TENOVATE GN

Clobetasol Propionate and Neomycin Sulphate Cream

QUALITATIVE AND QUANTITATIVE COMPOSITION

TENOVATE GN contains:

- Clobetasol Propionate I.P. 0.05% w/w
- Neomycin Sulphate I.P. 0.5 % w/w
- Imidurea I.P. 0.3% w/w (as preservative)
in a non-greasy base

PHARMACEUTICAL FORM

Cream.

CLINICAL PARTICULARS

Therapeutic Indications

TENOVATE GN is indicated in resistant dermatoses where secondary bacterial infection is present, suspected, or likely to occur e.g. psoriasis (excluding widespread plaque psoriasis), recalcitrant dermatoses.

Posology and Method of Administration

For topical use only.

Creams are especially appropriate for moist or weeping surfaces.

Adults and adolescents

Apply thinly and gently rub in using only enough to cover the entire affected area once or twice daily until improvement occurs. As with other highly active topical corticosteroid preparations, therapy should be discontinued when control is achieved. In the more responsive conditions this may be within a few days. If the condition worsens or does not improve within seven days, treatment and diagnosis should be re-evaluated. If a longer course is necessary, it is recommended that treatment should not be continued for more than four weeks. Repeated short courses of TENOVATE GN may be used to control exacerbations. If continuous corticosteroid treatment is necessary, a less potent preparation which does not contain neomycin sulphate should be used.

Allow adequate time for absorption after each application before applying an emollient.

Patients should be advised to wash their hands after applying TENOVATE GN, unless it is the hands that are being treated.
In very resistant lesions, especially where there is hyperkeratosis, the anti-inflammatory effect of TENOVATE GN can be enhanced, if necessary, by occluding the treatment area with polythene film. Overnight occlusion only is usually adequate to bring about a satisfactory response, thereafter improvement can usually be maintained by application without occlusion.

The maximum weekly dose should not exceed 50 g/week.

**Children aged 2 years and over**

TENOVATE GN is suitable for use in children (2 years and over) at the same dose as adults. A possibility of increased absorption exists in very young children, thus TENOVATE GN is contraindicated in neonates and infants (less than 2 years) (see *Contraindications*).

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 *Special Warnings and Special Precautions for Use*).

Care should be taken when using TENOVATE GN to ensure the amount applied is the minimum that provides therapeutic benefit.

**Elderly**

TENOVATE GN is suitable for use in the elderly. Caution should be exercised in cases where a decrease in renal function exists and significant systemic absorption of neomycin sulphate may occur (see *Special Warnings and Special Precautions for Use*). The minimum quantity should be used for the shortest duration to achieve the desired clinical benefit.

**Renal Impairment**

Dosage of TENOVATE GN should be reduced in patients with reduced renal function (see *Special Warnings and Special Precautions for Use*).

**Contraindications**

TENOVATE GN is contraindicated in patients who have demonstrated hypersensitivity to clobetasol propionate, neomycin sulphate, or any components of the formulation (see *Undesirable Effects*).

The following conditions should not be treated with TENOVATE GN

- Rosacea.
- Acne vulgaris.
- Perioral dermatitis.
- Pruritus without inflammation.
- Perianal and genital pruritus.
- Primary cutaneous viral infections (e.g., herpes simplex, chickenpox).
- Primary infected skin lesions caused by infection with fungi, bacteria or yeast.
- Secondary infections due to *Pseudomonas* or *Proteus* species;
- Otitis externa where the eardrum is perforated because of the risk of ototoxicity.
Due to the known ototoxic and nephrotoxic potential of neomycin sulphate, the use of TENOVATE GN in large quantities or on large areas for prolonged periods of time is contraindicated in circumstances where significant systemic absorption may occur.

A possibility of increased absorption exists in very young children, thus TENOVATE GN is contraindicated for use in neonates and infants (up to 2 years). In neonates and infants, absorption by immature skin may be enhanced and renal function may be immature.

**Special Warnings and Special Precautions for Use**

*Pseudomembranous colitis*

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 neomycin, 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 is 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 Undesirable Effects).

Risk factors for increased corticosteroidal systemic effects are:

- Potency and formulation of topical corticosteroid.
- Duration of exposure.
- Application to a large surface area.
- Use on occluded areas of skin e.g. on intertriginous areas or under occlusive dressings (nappies 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.

Visual disturbance has been reported by patients using systemic and/or topical corticosteroids. If a patient has blurred vision or other visual disturbances, consider evaluation of possible causes which may include cataract, glaucoma or central serous chorioretinopathy.

*Local hypersensitivity*

Local hypersensitivity reactions may resemble symptoms of the condition under treatment (see Undesirable Effects). If signs of hypersensitivity appear, application should be stopped immediately.
Use in Children

In comparison with adults, children 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.

Long-term continuous therapy should be avoided, particularly in children, as adrenal suppression can occur readily even without occlusion. If TENOVATE GN is required for use in children, it is recommended that the treatment should be limited to only a few days and reviewed weekly.

Application to the face

Application to the face is undesirable as, more than other areas of the body, this area may exhibit atrophic changes after prolonged treatment with potent topical corticosteroids. If used on the face, treatment should be limited to only a few days.

Application to 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 (see Undesirable Effects).

Use in Psoriasis

Topical corticosteroids may be hazardous in psoriasis for a number of reasons including rebound relapses, development of tolerance, risk of generalised pustular psoriasis (see Undesirable Effects) and development of local or systemic toxicity due to impaired barrier function of the skin. If used in psoriasis careful patient supervision is important.

Ototoxicity and nephrotoxicity

Following significant systemic absorption, aminoglycosides such as neomycin sulphate can cause irreversible ototoxicity. Neomycin sulphate also has nephrotoxic potential (see Contraindications).

Renal impairment

In renal impairment the plasma clearance of neomycin sulphate is reduced (see Posology and Method of Administration).

Contact sensitisation

Extended or recurrent application may increase the risk of contact sensitisation.

Dilution

Products which contain antimicrobial agents should not be diluted.

Infection
Extension of the infection may occur due to the masking effect of the corticosteroid. If infection persists, systemic chemotherapy may be required. Any spread of infection requires withdrawal of topical corticosteroid therapy.

**Infection risk with occlusion**

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

**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.

**Interactions with Other Medications and Other Forms of Interaction**

**CYP3A4 inhibitors**

Co-administered drugs that can inhibit CYP3A4 (e.g. ritonavir and 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.

**Neuromuscular blocking agents**

Following significant systemic absorption neomycin sulphate can intensify and prolong the respiratory depressant effects of neuromuscular blocking agents. However if used in accordance with the recommendations, systemic exposure to neomycin sulphate is expected to be minimal and the drug interactions are unlikely to be significant.

**Systemic aminoglycoside therapy**

Possibility of cumulative toxicity should be considered when neomycin sulphate is applied topically in combination with systemic aminoglycoside therapy.

**Pregnancy and Lactation**

**Fertility**

There are no data in humans to evaluate the effect of topical clobetasol propionate with neomycin sulphate on fertility.

Clobetasol propionate administered subcutaneously to rats had no effect upon mating performance; however, fertility was decreased at the highest dose (see Preclinical Safety Data). The relevance of this finding to humans has not been established.

**Pregnancy**
There are limited data from the use of clobetasol propionate and neomycin sulphate in pregnant women.

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

Neomycin present in maternal blood can cross the placenta and may give rise to a theoretical risk of foetal toxicity, thus the use of TENOVATE GN is not recommended in pregnancy.

**Lactation**

The safe use of clobetasol propionate during lactation has not been established. It is not known whether the topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable amounts in breast milk. Thus, use of TENOVATE GN is not recommended in lactation.

**Effects on Ability to Drive and Use Machines**

There have been no studies to investigate the effect of clobetasol propionate with neomycin sulphate 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 clobetasol propionate and neomycin sulphate.

**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), including isolated reports.

**Clinical trial data**

<table>
<thead>
<tr>
<th>Skin and Subcutaneous Tissue Disorders</th>
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<tbody>
<tr>
<td>Common:</td>
<td>Skin atrophy*, telangiectasis*</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Striae*</td>
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</tbody>
</table>

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

**Post-marketing data**

<table>
<thead>
<tr>
<th>Infections and Infestations</th>
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<tr>
<td>Very rare:</td>
<td>Opportunistic infection</td>
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<table>
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<tr>
<th>Immune System Disorders</th>
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<tr>
<td>Very rare:</td>
<td>Allergic reactions including anaphylaxis and hypersensitivity</td>
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<tr>
<th>Endocrine Disorders</th>
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<tr>
<td>Very rare:</td>
<td>Hypothalamic-pituitary adrenal (HPA) axis suppression: Cushingoid features (e.g. moon face,</td>
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<tr>
<td>Eye Disorders</td>
<td>Central obesity), delayed weight gain/growth retardation in children, osteoporosis, hyperglycaemia/glucosuria, hypertension, increased weight/obesity, decreased endogenous cortisol levels</td>
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**Eye Disorders**

Very rare: Cataract, central serous chorioretinopathy, glaucoma

**Skin and Subcutaneous Tissue Disorders**

Very rare: Skin thinning*, skin wrinkling*, skin dryness*, pigmentation changes*, hypertrichosis, exacerbation of underlying symptoms, allergic contact dermatitis/dermatitis, pustular psoriasis (see *Special Warnings and Special Precautions for Use*), erythema, rash, urticaria, alopecia*, trichorrhexis*, pruritus, local skin burning /skin pain, acne

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

**General Disorders and Administration Site Conditions**

Very rare: Application site irritation/pain

**Overdose**

**Symptoms and Signs**

Topically applied clobetasol propionate 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 *Special Warnings and Special Precautions for Use* and *Undesirable Effects*).

**Treatment**

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

Consideration should be given to significant systemic absorption of neomycin sulphate (see *Special Warnings and Special Precautions for Use and Interactions with Other Medications and Other Forms of Interaction*). If this is suspected, use of the product should be stopped and the patient's general status, hearing acuity, renal and neuromuscular functions should be monitored.

Blood levels of neomycin sulphate should also be determined. Haemodialysis may reduce the serum level of neomycin sulphate.

Further management should be as clinically indicated.
PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

*Clobetasol propionate*
Topical corticosteroids have anti-inflammatory, anti-pruritic, and vasoconstrictive properties.

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.

*Neomycin sulphate*
Neomycin sulphate interferes with bacterial protein synthesis by binding to 30S ribosomal subunits.

Neomycin sulphate has a bactericidal action against many Gram-negative bacteria but it lacks activity against *Pseudomonas aeruginosa*. It has partial activity against Gram-positive bacteria. It is used topically in the treatment of infections of the skin, ear, and eye due to susceptible *staphylococci* and other organisms.

Pharmacokinetic Properties

Absorption

*Clobetasol propionate*
Percutaneous penetration of clobetasol propionate varies among individuals and can be increased by the use of occlusive dressings, or when the skin is inflamed or diseased.

*Neomycin sulphate*
Absorption of neomycin sulphate has been reported to occur from wounds and inflamed skin. It is poorly absorbed from the gastrointestinal tract when administered orally.

Distribution

*Clobetasol propionate*
Mean peak plasma clobetasol propionate concentrations of 0.63 ng/ml occurred in one study 8 h after the second application (13 h after an initial application) of 30 g clobetasol propionate 0.05 % ointment to normal individuals with healthy skin. Following the application of a second dose of 30 g clobetasol propionate cream 0.05 % mean peak plasma concentrations were slightly higher than the ointment and occurred 10 h after application. In a separate study, mean peak plasma concentrations of approximately 2.3 ng/ml and 4.6 ng/ml occurred respectively in patients with psoriasis and eczema 3 h after a single application of 25 g clobetasol propionate 0.05 % ointment.

Clobetasol propionate is extensively bound to plasma proteins (> 90 %) and has a small volume of distribution.

*Neomycin sulphate*
Absorbed neomycin sulphate distributes to tissues and concentrates in the renal cortex.
**Metabolism**

*Clobetasol propionate*
Following percutaneous absorption of clobetasol propionate the drug probably follows the metabolic pathway of systemically administered corticosteroids. They are metabolised primarily in the liver. However, systemic metabolism of clobetasol propionate has never been fully characterised or quantified.

*Neomycin sulphate*
No data exist on the metabolism of neomycin sulphate following systemic absorption

**Elimination**

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

*Neomycin sulphate*
Absorbed neomycin sulphate is rapidly excreted by the kidneys as parent compound. It has been reported to have a half-life of 2 to 3 hours.

**Preclinical Safety Data**

Non-clinical studies have not been conducted with clobetasol propionate with neomycin sulphate.

Clobetasol propionate and neomycin sulphate individually have been evaluated in animal toxicity tests, and the following statements reflect the information available on the individual components.

**Carcinogenesis**

Carcinogenicity studies have not been conducted with clobetasol propionate individually.

**Genotoxicity**

*Clobetasol propionate*
Clobetasol propionate was not mutagenic in a range of *in vitro* bacterial cell assays.

*Neomycin sulphate*
Neomycin was negative in the Ames test, HGPRT mutation assay in Chinese hamster ovary (CHO) cells and mouse bone marrow micronucleus test.

**Reproductive Toxicology**

**Fertility**

*Clobetasol propionate*
In fertility studies, subcutaneous administration of clobetasol propionate to rats at doses of 6.25 to 50 μg/kg/day produced no effects on mating, and fertility was only decreased at 50 μg/kg/day.

Neomycin sulphate
The effect on fertility of neomycin sulphate has not been evaluated in animals.

Pregnancy

Clobetasol propionate
Subcutaneous administration of clobetasol propionate to mice (≥100 μg/kg/day), rats (400 μg/kg/day) or rabbits (1 to 10 μg/kg/day) during pregnancy produced foetal abnormalities including cleft palate and intrauterine growth retardation.

In the rat study, where some animals were allowed to litter, developmental delay was observed in the F1 generation at ≥100 μg/kg/day and survival was reduced at 400 μg/kg/day. No treatment related effects were observed in F1 reproductive performance or in the F2 generation.

Neomycin sulphate
The effect on fertility and pregnancy of neomycin sulphate has not been evaluated in animals.

PHARMACEUTICAL PARTICULARS

List of Excipients
Propylene glycol, Cetostearyl alcohol, Cetomacrogol 1000, Isopropyl myristate, Dimethicone 350, Sodium Citrate, Citric acid monohydrate, Imidurea (as preservative) and Purified water.

Incompatibilities
No incompatibilities have been identified.

Shelf Life
The expiry date is indicated on the label and packaging.

Special Precautions for Storage
Store at a temperature not exceeding 25°C. Do not freeze.

Keep out of reach of children.

Nature and Specification of Container
Aluminium tube in carton.

Instructions for Use/Handling
For external use only.
For further information, please contact:
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Adapted from: Clobetasol propionate with neomycin sulphate and nystatin (Dermovate-NN)
GDS 12 / IPI 05 dated 04 April 2018.