SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trimovate Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Trimovate Cream is a yellow water-miscible cream containing clobetasone 17-butyrate 0.05% w/w, oxytetracycline 3.0% w/w as calcium oxytetracycline and nystatin 100,000 units per gram.

Excipients with known effect:

Cetostearyl alcohol

Chlorocresol

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Cream

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clobetasone 17-butyrate is a moderately potent topical corticosteroid indicated for adults, elderly, children and infants for the relief of the inflammatory and pruritic manifestations of steroid responsive dermatoses. Nystatin is a polyene antifungal. Oxytetracycline is a broad spectrum antibiotic.

Topical preparations combining clobetasone with nystatin and oxytetracycline are indicated for the treatment and management of steroid responsive dermatoses where candidal or bacterial infection is present, suspected or likely to occur.

These include the following:

- Atopic dermatitis
- Nappy rash
- Intertrigo
- Anogenital pruritis
- Seborrhoeic dermatitis

4.2 Posology and method of administration

Adults, Elderly, Children and Infants

For topical use only.

Creams are especially appropriate for moist or weeping surfaces.

Apply thinly and gently rub in using only enough to cover the entire affected area once or twice a day for up to seven days.

If the infection worsens, treatment and diagnosis should be re-evaluated as soon as possible.

If the condition does not improve within seven days, treatment and diagnosis should be re-evaluated.

Treatment should not be continued for more than seven days without medical supervision.

Allow adequate time for absorption after each application before applying an emollient. Patients should be advised to wash their hands after applying clobetasone with nystatin and oxytetracycline, unless it is the hands that are being treated.

Rebound of pre-existing dermatoses can occur with abrupt discontinuation of topical corticosteroids especially with potent preparations. If further treatment is required to achieve control of the pre-existing dermatoses, it may be necessary to continue therapy with another corticosteroid preparation not containing nystatin and oxytetracycline

Children

Children are more likely to develop local and systemic side effects of topical corticosteroids and, in general, require shorter courses and less potent agents than adults (see Warnings and Precautions).

Care should be taken when using clobetasone with nystatin and oxytetracycline to ensure the amount applied is the minimum that provides therapeutic benefit.

Elderly

Clinical studies have not identified differences in responses between the elderly and younger patients. The greater frequency of decreased hepatic or renal function in the elderly may delay elimination if systemic absorption occurs. Therefore the minimum quantity should be used for the shortest duration to achieve the desired clinical benefit.

Renal / Hepatic Impairment

In case of systemic absorption (when application is over a large surface area for a prolonged period) metabolism and elimination may be delayed therefore increasing the risk of systemic toxicity. Therefore the minimum quantity should be used for the shortest duration to achieve the desired clinical benefit.

4.3 Contraindications

The following should not be treated with clobetasone with nystatin and oxytetracycline:
- Patients with known history of hypersensitivity to clobetasone butyrate, nystatin, oxytetracycline or any components of the formulation
- Primary cutaneous viral infections
- Primary infected skin lesions caused by infection with fungi, bacteria or yeasts
- Cutaneous infections caused by Acinetobacter species, methicillin resistant Staphylococcus aureus (MRSA), Pseudomonas species, Proteus species Serratia species or Streptococcus B.
- Rosacea
- Acne vulgaris
- Pruritus without inflammation.
- Perioral dermatitis

4.4 Special warnings and precautions for use

Instruct patients not to smoke or go near naked flames - risk of severe burns. Fabric (clothing, bedding, dressings etc.) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

<u>Pseudomembranous colitis</u>

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. Although this is less likely to occur with topically applied oxytetracycline, if prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression
Manifestations of hypercortisolism (Cushing's syndrome) and reversible hypothalamic-pituitary-adrenal (HPA) axis suppression can occur in some individuals as a result of increased systemic absorption of topical corticosteroids. If either of the above are observed, withdraw the drug gradually by reducing the frequency of application or by substituting a less potent corticosteroid. Abrupt withdrawal of treatment may result in glucocorticosteroid insufficiency (see section 4.8).

Risk factors for increased corticosteroidal systemic effects are:
- Potency and formulation of topical steroid
- Duration of exposure
- Application to a large surface area
- Use on occluded areas of skin e.g. on intertriginous areas or under occlusive dressings (in infants the nappy may act as an occlusive dressing).
- Increasing hydration of the stratum corneum
- Use on thin skin areas such as the face
- Use on broken skin or other conditions where the skin barrier may be impaired.

Paediatric population
In comparison with adults, children and infants may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic adverse effects. This is because children have an immature skin barrier and a greater surface area to body weight ratio compared with adults.

In infants and children under 12 years of age, long-term continuous topical corticosteroid therapy should be avoided where possible, as adrenal suppression can occur.

Infection risk with occlusion
Bacterial infection is encouraged by the warm, moist conditions within skin folds or caused by occlusive dressings. When using occlusive dressings, the skin should be cleansed before a fresh dressing is applied.

Infection
Extension of infection may occur due to the masking effect of the steroid. Any spread of infection requires withdrawal of topical corticosteroid therapy and administration of appropriate antimicrobial therapy.

Application to the face
Prolonged application to the face is undesirable as this area is more susceptible to atrophic changes.

Application to the eyelids
If applied to the eyelids, care is needed to ensure that the preparation does not enter the eye, as cataract and glaucoma might result from repeated exposure.

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents 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 which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Chronic leg ulcers
Topical corticosteroids are sometimes used to treat the dermatitis around chronic leg ulcers. However, this use may be associated with a higher occurrence of local hypersensitivity reactions and an increased risk of local infection.

Local hypersensitivity
Local hypersensitivity reactions may resemble symptoms of the condition under treatment (see section 4.8). If signs of hypersensitivity appear, application should be stopped immediately.

Contact sensitisation
Extended or recurrent application of clobetasone with nystatin and oxytetracycline may increase the risk of contact sensitisation.

Staining
Clobetasone with nystatin and oxytetracycline may cause slight staining of hair, skin or fabric, but this can be removed by washing. The application may be covered with a non-occlusive dressing to protect clothing.

Dilution
Products which contain antimicrobial agents should not be diluted.

Photosensitivity reactions
Photosensitivity reactions may occur in hypersensitive persons and such patients should be warned to avoid direct exposure to natural or artificial sunlight and to discontinue therapy at the first sign of skin discomfort.

Trimovate contains cetostearyl alcohol and chlorocresol
Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis). Chlorocresol may cause allergic reactions.

Long term continuous or inappropriate use of topical steroids can result in the development of rebound flares after stopping treatment (topical steroid withdrawal syndrome). A severe form of rebound flare can develop which takes the form of a dermatitis with intense redness, stinging and burning that can spread beyond the initial treatment area. It is more likely to occur when delicate skin sites such as the face and flexures are treated. Should there be a reoccurrence of the condition within days to

weeks after successful treatment a withdrawal reaction should be suspected. Reapplication should be with caution and specialist advice is recommended in these cases or other treatment options should be considered.

The label will state moderate steroid.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administered drugs that can inhibit CYP3A4 (e.g. ritonavir, itraconazole) have been shown to inhibit the metabolism of corticosteroids leading to increased systemic exposure. The extent to which this interaction is clinically relevant depends on the dose and route of administration of the corticosteroids and the potency of the CYP3A4 inhibitor.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are limited data from the use of clobetasone butyrate in pregnant women.

Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development (see section 5.3).The relevance of this finding to human beings has not been established.

Systemic administration of tetracyclines after the fourth month of pregnancy has been associated with discoloration of the child's teeth. However, during topical administration the amounts systemically absorbed are unlikely to be significant (see section 5.2).

Administration of clobetasone with nystatin and oxytetracycline during pregnancy should only be considered if the expected benefit to the mother outweighs the risk to the foetus. The minimum quantity should be used for the minimum duration.

Breast-feeding

The safe use of topical clobetasone with nystatin and oxytetracycline during lactation has not been established.

It is not known whether the topical administration of clobetasone with nystatin and oxytetracycline could result in sufficient systemic absorption to produce detectable amounts in breast milk.

Administration of clobetasone with nystatin and oxytetracycline during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant. If used during lactation, clobetasone with nystatin and oxytetracycline should not be applied to the breasts to avoid accidental ingestion by the infant.

Fertility

There are no data in humans to evaluate the effect of topical clobetasone with nystatin and oxytetracycline on fertility.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of clobetasone with nystatin and oxytetracycline on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the adverse reaction profile of topical clobetasone with nystatin and oxytetracycline.

4.8 Undesirable effects

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000), not known (cannot be estimated from the available data), including isolated reports.

Post-marketing data

Infections and Infestations
Not known: Opportunistic infection

Immune System Disorders
Not known: Hypersensitivity

Endocrine Disorders
Not known: Hypothalamic-pituitary adrenal (HPA) axis suppression: (see also Skin and Subcutaneous Tissue Disorders).
Cushingoid features (e.g. moon face, central obesity), delayed weight gain/growth retardation in children, osteoporosis, glaucoma, hyperglycaemia/glucosuria, cataract, hypertension, increased weight/obesity, decreased endogenous cortisol levels

Skin and Subcutaneous Tissue Disorders
Common or very common: Telangiectasia
Not known (cannot be estimated from available data):

Allergic contact dermatitis/dermatitis, urticaria, skin atrophy*/skin thinning, pigmentation changes*, exacerbation of underlying symptoms, local skin burning/skin pain, hypertrichosis, rash (including erythematous and macropapular), pruritus, erythema, photosensitivity reaction

Withdrawal reactions – redness of the skin which may extend to areas beyond the initial affected area, burning or stinging sensation, itch, skin, peeling, oozing pustules. (See section 4.4)

**Skin features related to hypothalamic-pituitary adrenal (HPA) axis suppression.*

General Disorders and Administration Site Conditions
Not known: Application site pain/reaction

Eye disorders
Not known: Vision, blurred

Vascular disorders
Not known: Vasodilation

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms and signs

Topically applied clobetasone with nystatin and oxytetracycline may be absorbed in sufficient amounts to produce systemic effects. Acute overdosage is very unlikely to occur, however, in the case of chronic overdosage or misuse the features of hypercortisolism may appear (see Warnings and Precautions, Adverse Reactions).

In case of accidental ingestion, professional assistance should be sought or a national poisons centre contacted immediately.

Treatment

In the event of chronic overdosage or misuse, topical corticosteroids should be withdrawn gradually by reducing the frequency of application or by substituting a less potent corticosteroid because of the risk of adrenal insufficiency .

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code

D07CB Corticosteroids, moderately potent, combinations with antibiotics

Mechanism of action

Clobetasone butyrate

Topical corticosteroids act as anti-inflammatory agents via multiple mechanisms to inhibit late phase allergic reactions including decreasing the density of mast cells, decreasing chemotaxis and activation of eosinophils, decreasing cytokine production by lymphocytes, monocytes, mast cells and eosinophils, and inhibiting the metabolism of arachidonic acid.

Nystatin

Nystatin acts by binding to sterols in the cell membrane of the fungus with a resultant change in membrane permeability allowing leakage of essential cellular constituents.

Oxytetracycline

Oxytetracycline is a broad spectrum antibiotic that is active against a wide variety of bacteria. However, some strains of bacteria have developed resistance and it is not effective against Acinetobacter species, methicillin resistant Staphylococcus aureus (MRSA), Pseudomonas species, Proteus species, Serratia species or Streptococcus B.

Oxytetracycline inhibits cell growth by inhibiting translation. It binds to the 30S ribosomal subunit and prevents the amino-acyl tRNA from binding to the A site of the ribosome. The binding is reversible in nature. Oxytetracycline is lipophilic and can pass through the cell membrane or passively diffuse through porin channels in the bacterial membrane.

Pharmacodynamic effects

Clobetasone butyrate

Topical corticosteroids have anti-inflammatory, antipruritic and vasoconstrictive properties.

Nystatin

Nystatin is fungistatic or fungicidal in a range of both pathogenic and non-pathogenic yeasts and fungi. It is inactive against organisms that do not contain sterols in their cell membrane (e.g. bacteria, protozoa, viruses).

Oxytetracycline

Oxytetracycline inhibits growth of susceptible bacteria via inhibition of protein synthesis.

5.2 Pharmacokinetic properties

Absorption

Clobetasone butyrate

Topical corticosteroids can be systemically absorbed from intact healthy skin. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusion, inflammation and/or other disease processes in the skin may also increase percutaneous absorption.

Nystatin

Systemic absorption of nystatin after topical application is reported to be minimal. In an ex vivo skin permeation study of nystatin ointment, less than 1% of the drug was shown to penetrate through the human skin.

Oxytetracycline

No data exist on systemic absorption of oxytetracycline following topical application. Serum levels of tetracycline, which has similar properties to oxytetracycline, after twice-daily application of tetracycline lotion in acne patients have been reported to be 0.1 µg/mL or less in most patients. Therefore, minimal systemic absorption is expected after topical application of oxytetracycline.

Distribution

Clobetasone butyrate

Once absorbed into the systemic circulation, corticosteroids are rapidly distributed to all body tissues.

Nystatin

No data exist on the distribution of nystatin following topical or systemic absorption.

Oxytetracycline

No data exist on the distribution of oxytetracycline following topical absorption. After single intravenous injection, the volume of distribution of oxytetracycline ranged from 1.82 to 1.92 L/kg. The plasma protein binding of oxytetracycline is approximately 35%.

Metabolism

Clobetasone butyrate

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. They are metabolised, primarily in the liver.

Nystatin

No data exist on the metabolism of nystatin following topical or systemic absorption.

Oxytetracycline

Only small amounts are metabolised to inactive metabolites in the liver.

Elimination

Clobetasone butyrate

Topical corticosteroids are excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

Nystatin

Nystatin is reported to be excreted almost entirely in the fecal route unchanged after oral administration.

Oxytetracycline

Most of the drug is excreted via the kidney and biliary system. The elimination half-life after single intravenous injection ranged from 8.5 to 9.6 hours in normal young men.

5.3 Preclinical safety data

Nonclinical studies have not been conducted with clobetasone with nystatin and oxytetracycline. Clobetasone butyrate, nystatin and oxytetracycline individually have been evaluated in animal toxicity tests, and the following statements reflect the information available on the individual components.

Carcinogenesis/mutagenesis

Clobetasone butyrate

Long-term animal studies have not been performed to evaluate the carcinogenic potential of topical clobetasone butyrate. Clobetasone butyrate was not mutagenic in vitro or in vivo.

Nystatin

Long-term animal studies have not been performed to evaluate the carcinogenic potential of nystatin. No specific studies have been conducted to investigate the genotoxic potential of nystatin.

Oxytetracycline

Dietary administration of oxytetracycline hydrochloride to mice (6,300 or 12,500 ppm) or rats (25,000 or 50,000 ppm) continuously for 2 years indicate that this antibiotic is not carcinogenic in rodents. Oxytetracycline was not mutagenic in a host-mediated assay in mice. Oxytetracycline was genotoxic in a mouse bone marrow micronucleus assay.

Reproductive Toxicology

Fertility

The effect on fertility of clobetasone butyrate, nystatin or oxytetracycline has not been evaluated in animals.

Pregnancy

Clobetasone butyrate

Topical application of clobetasone butyrate to rats at doses of 0.5 or 5 mg/kg/day, and subcutaneous administration to mice at doses ≥3 mg/kg/day or rabbits at doses ≥30 µg/kg/day during pregnancy resulted in foetal abnormalities including cleft palate, intrauterine growth retardation and foetal loss.

Nystatin

Oral administration of nystatin to rats (500 mg/kg/day) during pregnancy produced no foetal abnormalities.

Oxytetracycline

Oral administration of oxytetracycline hydrochloride to mice (≥1200 mg/kg/day) or rats (≥1325 mg/kg/day) during pregnancy produced maternal and foetal toxicity, but did not produce any treatment-related increase in foetal abnormalities. Intramuscular administration during pregnancy produced foetal toxicity and abnormalities in dogs (20.75 mg/kg/day), foetal toxicity in rabbits (41.5 mg/kg/day), but no effects in rats (41.5 mg/kg/day).

Administration of oxytetracycline hydrochloride to rats in their food at a dose of 10 mg/kg of feed from days 1 to 18 of lactation and rabbits at a dose of 1 mg/kg/day

dissolved in milk from days 2 to 28 of lactation increased milk production in both species.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Titanium Dioxide
Glyceryl Monostearate
Cetostearyl Alcohol
White Soft Paraffin
Polyoxyl 40 Stearate
Dimethicone 20
Glycerol
Chlorocresol
Sodium Metabisulphite
Sodium Acid Phosphate
Disodium Hydrogen Phosphate Anhydrous
Purified Water

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25^0C.

6.5 Nature and contents of container

25gm and 30gm collapsible latex banded aluminum tube, internally coated with epoxy resin based lacquer, with polypropylene cap.

6.6 Special precautions for disposal

Patients should be advised to wash their hands after applying clobetasone butyrate with nystatin and oxytetracycline, unless it is the hands that are being treated.

7 MARKETING AUTHORISATION HOLDER

Ennogen IP Ltd,

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Riverside Way,

Dartford,

DA1 5BS, UK.

8 MARKETING AUTHORISATION NUMBER(S)

PL 55612/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

19/07/2024