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

TENOVATE GN

1. GENERIC NAME

Clobetasol Propionate and Neomycin Sulphate Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains:

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

3. DOSAGE FORM AND STRENGTH

Cream.

4. CLINICAL PARTICULARS

4.1 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.

4.2 Posology and Method of Administration

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 for up to seven days, then change to another corticosteroid preparation not containing neomycin sulphate if further treatment is required. Allow adequate time for absorption after each application before applying an emollient.

In the more resistant lesions, such as the thickened plaques of psoriasis on elbows and knees, the effect of clobetasol propionate-neomycin sulphate 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 in such lesions; thereafter, improvement can usually be maintained by regular application without occlusion.

Treatment should not be continued for more than seven days without medical supervision. If the condition worsens or does not improve within seven days, treatment and diagnosis should be re-evaluated.

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 4.3 *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 4.4 *Special Warnings and Precautions for Use)*.

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

Elderly

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 Impairment

Dosage should be reduced in patients with reduced renal function (see 4.4 *Special Warnings and Precautions for Use*).

4.3 Contraindications

TENOVATE GN is contraindicated in children under 2 years of age.

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 (see 4.2 *Posology and Method of Administration)*.

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.
- Primary infected skin lesions caused by infection with fungi or bacteria or yeast.
- Secondary infections due to *Pseudomonas* or *Proteus* species;
- Otitis externa where the eardrum is perforated because of the risk of ototoxicity.

4.4 Special Warnings and Precautions for Use

Hypersensitivity

TENOVATE GN should be used with caution in patients with a history of local hypersensitivity to clobetasol, neomycin or to any of the excipients in the preparation. Local hypersensitivity reactions (see 4.8 *Undesirable Effects*) may resemble symptoms of the condition under treatment.

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 clobetasol propionate-neomycin sulphate. 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 4.8 *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 Disturbances

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.

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.

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

Use in Psoriasis

Topical corticosteroids should be used with caution in psoriasis as rebound relapses, development of tolerance, risk of generalised pustular psoriasis and development of local or systemic toxicity due to impaired barrier function of the skin have been reported in some cases (see 4.8 *Undesirable Effects*). If used in psoriasis careful patient supervision is important.

Dilution

Products which contain antimicrobial agents should not be diluted.

Contact sensitisation

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

Ototoxicity and nephrotoxicity

Following significant systemic absorption, aminoglycosides such as neomycin sulphate can cause irreversible ototoxicity. Neomycin sulphate also has nephrotoxic potential (see 4.3 *Contraindications*).

Renal impairment

In renal impairment the plasma clearance of neomycin sulphate is reduced (see 4.2 *Posology and Method of Administration*).

Application to the face

Application to the face is undesirable as this area is more susceptible to atrophic changes. 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 4.8 *Undesirable Effects*).

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 systemic antimicrobial therapy.

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.

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.

4.5 Drug Interactions

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.

Following significant systemic absorption, neomycin sulphate can intensify and prolong the respiratory depressant effects of neuromuscular blocking agents.

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

4.6 Use in Special Population

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 6 *Nonclinical Properties).*

Pregnancy

Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development (see 6 *Nonclinical properties)*. 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 (see 6 *Nonclinical properties)*. Thus use of *TENOVATE GN* is not recommended in pregnancy.

Lactation

The safe use of *TENOVATE GN* 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.

4.7 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.

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), including isolated reports.

Infections and Infestations	
Very rare:	Opportunistic infection

Immune System Disorders	
Very rare:	Local hypersensitivity

Endocrine Disorders	
Very rare:	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, hyper glycaemia/glucosuria, cataract, hypertension, increased weight/obesity, decreased endogenous cortisol levels

Eye Disorders	
Very rare:	Cataract, central serous chorioretinopathy, glaucoma

Skin and Subcutaneous Tissue Disorders	
Common:	Pruritus, local skin burning/pain of skin
Uncommon:	Skin atrophy*, striae*, telangiectasias**
Very rare:	Allergic contact dermatitis/dermatitis, erythema, rash, urticaria, acne, pustular psoriasis, skin thinning* / skin atrophy*, skin wrinkling*, skin dryness*, striae*, telangiectasias*, pigmentation changes*, hypertrichosis, exacerbation of underlying symptoms, alopecia*, trichorrhexis*

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

General Disorders and Administration Site Conditions	
Very rare:	Application site irritation/pain

4.9 Overdose

Symptoms and Signs

Topically applied clobetasol propionate- neomycin sulphate 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 4.4 *Special Warnings and Precautions for Use* and 4.8 *Undesirable Effects*).

Treatment

In the event of chronic overdose 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 glucocorticosteroid insufficiency.

Consideration should be given to significant systemic absorption of neomycin sulphate (see 4.4 *Special Warnings and Precautions for Use*). 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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.

5.2 Pharmacokinetic Properties

Absorption

Clobetasol propionate

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.

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.

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

The use of pharmacodynamic endpoints for assessing the systemic exposure of topical corticosteroids is necessary due to the fact that circulating levels are well below the level of detection.

Neomycin sulphate

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

Metabolism

Clobetasol propionate

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

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.

6. NONCLINICAL PROPERTIES

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

Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

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 pregnancy of neomycin sulphate has not been evaluated in animals.

7. DESCRIPTION

Contains:

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

8. 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.

8.1 Incompatibilities

No incompatibilities have been identified.

8.2 Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

Aluminium tube in carton.

8.4 Storage and Handling Information

Store at temperature not exceeding 25°C. Do not freeze.

Keep out of reach of children.

For external use only.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or their patients' parents) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *TENOVATE GN*. Patients (and/or patients' parents) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information, please contact:
GlaxoSmithKline Pharmaceuticals Limited.
Registered Office
Dr. Annie Besant Road, Worli,
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Manufacturing License number is indicated on the label and packaging.

12. DATE OF REVISION

28-July-2020

Version TEN-GN/PI/IN/2020/02

Adapted from

- *Betamethasone 17 valerate Neomycin sulphate GDS Version 12 dated 19 May 2020*
- *Clobetasol propionate (topical) GDS 15 / IPI 08 dated 15 July 2020*