Company Core Data Sheet for Brinzolamide Eye Drops, Suspension

Full Title:

Company Core Data Sheet for Brinzolamide 10 mg/ml Eye Drops, Suspension

Document Type	Company Core Data Sheet (CCDS)
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Approvals	See last page of this document.

1. NAME OF THE MEDICINAL PRODUCT

AZOPT

Brinzolamide 10 mg/ml Eye Drops, Suspension

**Alternative names may be applicable. Refer to local labeling.*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Brinzolamide 10 mg/ml, benzalkonium chloride 0.1 mg/ml, mannitol, carbomer 974P, tyloxapol, disodium edetate, sodium chloride, hydrochloric acid and/or sodium hydroxide and purified water.

**Information might differ in some countries. Refer to local labeling.*

3. PHARMACEUTICAL FORM

Eye drops, suspension.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Brinzolamide 10 mg/ml Eye Drops is a carbonic anhydrase inhibitor indicated to decrease elevated intraocular pressure in patients with ocular hypertension or 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 or prostaglandin analogues.

** Refer to the currently approved product labeling. Indication as per national approval.*

4.2. Posology and Method of Administration

Recommended Dose and Dosage Adjustment

The dosing of Brinzolamide 10 mg/ml Eye Drops for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma is as follows:

- One drop in the affected eye(s) 3 times daily.

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) 3 times daily.

Pediatric population

The safety and efficacy of Brinzolamide 10 mg/ml Eye Drops in patients below the age of 18 have not been established and its use is not recommended in these patients.

Hepatic and renal impairment

Brinzolamide 10 mg/ml Eye Drops has not been studied in patients with hepatic impairment and is therefore not recommended in such patients. Brinzolamide has not been studied in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2). Since brinzolamide and its major metabolite are excreted predominately by the kidney, brinzolamide is therefore contra-indicated is such patients. However, in patients with moderate renal impairment (creatinine clearance 30-60 mL/min/1.73 m^2) there is no need for dose adjustments with topical administration of brinzolamide 1%.

Geriatric population

No overall differences in safety or effectiveness have been observed between elderly and younger patients. No dose adjustment in elderly patients is necessary.

Method of administration

Brinzolamide 10 mg/ml Eye Drops is for ocular use. 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.

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.

After cap is removed, if tamper evident snap collar is loose, remove before using product.

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.

* *Refer to the currently approved product labeling. Posology is per national approval.*

4.3. Contraindications

- Hypersensitivity to the active substance, to any of the excipients or to sulphonamides.
- Severe renal impairment.
- Hyperchloraemic acidosis.

4.4. Special Warnings and Precautions for Use

- Hypersensitivity reactions common to all sulphonamide derivatives can occur in patients receiving [Brinzolamide 10 mg/ml Eye Drops, Suspension] as it is absorbed systemically. If signs of serious reactions or hypersensitivity occur, discontinue the use of this product.

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

- 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). Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.

- [Brinzolamide 10mg/ml Eye Drops, Suspension] 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 [Brinzolamide 10mg/ml Eye Drops, Suspension] and wait at least 15 minutes before reinsertion. *[Only for products containing benzalkonium chloride]*.

4.5. Interaction with other Medicinal Products and Other Forms of Interaction

[Brinzolamide 10mg/ml Eye Drops, Suspension] 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. NSAIDS and Salicylates) must be considered in patients receiving [Brinzolamide 10mg/ml Eye Drops, Suspension].

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 10mg/ml Eye Drops, Suspension]. The concomitant administration of [Brinzolamide 10mg/ml Eye Drops, Suspension] and oral carbonic anhydrase inhibitors is not recommended.

4.6. Fertility, Pregnancy and Lactation

Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of brinzolamide on male or female fertility. No effect on fertility was observed in rats after oral administration of brinzolamide.

Pregnancy

There are no or limited amount of data from the use of ophthalmic brinzolamide in pregnant women. Studies in animals with brinzolamide have shown reproductive toxicity following systemic administration. Animal studies using brinzolamide showed no teratogenicity at doses up to 18 mg/kg/day and 6 mg/kg/day in rats and rabbits respectively. Decrease in fetal body weight and an increase in developmental variations in rats were observed at an oral dose of 18 mg/kg/day (514 times recommended human ophthalmic dose). (See section 5.3).

[Brinzolamide 10 mg/mL Eye Drops, Suspension] is not recommended during pregnancy.*

Lactation

It is unknown whether brinzolamide/metabolites are excreted in human milk following topical ocular administration; however, a risk to the suckling child cannot be excluded. In animal studies following oral administration, minimal levels of brinzolamide were detected in breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from [Brinzolamide 10 mg/mL Eye Drops, Suspension] therapy taking in to account the benefit of breast-feeding for the child and the benefit of therapy for the woman. *

**Refer to regional guidelines on Pregnancy and Lactation for appropriate recommendation's statement.*

4.7. Effects on Ability to Drive and Use Machines

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

Additionally, nervous system disorders have been reported with the use of the product which may affect the ability to drive or use machines (see section 4.8).

4.8. Undesirable Effects

a. The following adverse reactions have been reported during clinical studies with [Brinzolamide 10mg/ml Eye Drops, Suspension] and are classified according to the subsequent convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000).

System Organ Classification	**Adverse reactions** **MedDRA Preferred Term (v. 19.1)**
Psychiatric disorders	*Uncommon:* depression *Rare:* insomnia
Nervous system disorders	*Uncommon:* dizziness, paresthesia, headache *Rare:* memory impairment, somnolence
Eye disorders	*Common:* vision blurred, eye irritation, eye pain, ocular discomfort, ocular hyperaemia *Uncommon:* corneal erosion, punctate keratitis, keratitis, conjunctivitis, conjunctivitis allergic, blepharitis, photophobia, dry eye, asthenopia, eye pruritus, lacrimation increased, eye discharge, eyelid margin crusting *Rare:* corneal oedema, diplopia, visual acuity reduced, photopsia, hypoaesthesia eye, periorbital oedema
Ear and labyrinth disorders	*Rare*: tinnitus
Cardiac disorders	*Rare:* angina pectoris, heart rate irregular

Respiratory, thoracic and mediastinal disorders	*Uncommon*: dyspnoea, epistaxis, rhinorrhoea, oropharyngeal pain, upper airway cough syndrome, throat irritation *Rare*: bronchial hyperreactivity, upper-respiratory tract congestion, sinus congestion, nasal congestion, cough, nasal dryness
Gastrointestinal disorders	*Common:* dysgeusia *Uncommon:* nausea, diarrhoea, dyspepsia, abdominal discomfort, dry mouth
Skin and subcutaneous tissue disorders	*Uncommon:* rash *Rare*: urticaria, alopecia, pruritus generalised
General disorders and administration site conditions	*Uncommon:* fatigue *Rare:* chest pain, feeling jittery, asthenia, irritability

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

System Organ Classification	**Adverse reactions** **MedDRA Preferred Term (v.19.1)**
Metabolism and nutrition disorders	Decreased appetite
Nervous system disorders	Hypoaesthesia
Vascular disorders	Blood pressure decreased
Musculoskeletal and connective tissue disorders	Arthralgia

4.9. Overdose

No specific reactions are to be expected with an ocular overdose of the product. In case of accidental ingestion, 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 AZOPT 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.

A clinical trial was conducted with AZOPT in 32 pediatric 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 AZOPT.

Among patients who were naive to IOP therapy (10 patients), the efficacy of AZOPT 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 AZOPT group.

5.2. Pharmacokinetic Properties

Absorption

After ocular administration of AZOPT® 1%, brinzolamide is systemically absorbed and accumulates in circulating red blood cells (RBCs) with a half-life of 111 days. RBCs concentration of brinzolamide after long term oral and ocular administration reaches a saturable mean concentration of 20 μM. This brinzolamide concentration is similar to the RBC concentration (22-27 μM) attained after oral dosing of brinzolamide, 1 mg BID for 32 weeks. In addition, the metabolite N-desacetyl brinzolamide also accumulates in RBCs after ocular and oral administration. However, the degree of carbonic anhydrase inhibition at these saturable levels is not sufficient for systemic effects. In addition, brinzolamide and N-desacetyl brinzolamide concentration in plasma after topical ocular dosing of AZOPT® 1% was typically near or below the limit of quantitation.

Distribution

Brinzolamide moderately binds to human plasma proteins (~60%); therefore the risk of drug interactions with compounds that also bind to plasma proteins is low. Brinzolamide moderately bind to melanin based on pigmented and non-pigmented rabbit studies. However, the half-life of brinzolamide in rabbit tissues is more influenced by its RBC binding than melanin binding.

Brinzolamide is distributed to ocular tissues after topical dosing of AZOPT® 1% to rabbits. After single topical doses, the higher concentrations are found in the anterior tissues compared to posterior tissues; whereas after multiple dosing, drug accumulates in many ocular tissues, due to its high affinity and tight binding to carbonic anhydrase II enzymes. This results in long half-lives in iris–ciliary body, choroid, retina, and lens which are similar to the half-life in blood (except in the lens which resulted in longer half-life than in blood). After multiple dosing, the accumulation of brinzolamide in posterior tissues such as retina and choroid is the result of blood circulation in these tissues, which result in long T_{max} as well as a long half-life. In contrast, aqueous humor, vitreous humor and plasma have relatively short half-lives and accumulation is absent after BID or TID dosing, which is the result from the lack of carbonic anhydrases in these tissues.

Metabolism

N-desethyl brinzolamide is the major human metabolite found in blood and urine. This metabolite is also a known inhibitor of carbonic anhydrase. Cytochrome P-450 CYP3A4 is the major enzyme responsible for the formation of this metabolite; additional P-450s appear to contribute to brinzolamide's clearance as well. Brinzolamide exhibits no inhibition of P-450s at concentrations up to and including 1000ng/ml, which is more than 100-fold higher than those in human plasma at steady state. In addition to N-desethyl brinzolamide, other metabolites, O-desmethyl brinzolamide and N-desmethoxypropyl brinzolamide also have been detected in human urine. These metabolites are not specific to human and have been identified in non-clinical species after oral brinzolamide administration as well. The isomerization of the R enantiomer to the S-enantiomer has not been observed.

Elimination

Brinzolamide is predominately cleared by the kidney as unchanged drug (60%) and other 20% is excreted in the urine as metabolites.

5.3. Preclinical Safety Data

Non-clinical data on brinzolamide reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Non-clinical developmental toxicity was observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Benzalkonium chloride
Mannitol (E421)
Carbomer 974P
Tyloxapol
Disodium edetate
Sodium chloride
Hydrochloric acid/sodium hydroxide (to adjust pH)
Purified water
Information might differ in some countries. Refer to local labeling.

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

Up to 36 months*

4 weeks after first opening.

** Information might differ in some countries. Refer to local labeling.*

6.4. Special Precautions for Storage

This medicinal product does not require any special storage conditions.

Information might differ/be more restricted in some countries, depending on local requirements and/or climate zone classification. Refer to local labeling.

6.5. Nature and Contents of Container

Low density polyethylene bottles with low density polyethylene plug and polypropylene screw caps (Droptainer).

Following fill volumes are available: 1.5 ml, 2.5 ml, 5 ml, 10 ml, 15 ml. For some of these fill volumes, outer cartons containing 1 or more bottles are available. Not all pack sizes may be marketed.

Information might differ in some countries or for different fill sizes / presentations. Refer to local labeling.

6.6. Instructions for Use and Handling <and Disposal>

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. CHANGES FROM PREVIOUS VERSION

CCDS TDOC-0017242 v2.0. The document has been adapted to current CCDS templates/standards.

Section 4.2 and 5.2- The following changes have been made (deletions in strikethrough) and new information (in Bold):

Section 4.2

Hepatic and renal impairment

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

Brinzolamide has not been studied in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2). Since brinzolamide and its major metabolite are excreted predominately by the kidney, brinzolamide is therefore contra-indicated is such patients. However, in patients with moderate renal impairment (creatinine clearance 30-60 mL/min/1.73 m^2) there is no need for dose adjustments with topical administration of brinzolamide 1%.

Section 5.2:

Elimination

Brinzolamide is predominately cleared by the kidney as unchanged drug (60%) and other 20% is ~~cleared by hepatic metabolism~~ **excreted in the urine as metabolites**.

No new and potentially significant safety findings have been identified, however, there is new safety information that is considered "minimum safety" which has been incorporated as part of this update.

Section 4.5:

- Interactions:

The following change (in bold) was introduced:

- [Brinzolamide 10mg/mL Eye Drops, Suspension] 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 **(i.e. NSAIDs and Salicylates)** must be considered in patients receiving [Brinzolamide 10 mg/mL Eye Drops, Suspension].

Section 4.6

Both the fertility and pregnancy statements have been updated as follows in strikethrough and bold. The recommendations for Pregnancy and Breastfeeding have been added.

- 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 male or female** ~~human~~ fertility. **No effect on fertility was observed in rats after oral administration of brinzolamide**.

- Pregnancy:

There are no or limited amount of data from the use of ophthalmic brinzolamide in pregnant women. Studies in animals with brinzolamide have shown reproductive toxicity following systemic administration. **Animal studies using brinzolamide showed no teratogenicity at doses up to 18 mg/kg/day and 6 mg/kg/day in rats and rabbits respectively**. **Decrease in fetal body weight and**

an increase in developmental variations in rats were observed at an oral dose of 18 mg/kg/day given orally (514 times recommended human ophthalmic dose). (See section 5.3)

[Brinzolamide 10 mg/mL Eye Drops, Suspension] is not recommended during pregnancy. *

- Breastfeeding:

It is unknown whether brinzolamide/metabolites are excreted in human milk following topical ocular administration; however, a risk to the suckling child cannot be excluded.

In animal studies following oral administration, minimal levels of brinzolamide were detected in breast milk.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from [Brinzolamide 10 mg/mL Eye Drops, Suspension] therapy taking in to account the benefit of breast-feeding for the child and the benefit of therapy for the woman. *

Section 4.8:

- Clinical Trials: Data from 4 clinical trials were added (C-10-033, C-10-039, C-10-040, C-14-03). No changes to the known safety profile of the product identified.
- Post-Marketing Surveillance: No terms added.

New CCDS. CCDS TDOC-0017242 v1.0.

The following changes have been made to the previous reference document (CCSI)- TDOC-0014825.

TDOC-0014825 v2.0, June 2013:

The following changes have been made which do not reflect any new and potential important safety findings for the product:

- The document has been adapted to current CCSI templates/standards.
- Section 4.6:
    - Fertility: Added information about non-clinical data that showed no effects on fertility.

- Breast-feeding: reworded as per CCSI standards. Added: “a risk to the suckling child cannot be excluded” and that “minimal levels” of brinzolamide were detected in animal breast milk.

- Section 4.8:

  Clinical Trials:

  - Terms that changed frequency:
    - Headache from common to uncommon
    - Dry eye and eye discharge from common to uncommon
    - Visual acuity reduced and periorbital oedema from uncommon to rare
    - Irritability from uncommon to rare
  - Terms that were added: **insomnia, eye irritation, conjunctivitis allergic, heart rate irregular, nasal dryness**, ***chest pain* and tinnitus****.

    *change in frequency: previously included from Post-marketing ADRs with unknown frequency in CCSI v1.0

  Post-Marketing Surveillance:

  - Terms that were added: **decreased appetite.**
  - Terms that were excluded: Tinnitus and chest pain were deleted from post-marketing table and added to clinical trials table with a frequency**. Medication residue** was combined with the already existing term eyelid margin crusting and excluded from CCSI.

TDOC-0014825 v1.0, Nov 2011:

Not applicable. New CCSI.

8. APPENDICES

Not applicable.