TRIDERM® CREAM

Qualitative and Quantitative Composition

Active substances: betamethasone (as dipropionate); clotrimazole, gentamicin (as sulphate).

1 gram of TRIDERM Cream contains: 0.643 mg betamethasone dipropionate, equivalent to 0.5 mg betamethasone, 10.00 mg clotrimazole and 1.00 mg gentamicin (as sulfate).

Excipients with known effect:
Propylene glycol – 10.0% w/w, cetostearyl alcohol – 7.2% w/w, benzyl alcohol – 1.0% w/w

Excipients:
White soft paraffin, propylene glycol, cetostearyl alcohol, liquid paraffin, cetomacrogol 1000, benzyl alcohol, sodium dihydrogen phosphate dihydrate, phosphoric acid, sodium hydroxide, purified water.

Pharmaceutical form
Cream

Therapeutic Indications

TRIDERM Cream is indicated for the treatment of corticosteroid-responsive dermatoses when complicated by infections caused by bacteria (sensitive to gentamicin) and fungi (sensitive to clotrimazole) or when the possibility of such infections is suspected. The cream is suitable for the use of oozing eczema.

Posology and Method of Administration

General
N/A

Dose
A thin film of TRIDERM Cream should be applied to cover completely the affected and surrounding skin areas twice daily, in the morning and at night. For treatment to be effective, TRIDERM Cream should be applied regularly.

Duration of Treatment
Duration of therapy varies depending upon the extent and location of disease and patient response. However, if clinical improvement is not achieved by three to four weeks, diagnosis should be reviewed.

Method of Administration

FOR DERMATOLOGIC USE ONLY

Contraindications

Skin infections [of viral, bacterial (incl. TB) and fungal aetiology] or syphilitic skin diseases, chicken pox (varicella), herpes infections (e.g. fever blisters), vaccine reactions, skin ulcers and acne are contraindicated in the case of locally applied corticosteroids.

Facial application is not recommended in the presence of rosacea or perioral dermatitis.

TRIDERM Cream is not indicated for use beneath occlusive dressings and in case of open wounds or damaged skin areas.

TRIDERM Cream should not be applied to mucous membranes, to the eyes or the area surrounding the eyes.

Hypersensitivity to the active substances or to any of the excipients used in the preparation, other aminoglycoside antibiotics (cross allergy to gentamicin) or imidazole derivatives (cross allergy to clotrimazole).

Warnings and precautions

If irritation or sensitization develops with the use of TRIDERM Cream, treatment should be discontinued and appropriate therapy instituted.

When applied topically, systemic absorption of the active substances may be increased if TRIDERM Cream is used extensively, particularly during prolonged use or if applied to damaged skin. Under such conditions, undesirable effects, which are seen following systemic application of the active substances, may occur. In such cases, particular caution is recommended in pediatric use.

During concomitant systemic administration of aminoglycoside antibiotics, it should be remembered that, in cases of increased dermal absorption, a cumulative toxic effect (ototoxicity, nephrotoxicity) is likely.
In particular, a possible cross reaction with other aminoglycoside antibiotics should be taken into consideration.

During long-term treatment with preparations containing antibiotics, non-susceptible microorganisms may develop. In such an event or at the onset of a superinfection appropriate treatment should be instituted.

High-dose, extensive or occlusive application of potent or highly-potent corticosteroids should only take place under regular, medical supervision; particularly in regard to the suppression of endogenous corticosteroid production and a possible metabolic effect.
Application onto open wounds and damaged skin should be avoided.

A period of 2-3 weeks continuous treatment should preferably not be exceeded.

Long-term continuous or improper use of topical steroids may result in rebound effects at the end of treatment (topical steroid withdrawal syndrome). A severe form of a rebound effect may develop in the form of dermatitis with intense redness, stinging, and burning that may extend beyond the original treated area. The probability of occurrence is greater when sensitive skin areas such as the face or flexures are treated. If there is a return of the original symptoms within days or weeks after successful treatment, a withdrawal reaction is suspected (see "Undesirable Effects"). Reapplication should only be done with caution and in these cases, specialist advice is to be sought or other treatment to be considered.

Highly potent, potent and medium-dose corticosteroids should be used with caution in the facial and genital region; treatment should not exceed one week in such cases.

Generally speaking, only low-dose corticosteroids should be used around the eyes (due to the risk of glaucoma).

Corticosteroids may mask the symptoms of an allergic reaction to one of the product ingredients.

The patient should be instructed to use the product solely in the treatment of his/her current skin condition, and not to pass it on to others.

Visual disturbance may occur with systemic and topical (including, intranasal, inhaled and intraocular) use of corticosteroid. If a patient appears with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes of the visual disturbances; these include among others cataract, glaucoma or rare diseases for example such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Use in pediatric patients

Use of this product in paediatric patients younger than 2 years of age is not recommended. When compared with adults, paediatric patients may demonstrate greater susceptibility to hypothalamic-pituitary-adrenal (HPA) axis suppression (induced by topical corticosteroids) and to exogenous corticosteroid effects, as absorption in children is greater due to the higher skin surface area to body weight ratio.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain and intracranial hypertension have been reported in children receiving topical corticosteroids. Symptoms of adrenal suppression in children include low plasma cortisol levels and absence of response to ACTH stimulation. Symptoms of intracranial hypertension include bulging fontanelles, headache and bilateral papilledema.

Ceto-stearyl alcohol

The medicinal product may cause a localised skin reaction (e.g. contact dermatitis) due to the presence of ceto-stearyl alcohol.

Propylene glycol

This medicinal product contains propylene glycol 100 mg per 1 gram of the cream. Propylene glycol may cause skin irritation.

Benzyl alcohol
This medicinal product contains benzyl alcohol 10 mg per 1 gram of the cream. Benzyl alcohol may cause allergic reactions or mild local irritation.

Interactions

When TRIDERM Cream is used in the genital or anal region, the presence of petroleum jelly and liquid paraffin (excipients used in the product) may diminish the tear resistance of concomitantly used latex condoms, thereby compromising their safety when in use.

Clotrimazole, when applied topically, may have an antagonistic effect with regard to amphotericin and other polyene antibiotics.

Pregnancy and Lactation

Pregnancy
There are no data on its use in human pregnancies.
Aminoglycosides cross the placental barrier and may harm the foetus if administered to pregnant women. There have been reports of total, irreversible, bilateral, congenital deafness in infants whose mothers received aminoglycosides (including gentamicin) during pregnancy. Sufficient data on the use of topically applied gentamicin during pregnancy is lacking.
Sufficient data on the use of clotrimazole during pregnancy is lacking. Animal studies have not demonstrated any risks with regard to the foetus (see section “Preclinical data”).
TRIDERM Cream should only be used in cases where it is absolutely necessary. TRIDERM Cream should not be used extensively, in large amounts or over prolonged periods of time.

Lactation
It is not known whether gentamicin, clotrimazole and topically applied corticosteroids pass into breast milk. However, systemically available corticosteroids are excreted in breast milk.
If applied to the breasts, TRIDERM Cream may not be used by nursing mothers.

Effects on ability to drive and use machines

The effect on the ability to drive and operate machinery has not been studied.

Undesirable Effects

Frequencies are presented as follows:
Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 '000, <1/1000), very rare (<1/10'000), frequency not known (cannot be estimated from the available data).

Endocrine disorders
Endogenous corticosteroid synthesis suppression; overactive adrenal glands with oedema.

Metabolism and nutrition disorders
Manifestation of latent diabetes mellitus.

Eye disorders
Blurred vision

Ear and labyrinth disorders / Renal and urinary disorders
In cases of concomitant systemic administration of aminoglycoside antibiotics, cumulative ototoxicity/ nephrotoxicity can be expected if TRIDERM Cream used extensively or on damaged skin.

Initiation of treatment
Skin and subcutaneous tissue disorders
Rare irritations, burning sensations, pruritus, skin dryness, hypersensitivity reactions to one of the ingredients used in the product and skin discoloration.

Extensive, occlusive and/or prolonged use
During extensive, occlusive and/or prolonged use, local skin changes may occur. During extensive use, systemic effects (adrenal suppression) may occur.
It should be remembered that patients are at greater risk of developing secondary infections as a result of diminished local resistance to infection.

Localised skin changes such as atrophy (particularly facial), telangiectasia, striae, striae distensae, cutaneous bleeding, purpura, steroid acne, rosacea-like/ perioral dermatitis, hypertrichosis and skin discoloration. It is not known whether the skin discoloration is reversible.
Uncommon *(≥1/1000, <1/100)*: contact sensitisation to gentamicin.

Not known
Withdrawal reactions - skin redness that may extend beyond the original affected area, a burning or stinging sensation, itching, peeling skin, oozing vesicles (see "Warnings and Precautions").

Possible photosensitisation was observed in some patients; however, it was impossible to reproduce this effect when gentamicin was reapplied, with subsequent exposure to UV irradiation.

Musculoskeletal and connective tissue disorders
Osteoporosis, growth retardation (in children).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

Overdose

Signs and Symptoms
Excessive or prolonged use of topical corticosteroids may lead to a suppression of the pituitary-adrenal function and may cause secondary adrenal insufficiency and symptoms of adrenal cortex hyperactivity, including Cushing's syndrome.

It cannot be excluded that a single excessive dose of gentamicin might induce such symptoms. Excessive and prolonged use of topically applied gentamicin may lead to an increased growth of fungi or non-susceptible bacteria at the site of skin lesions.

Treatment
Appropriate symptomatic treatment is indicated. Acute symptoms of adrenal cortex hyperactivity are usually reversible. Electrolyte imbalances should be treated where required. In cases of chronic toxicity, withdrawal of corticosteroids should be gradual.

If overgrowth by non-susceptible microorganisms occurs, stop treatment with TRIDERM Cream and institute appropriate antimycotic or antibacterial therapy.

Properties/effects

ATC code
D07CC01

Mechanism of action
TRIDERM Cream combines three modes of action, i.e. the anti-inflammatory action of betamethasone dipropionate, the antibacterial effect of gentamicin and the antimycotic effect of clotrimazole.

Pharmacodynamics
Betamethasone dipropionate is a potent (Class III) corticosteroid, with an anti-inflammatory, anti-allergic and antipruritic effect.
Gentamicin is an aminoglycoside antibiotic with a bactericidal action. It acts by inhibiting protein synthesis in susceptible bacteria. Gentamicin is active against many aerobic gram-negative and a few gram-positive bacteria. *In vitro*, gentamicin concentrations of 1-8 µg/mL inhibit most susceptible strains of *Escherichia coli, Haemophilus influenzae, Moraxella lacunata, Neisseria*, indole-positive and indole-negative *Proteus, Pseudomonas* (incl. most *Pseudomonas aeruginosa* strains), *Staphylococcus aureus, Staphylococcus epidermidis* and *Serratia*. Various species and strains of the same species may exhibit major differences in terms of *in vitro* susceptibility. Furthermore, *in vitro* susceptibility does not always correlate with *in vivo* susceptibility. Gentamicin is ineffective against most anaerobic bacteria, fungi and viruses. Gentamicin is only minimally effective against streptococci.

Resistance to gentamicin may develop in both gram-negative and gram-positive bacteria.

Clotrimazole is a synthetic, imidazole-type antimycotic. Its spectrum of activity includes a range of fungi that are pathogenic to humans and animals. Clotrimazole is effective against dermatophytes, yeasts and moulds. During *in vitro* tests, clotrimazole was shown to be effective against *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis* and *Candida* (including *Candida albicans*). On the basis of current knowledge, the antimycotic effect of Clotrimazole is based on the inhibition of ergosterol synthesis. Ergosterol is an essential component of fungal cell membranes.

Clinical efficacy

No data available.

Pharmacokinetics

No penetration or absorption studies have been performed on this medicinal product.

Absorption

Betamethasone

Its penetration and permeation rate depend on the site of application, skin condition, the galenic formulation being used, patient age and method of application.

Gentamicin

Absorption need hardly be considered when gentamicin is used on intact skin. However, increased percutaneous absorption should be taken into consideration in cases of keratin layer loss, inflammations and occlusive/ extensive application.

Clotrimazole

Following application, systemic absorption is low, with the majority of clotrimazole remaining in the stratum corneum. The following concentrations were observed at 6 hours following application of 1 % radioactive clotrimazole on intact and acutely inflamed skin: stratum corneum = 100 mcg/cm^3, reticular layer = 0.5-1 µg/cm^3, subcutis = 0.1 µg/cm^3.

Distribution

Under normal conditions, only a fraction of the locally applied amount of betamethasone is systemically available.

Metabolism

No data available.

Elimination

No data available.

Preclinical data

Betamethasone

In animal studies, topical application of corticosteroids was shown to have a teratogenic effect.

Corticosteroid studies using animal models have shown that bethamethasone is toxic to reproduction (cleft palate, skeletal malformations).

In reproduction toxicity studies on rats, prolonged gestation, prolonged labour and dystocia were recorded. Furthermore, a reduction in offspring survival was observed, as well as decreased body weight and a reduction in weight gain. There was no evidence of impaired fertility.

Mutagenicity and carcinogenicity have not been studied.

Gentamicin

In studies to evaluate the chronic toxicity of gentamicin, nephrotoxic and ototoxic effects have been observed in various species. To date, mutagenicity studies have revealed no mutagenic potential for the product; however, current data do not allow any definitive risk evaluation to be made. There have been no long-term studies on animals to evaluate the carcinogenic potential of the substance.

Clotrimazole

Studies on animal models have revealed no mutagenic, teratogenic or embryotoxic properties.

Other information

Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after first opening: 3 months.

Special precautions for storage

Store below 25°C.

Keep out of the reach and sight of children.

Packs sizes

15 g and 30 g tubes

Not all pack sizes may be marketed.

Manufacturer:

Organon LLC, NJ USA

License Holder and address:

Organon Pharma Israel Ltd., 1 Atir Yeda, Kfar Saba

License number:

105.13.28792

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