Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

GENAZOPT PLUS 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 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 genazopt plus in the affected eye(s) two times daily.

Missed dose

If a dose is missed, treatment should be continued with the next dose as planned.

Hepatic and/or renal impairment

Brinzolamide and brimonidine tartrate has not been studied in patients with hepatic impairment and caution is therefore recommended in this population (see section 4.4).

Brinzolamide and brimonidine tartrate 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 Brinzolamide and brimonidine tartrate and its metabolite are excreted predominantly by the kidney, Brinzolamide and brimonidine tartrate is contraindicated in such patients (see section 4.3).

Paediatric population

The safety and efficacy of Brinzolamide and brimonidine tartrate in children and adolescents aged 2 to 17 years have not been established. No data are available.

Brinzolamide and brimonidine tartrate is contraindicated in neonates and infants aged less than 2 years in the decrease of elevated intraocular pressure (IOP) with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction 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 nasolacrimal occlusion is used and the eyelids are closed for 2 minutes, 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.

Brinzolamide and brimonidine tartrate 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.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Hypersensitivity 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 Brinzolamide and brimonidine tartrate.

Ocular effects

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

The possible effect 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 (for further instructions on wearing contact lenses, see below under " Benzalkonium chloride"). Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.

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 Brinzolamide and brimonidine tartrate have not been studied. While the duration of IOP-lowering effect for Brinzolamide and brimonidine tartrate 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

Brinzolamide and brimonidine tartrate contains brinzolamide, a sulphonamide inhibitor of carbonic anhydrase and, although administered topically, is absorbed systemically. The same types of adverse drug reactions that are attributable to sulphonamides may occur with topical administration, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). 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, Brinzolamide and brimonidine tartrate should be withdrawn immediately .

Cardiac disorders

Following administration of Brinzolamide and brimonidine tartrate, 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 Brinzolamide and brimonidine tartrate or in patients with severe or unstable and uncontrolled cardiovascular disease (see section 4.5).

Brinzolamide and brimonidine tartrate 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. Brinzolamide and brimonidine tartrate 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).

Brinzolamide and brimonidine tartrate should be used with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis. Brinzolamide and brimonidine tartrate is contraindicated in patients with severe renal impairment (see section 4.3).

Hepatic impairment

Brinzolamide and brimonidine tartrate 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. GENAZOPT PLUS is absorbed systemically and this may therefore occur with topical administration (see section 4.7).

Paediatric population

The safety and efficacy of Brinzolamide and brimonidine tartrate in children and adolescents aged 2 to 17 years have 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. GENAZOPT PLUS is therefore contraindicated in children below 2 years of age (see section 4.3).

Treatment of children 2 years and above (especially 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).

Benzalkonium chloride

GENAZOPT PLUS 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 GENAZOPT PLUS and wait at least 15 minutes before reinsertion.

Benzalkonium chloride has been reported to cause eye irritation and symptoms of dry eyes and may affect the tear film and corneal surface. It should be used with caution in dry eye patients and in patients whose cornea may be compromised. Patients should be monitored in case of prolonged use.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with Brinzolamide and brimonidine tartrate eye drops.

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

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 GENAZOPT PLUS administration are available. However, caution 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 GENAZOPT PLUS, 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 GENAZOPT PLUS.

Caution is advised when initiating (or changing the dose of) 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 GENAZOPT PLUS.

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 GENAZOPT PLUS 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 in pregnant women. Brinzolamide was not teratogenic in rats and rabbits, following systemic administration (oral gavage). 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 foetal circulation to a limited extent (see section 5.3). GENAZOPT PLUS is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether topical GENAZOPT PLUS 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. GENAZOPT PLUS should not be used by women who are breast-feeding.

Fertility

Non-clinical data do not show any effects of brinzolamide or brimonidine on fertility. There are no data on the effect of topical ocular administration of GENAZOPT PLUS GENon human fertility.

4.7 Effects on ability to drive and use machines

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

GENAZOPT PLUS 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 GENAZOPT PLUS 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.

Tabulated summary of adverse reactions

The following adverse reactions have been reported during clinical studies with SIMBRANZA 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), very rare (<1/10,000) or not known (cannot be estimated from the available data). 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], sinusitis[2] Not known: rhinitis[2]
Blood and lymphatic system disorders	Uncommon: red blood cells 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], nightmares[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], hypoaesthesia 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], tinnitus[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 respiratory tract congestion[2], nasal congestion[1], rhinorrhoea[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 maculopapular[2], pruritus generalised[2], alopecia[2], skin tightness[2] Not known: Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (see section 4.4), 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 GENAZOPT PLUS [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 (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 the brinzolamide component of GENAZOPT PLUS. Nasolacrimal occlusion or gently closing the eyelid after instillation may help reduce the occurrence of this effect (see section 4.2).

GENAZOPT PLUS 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 GENAZOPT PLUS 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 GENAZOPT PLUS experienced decreases in blood pressure similar to those observed with the use of brimonidine as monotherapy.

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

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

Due to the brinzolamide component of GENAZOPT PLUS, 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 GENAZOPT PLUS in adults. The only adverse reaction 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 reactions following inadvertent ingestion with the brimonidine component of GENAZOPT PLUS 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: Ophthalmologicals, Antiglaucoma preparations and miotics, ATC code: S01EC54

Mechanism of action

GENAZOPT PLUS 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.

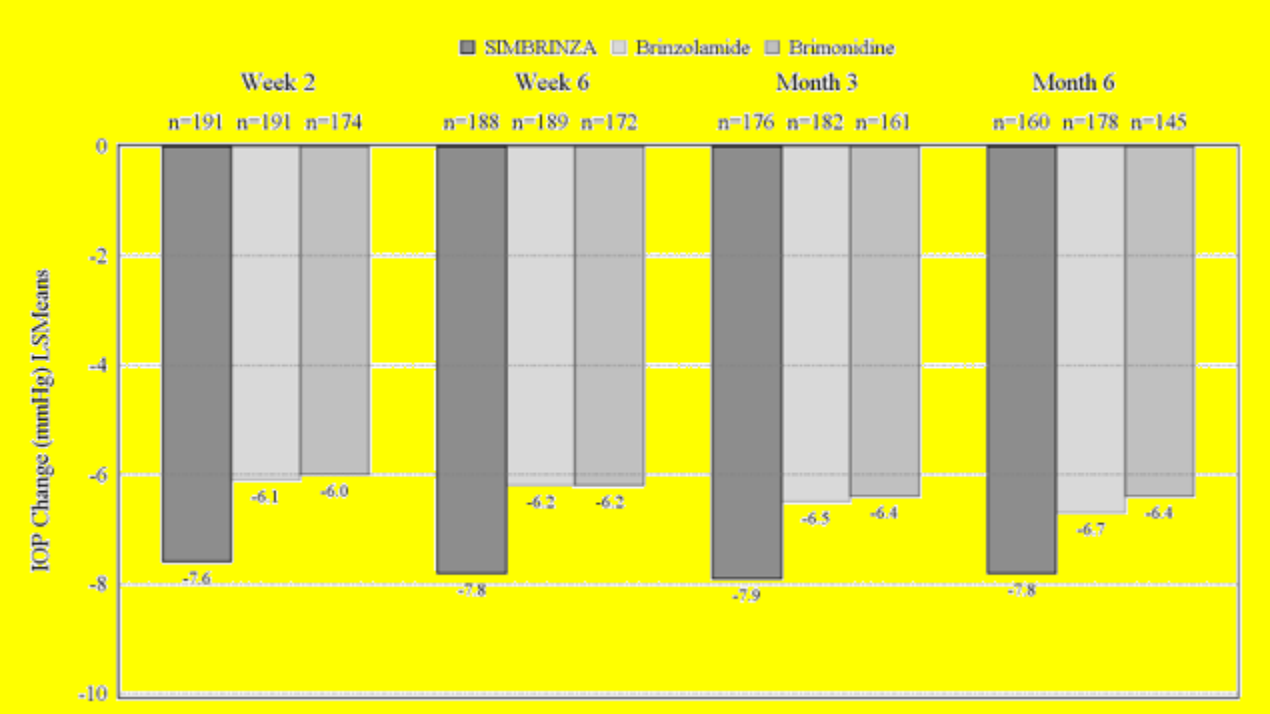
Pharmacodynamic effects

Clinical efficacy and safety

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 (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 (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 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 (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 71.6% in both study groups.

Adjunct therapy

Clinical data on the use of SIMBRINZA adjunctive to prostaglandin analogues (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.

There are no efficacy and safety data for adjunct therapy beyond 6 weeks.

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 GENAZOPT PLUS 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 were similar to those observed for brimonidine administered alone, with the exception of the twice daily GENAZOPT PLUS 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 (about 60%) bound 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 metabolised 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 analogue 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 metabolised 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)

GENAZOPT PLUS 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 GENAZOPT PLUS. 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 impairment, 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, single-dose toxicity, 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 µ g/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
24 months

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 containing 5 mL suspension.

Carton containing 1 or 3 bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing authorisation holder

GENERAL PHARMACEUTICALS LTD

8. Marketing authorisation number(s)

CTD10783

9. Date of first authorisation/renewal of the authorization

20/12/2023

10. Date of revision of the text

13/5/2025