BRINZOLAMIDE SK
eye drops, suspension

Summary of Product Characteristics

1. Name of the medicinal product

BRINZOLAMIDE SK 10 mg/ml eye drops, suspension

2. Qualitative and quantitative composition

Each ml of suspension contains 10 mg brinzolamide.

Excipient with known effect:

Each ml of suspension contains 0.15 mg benzalkonium chloride.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Eye drops, suspension.

White to off-white homogenous suspension.

4. Clinical particulars

4.1 Therapeutic indications

BRINZOLAMIDE SK is indicated to decrease elevated intraocular pressure in:

• ocular hypertension

• open-angle glaucoma

as monotherapy in adult patients unresponsive to beta-blockers or in adult patients in whom beta-blockers are contraindicated, or as adjunctive therapy to beta-blockers (see also section 5.1).

4.2 Posology and method of administration

Posology

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

Special populations

Elderly population

No dose adjustment in elderly patients is necessary.

Hepatic and renal impairment

BRINZOLAMIDE SK has not been studied in patients with hepatic impairment and is therefore not recommended in such patients.

BRINZOLAMIDE SK has not been studied in patients with severe renal impairment (creatinine clearance < 30 ml/min) or in patients with hyperchloraemic acidosis. Since brinzolamide and its main metabolite are excreted predominantly by the kidney, **BRINZOLAMIDE SK** is therefore contra-indicated in such patients (see also section 4.3).

Paediatric population

The safety and efficacy of **BRINZOLAMIDE SK** in infants, children and adolescents aged 0 to 17 years have not been established. Currently available data are described in sections 4.8 and 5.1. **BRINZOLAMIDE SK** is not recommended for use in infants, children and adolescents.

Method of administration

For ocular use.

Nasolacrimal occlusion or gently closing the eyelid after instillation is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic side effects.

Instruct the patient to shake the bottle well before use. After the cap is removed, if tamper evident snap collar is loose, remove before using the product.

To prevent contamination of the dropper tip and suspension, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Instruct patients to keep the bottle tightly closed when not in

use.

When substituting another ophthalmic antiglaucoma agent with **BRINZOLAMIDE SK**, discontinue the other agent and start the following day with **BRINZOLAMIDE SK**.

If more than one topical ophthalmic medicinal product is being used, the medicines 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 one drop in the affected eye(s) three times daily.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known hypersensitivity to sulphonamides (see also section 4.4).
- Severe renal impairment.
- Hyperchloraemic acidosis.

4.4 Special warnings and precautions for use

Systemic effects

BRINZOLAMIDE SK is 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 SK** should be withdrawn immediately

Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. Use with caution in patients with risk of renal impairment because the possible risk of metabolic acidosis (see section 4.2).

Brinzolamide has not been studied in pre-term infants (less than 36 weeks gestational age) or those less than 1 week of age. Patients with significant renal tubular immaturity or abnormalities should only receive brinzolamide after careful consideration of the risk benefit balance because of the possible risk of metabolic acidosis.

Oral carbonic anhydrase inhibitors may impair the ability to perform tasks requiring mental alertness and/or physical coordination. **BRINZOLAMIDE SK** is absorbed systemically and therefore this may occur with topical administration.

Concomitant therapy

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 **BRINZOLAMIDE SK**. The concomitant administration of **BRINZOLAMIDE SK** and oral carbonic anhydrase inhibitors has not been studied and is not recommended (see also section 4.5).

brinzolamide was primarily evaluated in concomitant administration with timolol during adjunctive glaucoma therapy. Additionally the IOP-reducing effect of **brinzolamide** as adjunctive therapy to the prostaglandin analogue travoprost has been studied. No long term data are available on the use of **BRINZOLAMIDE SK** as adjunctive therapy to travoprost(see also section 5.1).

There is limited experience with **BRINZOLAMIDE SK** in the treatment of patients with pseudoexfoliative glaucoma or pigmentary glaucoma. Caution should be used in treating these patients and close monitoring of intraocular pressure (IOP) is recommended. **brinzolamide** 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.

Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since **BRINZOLAMIDE SK** contains benzalkonium chloride, close monitoring is required with frequent or prolonged use in dry eye patients, or in conditions where the cornea is compromised.

brinzolamide has not been studied in patients wearing contact lenses. **BRINZOLAMIDE SK** contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses is to be avoided. Patients must be instructed to remove contact lenses prior to the application of **BRINZOLAMIDE SK** and wait at least 15 minutes after instillation of the dose before reinsertion.

Potential rebound effects following cessation of treatment with **BRINZOLAMIDE SK** have not been studied; the IOP-

lowering effect is expected to last for 5-7 days.

Paediatric population

The safety and efficacy of **BRINZOLAMIDE SK** in infants, children and adolescents aged 0 to 17 years have not been established and its use is not recommended in infants, children or adolescents

4.5 Interaction with other medicinal products and other forms of interaction

Specific interaction studies with other medicinal products have not been performed with **brinzolamide**.

In clinical studies, **brinzolamide** was used concomitantly with prostaglandin analogues and timolol ophthalmic preparations without evidence of adverse interactions. Association between **brinzolamide** and miotics or adrenergic agonists has not been evaluated during adjunctive glaucoma therapy.

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 **brinzolamide**.

The cytochrome P-450 isozymes responsible for metabolism of brinzolamide include CYP3A4 (main), CYP2A6, 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 ophthalmic brinzolamide in pregnant women. Studies in animals have shown reproductive toxicity following systemic administration (see also section 5.3).

BRINZOLAMIDE SK is not recommended during pregnancy and in women of childbearing potential not using

contraception. Breast-feeding

It is unknown whether brinzolamide/metabolites are excreted in human milk following topical ocular administration. Animal studies have shown the excretion of minimal levels of brinzolamide in breast milk following oral administration.

A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from **BRINZOLAMIDE SK** therapy taking in to account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies with brinzolamide demonstrated no effect on fertility. Studies have not been performed to evaluate the effect of topical ocular administration of brinzolamide on human fertility.

4.7 Effects on ability to drive and use machines

BRINZOLAMIDE SK has a minor influence on the ability to drive and use machines.

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines (see also section 4.8). 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 to perform tasks requiring mental alertness and/or physical coordination (see also section 4.4 and section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In clinical studies involving 2732 patients treated with **brinzolamide** as monotherapy or adjunctive therapy to timolol maleate 5 mg/ml, the most frequently reported treatment-related adverse reactions were: dysgeusia (6.0%) (bitter or unusual taste, see description below) and temporary blurred vision (5.4%) upon instillation, lasting from a few seconds to a few minutes (see also section 4.7).

Tabulated summary of adverse reactions

The following adverse reactions have been reported with brinzolamide 10mg/ml eye drops, suspension and are classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), 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. The adverse reactions were obtained from clinical trials and post-marketing spontaneous reports.

System Organ Classification	MedDRA Preferred Term (v.15.1)
Infections and infestations	Uncommon: nasopharyngitis, pharyngitis, sinusitis Not Known: rhinitis
Blood and lymphatic system disorders	Uncommon: red blood cell count decreased, blood chloride increased
Immune system disorders	Not Known: hypersensitivity
Metabolism and nutrition disorders	Not known: decreased appetite
Psychiatric disorders	Uncommon: apathy, depression, depressed mood, libido decreased, nightmare, nervousness Rare: insomnia
Nervous system disorders	Uncommon: motor dysfunction, amnesia, dizziness, paraesthesia, headache Rare: memory impairment, somnolence Not Known: tremor, hypoaesthesia, ageusia
Eye disorders	Common: blurred vision, eye irritation, eye pain, foreign body sensation in eyes, ocular hyperaemia Uncommon: corneal erosion, keratitis, punctate keratitis, keratopathy, deposit eye, corneal staining, corneal epithelium defect, corneal epithelium disorder, blepharitis, eye pruritus, conjunctivitis, eye swelling, meibomianitis, glare, photophobiadry eye, allergic conjunctivitis, pterygium, scleral pigmentation, asthenopia, ocular discomfort, abnormal sensation in eye, keratoconjunctivitis sicca, subconjunctival cyst, conjunctival hyperaemia, eyelids pruritus, eye discharge, eyelid margin crusting, lacrimation increased Rare: corneal oedema, diplopia, visual acuity reduced, photopsia, hypoaesthesia eye, periorbital oedema, intraocular pressure increased, optic nerve cup/disc ratio increased Not Known: corneal disorder, visual disturbance, eye allergy, madarosis, eyelid disorder, erythema of eyelid
Ear and labyrinth disorders	Rare: tinnitus Not Known: vertigo
Cardiac disorders	Uncommon: cardio-respiratory distress, bradycardia, palpitations Rare: angina pectoris, heart rate irregular Not Known: arrhythmia, tachycardia, hypertension, blood pressure increased, blood pressure decreased, heart rate increased
Respiratory, thoracic and mediastinal disorders	Uncommon: dyspnoea, epistaxis, oropharyngeal pain, pharyngolaryngeal pain, throat irritation, upper airway cough syndrome, rhinorrhoea, sneezing Rare: bronchial hyperreactivity, upper respiratory tract congestion, sinus congestion, nasal congestion, cough, nasal dryness Not Known: asthma
Gastrointestinal disorders	Common: dysgeusia Uncommon: oesophagitis, diarrhoea, nausea, vomiting, dyspepsia, upper abdominal pain, abdominal discomfort, stomach discomfort, flatulence, frequent bowel movements, gastrointestinal disorder, hypoaesthesia oral, paraesthesia oral, dry mouth
Hepato-biliary disorders	Not Known: liver function test abnormal

Skin and subcutaneous tissue disorders	Uncommon: rash, rash maculo-papular, skin tightness Rare: urticaria, alopecia, pruritus generalised Not Known: Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (see section 4.4), dermatitis, erythema
Musculoskeletal and connective tissue disorders	Uncommon: back pain, muscle spasms, myalgia Not Known: arthralgia, pain in extremity
Renal and urinary disorders	Uncommon: renal pain Not Known: pollakiuria
Reproductive system and breast disorders	Uncommon: erectile dysfunction
General disorders and administration site conditions	Uncommon: pain, chest discomfort, fatigue, feeling abnormal Rare: chest pain, feeling jittery, asthenia, irritability Not Known: peripheral oedema, malaise
Injury, poisoning and procedural complications	Uncommon: foreign body in eye

Description of selected adverse events

Dysgeusia (bitter or unusual taste in the mouth following instillation) was the most frequently reported systemic adverse reaction associated with the use of **brinzolamide** during clinical studies. It is likely caused by passage of the eye drops in the nasopharynx via the nasolacrimal canal. Nasolacrimal occlusion or gently closing the eyelid after instillation may help reduce the incidence of this effect (see also section 4.2).

brinzolamide 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 that are attributable to oral carbonic anhydrase inhibitors may occur with topical administration.

No unexpected adverse reactions have been observed with **brinzolamide** when used as adjunctive therapy to travoprost. The adverse reactions seen with the adjunctive therapy have been observed with each active substance alone.

Paediatric population

In small short-term clinical trials, approximately 12.5% of paediatric patients were observed to experience adverse reactions, the majority of which were local, non-serious ocular reactions such as conjunctival hyperaemia, eye irritation, eye discharge, and lacrimation increased (see also section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://sideeffects.health.gov.il

4.9 Overdose

No case of overdose has been reported.

Treatment should be symptomatic and supportive. 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, carbonic anhydrase inhibitors, ATC code: S01EC04

Mechanism of action

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body, including the eye. Carbonic anhydrase catalyses the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid.

Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humour secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP) which is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. Brinzolamide, an inhibitor of carbonic anhydrase II (CA-II), the predominant iso-enzyme in the eye, with an *in vitro* IC_{50} of 3.2 nM and a K_i of 0.13 nM against CA-II.

Clinical efficacy and safety

The IOP-reducing effect of **brinzolamide** as adjunctive therapy to the prostaglandin analogue travoprost was studied. Following a 4 week run-in with travoprost, patients with an IOP ≥19 mmHg were randomized to receive added treatment with brinzolamide or timolol. An additional decrease in mean diurnal IOP of 3.2 to 3.4 mmHg for the brinzolamide group and 3.2 to 4.2 mmHg for the timolol group were observed. There was an overall higher incidence of non-serious ocular adverse reactions, mainly related to signs of local irritation, in the brinzolamide/travoprost groups. The events were mild and did not affect the overall discontinuation rates in the studies (see also section 4.8).

A clinical trial was conducted with **brinzolamide** in 32 paediatric patients less than 6 years of age, diagnosed with glaucoma or ocular hypertension. Some patients were naive to IOP therapy whilst others were on other IOP-lowering medicinal product(s). Those who had been on previous IOP medicinal product(s) were not required to discontinue their IOP medicinal product(s) until initiation of monotherapy with **brinzolamide**.

Among patients who were naive to IOP therapy (10 patients), the efficacy of **brinzolamide** was similar to that seen previously in adults, with mean IOP reductions from baseline ranging up to 5 mmHg. Among patients who were on topical IOP- lowering medicinal product(s) (22 patients), mean IOP increased slightly from baseline in the **brinzolamide** group.

5.2 Pharmacokinetic properties

Following topical ocular administration, brinzolamide is absorbed into the systemic circulation. Due to its high affinity for CA-II, brinzolamide distributes extensively into the red blood cells (RBCs) and exhibits a long half-life in whole blood (mean of approximately 24 weeks). In humans, the metabolite N-desethylbrinzolamide is formed, which also binds to CA and accumulates in RBCs. This metabolite binds mainly to CA-I in the presence of brinzolamide. In plasma, both brinzolamide and N-desethylbrinzolamide concentrations are low and generally below assay quantitation limits (<7.5 ng/ml).

Binding to plasma proteins is not extensive (about 60%). Brinzolamide is eliminated primarily by renal excretion (approximately 60%). About 20% of the dose has been accounted for in urine as metabolite. Brinzolamide and N-desethylbrinzolamide are the predominant components in the urine along with trace levels (<1%) of the N-desmethoxypropyl and O-desmethyl metabolites.

In an oral pharmacokinetic study, healthy volunteers received 1 mg capsules of brinzolamide twice daily for up to 32 weeks and RBC CA activity was measured to assess the degree of systemic CA inhibition.

Brinzolamide saturation of RBC CA-II was achieved within 4 weeks (RBC concentrations of approximately 20 µM). N-Desethylbrinzolamide accumulated in RBCs to steady state within 20-28 weeks reaching concentrations ranging from 6-30 µM. The inhibition of total RBC CA activity at steady state was approximately 70-75%.

Subjects with moderate renal impairment (creatinine clearance of 30-60 ml/minute) were administered 1 mg of brinzolamide twice daily orally for up to 54 weeks. Brinzolamide RBC concentration ranged from about 20 to 40 µM by week 4 of treatment. At steady-state, brinzolamide and its metabolite RBC concentrations ranged from 22.0 to 46.1 and 17.1 to 88.6 µM, respectively.

N-desethylbrinzolamide RBC concentrations increased and total RBC CA activity decreased with decreasing creatinine clearance but brinzolamide RBC concentrations and CA-II activity remained unchanged. In subjects with the highest degree of renal impairment inhibition of total CA activity was greater although it was inferior to 90% at steady-state.

In a topical ocular study, at steady-state, brinzolamide RBC concentrations were similar to those found in the oral study, but levels of N-desethylbrinzolamide were lower. Carbonic anhydrase activity was approximately 40-70% of predose levels.

5.3 Preclinical safety data

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

Developmental toxicity studies in rabbits with oral doses of brinzolamide of up to 6 mg/kg/day (125 times the recommended human ophthalmic dose) revealed no effect on foetal development despite significant maternal toxicity. Similar studies in rats resulted in slightly reduced ossification of skull and sternebrae of foetuses of dams receiving brinzolamide at doses of 18 mg/kg/day (375 times the recommended human ophthalmic dose), but not 6 mg/kg/day. These findings occurred at doses that caused 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 receiving brinzolamide orally ranging from a slight decrease (about 5-6%) at 2 mg/kg/day to nearly 14% at 18 mg/kg/day. During lactation, the no adverse effect level in the offspring was 5 mg/kg/day.

6. Pharmaceutical particulars

6.1 List of excipients

Benzalkonium chloride

Mannitol (E421)

Carbomer 974P

Sodium chloride

disodium Edetate

Hydrochloric acid/sodium hydroxide (to adjust pH)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.4 weeks after first opening.

6.4 Special precautions for storage

store below 25ºC. protect from light, keep in the external carton pack.

6.5 Nature and contents of container

5 ml opaque low density polyethylene bottles with polypropylene screw caps (droptainer).

The following pack sizes are available: outer cartons containing 1 x 5 ml, bottles.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

K.S. KIM INTERNATIONAL (SK- PHARMA) LTD., ISRAEL
94 YIGAL ALON STR., TEL-AVIV-YAFO, 6789139

MANUFACTURER

AZAD PHARMA AG, SWITZERLAND

BAHNHOFSTRASSE 9, CH-3125 TOFFEN, SWITZERLAND

8. Marketing authorisation number(s)

9. 163-25-35121Date of first authorisation/renewal of the authorisation

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