ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SIMBRINZA 10 mg/mL + 2 mg/mL eye drops, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of suspension contains 10 mg of brinzolamide and 2 mg of brimonidine tartrate equivalent to 1.3 mg of brimonidine.

Excipient(s) with known effect:
Each mL of suspension contains 0.03 mg of benzalkonium chloride.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Decrease of elevated intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction(see section 5.1).

4.2 Posology and method of administration

Posology

Use in adults, including the elderly
The recommended dose is one drop of SIMBRINZA in the affected eye(s) two times daily.

Hepatic and/or renal impairment
SIMBRINZA has not been studied in patients with hepatic impairment and caution is therefore recommended in this population (see section 4.4).

SIMBRINZA has not been studied in patients with severe renal impairment (CrCl < 30 mL/min) or in patients with hyperchloraemic acidosis. Since the brinzolamide component of SIMBRINZA and its metabolite are excreted predominantly by the kidney, SIMBRINZA is contraindicated in such patients (see sections 4.3).

Paediatric population
The safety and efficacy of SIMBRINZA in children and adolescents aged 2 to 17 years has not been established. No data are available. SIMBRINZA is not recommended in children or adolescents (see section 4.4).

SIMBRINZA must not be used in neonates and infants aged less than 2 years because of safety concerns (see section 4.3).

Method of administration
For ocular use.

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

When using nasolacrimal occlusion and closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity (see section 4.4).

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

SIMBRINZA may be used concomitantly with other topical ophthalmic medicinal products to lower intraocular pressure. If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart.

If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed 1 drop in the affected eye(s) 2 times daily.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 or to sulphonamides (see section 4.4).
Patients receiving monoamine oxidase (MAO) inhibitor therapy (see section 4.5)
Patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin) (see section 4.5)
Patients with severe renal impairment (see section 4.4)
Patients with hyperchloraemic acidosis
Neonates and infants under the age of 2 years (see section 4.4)

4.4 Special warnings and precautions for use

The medicinal product should not be injected. Patients should be instructed not to swallow SIMBRINZA.

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

The possible role of brinzolamide on corneal endothelial function has not been investigated in patients with compromised corneas (particularly in patients with low endothelial cell count). Specifically, patients wearing contact lenses have not been studied and careful monitoring of these patients when using brinzolamide is recommended, since carbonic anhydrase inhibitors may affect corneal hydration and wearing contact lenses might increase the risk for the cornea. Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended. SIMBRINZA may be used while wearing contact lenses with careful monitoring (see below under 'Benzalkonium chloride').

Brimonidine tartrate 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 potential effects following cessation of treatment with SIMBRINZA have not been studied. While the duration of IOP-lowering effect for SIMBRINZA has not been studied, the IOP-lowering effect of brinzolamide is expected to last for 5-7 days. The IOP-lowering effect of brimonidine may be longer.

Systemic effects
SIMBRINZA contains brinzolamide, a sulphonamide inhibitor of carbonic anhydrase and, although administered topically, is absorbed systemically. The same types of adverse reactions that are attributable to sulphonamides may occur with topical administration. If signs of serious reactions or hypersensitivity occur, the use of this medicinal product should be discontinued.

Cardiac disorders

Following administration of SIMBRINZA, small decreases in blood pressure were observed in some patients. Caution is advised when using medicinal products such as antihypertensives and/or cardiac glycosides concomitantly with SIMBRINZA or in patients with severe or unstable and uncontrolled cardiovascular disease (see section 4.5)

SIMBRINZA should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

Acid/base disturbances
Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. SIMBRINZA contains brinzolamide, an inhibitor of carbonic anhydrase, and although administered topically, is absorbed systemically. The same types of adverse reactions that are attributable to oral carbonic inhibitors (i.e., acid-base disturbances) may occur with topical administration (see section 4.5).

Use with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis. SIMBRINZA is contraindicated in patients with severe renal impairment (see section 4.3).

Hepatic impairment
SIMBRINZA has not been studied in patients with hepatic impairment; caution should be used in treating such patients (see section 4.2).

Mental alertness
Oral carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination in elderly patients. SIMBRINZA is absorbed systemically and therefore this may occur with topical administration (see section 4.7).

Benzalkonium chloride
SIMBRINZA contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses should be avoided. Patients must be instructed to remove contact lens prior to application of SIMBRINZA and wait at least 15 minutes before reinsertion.

Benzalkonium chloride has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent or prolonged use.

Paediatric population
The safety and efficacy of SIMBRINZA in children and adolescents aged 2 to 17 years has not been established. Symptoms of brimonidine overdose (including loss of consciousness, hypotension, hypotonia, bradycardia, hypothermia, cyanosis and apnoea) have been reported in neonates and infants receiving brimonidine eye drops as part of medical treatment of congenital glaucoma. SIMBRINZA is therefore contraindicated in children below 2 years of age (see section 4.3).

Treatment of children 2 years and above (especially in those in the 2-7 age range and/or weighing < 20 kg) is not recommended because of the potential for central nervous system-related side effects (see section 4.9).

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with SIMBRINZA.

SIMBRINZA is contraindicated in patients receiving monoamine oxidase inhibitors and patients on antidepressants which affect noradrenagic transmission (e.g. tricyclic antidepressants and mianserin), (see section 4.3). Tricyclic antidepressants may blunt the ocular hypotensive response of SIMBRINZA.

Caution is advised due to the possibility of an additive or potentiating effect with CNS depressants (e.g. alcohol, barbiturates, opiates, sedatives, or anaesthetics).

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, serotonin-norepinephrine reuptake inhibitors).

Alpha adrenergic agonists (e.g., brimonidine tartrate), as a class, may reduce pulse and blood pressure. Following administration of SIMBRINZA, small decreases in blood pressure were observed in some patients. Caution is advised when using medicinal products such as antihypertensives and/or cardiac glycosides concomitantly with SIMBRINZA.

Caution is advised when initiating (or changing the dose of) a concomitant systemic medicinal products (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).

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 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of SIMBRINZA in pregnant women. Brinzolamide was teratogenic in rats, but not rabbits, following systemic administration. Animal studies with oral brimonidine do not indicate direct harmful effects with respect to reproductive toxicity. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. SIMBRINZA is not recommended during pregnancy and in women of child bearing potential not using contraception.

Breast-feeding
It is unknown whether topical SIMBRINZA is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown that following oral administration, minimal levels of brinzolamide are excreted in breast milk. Brimonidine administered orally is excreted in breast milk. SIMBRINZA should not be used by women nursing infants.

Fertility
Nonclinical data do not show any effects of brinzolamide or brimonidine on fertility. There are no data on the effect of topical ocular administration of SIMBRINZA on human fertility.

4.7 Effects on ability to drive and use machines

SIMBRINZA has a moderate influence on the ability to drive and use machines.

SIMBRINZA may cause dizziness, fatigue and/or drowsiness, which may impair the ability to drive or use machines.

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

Oral carbonic anhydrase inhibitors may impair the ability of elderly patients to perform tasks requiring mental alertness and/or physical coordination (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

In clinical trials involving SIMBRINZA dosed twice-daily the most common adverse reactions were ocular hyperaemia and ocular allergic type reactions occurring in approximately 6-7% of patients, and dysgeusia (bitter or unusual taste in the mouth following instillation) occurring in approximately 3% of patients. The safety profile of SIMBRINZA was similar to that of the individual components (brinzolamide 10 mg/mL and brimonidine 2 mg/mL).

Tabulated summary of adverse reactions

The following adverse reactions have been reported during clinical studies with SIMBRINZA twice-daily dosing and during clinical studies and post-marketing surveillance with the individual components brinzolamide and brimonidine. They are classified according to the subsequent convention: 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) and very rare (<1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	**Adverse reactions**
Infections and infestations	Uncommon: nasopharyngitis[2], pharyngitis[2], sinusitus[2] Not known: rhinitis[2]
Blood and lymphatic system disorders	Uncommon: red blood cell decreased[2], blood chloride increased[2]
Immune system disorders	Uncommon: hypersensitivity[3]
Psychiatric disorders	Uncommon: apathy[2], depression[2,3], depressed mood[2], insomnia[1], libido decreased[2], nightmare[2], nervousness[2]
Nervous system disorders	Common: somnolence[1], dizziness[3], dysgeusia[1] Uncommon: headache[1], motor dysfunction[2], amnesia[2], memory impairment[2], paraesthesia[2] Very rare: syncope[3] Not known: tremor[2], hypoaesthesia[2], ageusia[2]
Eye disorders	Common: eye allergy[1], keratitis[1], eye pain[1], ocular discomfort[1], blurred vision[1], abnormal vision[3], ocular hyperaemia[1], conjunctival blanching[3] Uncommon: corneal erosion[1], corneal oedema[2], blepharitis[1], corneal deposits (keratic precipitates) [1], conjunctival disorder (papillae) [1], photophobia[1], photopsia[2], eye swelling[2], eyelid oedema[1], conjunctival oedema[1], dry eye[1], eye discharge[1], visual acuity reduced[2], lacrimation increased[1], pterygium[2], erythema of eyelid[1], meibomianitis[2], diplopia[2], glare[2], hypoaesthsia eye[2], scleral pigmentation[2], subconjunctival cyst[2],abnormal sensation in eye[1], asthenopia[1] Very rare: uveitis[3], miosis[3] Not known: visual disturbances[2], madarosis[2]
Ear and labyrinth disorders	Uncommon: vertigo[1], tinitus[2]
Cardiac disorders	Uncommon: cardio-respiratory distress[2], angina pectoris[2], arrhythmia[3], palpitations[2,3], heart rate irregular[2], bradycardia[2,3], tachycardia[3]
Vascular disorders	Uncommon: hypotension[1] Very rare: hypertension[3]
Respiratory, thoracic and mediastinal disorders	Uncommon: dyspnoea[2], bronchial hyperactivity[2], pharyngolaryngeal pain[2], dry throat[1], cough[2], epistaxis[2], upper

System Organ Classification	Adverse reactions
	respiratory tract congestion[2], nasal congestion[1], rhinorrhea[2], throat irritation[2], nasal dryness[1], postnasal drip[1], sneezing[2] Not known: asthma[2]
Gastrointestinal disorders	Common: dry mouth[1] Uncommon: dyspepsia[1], oesophagitis[2], abdominal discomfort[1], , diarrhoea[2], vomiting[2], nausea[2], frequent bowel movements[2], flatulence[2], hypoaesthesia oral[2], paraesthesia oral[1]
Hepatobiliary disorders	Not known: liver function test abnormal[2]
Skin and subcutaneous tissue disorders	Uncommon: dermatitis contact[1], urticaria[2], rash[2], rash maculo-papular[2], pruritus generalized[2], alopecia[2], skin tightness[2] Not known: face oedema[3], dermatitis[2,3], erythema[2,3]
Musculoskeletal and connective tissue disorders	Uncommon: back pain[2], muscle spasms[2], myalgia[2] Not known: arthralgia[2], pain in extremity[2]
Renal and urinary disorders	Uncommon: renal pain[2] Not known: pollakiuria[2]
Reproductive system and breast disorders	Uncommon: erectile dysfunction[2]
General disorders and administration site conditions	Uncommon: pain[2], chest discomfort[2], feeling abnormal[2], feeling jittery[2], irritability[2], medication residue[1] Not known: chest pain[2], peripheral oedema[2,3]

[1] adverse reaction observed with Simbrinza
[2] additional adverse reaction observed with brinzolamide monotherapy
[3] additional adverse reaction observed with brimonidine monotherapy

Description of selected adverse reactions
Dysgeusia was the most common systemic adverse reaction associated with the use of SIMBRINZA (3.4%). It is likely to be caused by passage of the eye drops in the nasopharynx via the nasolacrimal canal and is mainly attributable to brinzolamide component of SIMBRINZA. Nasolacrimal occlusion or gently closing the eyelid after instillation may help reduce the occurrence of this effect (see section 4.2).

SIMBRINZA contains brinzolamide which is a sulphonamide inhibitor of carbonic anhydrase with systemic absorption. Gastrointestinal, nervous system, haematological, renal and metabolic effects are generally associated with systemic carbonic anhydrase inhibitors. The same type of adverse reactions attributable to oral carbonic anhydrase inhibitors may occur with topical administration.

Adverse reactions commonly associated with the brimonidine component of SIMBRINZA include the development of ocular allergic type reactions, fatigue and/or drowsiness, and dry mouth. The use of brimonidine has been associated with minimal decreases in blood pressure. Some patients who dosed with SIMBRINZA experienced decreases in blood pressure similar to those observed with the use of brimonidine as monotherapy.

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 via the national reporting system listed in Appendix V.

4.9 Overdose

If overdose with SIMBRINZA occurs treatment should be symptomatic and supportive. The patient's airway should be maintained.

Due to the brinzolamide component of SIMBRINZA, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels must be monitored.

There is very limited information regarding accidental ingestion with the brimonidine component of SIMBRINZA in adults. The only adverse event reported to date was hypotension. It was reported that the hypotensive episode was followed by rebound hypertension.

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.

Paediatric population
Serious adverse effects following inadvertent ingestion with the brimonidine 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. All subjects were reported to have made a full recovery, usually within 6-24 hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned ATC code: not yet assigned

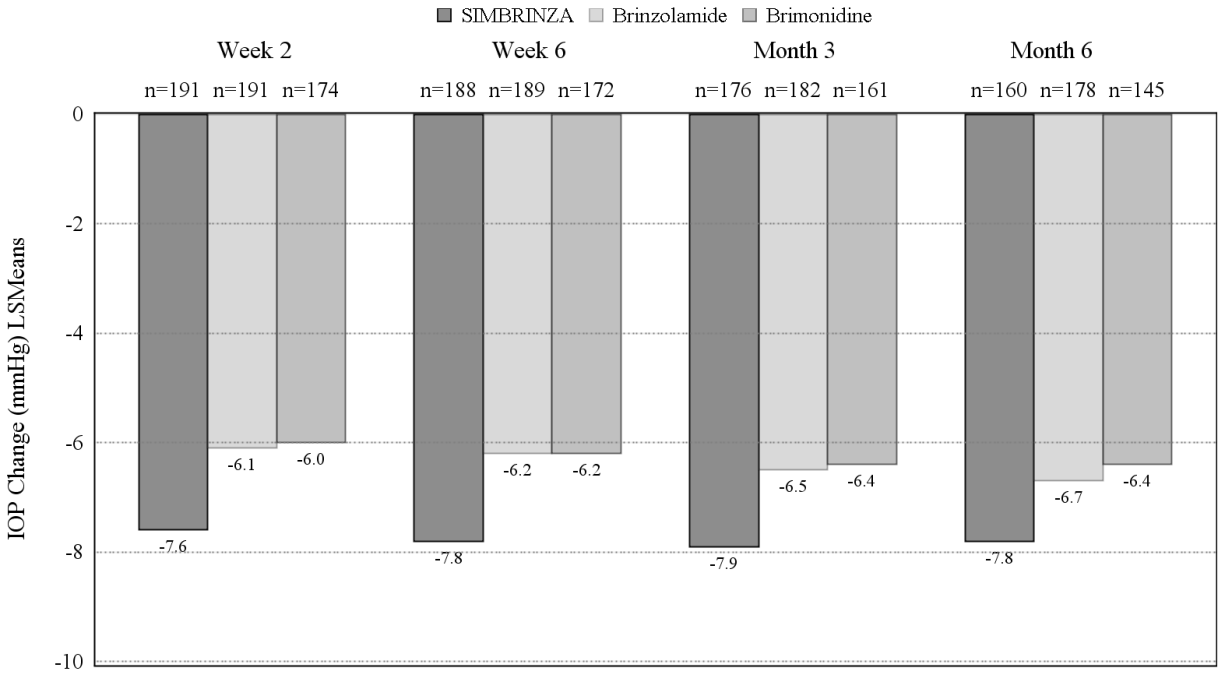
Mechanism of action
SIMBRINZA contains two active substances: brinzolamide and brimonidine tartrate. These two components lower intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) and ocular hypertension (OHT) by suppressing the formation of aqueous humour from the ciliary process in the eye. Although both brinzolamide and brimonidine lower IOP by suppressing aqueous humour formation, their mechanisms of action are different.

Brinzolamide acts by inhibiting the enzyme carbonic anhydrase (CA-II) in the ciliary epithelium that reduces the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport across the ciliary epithelium, resulting in decreased aqueous humour formation. Brimonidine, an alpha-2 adrenergic agonist, inhibits the enzyme adenylate cyclase and suppresses the cAMP-dependent formation of aqueous humour. Additionally, administration of brimonidine results in an increase in uveoscleral outflow.

Pharmacodynamic effects

Clinical efficacy and safety
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 (Figure 1).

Figure 1. Mean[a] Diurnal (9 AM, +2 Hrs, +7 Hrs) IOP Change from Baseline (mmHg)—Contribution of Elements Study



[a]Least squares means derived from a statistical model that accounts for study site, 9 AM baseline IOP stratum, and correlated IOP measurements within patient.

All treatment differences (SIMBRINZA versus individual components) were statistically significant with p=0.0001 or less.

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 9 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 61.7% in the SIMBRINZA group, 40.1% in the Brinzolamide group, and 40.0% 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 (Table 1).

Table 1. Comparison of Mean Diurnal IOP (mmHg) Change from Baseline– Non-inferiority Study

Visit	SIMBRINZA Mean[a]	Brinzolamide + Brimonidine Mean[a]	Difference Mean[a] (95% CI)
Week 2	-8.4 (n=394)	-8.4 (n=384)	-0.0 (-0.4, 0.3)
Week 6	-8.5 (n=384)	-8.4 (n=377)	-0.1 (-0.4, 0.2)
Month 3	-8.5 (n=384)	-8.3 (n=373)	-0.1 (-0.5, 0.2)
Month 6	-8.1 (n=346)	-8.2 (n=330)	0.1 (-0.3, 0.4)

[a] Least squares means derived from a statistical model that accounts for study site, 9 AM baseline IOP stratum, and correlated IOP measurements within patient

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 65.6% in the SIMBRINZA group and 63.7% Brinzolamide + Brimonidine groups.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with SIMBRINZA in all subsets of the paediatric population in the treatment of glaucoma and ocular hypertension (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Brimonidine is rapidly absorbed into the eye following topical administration. In rabbits, maximum ocular concentrations were achieved in less than one hour in most cases. Maximum human plasma concentrations are < 1 ng/mL and achieved within < 1 hour. Plasma levels decline with a half-life of approximately 2-3 hours. No accumulation occurs during chronic administration.

In a topical ocular clinical study comparing the systemic pharmacokinetics of SIMBRINZA administered two or three times daily to brinzolamide and brimonidine administered individually using the same two posologies, 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 with the exception of the twice daily SIMBRINZA treatment group, for which the mean $AUC_{0\text{-}12\ hours}$ was about 25% lower than that for brimonidine alone administered twice daily.

Distribution
Studies in rabbits showed that maximum brinzolamide ocular concentrations following topical administration are in the anterior tissues such as cornea, conjunctiva, aqueous humour and iris-ciliary body. Retention in ocular tissues is prolonged due to binding to carbonic anhydrase. Brinzolamide is moderately bound (about 60%) to human plasma proteins.

Brimonidine exhibits affinity for pigmented ocular tissues, particularly iris-ciliary body, due to its known melanin binding properties. However, clinical and non-clinical safety data show it to be well-tolerated and safe during chronic administration

Biotransformation
Brinzolamide is metabolized by hepatic cytochrome P450 isozymes, specifically CYP3A4, CYP2A6, CYP2B6, CYP2C8 and CYP2C9. The primary metabolite is N-desethylbrinzolamide 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.

Brimonidine is extensively metabolized by hepatic aldehyde oxidase with formation of 2-oxobrimonidine, 3-oxobrimonidine and 2,3-dioxobrimonidine being the major metabolites. Oxidative cleavage of the imidazoline ring to 5-bromo-6-guanidinoquinoxaline is also observed.

Elimination

Brinzolamide is primarily eliminated in urine unchanged. 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 30%), primarily as metabolites.

Brimonidine is primarily eliminated in the urine as metabolites. In rats and monkeys, urinary metabolites accounted for 60 to 75% of oral or intravenous doses.

Linearity/non-linearity
Brinzolamide pharmacokinetics are inherently non-linear due to saturable binding to carbonic anhydrase in whole blood and various tissues. Steady-state exposure does not increase in a dose-proportional manner.

In contrast, brimonidine exhibits linear pharmacokinetics over the clinically therapeutic dose range.

Pharmacokinetic/pharmacodynamic relationship(s)
SIMBRINZA is intended for local action within the eye. Assessment of human ocular exposure at efficacious doses is not feasible. The pharmacokinetic/pharmacodynamic relationship in humans for IOP-lowering has not been established.

Other special populations
Studies to determine the effects of age, race, and renal or hepatic impairment have not been conducted with SIMBRINZA. A study of brinzolamide in Japanese versus non-Japanese subjects showed similar systemic pharmacokinetics between the two groups. In a study of brinzolamide in subjects with renal imapirment, a 1.6- to 2.8-fold increase in the systemic exposure to brinzolamide and N-desethylbrinzolamide between normal and moderately renally-impaired subjects was demonstrated. This increase in steady-state RBC concentrations of substance-related material did not inhibit RBC carbonic anhydrase activity to levels that are associated with systemic side effects. However, the combination product is not recommended for patients with severe renal impairment (creatinine clearance < 30 mL/minute).

The C_{max}, AUC and elimination half-life of brimonidine are similar in elderly (>65 years of age) subjects compared to young adults. The effects of renal and hepatic impairment on the systemic pharmacokinetics of brimonidine have not been evaluated. Given the low systemic exposure to brimonidine following topical ocular administration, it is expected that changes in plasma exposure would not be clinically relevant.

Paediatric population
The systemic pharmacokinetics of brinzolamide and brimonidine, alone or in combination, in paediatric patients have not been studied.

5.3 Preclinical safety data

Brinzolamide
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Effects in non-clinical reproduction and development toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. In rabbits, oral, maternally toxic, doses of brinzolamide of up to 6 mg/kg/day (261 times the recommended daily clinical dose of 23 µg/kg/day) revealed no effect on foetal development. In rats doses of 18 mg/kg/day (783 times the recommended daily clinical dose), but not 6 mg/kg/day, resulted in slightly reduced ossification of skull and sternebrae of foetuses. These findings were associated with metabolic acidosis with decreased body weight gain in dams and decreased foetal weights. Dose related decreases in foetal weights were observed in pups of dams given 2 to 18 mg/kg/day. During lactation, the no adverse effect level in the offspring was 5 mg/kg/day.

Brimonidine
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Propylene glycol
Carbomer 974P
Boric acid
Mannitol
Sodium chloride
Tyloxapol
Hydrochloric acid and/or sodium hydroxide (to adjust pH)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

4 weeks after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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 (Drop-Tainer) 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 for disposal.

7. MARKETING AUTHORISATION HOLDER

Alcon Laboratories (UK) Ltd
Frimley Business Park
Frimley, Camberley
Surrey GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/933/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Alcon-Couvreur N.V.
Rijksweg 14
BE-2870 Puurs
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 5 ml BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

SIMBRINZA 10 mg/ml + 2 mg/ml eye drops, suspension
Brinzolamide/brimonidine tartrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of suspension contains 10 mg brinzolamide and 2 mg brimonidine tartrate

3. LIST OF EXCIPIENTS

Benzalkonium chloride, propylene glycol, carbomer 974P, boric acid, mannitol, sodium chloride, tyloxapol, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water.

See the package leaflet for further details.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, suspension
1 x 5 ml
3 x 5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake well before use.
Read the package leaflet before use.
Ocular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp
Discard 4 weeks after first opening.
Opened:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alcon Laboratories (UK) Ltd.
Frimley Business Park
Frimley, Camberley
Surrey GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/933/001 1 x 5 ml
EU/1/14/933/002 3 x 5 ml

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

simbrinza

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

SIMBRINZA 10 mg/ml + 2 mg/ml eye drops
Brinzolamide/brimonidine tartrate

Ocular use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

SIMBRINZA 10 mg/ml + 2 mg/ml eye drops, suspension
Brinzolamide/brimonidine tartrate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, optometrist (optician) or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, optometrist (optician) or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What SIMBRINZA is and what it is used for

SIMBRINZA contains two active substances, brinzolamide and brimonidine tartrate. Brinzolamide belongs to a group of medicines called 'carbonic anhydrase inhibitors' and brimonidine tartrate belongs to a group of medicines called 'alpha-2 adrenergic receptor agonists'. Both substances work together to reduce pressure within the eye.

SIMBRINZA is used to lower pressure in the eyes in adult patients (aged more than 18 years) who have eye conditions known as glaucoma or ocular hypertension and whose high pressure in the eyes cannot be controlled effectively by one medicine alone.

2. What you need to know before you use SIMBRINZA

Do not use SIMBRINZA:

- if you are allergic to brinzolamide or brimonidine tartrate or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to sulphonamides (examples include medicines used to treat diabetes and infections and also diuretics (water tablets))
- if you are taking monoamine oxidase (MAO) inhibitors (examples include medicines to treat depression or Parkinson's disease) or certain antidepressants. You must inform your doctor if you are taking any antidepressant medicines
- if you have severe kidney problems
- if you have too much acidity in your blood (a condition called hyperchloraemic acidosis)
- in babies and infants aged less than 2 years.

Warnings and precautions

Talk to your doctor, optometrist (optician) or pharmacist before using SIMBRINZA if you have now or have had in the past:
- liver problems

- a type of high pressure in the eyes called narrow-angle glaucoma
- dry eyes or cornea problems
- coronary heart disease (symptoms can include chest pain or tightness, breathlessness or choking), heart failure, high or low blood pressure
- depression
- disturbed or poor blood circulation (such as Raynaud's disease or Raynaud's syndrome or cerebral insufficiency)

If you wear soft contact lenses, do not use the drops with your lenses in. See section 'Wearing contact lenses - SIMBRINZA contains benzalkonium chloride' below).

Children and adolescents

SIMBRINZA is not recommended for children and adolescents under 18 years of age. It is particularly important that the medicine is not used in children under the age of 2 years (see section 'Do not use SIMBRINZA' above). SIMBRINZA should not be used in children due to the potential for serious side effects (see section 3).

Other medicines and SIMBRINZA

Tell your doctor, optometrist (optician) or pharmacist if you are using, have recently used, or might use any other medicines.

SIMBRINZA can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma.

Tell your doctor if you are taking or intend to take any of the following medicines:
- medicines to lower blood pressure
- heart medicines including digoxin (used to treat heart conditions)
- other medicines for glaucoma that also treat altitude sickness known as acetazolamide, methazolamide and dorzolamide
- medicines that can affect the metabolism like chlorpromazine, methylphenidate and reserpine
- antiviral, antiretroviral (type of medicines used to treat Human Immunodeficiency Virus (HIV)) or antibiotic medicines
- antiyeast or antifungal medicines
- monoamine oxidase (MAO) inhibitors, or antidepressants including amitriptyline, nortriptyline, clomipramine, mianserin, venlafaxine and duloxetine
- anasthetics
- sedatives, opiates, or barbiturates
- or if the dose of any of your current medicines is changed.

Simbrinza with alcohol

If you are regularly consuming alcohol, ask your doctor, optometrist (optician) or pharmacist for advice before taking this medicine. Simbrinza can be affected by alcohol.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, optometrist (optician) or pharmacist for advice before taking this medicine. Women who may become pregnant are advised to use effective contraception during SIMBRINZA treatment. The use of SIMBRINZA is not recommended during pregnancy. Do not use SIMBRINZA unless clearly indicated by your doctor.

If you are breast-feeding, SIMBRINZA may pass into your milk. The use of SIMBRINZA is not recommended during breast-feeding.

Driving and using machines

You may find that your vision is blurred or abnormal for a time just after using SIMBRINZA. SIMBRINZA may also cause dizziness, drowsiness or tiredness in some patients.

Do not drive or use machines until the symptoms are cleared.

Wearing contact lenses - SIMBRINZA contains benzalkonium chloride

There is a preservative in SIMBRINZA (called benzalkonium chloride) that may cause eye irritation and is known todiscolour soft **contact lenses**. Avoid contact with soft contact lenses.. Remove contact lenses prior to application and wait at least 15 minutes after using SIMBRINZA before putting your contact lenses back in.

3. How to use SIMBRINZA

Always use this medicine exactly as your doctor, optometrist (optician) or pharmacist has told you. Check with your doctor, optometrist (optician) or pharmacist if you are not sure.

Only use SIMBRINZA for your eyes. Do not swallow or inject.

The recommended dose is one drop in the affected eye or eyes two times a day. Use at the same time each day.

How to use

Wash your hands before you start.

1

2

Shake well before use.
Twist off the bottle cap. After the cap is removed, if the tamper evident snap collar is loose, remove it before using the medicine.
Do not touch the dropper with your fingers when opening or closing the bottle. It could infect the drops.
Hold the bottle, pointing down, between your thumb and fingers.
Tilt your head back.
Pull down your lower eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye.
The drop will go in here (picture 1).
Bring the bottle tip close to the eye. Do this in front of a mirror if it helps.
Do not touch your eye or eyelid, surrounding areas or other surfaces with the dropper. It could infect the drops.
Gently press on the base of the bottle to release one drop of SIMBRINZA at a time.
Do not squeeze the bottle: it is designed so that a gentle press on the bottom is all that it needs (picture 2).

To reduce the amount of medicine that could come into the rest of the body after application of eye drops close your eye and apply gentle pressure to the corner of the eye next to the nose with a finger for at least 2 minutes.

If you use drops in both eyes, repeat the steps for your other eye. It is not necessary to close and shake the bottle before you use the drops for your other eye. Close the bottle cap firmly immediately after use.

If you are using other eye drops, wait at least five minutes between using SIMBRINZA and the other drops.

If a drop misses your eye, try again.

If you use more SIMBRINZA than you should
Rinse your eye with warm water. Do not put in any more drops until it is time for your next regular dose.

Adults who accidentally swallowed medicines containing brimonidine experienced a decreased heart rate, decreased blood pressure which may be followed by increased blood pressure, heart failure, difficulty breathing and effects in the nervous system. Should this happen, contact your doctor immediately.

Serious side effects have been reported in children who accidently swallowed medicines containing brimonidine. Signs included sleepiness, floppiness, low body temperature, paleness and breathing difficulties. Should this happen, contact your doctor immediately.

If SIMBRINZA has been accidentally swallowed then you should contact your doctor immediately.

If you forget to use SIMBRINZA
Continue with the next dose as planned. Do not use a double dose to make up for a forgotten dose. Do not use more than one drop in the affected eye(s) two times a day.

If you stop using SIMBRINZA
Do not stop using SIMBRINZA without first speaking to your doctor. If you stop using SIMBRINZA the pressure in your eye will not be controlled which could lead to loss of sight.

If you have any further questions on the use of this medicine, ask your doctor, optometrist (optician) or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience any of the following side effects, please stop using this medicine and seek immediate medical attention as these could be signs of a reaction to the medicine. The frequency of an allergic reaction to the medicine is not known (frequency cannot be estimated from the available data).

- Severe skin reactions, including rash or redness or itching on your body or eyes
- Trouble breathing
- Chest pain, irregular heart beat

Contact your doctor immediately if you develop extreme tiredness or dizziness.

The following side effects have been observed with SIMBRINZA and other medicines containing brinzolamide or brimonidine alone.

Common side effects (may affect up to 1 in 10 people)

- Effects in the eye: allergic conjunctivitis (eye allergy), eye surface inflammation, eye pain, eye discomfort, blurred or abnormal vision, eye redness

- General side effects: drowsiness, dizziness, bad taste in mouth, dry mouth

Uncommon side effects (may affect up to 1 in 100 people)

- Effects in the eye: eye surface damage with loss of cells, inflammation of the eyelid, deposits on the eye surface, sensitivity to light, swelling of the eye (affecting the cornea or eyelid), dry eye, eye discharge, watery eye, eyelid redness, abnormal or decreased sensation in eye, tired eye, reduced vision, double vision, product particles in eyes.

- General side effects: decreased blood pressure, chest pain, irregular heartbeat, slow or fast heart rate, palpitations, difficulty sleeping (insomnia), nightmares, depression, generalised weakness, headache, dizziness, nervousness, irritability, general feeling of being unwell, memory loss, shortness of breath, asthma, nose bleeds, cold symptoms, dry nose or throat, sore throat, throat irritation, cough, runny nose, stuffy nose, sneezing, sinus infection, chest congestion, ringing in ear, indigestion, intestinal gas or stomach ache, nausea, diarrhoea, vomiting, abnormal sensation in mouth, increased allergic symptoms on skin, rash, abnormal skin sensation, hair loss, generalised itching, increased blood chlorine levels, or decreased red blood cell count as seen in a blood test, pain, back pain, muscle pain or spasm, kidney pain such as lower back pain, decreased libido, male sexual difficulty.

Very rare (may affect up to 1 in 10,000 people)

- Effects in the eye: decreased pupil size

- General side effects: fainting, increased blood pressure

Not known (frequency cannot be estimated from the available data)

- Effects in the eye: decreased growth of eyelashes

- General side effects: tremor, decreased sensation, loss of taste, abnormal liver function values as seen in a blood test, swelling of the face, joint pain, frequent urination, chest pain, swelling of the extremities.

Reporting of side effects
If you get any side effects, talk to your doctor, optometrist (optician) or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store SIMBRINZA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Throw away the bottle 4 weeks after first opening to prevent infections and use a new bottle. Write down the date of opening on the carton label in the space provided.

Do not throw away any medicines via wastewater or household waste. Ask your optometrist (optician) or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What SIMBRINZA contains
- The active substances are brinzolamide and brimonidine tartrate. One ml of suspension contains 10 mg of brinzolamide and 2 mg of brimonidine tartrate equivalent to 1.3 mg brimonidine.

- The other ingredients are benzalkonium chloride (see section 2 ‘Wearing contact lenses - SIMBRINZA contains benzalkonium chloride’), propylene glycol, carbomer 974P, boric acid, mannitol, sodium chloride, tyloxapol, hydrochloric acid and/or sodium hydroxide and purified water.

Tiny amounts of hydrochloric acid and/or sodium hydroxide are added to keep acidity levels (pH levels) normal.

What SIMBRINZA looks like and contents of the pack
SIMBRINZA eye drops, suspension, is a liquid (white-to-off-white suspension) supplied in a pack containing one or three 5 ml plastic bottles with screw cap. Not all pack sizes may be marketed.

Marketing Authorisation Holder
Alcon Laboratories (UK) Ltd.
Frimley Business Park
Frimley, Camberley
Surrey GU16 7SR
United Kingdom

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

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.