For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

TENOVATE™ NM

Clobetasol Propionate, Neomycin Sulphate and Miconazole Nitrate Cream

QUALITATIVE AND QUANTITATIVE COMPOSITION

TENOVATE NM contains:

Clobetasol propionate IP	0.05% w/w
Neomycin sulphate IP	0.5 % w/w
Miconazole nitrate IP	2.0 % w/w
Imidurea IP (as preservative) in a cream base	0.3% w/w

PHARMACEUTICAL FORM

Cream.

CLINICAL PARTICULARS

Therapeutic Indications

TENOVATE NM is indicated in resistant dermatoses where secondary bacterial infection and/or fungal infection is present, suspected, or likely to occur.

e.g., psoriasis (excluding widespread plaque psoriasis), recalcitrant eczemas.

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 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. However, treatment should not be continued for more than seven days without medical supervision. Repeated short courses of *TENOVATE NM* 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 NM*, unless it is the hands that are being treated.

In very resistant lesions, especially where there is hyperkeratosis, the anti-inflammatory effect of *TENOVATE NM* 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.

C***hildren aged 2 years and over***

TENOVATE NM 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 NM* 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 NM* to ensure the amount applied is the minimum that provides therapeutic benefit.

Elderly

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

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.

Contraindications

The following conditions should not be treated with *TENOVATE NM*:

- Hypersensitivity to any of the ingredients of the preparation.
- 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 NM* in large quantities or on large areas for prolonged periods of time is not recommended in circumstances where significant systemic absorption may occur.

A possibility of increased absorption exists in very young children, thus *TENOVATE NM* is not recommended 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.

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 NM* 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 sensitization

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.

If a reaction suggesting sensitivity or irritation should occur, the treatment should be discontinued.

Interactions with Other Medications and Other Forms of Interactions

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.

Miconazole administered systemically is known to inhibit CYP3A4/2C9. Due to the limited systemic availability after topical application, clinically relevant interactions are rare. However, in patients on oral anticoagulants, such as warfarin, caution should be exercised and anticoagulant effect should be monitored.

Pregnancy and Lactation

Fertility

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

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

Pregnancy

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

Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development (see *Pre-clinical Safety Data*). 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.

In animals miconazole nitrate has shown no teratogenic effects but is fetotoxic at high oral doses. Only small amounts of miconazole nitrate are absorbed following topical administration.

Thus the use of *TENOVATE NM* is not recommended in pregnancy.

Lactation

The safe use of clobetasol propionate, neomycin sulphate and miconazole 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.

Topically applied miconazole is minimally absorbed into the systemic circulation, and it is not known whether miconazole is excreted in human breast milk

Thus use of *TENOVATE NM* 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 and miconazole nitrate 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 with neomycin sulphate and miconazole nitrate.

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.

Clobetasol propionate

Clinical trial data

Skin and Subcutaneous Tissue Disorders	
Common:	Skin atrophy*, telangiectasis*
Uncommon:	Striae*

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

Post-marketing data

Infections and Infestations	
Very rare:	Opportunistic infection

Immune System Disorders	
Very rare:	Allergic reactions including anaphylaxis and hypersensitivity

Endocrine Disorders	
Very rare:	Hypothalamic-pituitary adrenal (HPA) axis suppression: 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	
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

Neomycin sulphate

The incidence of allergic hypersensitivity reactions to neomycin sulphate in the general population is low. There is, however, an increased incidence of hypersensitivity to neomycin in certain selected groups of patients in dermatological practice particularly those with venous stasis eczema and ulceration.

Allergic hypersensitivity to neomycin sulphate following topical application may manifest itself as a reddening and scaling of the affected skin, as an eczematous exacerbation of the lesion or as a failure of the lesion to heal.

Miconazole nitrate

Adverse drug reactions reported among 834 patients who received miconazole nitrate 2% cream (n=426) and/or placebo cream base (n=408) in 21 double-blind clinical trials are presented in Table 1 below. Moreover, adverse drug reactions from spontaneous reports during the worldwide post-marketing experience with miconazole nitrate 2% cream that meet threshold criteria are included in Table 1. The adverse drug reactions are ranked by frequency, using the following convention:
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)

Adverse reactions obtained from clinical studies and post-marketing surveillance are presented by frequency category based on incidence in clinical trials or epidemiology studies, when known.

Table 1: Adverse reactions reported in clinical trials and post-marketing experience

System Organ Class	**Adverse Reactions**	
	Frequency Category	
	Uncommon (≥1/1,000 to <1/100)	**Not known**
Immune System Disorders		Anaphylactic reaction Hypersensitivity Angioneurotic edema
Skin and Subcutaneous Tissue Disorders	Skin burning sensation Skin inflammation Skin hypopigmentation	Urticaria Contact dermatitis Rash Erythema Pruritus
General Disorders and Administration Site Conditions	Application site irritation Application site burning Application site pruritus Application site reaction NOS Application site warmth	

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, 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*, *Interactions with Other Medications and Other Forms of Interactions*). 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.

Excessive topical use of miconazole nitrate can result in skin irritation, which usually disappears after discontinuation of therapy.

TENOVATE NM is intended for cutaneous use, not for oral use. If accidental ingestion of large quantities of the product occurs, use appropriate supportive care.

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.

Miconazole Nitrate

Miconazole nitrate is an imidazole antifungal agent and may act by interfering with the permeability of the fungal cell membrane. It possesses a wide antifungal spectrum and has some antibacterial activity.

Pharmacokinetics

Clobetasol propionate

Absorption

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.

Distribution

Mean peak plasma clobetasol propionate concentrations of 0.63 ng/ml occurred in one study 8 hours after the second application (13 hours 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 hours 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 hours 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.

Metabolism

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.

Elimination

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

Neomycin sulphate

Absorption

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

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

Metabolism

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

Elimination

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.

Miconazole nitrate

Absorption

There is little absorption through skin or mucous membranes when miconazole nitrate is applied topically.

Distribution

Absorbed miconazole is bound to plasma proteins (88.2%) and red blood cells (10.6%).

Metabolism & Elimination

The small amount of miconazole that is absorbed is eliminated predominantly in faeces as both unchanged drug and metabolites.

Preclinical Safety Data

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

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

Clobetasol propionate

Carcinogenicity studies have not been conducted with clobetasol propionate individually.

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

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.

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

Carcinogenicity studies have not been conducted with neomycin sulphate individually.

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

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

Miconazole nitrate

Preclinical data on miconazole reveal no special hazard for humans based on conventional studies of local irritation, single and repeated dose toxicity, genotoxicity and toxicity to reproduction

Also see *Pregnancy and Lactation.*

PHARMACEUTICAL PARTICULARS

List of Excipients

Imidurea, Propylene glycol, Cetostearyl alcohol, Cetomacrogol 1000, Isopropyl Myristate , Dimethicone 350, Sodium citrate, Citric acid monohydrate and Purified Water.

Incompatibilities

No incompatibilities have been identified.

Shelf Life

18 months.

The expiry date is indicated on the label and packaging.

Special Precautions for Storage

Store below 25°C. Do not freeze.

Keep out of reach of children.

Nature and Specification of Container

Aluminium tube in a carton.

Instructions for Use/Handling

For external use only.

Patients should be advised to wash their hands after applying *TENOVATE NM*, unless it is the hands that are being treated.

For further information please contact:
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TENOVATE is a trademark of GlaxoSmithKline.

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