SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dexamphenicol 5 mg/ml+1 mg/ml, eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances in 1 ml solution: Chloramphenicol 5 mg and Dexamethasone sodium phosphate equivalent to Dexamethasone 1 mg.

Excipient with known effect: benzalkonium chloride

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Appearance: colourless to pale yellow opalescent liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dexamphenicol eye drops are intended for inflammation of the anterior segment where corticosteroids are indicated and when complicated with secondary bacterial infection caused by microorganisms susceptible to chloramphenicol or when the possibility of such infection is suspected.

Consideration should be given to official local guidance on the appropriate use of antibacterial agents before initiating treatment with this product.

4.2 Posology and method of administration

Posology

Adults
1 drop of solution to be instilled in the affected eye/eyes 3-5 times daily.
The dose may be increased to 1 drop every hour in severe cases.

The recommended duration of treatment should not exceed 10 days.

Elderly (over 65 years)
No dose adjustment is required in this patient group.

Paediatric population
There are no data from controlled trials in the paediatric population.
Administration of this product in infants aged from 28 days to three months and children aged less than 2 years should only be indicated in exceptional cases, given the possible systemic adverse affects (see section 4.4).

The product should not be given to infants aged less than 28 days (infants aged from 0 to 27 days) (see section 4.3).

Method of administration
The drops should be instilled in the conjunctival sac and in order to reduce the absorption of the medicinal product through the nasal mucosa and potentiate the local activity, particularly in neonates, infants and children, the nasolacrimal duct should be pressed with fingers for 2-3 minutes or the eyes closed for 3 minutes after the instillation.

The applicator tip must not be in contact with the eyelids, the adjacent skin around the eyes or other surfaces to avoid contamination when instilling the eye drops in the affected eye/eyes.

In the event of concomitant administration with other medicinal product intended for ocular use, the applications should be performed at least 5 minutes apart.

4.3 Contraindications

- Hypersensitivity to dexamethasone, chloramphenicol or to any of the excipients listed in section 6.1.
- Corneal impairment not associated with bacterial infection and ulcerative processes;
- Herpes simplex and other viral infections;
- Mycosis and other fungal infections;
- Blood disorders associated with bone marrow suppression;
- Family history of bone marrow suppression;
- Hepatic impairment;
- Infants aged less than 28 days (from 0 to 27 days).

4.4 Special warnings and precautions for use

The product is intended for topical ocular administration only. The solution is not intended for subconjunctival or direct administration into the anterior chamber.

The occurrence of bone marrow aplasia (although in very rare cases) associated with long-term use of chloramphenicol, including topical ocular administration cannot be excluded. Irreversible form of aplasia might occur after a latent period of weeks and months.

Prolonged use might result in a secondary ocular infection or overgrowth of non-susceptible bacteria. As with other corticosteroids dexamethasone may in turn mask the symptoms or the exacerbation of an ocular infection due to its pronounced anti-inflammatory effect.
As with other antibiotics, monitoring is recommended for symptoms of superinfections caused by non-susceptible organisms, including fungi.

In the event of superinfection, appropriate alternative treatment should be applied.

Prolonged use of corticosteroids intended for ocular use may increase the intraocular pressure. Patients with glaucoma or similar predisposition require regular monitoring of intraocular pressure, especially in long-term therapy.

Intensive prolonged therapy with corticosteroids for topical use, including dexamethasone, may lead to development or exacerbation of posterior subcapsular cataract.
The risk of posterior subcapsular cataracts and increased intraocular pressure is higher in patients with diabetes mellitus, and therefore the administration of the product in this patient group should be undertaken with caution.

Ocular administration of corticosteroids immediately after cataract removal surgery may result in a delayed healing and increased incidence of bullae formation.

The duration of treatment with this product should not exceed 10 days. In the absence of relevant clinical response after a three-day treatment, another therapeutic regimen should be considered.

There have been reports of perforation of the sclera and cornea associated with chronic use of topical corticosteroid products, especially in the event of diseases, leading to thinning of these eye structures.

Caution should be exercised during co-administration in the eye of topical corticosteroids and NSAIDs (see section 4.5).

When symptoms of bacterial ocular infection occur or such an infection is suspected, wearing contact lenses is contraindicated and patients should be instructed accordingly by their physician.

The product contains benzalkonium chloride as an excipient, which may cause eye irritation.
Contact with soft contact lenses should be avoided. The latter should be removed prior to application and re-inserted within at least 15 minutes.
Benzalkonium chloride is known to discolour soft contact lenses.

Paediatric population
Safety data in infants and children are limited, and therefore this medicinal product should be used with caution in infants aged from 28 days to three months and children aged less than 2 years.

4.5 Interaction with other medicinal products and other forms of interaction

This medicinal product must not be administered concomitantly with topical bactericidal antibiotics (cephalosporins, gentamicin, tetracycline, polymyxin B, vancomycin, sulfadiazine, etc.) since these may inhibit the bacteriostatic effect of chloramphenicol.

The use of this product is not acceptable during treatment with products for systemic use that may cause bone marrow suppression (sulphonylureas antidiabetic agents, coumarin derivatives, hydantoin, methotrexate).

Concomitant use of topical corticosteroids and NSAIDs intended for ocular use in patients with a history of corneal inflammation is not recommended and caution is required.

In patients treated concomitantly with multiple products intended for topical ocular administration, it is necessary to provide an interval of not less than 5 minutes between the applications in order to avoid possible interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy
Results of experimental studies in animals have shown evidence of adverse effects of chloramphenicol on the foetus (see section 5.3).

The use of chloramphenicol during pregnancy in humans may cause Grey baby syndrome.

In animal studies, topical ocular administration of therapeutic doses of dexamethasone may have teratogenic effects (see section 5.3).

There are no data from controlled prospective clinical trials in women, and therefore the product should not be used during pregnancy.

Breastfeeding
Chloramphenicol is excreted in breast milk and may cause bone marrow toxicity in infants therefore its use during breastfeeding is contraindicated.

4.7 Effects on ability to drive and use machines

As with all products for ophthalmic use, the application of Dexamphenicol eye drops may cause transient blurred vision or other disturbances which may affect the ability to drive or use machines.
In the event of blurred vision following application, the patient should be instructed to wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Undesirable effects may be associated with the presence of both chloramphenicol and dexamethasone in the composition of the product.

There are no post-marketing clinical trial data on potentiated toxicity between the two active substances.

Blood and lymphatic system disorders
There have been rare literature reports of irreversible blood dyscrasias (aplastic anemia, pancytopenia, leukopenia, thrombocytopenia, and agranulocytosis) with fatal outcome associated with the use of products for topical ophthalmic administration containing chloramphenicol.

Immune system disorders
There are literary data for anaphylactic reactions following topical ocular use of chloramphenicol.

There are rare reports of allergic reactions in the form of eczema affecting the corners of the mouth.

Nervous system disorders
In rare cases, a reversible optic neuritis may occur after ocular administration of chloramphenicol.

Eye disorders
The most commonly reported reactions are pruritus, conjunctival hyperemia, redness, oedema, foreign body sensation or other signs of irritation that were absent prior to treatment.

There are reports of burning and stinging as well as blurred vision following eye drops instillation.

Adverse reactions associated with the use of dexamethasone include increased intraocular pressure with possible development of glaucoma and subsequent impairment of the optic nerve and visual acuity and visual field loss, formation of posterior subcapsular cataracts, secondary ocular infection due to an inhibited response of the recipient.

Delayed wound healing, thinning of the cornea and /or perforation of the bulbus as well as development of ptosis and mydriasis are likely to occur.

Gastrointestinal disorders
Dysgeusia associated with the presence of chloramphenicol in the medicinal product.

There are case reports of systemic effects after topical ocular long-term administration of corticosteroids in high doses.

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 likelihood of overdose associated with topical application of the product is minimal. There are no reports of overdose.

In the event of ingestion of the vial contents, measures should be taken to delay and reduce the extent of absorption of active substances.
There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; anti-inflammatory agents and anti-infectives in combination; corticosteroids and anti-infectives in combination, ATC code: S01CA01

Mechanism of action
Dexamethasone inhibits phospholipase A2, the first step in the synthesis of prostaglandins, thereby preventing their formation, including that of leukotrienes, and other mediators of inflammation.

It inhibits the chemotactic migration of neutrophils into the inflammatory site and reduces the number and activity of lymphocytes.

Chloramphenicol is a bacteriostatic, broad spectrum antibiotic of low molecular weight, the activity of which is related to the selective inhibition of protein synthesis in the bacterial cell.

Pharmacodynamic effects
Dexamethasone has a pronounced anti-inflammatory effect that exceeds almost 25 times that of hydrocortisone. It exerts anti-allergic and antipruritic effects.

The antibacterial spectrum of chloramphenicol includes Gram-positive and Gram-negative bacteria: *Staphylococcus aureus, Streptococci*, incl. *Streptococcus pneumoniae, Haemophilus influenzae, Escherichia coli*, some strains of *Klebsiella / Enterobacter, Moraxella lacunata,* and some strains of *Neisseria.*

Susceptibility of chloramphenicol to *Pseudomonas aeruginosa* and *Serratia marcescens* is uncertain.

In vitro and *in vivo* resistance was found in certain strains of *Staphylococci, Salmonella, Shigella, E. coli, Pseudomonas aeruginosa*. The resistance is due to plasmid-mediated factors.

In vitro tests for determining susceptibility of bacteria isolated from eye surfaces with clinical symptoms of infection against various antibacterial agents have shown that chloramphenicol has the highest activity among all tested antibiotics, and minimal resistance.

5.2 Pharmacokinetic properties

After topical application into the eye, dexamethasone is absorbed rapidly and extensively, attaining high concentrations in ocular tissues and fluids.

Chloramphenicol quickly penetrates human cornea, and can be detected in the chamber fluid up to 5 hours after the administration, by attaining concentrations in the range of 3.5 – 6.7 mcg/ml up to 1-2 hours after application.

Systemic concentrations of chloramphenicol have not been detected following ocular administration of a solution (5 mg / ml), administered as 1 drop four times daily for 14 days, which however does not exclude the possibility of systemic absorption.

5.3 Preclinical safety data

Systemic administration of chloramphenicol at high doses in rats caused embryotoxic effects (retardation) accompanied by not very pronounced teratogenic effect.

In general corticosteroids, including dexamethasone, are known to exert a teratogenic effect in animals when administered systemically at relatively low doses. If administered during pregnancy they caused congenital abnormalities, such as cleft palate, deformities of the forearms, phocomelia and anasarca.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium phosphate dihydrate
Sodium dihydrogen phosphate dihydrate
Disodium edetate
Macrogol 400
Macrogol glycerol ricinoleate
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 (two) years from date of manufacture.
28 (twenty eight) days after opening of the bottle.

6.4 Special precautions for storage

Prior to first opening: Store in a refrigerator (2°C -8°C).
After first opening: store below 25°C.
Store in the original package.
Keep out of the reach of children.

6.5 Nature and contents of container

White plastic bottle with applicator-dropper, closed with a screw cap with a protective ring.

1 (one) bottle of 5 ml together with a package leaflet is packed in a cardboard box.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

10.2013