SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BetazonTrio 0.5 mg/g+10 mg/g+1 mg/g ointment

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances per 1 g of ointment:
Betamethasone dipropionate 0.643 mg, equivalent to betamethasone 0.500 mg
Clotrimazole 10.0 mg
Gentamicin sulfate equivalent to 1.0 mg gentamicin

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ointment.

Appearance: uniform ointment without air bubbles of white or off-white color.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Topical treatment in adults and children aged 3 years and older of corticosteroid-responsive dermatoses, when complicated with secondary infection caused by microorganisms susceptible to clotrimazole and gentamicin or when the possibility of such infection is suspected.

4.2 Posology and method of administration

Adults
A small amount of the product should be applied two times daily (morning and evening) to the affected skin area and the immediately adjacent skin area.

Children and adolescents
Adverse reactions associated with the use of the product are more common in children, therefore it should be used in accordance with the exact instructions given by the physician.

Older people
No dose adjustment is required in older people.

Method of administration
A thin film of the product should be applied, possibly by a gentle massage to facilitate penetration. Application of the least possible amount, required for achieving a therapeutic effect is recommended.

The duration of application depends on the extent and location of the disease and the patient's response to treatment.

Reassessment of the diagnosis is required if clinical improvement is not observed within 3-4 weeks of treatment.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

- Some skin infections (herpes simplex, herpes zoster, varicella, syphilis and tuberculosis of skin, acne vulgaris, rosacea);
- Perioral dermatitis;
- Perianal and genital pruritus;
- Children under 3 years.

4.4 Special warnings and precautions for use

Prolonged and intensive treatment with highly active corticosteroids may cause local atrophic skin changes and dilation of superficial blood vessels. This should be taken into consideration during prolonged application of the product on the facial skin surface, especially in the treatment of psoriasis, lupus erythematosus and severe eczema.

Prolonged use of topical antibiotics, incl. gentamicin and clotrimazole, could lead to development of resistance and susceptibility to superinfection. If such is suspected, treatment with the product should be discontinued and appropriate therapy undertaken with another antibacterial product. The use of occlusive dressings favors the development of infection in the affected skin areas.

There is cross-resistance between various aminoglycosides.

Prolonged use of topical corticosteroid preparations, their application in high doses or over large skin areas can result in significant systemic absorption, which in turn may cause suppression of the hypothalamic-pituitary-adrenal system, with the development of clinical manifestations of hypercortisolism. These events are more common in children or with the frequent use of occlusive dressing (diapers can have a similar effect).

The use of topical corticosteroids in the treatment of psoriasis vulgaris may result in chronification, tolerance, risk of generalized pustular psoriasis and local or systemic toxicity due to impaired barrier function of the skin.

In the event of hypersensitivity reactions or symptoms of superinfection, the product should be discontinued.

The product should be used with caution in the eye and contact with the eyeball surfaces should be avoided, as it might cause glaucoma.

Long-term application of gentamicin on large skin areas or areas of impaired skin integrity may lead to significant absorption and related systemic effects.

The product should not be applied to open wounds or impaired skin integrity.

Paediatric population
As a result of the increased absorption due to the greater ratio of skin area/body weight children may be more sensitive than adults to topical corticosteroid- associated suppression of hypothalamic-pituitary-adrenal axis and to glucocorticosteroid effects.
Limited duration of application is required in these patient groups (4-5 days).
In children treated with topical corticosteroids, there were reports for suppression of the hypothalamic-pituitary-adrenal axis, Cushing syndrome, growth retardation, delayed weight gain, and increased intracranial pressure.

4.5 Interaction with other medicinal products and other forms of interaction

Not known.

4.6 Fertility, pregnancy and lactation

Pregnancy
Application of topical corticosteroids in animals may lead to abnormalities in the fetus however there is no confirmed data on the relationship between the use of such products and teratogenic effects in humans.
Nevertheless prolonged use of the product, especially on large skin areas in pregnant women is not recommended and should only be used after careful evaluation of the benefit to the mother/risk to the fetus.

Breastfeeding
The safe use of this product in neonates and infants has not been established, and therefore caution is required when this product is used in these patient groups. It is recommended to discontinue breastfeeding during treatment with this product or discontinue therapy if possible.

4.7 Effects on ability to drive and use machines

BetazonTrio ointment has no effect on the ability to drive and use machines.

4.8 Undesirable effects

Immune system disorders
Redness, pruritus, irritation, rashes, skin inflammation

Endocrine disorders
Manifestations of hypercortisolism

Vascular disorders
Dilation of the superficial cutaneous blood vessels

Skin and subcutaneous tissue disorders
Atrophic skin changes, appearance of stretch marks, especially with the use of occlusive dressings and application in skin folds, hypopigmentation, hypertrichosis, allergic contact dermatitis, perioral dermatitis, maceration of the skin, pustular form of psoriasis vulgaris, secondary infections.

General disorders and administration site conditions
Local burning sensation or pruritus at the application site, erythema, skin depigmentation.

4.9 Overdose

Acute overdose with topical corticosteroids is unlikely to occur. During chronic continuous use on large skin surfaces or incorrect application symptoms of hypercortisolism may occur. In these cases gradual discontinuation is required as well as medical supervision for possible symptoms of adrenal insufficiency. Treatment should be symptomatic.

In case of accidental ingestion of the product, treatment should be identical to that of an overdose of corticosteroid products intended for oral administration.

Overdose with clotrimazole is unlikely to occur.

A single overdose of gentamicin is not expected to cause clinical symptoms. Long-term or excessive use of gentamicin can lead to expansion of the lesions caused by antibiotic-resistant microorganisms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dermatologicals, corticosteroids in combination with antibiotics, ATC code: D07CC01

Topical application of betamethasone is characterized by rapid, continuous and pronounced anti-inflammatory, antipruritic and vasoconstrictive effects. The presence of fluorine in its chemical structure enhances its anti-inflammatory activity which exceeds that of hydrocortisone almost 30 times; it has no mineralocorticoid activity. When applied topically, it does not lead to delayed healing of the skin lesions.

Clotrimazole has a broad spectrum antifungal activity. It is active against brewers' yeast, dermatophytes, *Aspergilus, Scopulariopsis, Trichophyton mentagrophytes, Trichophyton guinckeanum, Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis, Candida albicans*.

Gentamicin is a broad spectrum antibiotic with bactericidal activity. It is highly effective as an antibacterial agent. Its antimicrobial activity is higher than that of neomycin and kanamycin. Susceptible to its activity are bacteria from the Streptococci group (group A β-hemolytic and α-hemolytic), *Staphylococcus aureus* (coagulase-a-positive, coagulase negative and penicillinase-producing strains) and a number of gram-negative bacteria, such as *Pseudomonas aeruginosa, Aerobacter aerogenes, Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae*.

5.2 Pharmacokinetic properties

The extent of skin absorption is determined by the quality and composition of the vehicle, the integrity of the epidermis and the presence of occlusive dressing.

Topical corticosteroids are absorbed through intact skin as well. Inflammatory and other disease processes, and particularly the presence of atrophic skin changes facilitate the absorption.

Once in the systemic circulation the pharmacokinetic behavior of topical corticosteroids is similar to that of the products for systemic administration. They bind to plasma proteins and are metabolized primarily in the liver. The major route of elimination is renal.

When clotrimazole is applied topically to the skin the degree of systemic absorption is negligible and blood concentrations are of no relevant clinical significance.

If administered to intact skin gentamicin is not absorbed, but after prolonged use or over large skin surfaces, as well as on skin with impaired integrity is possible to pass into the blood. It is excreted unchanged in the urine.

5.3 Preclinical safety data

Betamethasone dipropionate
LD_{50} values of oral betamethasone in rats -> 4000 g/kg body weight. Acute intoxication is manifested by changes in behavior, changes affecting the skin and skin appendages.

It is known that corticosteroids in general exert teratogenic effects in experimental animals when administered systemically at relatively low doses. When administered during pregnancy they cause congenital abnormalities, such as palatoschisis, deformities of the forearms, phocomelia and anasarca.

Clotrimazole
LD_{50} values of oral clotiramozole in rats -> 708 mg/kg body weight
There is no convincing evidence for the absence of embryotoxic and teratogenic effects in experimental animals following exposure to clotrimazole.

Gentamicin sulfate

LD_{50} values of gentamicin sulfate in rats - 630 mg/kg bodyweight
There are no data for teratogenic effect of gentamicin in rats following intramuscular administration.
There are reports of damage to the auditory and vestibular nerve following high dose long-term treatment, especially in the second and third trimesters of pregnancy.
There is no evidence of carcinogenic and mutagenic effect.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Paraffin, liquid
Paraffin, white soft

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 (three) years from the manufacturing date
Shelf life after first opening of the container- 28 days

6.4 Special precautions for storage

Store below 25°C.
Keep this medicinal product out of the sight and reach of children.

6.5 Nature and contents of container

15 g BetazonTrio cream in aluminum tubes, polished, sealed with plastic screw cap with latex ring at the bottom edge of the tube.

One tube with a package leaflet is packed in a cardboard box.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Antibiotic-Razgrad AD
68 Aprilsko Vastanie blvd., office 201
Razgrad, Bulgaria
084 613318

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

October, 2014