SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Moxifloxan 5 mg/ml, eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance in 1 ml moxifloxacin hydrochloride eq. to 5 mg moxifloxacin.

Excipients: for the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution

Appearance: clear liquid with light yellow to light greenish-yellow color

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Topical treatment of bacterial conjunctivitis caused by moxifloxacin suceptible strains (see sections 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterials.

4.2 Posology and method of administration

The product is intended for topical ocular administration only. It is not intended for injection. The solution should be administered subconjunctivally or administered directly into the anterior chamber.

Posology

Use in adults, incl. the elderly (over 65 years)
The dose is one drop in the affected eye / eyes, three times daily.
The infection usually improves within 5 days; treatment should be continued then for another 2-3 days. If there is no improvement within up to 5 days after initiation of treatment, diagnosis and/or treatment should be reconsidered. The duration of treatment depends on the severity of the condition and on the clinical and bacteriological development of the infection.

Paediatric population
No adjustment is necessary in the indicated dose.

Patients with hepatic and renal impairment
No adjustment is necessary in the indicated dose.

Method of administration
Ocular use

To protect the dropper tip and the solution from contamination, the eyelids, adjacent areas or other surfaces should not come into contact with the tip of the dropper.

To prevent absorption of the medicinal product through the nasal mucosa, especially in newborn infants (neonates) or children the nasolacrimal duct must be pressed with a finger after instilling the drops for 2 to 3 minutes.

If more than one medicinal products for ocular use are to be instilled, this should be done at least 5 minutes apart.

4.3 Contraindications

Hypersensitivity to moxifloxacin, to other quinolones or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

There are serious, sometimes fatal hypersensitivity (anaphylactic) reactions in patients with systemic administration of quinolones, including after the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (incl. laryngeal, pharyngeal and facial edema), airway obstruction, dyspnea, urticaria and pruritus (see section 4.8).

The product should be discontinued in the event of an allergic reaction associated with the use of Moxifloxan. Serious acute hypersensitivity reactions to moxifloxacin or any of the other ingredients of the product may require emergency treatment (e.g. subcutaneous administration of adrenaline). If necessary, intravenous glucocorticoids, oxygen therapy, control and maintenance of breathing should be applied where clinically indicated.

As with other antibacterial agents, long term administration of moxifloxacin can result in overgrowth of non-susceptible organisms, including fungi. Should superinfection appear, the use of the product must be discontinued and appropriate alternative treatment initiated.

Systemic therapy with fluoroquinolones, including moxifloxacin may lead to inflammation and tendon rupture, particularly in elderly patients and patients treated with corticosteroids. After ocular administration of moxifloxacin, plasma concentrations are significantly lower than after oral administration of therapeutic doses; nevertheless this should be carefully considered and treatment should be discontinued at the first sign of tendon inflammation.

The data on safety and efficacy in the treatment of conjunctivitis in neonates are very limited. Therefore, this medicinal product is not recommended for use in the treatment of conjunctivitis in neonates.

Moxifloxan should not be used for the prevention or empirical treatment of gonococcal, incl. gonococcal ophthalmia of the newborn due to widespread resistance of fluoroquinolones against *Neisseria gonorrhoeae*. Patients with ocular infections caused by *Neisseria gonorrhoeae*, must be subjected to an appropriate systemic treatment.

The use of this product in children less than 2 years with conjunctivitis caused by *Chlamydia trachomatis* is not recommended due to lack of evidence of efficacy and safety. Children over 2 years of age with eye infections caused by *Chlamydia trachomatis*, should receive appropriate systemic treatment.

Neonates with ophthalmia neonatorum should be subject to appropriate treatment, incl. systemic treatment in cases of *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

Patients should be instructed not to wear contact lenses in case of signs and symptoms of bacterial ocular infection.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with moxifloxacin 5 mg/ml eye drops, solution. Given the low systemic concentration of moxifloxacin following topical ocular administration (see. 5.2), drug interactions are unlikely to occur.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data on the use of moxifloxacin-containing eye drops in pregnant women. Due to the negligible systemic exposure no adverse effects on pregnancy and foetus can be expected. This product can be used during pregnancy.

Breastfeeding
It is not known whether ocular moxifloxacin is excreted in breast milk. Studies in animals have shown excretion of small amounts in breast milk after systemic administration. When used in therapeutic doses Moxifloxan is not expected to cause any adverse effects on the infant. This product can be used during breastfeeding.

4.7 Effects on ability to drive and use machines

As with all products for ophthalmic use, transient blurred vision or other disturbances may affect the ability to drive or use machines. If blurred vision occurs following the application of the drops, the patient must wait until the vision clears before driving or using machines.

4.8 Undesirable effects

No serious ocular or systemic adverse reactions have been reported in clinical trials. The most commonly reported adverse reactions were eye irritation and eye pain (1% and 2%) with moderate severity, which usually did not require treatment discontinuation.

The following convention is used for classification of adverse effects in terms of frequency: 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), not known (frequency cannot be estimated from the available data).

Within each frequency grouping, adverse drug reactions are listed in order of decreasing seriousness.

Blood and lymphatic system disorders
Rare: decreased haemoglobin.

Immune system disorders
Not known: hypersensitivity.

Nervous system disorders
Uncommon: headache.
Rare: paresthesia.
Not known: dizziness

Eye disorders
Common: eye pain, eye irritation.
Uncommon: punctate keratitis, dry eye, ocular hyperaemia, eye pruritus, conjunctival haemorrhage, discomfort, eyelid oedema
Rare: corneal epithelial defects, corneal disorder, conjunctivitis, blepharitis, eye swelling, conjunctival oedema, blurred vision, decreased visual acuity, asthenopia, eyelid erythema.
Not known: endophthalmitis, ulcerative keratitis, corneal erosion, abrasion of the cornea, increased intraocular pressure, opacification of the cornea, corneal infiltrates and deposits, eye allergy, keratitis, corneal oedema, photophobia, corneal disorder, eyelid oedema, increased lacrimation, eye discharge, foreign body sensation.

Cardiac disorders
Not known: palpitations

Respiratory, thoracic and mediastinal disorders
Rare: nasal discomfort, pharyngolaryngeal pain, foreign body sensation in the throat.
Not known: dyspnoea.

Gastrointestinal disorders
Uncommon: dysgeusia
Rare: vomiting
Not known: nausea.

Hepato-biliary disorders
Rare: increased levels of ALAT, GGT.

Skin and subcutaneous tissue disorders
Not known: erythema, rash, pruritus, urticaria.

Paediatric population
Data from clinical studies, incl. in newborns shows that the type and severity of adverse reactions in children are similar to those in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

The limited retaining capacity of the conjunctival sac for ophthalmic products practically rules out any possible overdose with moxifloxacin.

The entire amount of moxifloxacin in a single pack is too small to cause adverse reactions after accidental ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; anti-infectives; other anti-infectives, ATC code: S01AX22

Mechanism of action
Moxifloxacin is a fourth generation fluoroquinolone. Like other fluoroquinolones, it inhibits DNA gyrase and topoisomerase IV, required for replication of bacterial DNA, recombination and recovery.

Resistance
Resistance to moxifloxacin, like other fluoroquinolones, mainly occurs as a result of a chromosomal gene mutations encoding DNA gyrase and topoisomerase IV. In gram-negative microorganisms, it may be due to mutations in *mar* (multiple antibiotic resistance) and *qnr* (quinolone resistance) gene systems. The resistance is also associated with bacterial expression of efflux proteins, and inactivate enzymes. Cross-resistance to beta-lactam antibiotics, macrolides and aminoglycosides is not expected due to differences in their mechanism of action.

Susceptibility testing range

There are no pharmacological data which correlate with the clinical outcome of the use of topical moxifloxacin. As a result, the European Committee of antimicrobial susceptibility testing (EUCAST) proposed the following epidemiological limits (ECOFF mg / l), derived from MIC distribution curves, to demonstrate susceptibility to topical moxifloxacin.

Corynebacterium	ND
Staphylococcus aureus	0.25 mg/l
Staphylococcus coag-neg.	0.25 mg/l
Streptococcus pneumoniae	0.5 mg/l
Streptococcus pyogenes	0.5 mg/l
Streptococcus, viridans group	0.5 mg/l
Enterobacter spp.	0.25 mg/l
Haemophilus influenzae	0.125 mg/l
Klebsiella spp.	0.25 mg/l
Moraxella catarrhalis	0.25 mg/l
Morganella morganii	0.25 mg/l
Neisseria gonorrhoeae	0.032 mg/l
Pseudomonas aeruginosa	4 mg/l
Serratia marcescens	1 mg/l

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of moxifloxacin in at least some types of infections is questionable.

Antimicrobial spectrum

Commonly susceptible species
Aerobic Gram-positive microorganisms *Corynebacterium* species incl. *Corynebacterium diphtheriae* *Staphylococcus aureus* (methicillin susceptible) *Streptococcus pneumoniae* *Streptococcus pyogenes* *Streptococcus viridans* group **Aerobic Gram-negative microorganisms** *Enterobacter cloacae* *Haemophilus influenzae* *Klebsiella oxytoca* *Moraxella catarrhalis* *Serratia marcescens* **Anaerobic microorganisms:** *Proprionibacterium acnes* **Other microorganisms:** *Chlamydia trachomatis*
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms Staphylococcus aureus (methicillin resistant) Staphylococcus, coagulase-negative species (methicillin resistant) **Aerobic Gram-negative microorganisms** Neisseria gonorrhoeae Other microorganisms:

None

5.2 Pharmacokinetic properties

Topical moxifloxacin instilled into the eye is absorbed to a moderate extent. Following tid application of the product in both eyes for 4 days under steady-state conditions C_{max} values were about 2.7 ng / ml and AUC 41.9 ng.h / ml respectively. These values were 1600 and 1200 times lower than those obtained after oral administration of therapeutic doses of 400 mg moxifloxacin. The estimated plasma half-life of moxifloxacin was 13 hours.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

As with other quinolones, moxifloxacin is genotoxic *in vitro* in bacteria and mammalian cells. Since these effects can be traced by interaction with the bacterial gyrase and in significantly higher concentrations in the interaction with Topoisomerase II in mammalian cells, it can be assumed that there is a threshold of genotoxicity. Regardless of the high doses of moxifloxacin in *in vivo* testing evidence of genotoxicity cannot be found. Therapeutic doses in humans therefore provide adequate safety range. There was no indication of carcinogenic effect in initial production model in rats.

Unlike other quinolones, moxifloxacin showed no phototoxic and photogenotoxic properties in extensive i*n vitro* and *in vivo* studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Boric acid
Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 (three) years from date of manufacture.
Shelf life after first opening: 28 days

6.4 Special precautions for storage

Store below 25°C.
Store in a tightly closed bottle.
Do not freeze.

6.5 Nature and contents of container

Sterile white plastic vials closed with a plastic dropper and sealed with sterile screw cap with a protective ring.

Contents of the pack: 1 (one) vial, together with a package leaflet in a cardboard box.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Antibitic-Razgrad AD
Office 201, 68 “Aprilsko vastanie” Blvd
Razgrad 7200
Bulgaria

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

06/2015