MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

Patient information leaflet
Brinamide

Eye Drops (suspension) 10 mg/ml

/stamp: AGREED with the Ministry of Health of the Republic of Belarus. The order of the Ministry of Health of the Republic of Belarus dated 16/05/2016 No 455/
KLS No. 4 dated 27.04.16

Invented name: Brinamide
International Nonproprietary Name: Brinzolamide
Dosage Form: eye drops (suspension) 10 mg/ml
Description: homogenous suspension from white to almost white colour.
1 ml of suspension contains:
Active substance
Brinzolamide – 10 mg
Excipients: benzylalkonium chloride, mannitol, 974P carbomer, disodium edetate, sodium chloride, sodium hydroxide and/or hydrochloric acid for pH dilution, purified water.
Pharmacotherapeutic group: antiglaucomic drugs and miotics, carbonic anhydrase inhibitors
ATC code: S01EC04.
Pharmacological properties
Pharmacodynamics
Mechanism of action
Carbonic anhydrase is a ferment, which is presented in many human body tissues, including eye tissues. Carbonic anhydrase acts as a reversible reaction catalyst, including carbon dioxide hydration and carbonic acid dehydration. Eye ciliary body carbonic anhydrase inhibition leads to the intraocular liquid secretion decrease mainly by bicarbonate ions formation reduction followed by sodium level and liquid transportation decrease. The result of such action is that the intraocular pressure (IOP) decrease, which is the main risk factor of pathogenesis of the ophthalmic nerve damage and visual field loss at glaucoma. Brinzolamide is a carbonic anhydrase II inhibitor, which is the major eye isoferment, with IC_{50} compound equal to 3.2 nM and K_i compound equal to 0.13 nM *in vitro* in regard to carbonic anhydrase II.
Clinical efficacy and safety
Brinzolamide IOP lowering effect has been studied as a concomitant therapy drug to Prostaglandine analogue – Travoprost. After 4 weeks of initial Travoprost therapy, the patients with IOP ≥ 19 mm HG were randomly divided into sub-groups, that were receiving Brinzolamide or Timolol additional therapy. The additional decrease of average daily IOP by 3.2 – 3.4 mm HG was observed in the patient group, getting Brinzolamide therapy, and by 3.2 – 4.2 mm HG in the patient group, getting Timolol therapy. The frequency of non-serious adverse reactions in vision organs, mainly connected with signs of local irritation, was higher in the patient group, getting Brinzolamide/Travoprost therapy. The severity of the adverse reactions was low, and the adverse reactions did not influence the general indicators of the therapy cessation during these studies.
Pediatric use
Clinical studies of Brinzolamide have been conducted with participation of 32 pediatric patients, younger than 6 years old, having been diagnosed with glaucoma or eye hypertension.

Some patients did not receive any IOP-reducing drug therapy, while others have been administered IOP reducing medicine. The patients, who had been previously administered IOP-reducing medicine, didn't require drug administration cessation before the beginning of Brinzolamide monotherapy. Brinzolamide efficiency was the same in 10 patients, who had not previously received any IOP reducing drug therapy, as in adult patients examined earlier, with the initial level of average IOP reduction to 5 mm HG. Among the patients (22 patients) who had previously received local IOP-reducing drug therapy, the average IOP slightly increased as compared with the initial level in the patients group, who had been administered Brinzolamide.

/stamp: AGREED with the Ministry of Health of the Republic of Belarus. The order of the Ministry of Health of the Republic of Belarus

Pharmacokinetics

Adsorption

After local application, Brinzolamide gets into the system circulation.

Distribution

Due to its high similarity to carbonic anhydrase II, Brinzolamide is quickly distributed between erythrocytes, and is characterized by the prolonged period of blood-circulating half-life (on average, about 24 weeks).

Metabolism

Metabolite N-deethylbrinzolamide, which is also bound with carbonic anhydrase and cumulated in erythrocytes, is formed in a human body. This metabolite is bound mainly with carbonic anhydrase I in Brinzolamide presence. Brinzolamide and N-deethylbrinzolamide plasma concentrations are low, and, as a rule, they are lower than the limit of quantification (< 7.5 ng/ml).

Plasma proteins binding is not extensive (about 60%).

Elimination

Brinzolamide is eliminated mainly with urine (about 60%). About 20% of the drug dosage is eliminated with urine in the form of metabolites. Brinzolamide and N-deethylbrinzolamide, as well as low amounts (< 1%) of N-demethoxypropyl and O-demethylated metabolite, are mainly detected in urine.

During the drug pharmacokinetics studies, healthy volunteers were prescribed oral capsules, with dosage of 1 mg of brinzolamide twice a day for 32 weeks. In order to evaluate the system carbonic anhydrase inhibition level, carbonic anhydrase erythrocytes activity was measured.

Carbonic anhydrase II of erythrocytes saturation with brinzolamide was reached within 4 weeks (with erythrocytes concentration about 20 μM). N-deethylbrinzolamide was cumulated in erythrocytes till its stable concentration totaled 6-30 μM for 20-28 weeks. Total activity of erythrocytes carbonic anhydrase inhibition under balanced conditions was about 70 – 75%.

Pharmacokinetics in particular medical cases

Patients with moderate *renal insufficiency* (creatinine clearance 30-60 ml/min) were prescribed 1 mg of Brinzolamide for oral application twice a day for 54 weeks. Brinzolamide concentration in erythrocytes by the beginning of the 4^{th} week of therapy was from 20 till 40 μM. Under balanced conditions the concentrations of brinzolamide and its metabolite in erythrocytes were within the range of 22.0 – 46.1 and 17.1 – 88.6 μM, respectively. N-deethylbrinzolamide concentrations in erythrocytes increased and the total carbonic anhydrase activity in erythrocytes decreased while the creatinine clearance lowered, however brinzolamide concentration in erythrocytes and carbonic anhydrase II activity remained unchanged. In patients with significant renal insufficiency, the total carbonic anhydrase inhibition level was higher, though it did not exceed 90% under balanced conditions.

During the studies of local application in ophthalmology, brinzolamide concentration in erythrocytes under balanced conditions remained on the same level as its concentration, determined at oral administration; however N-deethylbrinzolamide concentration was lower. Carbonic anhydrase activity was about 40 – 70% as compared with the initial level.

Indications for use

The lowering of the increased intraocular pressure at intraocular hypertension, open-angle glaucoma, as monotherapy at adult patients, not sensitive to beta-blockers, or as concomitant therapy by beta-blockers or prostaglandin analogues.

/stamp: AGREED with the Ministry of Health of the Republic of Belarus. The order of the Ministry of Health of the Republic of Belarus

Contraindications

- Increased sensibility to any of the Brinamide drug product compounds;
- Detected increased sensitivity to sulfonamides;
- Severe renal insufficiency;
- Hyperchloremic acidosis.

Precautions

System action

Brinamide is a sulfonamide carbonic anhydrase inhibitor and, despite of its local application, it is absorbed systematically. If applied locally, the adverse drug reactions, characteristic of sulfonamides, can be observed. If serious adverse drug reactions or an increased sensitivity are observed, the Brinamide drug product administration should be stopped.

If oral carbonic anhydrase inhibitors were administered, the cases of acid-alkaline balance disturbance were reported. The patients with renal insufficiency development risk should be administered Brinamide with caution because of possible metabolic acidosis risk.

Brinzolamide effect in premature infants (with the gestation term less than 36 weeks) or children younger than 1 week, was not studied. Patients with the significant hypotrophy or renal tubules function disturbances should be administered Brinzolamide only after a careful evaluation of risk-benefit ratio because of the metabolic acidosis risk.

Carbonic anhydrase inhibitors for oral application can influence the activity, which require increased attention and/or coordination of movements. As Brinamide eye drops characterized by system adsorption, such action can also be observed if applied locally.

Concomitant therapy

When using brinzolamide patients getting oral carbonic anhydrase inhibitors therapy and brinzolamide are at risk of additive effect of carbonic anhydrase inhibition. Concomitant oral administration of Brinamide and carbonic anhydrase is not recommended, as it was not studied.

Firstly, brinzolamide action was studied at simultaneous Timolol use as an additional therapy for a glaucoma treatment. In addition to this, brinzolamide effect for the elevated intraocular pressure decrease for concomitant therapy to Prostoglandine analogue – Travoprost – was studied. There are no data on long-term brinzolamide administration as additional therapy to Travoprost.

There are scarce data on brinzolamide application in patients with pseudoexfoliative glaucoma or pigment glaucoma treatment. Treatment of such patients should be careful; constant monitoring of intraocular pressure level is recommended. Brinzolamide action was not studied at patients with narrow-angle glaucoma. Brinzolamide use is not recommended for such patients.

Possible brinzolamide effect at cornea endothelium function in patients with cornea function disturbances (in particular, in patients with low endothelium cell amount) was not studied.

Brinzolamide usage by the patients, wearing contact lenses, was not studied. Such patients should be carefully monitored, as carbonic anhydrase inhibitors can influence cornea hydration, and contact lenses can increase the risk of cornea impact. Careful monitoring of patients with cornea function disturbance, for example, patients with diabetes mellitus or cornea dystrophy, is recommended.
There are data, that benzalkonium chloride, used as preserving agent in ophthalmology products, causes droplet keratopathy and/or toxic ulcerous ceratopathy. As Brinamode drug product contains benzalkonium chloride, the patients with eye dryness or cornea damage should be carefully monitored.

/stamp: AGREED with the Ministry of Health of the Republic of Belarus. The order of the Ministry of Health of the Republic of Belarus

Brinamide used by the patient wearing *contact lenses*, was not studied. The suspension contains benzalkonium chloride, which can cause eye irritation and de-colour soft contact lenses. The drug should not contact with lenses. Patient should be warned that contact lenses must be removed before Bronamide eye drops application and used not earlier than 15 minutes later.
Possible inverted effects after brinzolamide application cessation were not studied. The supposed duration of the increased intraocular pressure lowering effect is 5-7 days.
Pediatric use
Safety and effectiveness of Brinamide drug product application in infants, children and teenagers aged 0-17, are not established, so drug product use for this age group treatment is not recommended.
Drug use during pregnancy and breastfeeding
Data on brinzolamide ophthalmology use by pregnant women are either absent, or scarce. Animal studies showed toxic effect on reproduction function during its system application. Bronamide administration is not recommended for pregnant women and also for reproductive age women, who do not use contraceptives.
It is unknown whether brinzolamide and its metabolites get into breast milk in case of the local ophthalmological application. During animals studies, small amounts of brinzolamide getting into the breast milk when applied orally, were detected.
A risk for the newborns/infants cannot be excluded. When making a decision on terminating breast feeding or Brinamide application cessation/refusal, the ratio of breast feeding benefit for a child and the benefit for a woman therapy should be evaluated.
The animal studies didn't show any fertility effect. Human studies on fertility effect with brinzolamid ophthalmological local application were not conducted.
The ability to drive a vehicle and work with mechanisms.
Temporary vision haziness or other vision disturbances can influence the possibility to drive a car and work with mechanisms. In case of blurred vision after applying the eye drops, it is necessary to wait till the eye vision is restored before driving a car or working with mechanisms.
At carbonic anhydrase inhibitors oral administration, a patients' performance, which requires mental activity and/or physical coordination, can be lowered.
Mode of application and dosage
Dosage
When the drug is applied as monotherapy or concomitant therapy, one drop of Brinamide is instilled into the conjunctival sac of the affected eye twice a day. Some patients are prescribed one drop three times a day for a better treatment response.
The dosage correction for *elderly patients* is not required.

Brinzolamide application *in patients with renal insufficiency* was not studied, thus not recommended.
Brinzolamide application in *patients with a severe renal insufficiency* (creatinine clearance lower than 30 ml/min) or at *patients with hyperchloremic acidosis* was not studied. As brinzolamide and its main metabolite are eliminated by kidneys, the drug product administration is contraindicated for such patients.
Mode of application
For local application in ophthalmology.

/stamp: AGREED with the Ministry of Health of the Republic of Belarus. The order of the Ministry of Health of the Republic of Belarus

When any antiglaucomic drug product is replaced by Brinamide, the drug product administration should be stopped and Brinamide administration should be started on the following day.
The vial with the drug product should be well-shaken before use. After the cap is opened, the protective ring, regulating the first opening, is removed.
Before the eye drops application *contact lenses* should be taken off and put on 15 minutes later after Brinamide application.
In order to prevent the dropping-tip of the vial and the suspension from contamination, care should be taken and the dropping vial should not touch the eyelid, adjacent areas and other surfaces.
It is recommended to press slightly the inner eye corner after the drug instillation for nasolacrymal duct covering, or slightly open the eyelids. Such actions can lower the system absorption of the opthalmological drug product for the local use and, as a result, decrease the system adverse reactions.
The vial should be stored tightly closed.
If more than one drug product for ophthalmology application is used they should be applied independently, with the interval between instillations not less than 5 minutes. Eye ointments are the last to be applied.
If *a drug product administration was missed*, the administration should be restarted from the next dose according to the schedule. The dose should not exceed 1 drop into the conjunctival sac three times a day.
Side effect
In clinical trials with 2732 patients, who were administered brinzolamide as a monotherapy or in combination with timolol maleate 5 mg/ml, the following side effects were reported the most frequently: dysgeusia (6.0%) (bitter or unusual after-taste in the mouth after instillation), temporary blurred vision (5.4%) after instillation with the duration from several seconds till several minutes.
Frequent side reactions (from ≥1/100 till <1/10):
Concerning organs of vision: vision disturbance, eye irritation, eye pain, the foreign body sensation in the eye, eye hyperemia.
Concerning digestive system: dysgeusia (bitter or unusual after-taste in the mouth after instillation).
Infrequent side effects (from ≥1/1000 till <1/100):
Infectious and invasive diseases: nasopharyngitis, pharyngitis, sinusitis.
Concerning blood and lymphatic system: the decreased amount of red blood cells, hyperchloremia.
Concerning nervous system: dyskinesia, amnesia, giddiness, paresthesia, headache, apathy, depression, suppressed mood, decrease libido, nightmares, anxiety.

Concerning organs of vision: cornea erosion, keratitis, droplet keratitis, keratopathy, eye deposits, cornea colouring, cornea epithelium damage, cornea epithelium damage, blepharitis, eye itching, conjunctivitis, eye edema, meimobite, blicks, photophobia, allergic conjunctivitis, pterygium, sclerae pigmentation, asthenopia, eye discomfort, eye feeling disturbance, dry keratoconjunctivitis, subconjunctival cyst, conjunctiva hyperemia, eyelids itching, eye discharge, eyelid margin skin flacking, watery eyes.
Concerning cardiovascular system: cardiac-respiratory insufficiency, bradycardia, heat beating.
From the side of breathing system, chest and mediastinum: apnoea, nasal bleeding, oropharynx pain, pharyngolaryneal pain, throat irritation, upper airways, cough, rhinorrhea, sneezing.
Concerning digestive system: esophagitis, diarrhea, nausea, vomiting, dyspepsia, pain in the upper belly part, stomach discomfort, flatulency, frequent feces, gastric diseases, hypoesthesia or paresthesia of the mouth cavity, dryness in the mouth.

/stamp: AGREED with the Ministry of Health of the Republic of Belarus. The order of the Ministry of Health of the Republic of Belarus

Concerning skin and subdermal tissues: rash, maculopapular rash, skin tightness.
Concerning skeletal and muscular system and connective tissue: back ache, muscular spasms, myalgia.
Concerning urinary system: pain at the kidneys area.
Concerning reproductive system: erection dysfunction.
General and local reactions: pain, discomfort in the chest area, asthenia, ailment.
Traumas, toxication and prescription complications: foreign body sensation in the eye.
Rare side effects (from ≥1/10000 till <1/1000):
Concerning nervous system: memory disorder, drowsiness, insomnia.
Concerning hearing organs and vestibular apparatus: ringing in the ears.
Concerning cardiovascular system: angina, irregular heart rhythm.
Concerning respiratory system, chest and mediastinum: bronchial hyperreactivity, upper airways obstruction, sinus congestion, nasal congestion, cough, nasal dryness.
Concerning skin and subdermal tissues: hives, alopecia, generalized pruritus.
General and local reactions: pain in the chest, feeling of anxiety, asthenia, nervousness.
Unknown side effects (can't be evaluated according to the present data):
Infections and invasions: rhinitis.
Concerning the immune system: hypersensitivity.
Concerning the digestive system: appetite decrease.
Concerning the nervous system: tremor, hypoesthesia, ageusia.
Concerning organs of vision: cornea disturbances, vision disturbance, eye allergy, madarosis, eyelids disturbances, eyelids erythema.
Concerning hearing organs and vestibular apparatus: vertigo.
Concerning cardio-vascular system: arrhythmia, tachycardia, arterial hypertension, increased arterial pressure, decrease arterial pressure, increase heart rate.
Concerning respiratory system, chest and mediastinum: asthma.
Disturbances from the side of liver and bile ducts: fictional probes deviations from normal values.
Concerning skin and subdermal tissues: dermatitis, erythema.
Concerning skeletal and muscular system and connective tissue: arthralgia, pain in extremity.
Concerning urinary system: pollakiuria.
General and local reactions: peripheral oedema, ailment.

Description of some side effects.
According to the clinical investigations data, dysgeusia (bitter or unusual after-taste in the mouth after instillation) is the most frequent system side effect, connected with brinzolamide administration. Most probably, it is connected with eye drops getting into the pharyngonasal cavity through the nasolacrymal duct. In order to reduce this side effect, it is recommended to press the inner eye corner slightly after the drug instillation for nasolacrymal duct covering, or slightly open the eyelids.
Brinamide is a sylphonamide carbonic anhydrase inhibitor with system absorption. Adverse side effects concerning gastrointestinal tract, nervous system, blood system, kidneys, and metabolism-connected effects are usually connected with carbonic anhydrase administration. When applied locally, the adverse reactions similar to those of peroral carbonic anhydrase administration are possible.
Using brinzolamide as a concomitant therapy to Travoprost had no unexpected side effects. The adverse effects, registered within a combined therapy, are also observed at each of the drugs' monotherapy application.

/stamp: AGREED with the Ministry of Health of the Republic of Belarus. The order of the Ministry of Health of the Republic of Belarus

Children
During small short-term clinical trials, the side effects were observed in 12.5% pediatric patients, the majority of which were local non-serious ophthalmological reactions, such as conjunctiva hyperemia, eyes irritation, lacrimation increase.

Overdosing
The drug overdosing symptoms were not reported.
The treatment should be symptomatic and supporting. Electrolyte balance disturbance, acidosis development, side effects concerning nervous system may appear. Electrolytes level (particularly, potassium) in blood serum and blood pH should be monitored.

Other drugs interaction
Special studies of possible brinzolamide interaction with other drugs were nor conducted. During clinical trials brinzolamide was used in combination with Prostaglandin analogues and timolol-based ophthalmological drugs. Adverse drugs interactions cases were not registered. Brinzolamide interaction with miotics or adrenergic receptors agonists at combined glaucoma therapy were not conducted.
Brinzolamide is a carbonic anhydrase inhibitor, and at its local application, it has system absorption. At carbonic anhydrase peroral administration, some cases of acid-alkaline balance disturbances were registered. The possibility of such interaction in case pf Brinamide drug product application should be considered.
Cytochrome P-450 isoferments, responsible for brinzolamide metabolism, include CYP2A6, CYP2C8 and CYP2C9. CYP3A4 inhibitors, such as ketoconazole, intraconazole, clotrimazole, ritonavir and troleandomycin should be expected to inhibit brinzolamide metabolism, connected with CYP3A4 isoferment. The concomitant CYP3A4 inhibitors should be used with caution. However, brinzolamide accumulation is unlikely, as it is eliminated mainly through kidneys. Brinzolamide is not cytochrome P-450 isoferments inhibitor.

Storage conditions and shelf-life
The drug should be stored protected from light at the temperature not lower than 25 ^{o}C.
The drug should be kept out of reach of children.
Shelf life is 2 years. It should not be used after the shelf-life expiration, indicated on the package. After the vial is opened, the suspension shall be used within 28 days.

Dispensing requirements
The drug product is dispensed on prescription.
Package
1 vial with a package insert in a cardboard packaging.
Manufacturing company
Lusomedicamenta Sociedade Tecnica Farmaceutica, S.A., Portuguese
Packaged by:
TriplePharm, JLLC, Minskaya street, building 2B, 223141, Logoisk, Minsk region, Republic of Belarus, tel./fax: (+375) 1774 43 181, e-mail: triplepharm@gmail.com