg 14C-brimonidine (26 times the MROHD) to lactating rats, radioactivity was detected in milk at concentrations similar or higher than in the rat maternal plasma.

Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of Simbrinza on human fertility. In rats, no effects on fertility were noted with brinzolamide (up to 375 times the MROHD based on BW) and brimonidine (up to 60-times the human AUC) (see section 5.3 Non-clinical safety data). No effects on male or female fertility are anticipated from the topical ocular use of Simbrinza.

4.7 Effects on ability to drive and use machines

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient must wait until the vision clears before driving or using machinery.

Simbrinza may cause fatigue and somnolence in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

4.8 Undesirable effects

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10);

common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-1 Percentage of patients with adverse drug reactions in clinical trials

System organ classification	Adverse drug reaction	Frequency category
Nervous system disorders	somnolence, dysgeusia	Common
	dizziness, headache	Uncommon
Eye disorders	conjunctivitis, conjunctivitis allergic, eye allergy, vision blurred, eye pain, eye irritation, dry eye, eye pruritus, ocular hyperemia blepharitis, ocular discomfort	Common
	corneal erosion, keratitis, punctate keratitis, blepharitis allergic, conjunctival follicle, photophobia, eye discharge, lacrimation increased, asthenopia, erythema of eyelid	Uncommon
	visual acuity reduced, lacrimation decreased	Rare
Ear and labyrinth disorders	vertigo	Uncommon
Vascular disorders	hypotension, blood pressure decreased	Uncommon
Respiratory, thoracic and mediastinal disorders	nasal dryness	Uncommon
	upper-airway cough syndrome, nasal congestion, dry throat	Rare
Gastrointestinal disorders	dry mouth	Common
	nausea, dyspepsia, abdominal discomfort	Rare
Skin and subcutaneous tissue disorders	dermatitis allergic	Uncommon
General disorders and administration site conditions	asthenia, fatigue, medication residue present	Uncommon

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Simbrinza via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 7-2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

System organ classification	Adverse drug reaction
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

In case of accidental ingestion, effects of brinzolamide toxicity may include electrolyte imbalance, development of an acidotic state, and possible nervous system effects. Serum electrolyte levels (particularly potassium) and blood pH levels must be monitored.

Oral overdoses of other alpha-2-agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression and seizure.

Treatment of an overdose includes supportive and symptomatic therapy. The patient's airway should be maintained.

Paediatric population
Serious adverse effects following inadvertent ingestion with the brimonidine tartrate component of Simbrinza by paediatric subjects have been reported. The subjects experienced symptoms of CNS depression, typically temporary coma or low level of consciousness, lethargy, somnolence, hypotonia, bradycardia, hypothermia, pallor, respiratory depression and apnoea, and required admission to intensive care with intubation if indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparation and miotics, ATC code: S01EC54.

Mechanism of action

Simbrinza is comprised of 2 components: brinzolamide (carbonic anhydrase inhibitor) and brimonidine tartrate (alpha-2 adrenergic receptor agonist). Each of these 2 components decreases elevated IOP by different mechanisms of action.

Brinzolamide is a topical ocular carbonic anhydrase inhibitor (CAI). Carbonic anhydrase is an enzyme found in many tissues of the body including the eye. CAIs inhibit carbonic anhydrase, mainly isozyme II, in the ciliary epithelium and reduce the production of bicarbonate ion, which is a critical component for active ion transport in aqueous formation. A reduction in bicarbonate ion by CAIs diminishes sodium and fluid transport across the ciliary epithelium and decreases aqueous humor production. Brinzolamide has a peak ocular hypotensive effect occurring at 2 to 3 hours post dose. Brimonidine, a selective alpha-2 adrenergic agonist, selectively activates the alpha-2 adrenergic receptor of the ciliary epithelium. Activation of this receptor activates the inhibitory GTP-binding protein, which then inhibits the enzyme adenylyl cyclase. This leads to a reduction in intracellular cyclic AMP levels and eventually suppresses aqueous humor production. It has been demonstrated that brimonidine also stimulates uveoscleral outflow. Initial administration of brimonidine reduces aqueous humor production. However, increase in uveoscleral outflow becomes the predominant effect with chronic administration.

Brimonidine tartrate has a peak ocular hypotensive effect occurring at 2 hours post dose.

The combination of brinzolamide/ brimonidine results in a reduction in IOP, a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.

Pharmacodynamic effects

Clinical efficacy and safety

Data from twice daily studies

Monotherapy

In a 6-month, controlled, contribution of elements clinical study enrolling 560 patients with open-angle glaucoma (including pseudoexfoliation or pigment dispersion component) and/or ocular hypertension who, in the investigator's opinion, were insufficiently controlled on monotherapy or already on multiple IOP-lowering medicinal products, and who had mean baseline diurnal IOP of 26 mmHg, the mean diurnal IOP-lowering effect of Simbrinza dosed twice daily was approximately 8 mmHg. Statistically superior reductions in the mean diurnal IOP were observed with Simbrinza compared to brinzolamide 10 mg/mL or brimonidine 2 mg/mL dosed twice daily at all visits throughout the study. Mean IOP reductions from baseline at each time point at each visit were greater with Simbrinza (6 to 9 mmHg) than monotherapy with either brinzolamide (5 to 7 mmHg) or brimonidine (4 to 7 mmHg). Mean percent IOP reductions from baseline with Simbrinza ranged from 23 to 34%. The percentages of patients with an IOP measurement less than 18 mmHg were greater in the Simbrinza group than in the brinzolamide group at 11 of 12 assessments through Month 6 and were greater in the Simbrinza group than in the brimonidine group at all 12 assessments through Month 6. At the + 2 h time point (the time corresponding to the morning efficacy peak) for the primary efficacy visit at Month 3, the percentage of patients with an IOP less than 18 mmHg was 68.8% in the Simbrinza group, 42.3% in the brinzolamide group, and 44.0% in the brimonidine group.
In a 6-month, controlled, non-inferiority clinical study enrolling 890 patients with open-angle glaucoma (including pseudoexfoliation or pigment dispersion component) and/or ocular hypertension who, in the investigator's opinion, were insufficiently controlled on monotherapy or already on multiple IOP-lowering medicinal products, and who had mean baseline diurnal IOP of 26 to 27 mmHg, non-inferiority of Simbrinza compared to brinzolamide 10 mg/mL + brimonidine 2 mg/mL dosed concomitantly was demonstrated at all visits throughout the study with respect to mean diurnal IOP reduction from baseline. Mean IOP reductions from baseline at each time point at each visit with Simbrinza or the individual components administered concomitantly were similar (7 to 10 mmHg). Mean percent IOP reductions from baseline with Simbrinza ranged from 25 to 37%.The percentages of patients with an IOP measurement less than 18 mmHg were similar across study visits for the same time point through Month 6 in the Simbrinza and brinzolamide + brimonidine groups. At the + 2 h time point (the time corresponding to the morning efficacy peak) for the primary efficacy visit at Month 3, the percentage of patients with an IOP less than 18 mmHg was 71.6% in both study groups.

Adjunct therapy

Clinical data on the use of Simbrinza adjunctive to prostaglandin analogs (PGA) also showed superior IOP-lowering efficacy of Simbrinza + PGA compared with the PGA alone. In study CQVJ499A2401, Simbrinza + PGA (i.e., travoprost, latanoprost, or bimatoprost) demonstrated superior IOP-lowering efficacy from baseline compared to Vehicle + PGA after 6 weeks of treatment, with between-treatment difference in model adjusted mean change from baseline in diurnal IOP of -3.44 mmHg (95% CI, -4.2, -2.7; p-value <0.001).
Clinical data on the use of Simbrinza adjunctive to travoprost-timolol maleate fixed dose combination eye drops, solution also showed superior IOP-lowering efficacy of Simbrinza+ travoprost-timolol maleate eye drops compared with the travoprost-timolol maleate alone. In study CQVJ499A2402,

Simbrinza + travoprost-timolol maleate eye drops demonstrated superior IOP-lowering efficacy from baseline compared to Vehicle + travoprost-timolol maleate eye drops after 6 weeks of treatment, with between-treatment difference in model adjusted mean change from baseline in diurnal IOP of -2.15 mmHg (95% CI, -2.8, -1.5; p-value <0.001).
The safety profile of Simbrinza in adjunct therapy was similar to that observed with Simbrinza monotherapy.

Data from three times daily studies
Monotherapy
Two clinical trials of 3 months duration were conducted in patients with open-angle glaucoma or ocular hypertension to compare the IOP-lowering effect of Simbrinza dosed three times daily to individually administered 1% brinzolamide three times daily and 0.2% brimonidine tartrate three times daily (TID).
The IOP-lowering effect of Simbrinza ophthalmic suspension was 1 to 3 mmHg greater than monotherapy with either 1% brinzolamide or 0.2% brimonidine tartrate throughout the duration of the trials.

Adjunct therapy
Clinical data on the use of Simbrinza adjunctive to PGA also showed superior IOP-lowering efficacy of Simbrinza + PGA compared with the PGA alone. In study M-13-019, Simbrinza + travoprost ophthalmic solution, 0.004% (adjunctive therapy to PGA) was superior to Vehicle + travoprost ophthalmic solution, 0.004% (PGA monotherapy) in lowering diurnal IOP at Week 6. The mean diurnal IOP was significantly less (p <0.0001) in patients treated with Simbrinza + travoprost ophthalmic solution, 0.004% than in patients treated with Vehicle + travoprost ophthalmic solution, 0.004% (LS mean diurnal IOP of 17.55 and 20.71 mmHg, respectively). The treatment group difference based upon LS means was -3.16 mmHg (CI = -4.16 to -2.27) in favour of Simbrinza + travoprost. In study M-13 020, Simbrinza + PGA (adjunctive therapy) was also superior to Vehicle + PGA (PGA monotherapy) in regard to mean diurnal IOP at Week 6. The mean diurnal IOP was significantly less (p <0.0001) in patients treated with Simbrinza + PGA than in patients treated with Vehicle + PGA (LS mean diurnal IOP of 17.07 and 20.51 mmHg, respectively). The treatment group difference based upon LS means was 3.44 mmHg (CI = -4.45 to -2.42) in favour of Simbrinza + PGA.
The safety profile of Simbrinza in adjunct therapy was similar to that observed with Simbrinza monotherapy.

5.2 Pharmacokinetic properties

Absorption

Brinzolamide is absorbed through the cornea following topical ocular administration. The drug is also absorbed into the systemic circulation where it binds strongly to carbonic anhydrase in red blood cells (RBCs). Plasma drug concentrations are low. Whole blood elimination half-life is prolonged (>100 days) in humans due to RBC carbonic anhydrase binding, resulting in significant accumulation of brinzolamide in the blood.

Plasma brimonidine concentrations achieve peak levels within 0.5 to 2.5 hours and decline with a systemic half-life of approximately 2 hours.

In a topical ocular clinical study comparing the systemic pharmacokinetics of brinzolamide/ brimonidine Eye Drops, suspension to brinzolamide and brimonidine administered individually, the

steady-state whole blood brinzolamide and N-desethylbrinzolamide pharmacokinetics were similar between the combination product and brinzolamide administered alone. Likewise, the steady-state plasma pharmacokinetics of brimonidine from the combination was similar to that observed for brimonidine administered alone.

Distribution

Studies in rabbits showed that during a course of topical ocular twice daily administration, brinzolamide significantly accumulates in the iris-ciliary body (ICB), choroid, and especially retina, while brimonidine significantly accumulates in choroid, retina and especially the ICB. Data in pigmented rabbits topically administered radiolabelled brinzolamide showed highest ocular radioactivity levels in the ICB with maximum aqueous humor and choroid levels about 6-fold lower than those in the ICB. Peak retinal exposure was about 11-fold lower than that of the ICB.

Circulating brinzolamide is primarily bound to RBCs while the much lower concentrations in human plasma are about 60% protein-bound.

Accumulation of brimonidine in the iris, ciliary body, and choroid/retina was reported in cynomolgus monkeys when 0.5% brimonidine was administrated twice daily topically in the eye. A similar trend was seen in pigmented rabbits, where extensive accumulation and prolonged retention were observed in iris-ciliary body and choroid. These phenomena are presumably due to the known melanin-binding properties of brimonidine.

Biotransformation/metabolism

Brinzolamide is metabolized by hepatic cytochrome P450 isozymes, specifically CYP3A4, CYP2A6, CYP2B6, CYP2C8 and CYP2C9. The primary metabolite is N-desethyl-brinzolamide followed by the N-desmethoxypropyl and O-desmethyl metabolites as well as an N-propionic acid analog formed by oxidation of the N-propyl side chain of O-desmethyl brinzolamide. Brinzolamide and N-desethylbrinzolamide do not inhibit cytochrome P450 isozymes at concentrations at least 100-fold above maximum systemic levels.
In humans, brimonidine is primarily metabolized by the liver, most likely by cytochrome P450 and aldehyde oxidase. The principle metabolic pathways of brimonidine are alpha(N)-oxidation to 2-oxobrimonidine, 3-oxobrimonidine and 2,3-dioxobrimonidine and oxidative cleavage of the imadazoline ring to yield 5-bromo-6-guanidinoquinoxaline.

Elimination

Brinzolamide is primarily eliminated in urine as unchanged drug. In humans, urinary brinzolamide and N-desethylbrinzolamide accounted for about 60% and 6% of the dose, respectively. Data in rats showed some biliary excretion (about 20%), primarily as metabolites.

In humans, brimonidine tartrate is eliminated rapidly via extensive systemic metabolism; there is no marked systemic accumulation after multiple dosing. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87% of an orally administered radioactive dose was eliminated within 120 hours, with 74% found in the urine in the first 96 hours.

Linearity/non-linearity

Due to its tight and saturable binding to carbonic anhydrase in RBCs and various tissues, the pharmacokinetics of brinzolamide are inherently non-linear. In contrast, brimonidine kinetics are

linear as evidenced by aqueous humor data from cataract patients showing a dose- proportional increase in ocular exposure with increasing topical dose.

Pharmacokinetic/pharmacodynamic relationship(s)

Although brinzolamide has prolonged retention in the ICB and other tissues containing carbonic anhydrase with half-lives >30 days in the ICB of both pigmented and albino rabbits, its IOP-lowering effect is considerably shorter (about 12 hours). This is due to the fact that >99% of carbonic anhydrase must be bound to drug for the pharmacological effects to be observed.

Increased IOP-lowering efficacy with increasing brimonidine dose was demonstrated following administration after single topical administrations of 0.08, 0.2 or 0.5% brimonidine solution to patients with glaucoma or ocular hypertension, with mean IOP reductions from baseline ranging from 16.1 to 30.1% across the dose range.

5.3 Preclinical safety data

Non-clinical data for brinzolamide or brimonidine revealed no special hazard for humans based on single-dose toxicity, repeated-dose toxicity, genotoxicity, and carcinogenicity studies and topical ocular irritation studies. For information on reproductive and developmental toxicity, see section 4.6.

Brinzolamide
In a rat fertility study, oral administration of brinzolamide did not reveal any adverse effects on the fertility or reproductive capacity of males or females at doses up to 18 mg/kg/day (up to 375 times the MROHD based on BW and 60 times the MROHD based on BSA).

Brimonidine
In reproductive studies performed in rats with oral doses of 0.66 mg brimonidine base/kg/day (corresponding to 60-times the human AUC, following administration of one drop of 0.15% brimonidine to both eyes three times daily), fertility was not impaired.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Propylene glycol
Carbomer 974P
Boric acid
Mannitol, sodium chloride
Tyloxapol
Sodium hydroxide and/or hydrochloric acid
Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

4 weeks after first opening.

6.4 Special precautions for storage

Do not store above 30°C.
Keep out of the reach and sight of children.

6.5 Nature and contents of container

8 ml round, opaque, low-density polyethylene (LDPE) bottles with a LDPE dropper tip and white polypropylene screw cap containing 5 ml suspension.
Carton containing 1 or 3 bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

NVS Kenya Limited
27th Floor Britam Towers,
Upper Hill,
Box 46057 00100 GPO Nairobi, Kenya

Manufacturer
Alcon-Couvreur N.V.
Rijksweg 14
B-2870 Puurs
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Prescription only medication.
Rwanda: FDA-HMP-MA-1478

9. DATE OF FIRST AUTHORISATION

Rwanda: 20 July 2024

12. DATE OF REVISION OF THE TEXT

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