NOVARTIS

1. NAME OF THE MEDICINAL PRODUCT

SIMBRINZA® (10 mg/mL brinzolamide + 2 mg/mL brimonidine tartrate) 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.
Preservative: 1 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.
White-to-off-white uniform suspension.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

SIMBRINZA® eye drops contains brinzolamide, a carbonic anhydrase (CA-II) inhibitor, and brimonidine tartrate, an alpha-2 adrenergic agonist.
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 1 drop of SIMBRINZA eye drops in the affected eye(s) 2 times daily.

Use in children and adolescents
The safety and efficacy of SIMBRINZA eye drops in children and adolescents aged 2 to 17 years has not been established. No data are available. SIMBRINZA eye drops is not recommended in children or adolescents (see section 4.4).
SIMBRINZA eye drops must not be used in neonates and infants aged less than 2 years because of safety concerns (see section 4.3).

Use in patients with hepatic and/or renal impairment
SIMBRINZA eye drops has not been studied in patients with hepatic impairment and caution is therefore recommended in this population (see section 4.4).
SIMBRINZA eye drops 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 eye drops and its metabolite are excreted predominantly by the kidney, SIMBRINZA eye drops is contraindicated in such patients (see section 4.3).

Method of administration

For ocular use.

Patients should be instructed to shake the bottle well before use.
After cap is removed, if tamper evident snap collar is loose, this should be removed before using the product.
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 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.
SIMBRINZA eye drops 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. Eye ointments should be administered last.
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.
When substituting another ophthalmic antiglaucoma agent with SIMBRINZA eye drops, the other agent should be discontinued and SIMRBINZA eye drops should be started the following day.

4.3. Contraindications

- Hypersensitivity to the active substances 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 younger than 2 years old (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 eye drops.

Ocular effects

- SIMBRINZA eye drops has not been studied in patients with narrow-angle glaucoma and its use is not recommended in thesepatients.
- 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. Specifically, patients wearing contact lenses have not been studied and careful monitoring of these patients when using brinzolamide is recommended, since wearing contact lenses might increase the risk for the cornea.
- SIMBRINZA eye drops 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 potential effects following cessation of treatment with SIMBRINZA eye drops have not

been studied. While the duration of IOP-lowering effect for SIMBRINZA eye drops 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 eye drops contains brinzolamide, a sulphonamide inhibitor of carbonic anhydrase. Hypersensitivity reactions reported with sulphonamide derivatives, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can occur in patients receiving SIMBRINZA eye drops 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

- Although brimonidine has a minimal effect on blood pressure of patients in clinical studies, caution should be taken in treating patients with severe or unstable and uncontrolled cardiovascular disorders due to the brimonidine-tartrate component. Caution is also advised when using medicinal products such as antihypertensives and/or cardiac glycosides concomitantly with SIMBRINZA eye drops (see section 4.5).
- SIMBRINZA eye drops 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 eye drops 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 eye drops is contraindicated in patients with severe renal impairment (see section 4.3).

Hepatic impairment

- SIMBRINZA eye drops has not been studied in patients with hepatic impairment; caution should be exercised 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 eye drops is absorbed systemically and therefore this may occur with topical administration (see section 4.7).

Benzalkonium chloride

- SIMBRINZA eye drops contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of SIMBRINZA eye drops and wait at least 15 minutes beforereinsertion.
- Benzalkonium chloride has also been reported to cause punctate keratopathy and/or toxic ulcerative

keratopathy. Close monitoring is required with frequent or prolonged use.

Pediatric population

- The safety and efficacy of SIMBRINZA eye drops 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 eye drops is therefore contraindicated in children under 2 years of age (see section 4.3).
- SIMBRINZA eye drops is not recommended in children or adolescents aged 2 to 17 years (especially in those in the 2-7 age range and/or weighing < 20 kg) because of the potential for central nervous system (CNS) depression due to brimonidine tartrate component (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 eye drops.
- SIMBRINZA eye drops is contraindicated in patients receiving monoamine oxidase inhibitors and patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin) (see section 4.3).
- 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 in patients taking tricyclic antidepressants as these agents may blunt the ocular hypotensive response of SIMBRINZA eye drops. No data on the level of circulating catecholamines after SIMBRINZA eye drops 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 eye drops, small decreases in blood pressure were observed in some patients. Caution is advised with concomitant use of drugs such as antihypertensives and/or cardiac glycosides with similar cardiovascular effects (drugs that cause hypotension).
- Caution is advised when initiating (or changing the dose of) 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).
- 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 eye drops.
- 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 eye drops and oral carbonic anhydrase inhibitors is notrecommended.
- 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 adequate or well controlled studies regarding the ocular use of SIMBRINZA eye drops in pregnant women. 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 fetal toxicity at 375 times the maximum recommended ophthalmic human dose (MROHD) based on body weight (BW). In rabbits, no fetal 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 fetus.

Data

Animal data

Brinzolamide

Embryofetal 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 fetal 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).

Embryofetal 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 feces 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 fetal 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 behavior, 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 fetal tissues were 3- to 10-fold less than those measured in the dams.

Brimonidine

In embryofetal 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 fetus corresponding to 107-times the maximal plasma concentrations (C_{max}) in humans treated with one drop of Simbrinza in both eyes three times daily.

In embryofetal 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, fetal toxicity, or teratogenicity were observed up to the highest tested dose of 3.3 mg base/kg/day, corresponding to 27-times the C_{max} 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 behavior) of F1 and F2 generations were not affected up to the dose of 0.66 mg/kg/day. 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 fetal circulation to a limited extent, producing 14C-brimonidine concentrations in fetal blood that were 10-27% of that in maternal blood.

Lactation

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.

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.

Data

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 eye drops 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).

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

SIMBRINZA eye drops has a moderate influence on the ability to drive and use machines. SIMBRINZA eye drops may cause dizziness, fatigue and/or somnolence in some patients, which may impair the ability to drive or use 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). Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

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.

4.8. Undesirable effects

Summary of the safety profile

In clinical trials, the most frequently reported adverse drug reactions were vision blurred, ocular hyperaemia and dysgeusia (bitter or unusual taste in the mouth following instillation), occurring in 3% to 4% of patients. The safety profile of SIMBRINZA eye drops was similar to that of the individual components (brinzolamide 10 mg/mL and brimonidine 2 mg/mL).

Tabulated summary of adverse reactions

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) and not known (frequency cannot be estimated from the available data; data is from post-marketing surveillance).

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[3], depressed mood[2], libido decreased[2], nightmare[2],nervousness[2] *Rare:* insomnia[1]

Nervous system disorders	*Common:* somnolence[1], dysgeusia[1] *Uncommon:* dizziness[1], 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:* conjunctivitis[1], conjunctivitis allergic[1], eye allergy[1], blepharitis[1], vision blurred[1], abnormal vision[3], eye pain[1], eye irritation[1], dry eye[1], eye pruritus[1], ocular hyperaemia[1], ocular discomfort[1], conjunctivalblanching[3] *Uncommon:* corneal erosion[1], keratitis[1], punctate keratitis[1], diplopia[2], corneal oedema[2], eye swelling[2], eye discharge[1], photopsia[2], photophobia[1], glare[2], hypoaesthesia eye[2], lacrimation increased[1], pterygium[2], erythema of eyelid[1], meibomianitis[2], blepharitis allergic[1], conjunctival follicle[1], conjunctival disorder (papillae)[1], subconjunctival cyst[2], scleral pigmentation[2],asthenopia[1] *Rare:* visual acuity reduced[1], corneal deposits (keratic precipitates)[1], conjunctival oedema[1], lacrimation decreased[1], abnormal sensation in eye[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], blood pressure decreased[1] *Very rare:* hypertension[3]

System Organ Classification	Adverse reactions
Respiratory, thoracic and mediastinal disorders	*Uncommon:* dyspnoea[2], bronchial hyperactivity[2], pharyngolaryngeal pain[2], cough[2], epistaxis[2], upper respiratory tract congestion[2], rhinorrhea[2], throat irritation[2], nasal dryness[1], postnasal drip[1], sneezing[2] *Rare:* upper-airway cough syndrome[1], nasal congestion[1], dry throat[1] *Not known:* asthma[2]
Gastrointestinal disorders	*Common:* dry mouth[1] *Uncommon:* oesophagitis[2],diarrhoea[2], vomiting[2], frequent bowel movements[2], flatulence[2], hypoaesthesia oral[2] *Rare:* nausea[1], dyspepsia[1], abdominal discomfort[1], paraesthesia oral[1]
Hepatobiliary disorders	*Not known:* liver function test abnormal[2]
Skin and subcutaneous tissue disorders	*Uncommon:* dermatitis allergic[1], urticaria[2], rash[2], rash maculo-papular[2], pruritus generalized[2], alopecia[2], skin tightness[2] *Not known:* Stevens-Johnson syndrome (SJS)[2], toxic epidermal necrolysis (TEN)[2], 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], asthenia[1], fatigue[1], feeling jittery[2], irritability[2], medication residue present[1] *Not known:* chest pain[2], peripheral oedema[2,3]

[1] adverse reaction observed with SIMBRINZA eye drops

[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 eye drops (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 eye drops. Nasolacrimal occlusion or gently closing the eyelid after instillation may help reduce the occurrence of this effect (see section 4.2).

SIMBRINZA eye drops 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 eye drops 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 eye drops experienced decreases in blood pressure similar to those observed with the use of brimonidine as monotherapy.

4.9. Overdose

An ocular overdose of SIMBRINZA may be flushed from the eye(s) with lukewarm water.

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.

There is very limited information regarding accidental ingestion with the brimonidine component of SIMBRINZA eye drops 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.

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

Pediatric population

Serious adverse effects following inadvertent ingestion with the brimonidine tartrate component of SIMBRINZA eye drops by pediatric 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: Ophthalmologicals, Antiglaucoma preparation and miotics ATC code: S01EC54

Mechanism of action

SIMBRINZA eye drops contains two active substances: brinzolamide (carbonic anhydrase inhibitor) and brimonidine tartrate (alpha-2 adrenergic receptor agonist). 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 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.

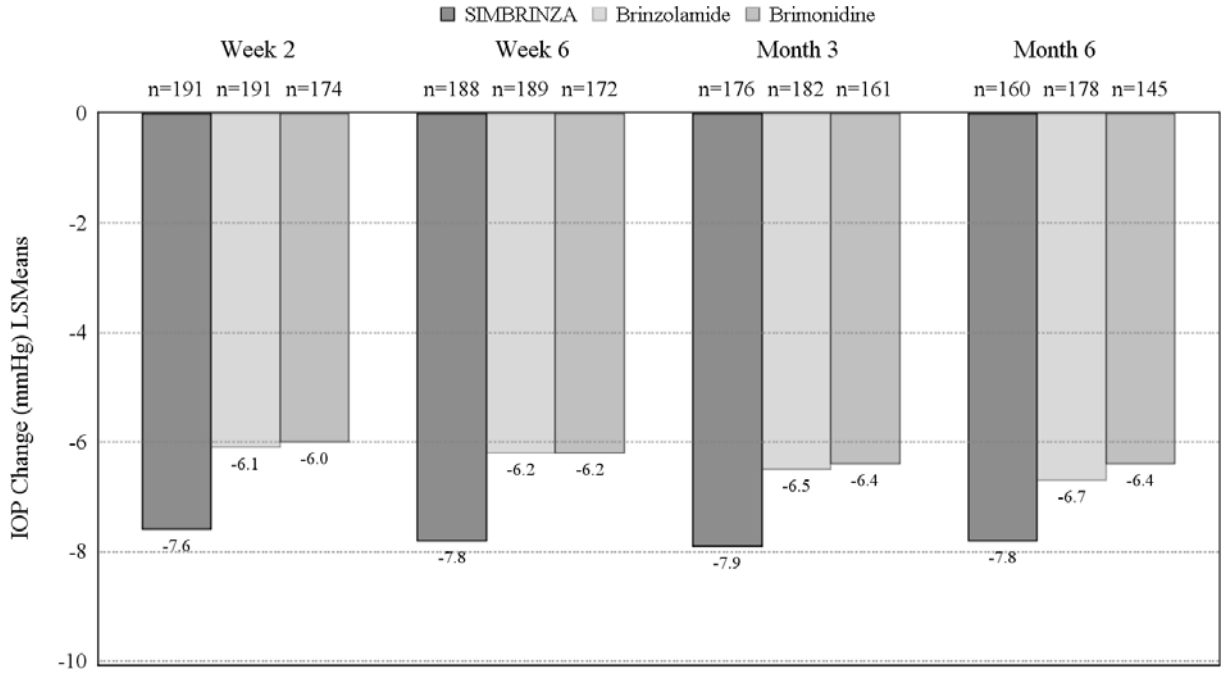
Pharmacodynamic effects

Clinical efficacy and safety

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 eye drops dosed twice daily was approximately 8 mmHg. Statistically superior reductions in the mean diurnal IOP were observed with SIMBRINZA eye drops 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 eye drops 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 eye drops (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 eye drops ranged from 23 to 34%. The percentages of patients with an IOP measurement less than 18 mmHg were greater in the SIMBRINZA eye drops group than in the brinzolamide group at 11 of 12 assessments through Month 6 and were greater in the SIMBRINZA eye drops 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 eye drops 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 eye drops 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 eye drops 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 eye drops or the individual components administered concomitantly were similar (7 to 10 mmHg). Mean percent IOP reductions from baseline with SIMBRINZA eye drops 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 eye drops 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 (ie, 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.

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, resulting in significant accumulation of brinzolamide in the blood.

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. In humans, plasma brimonidine concentrations achieve peak levels within 0.5 to 2.5 hours and decline with a systemic half-life of approximately 2 hours. No accumulation occurs during chronic administration.

In a topical ocular clinical study comparing the systemic pharmacokinetics of SIMBRINZA eye drops 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 eye drops 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 during a course of topical ocular twice daily administration, brinzolamide significantly accumulates in the anterior tissues such as cornea, conjunctiva, aqueous humour, iris- ciliary body (ICB), choroid, and especially retina. Retention in ocular tissues is prolonged due to binding to carbonic anhydrase. Brimonidine exhibits affinity for pigmented ocular tissues and significantly accumulates in choroid, retina and especially the

ICB. However, clinical and non- clinical safety data show it to be well-tolerated and safe during chronic administration.

Data in pigmented rabbits topically administered radiolabeled 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

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.

In humans, brimonidine is primarily metabolized by the liver, most likely by cytochrome P450 and aldehyde oxidase, with alpha(N)-oxidation to 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.

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. 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 its tight and saturable binding to carbonic anhydrase in RBCs 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, as evidenced by aqueous humour data from cataract patients showing a dose-proportional increase in ocular exposure with increasing topicaldose.

Pharmacokinetic/pharmacodynamic relationship(s)

SIMBRINZA eye drops 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.

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.

Other special populations

Studies to determine the effects of age, race, and renal or hepatic impairment have not been conducted with SIMBRINZA eye drops. 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.

Pediatric population

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

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 administation 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 (to adjust pH) and/or hydrochloric acid and purified water.

6.2. Incompatibilities

Not applicable.

6.3. Special precautions for storage

Do not store above 30°C.
Do not use this medicine after the expiry date which is stated on the packaging. Discard 1 month after first opening.
Do not store above 25°C after first opening.
Keep this medicine out of the sight and reach of children.

6.4. Nature and contents of container

Plastic dispenser containing 5 mL.

6.5. Special precautions for disposal and other handling

No special requirements.

Novartis Pharma AG, Basel, Switzerland