Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Clobetasol Propionate, Neomycin Sulphate & Miconazole Nitrate Cream
(Brand Name: SONADERM ® -NM Cream)

2. Qualitative and Quantitative Composition

Clobetasol Propionate IP …… 0.05% w/w
Neomycin Sulphate IP …… 0.5% w/w
Miconazole Nitrate IP ……..… 2 % w/w
Chlorocresol IP (as preservative) …… 0.1% w/w
Cream base ……..… q.s.

3. Dosage Form and Strength

Dosage Form: Cream.
Dosage Strength: Clobetasol Propionate 0.05%, Neomycin Sulphate 0.5%, and Miconazole Nitrate 2%.

4. Clinical Particulars

4.1 Therapeutic Indication

SONADERM-NM Cream is indicated for resistant dermatoses where secondary bacterial and /or fungal infection is present, suspected or likely to occur.

4.2Posology and Method of Administration

For topical use in adults and children over 2 years of age.
Sufficient amount of cream should be applied to cover the affected areas twice daily (morning and evening). Rub the cream in gently and completely.
SONADERM-NM Cream shall not be used continuously for more than one week without re-evaluation by the physician. The total dosage should not exceed 50 grams per week because of the potential of the clobetasol propionate to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Further, treatment beyond 2 consecutive weeks is not recommended. Repeated short courses may be used to control exacerbations.
Or, as prescribed by the physician.

4.3Contraindications

SONADERM-NM Cream is contraindicated in following cases:

- Hypersensitivity to clobetasol propionate or to neomycin sulphate or to miconazole nitrate or to any component of the formulation.
- Rosacea.

- Acne vulgaris.
- Perioral dermatitis.
- Perianal and genital pruritus.
- Primary cutaneous viral infections (e.g., herpes simplex, chickenpox).
- Otitis externa with a perforated eardrum (because of risk of ototoxicity).

4.4Special Warnings and Precautions for Use

For external use only.

SONADERM-NM Cream must not come in contact with the eyes. Also, it should not be used with occlusive dressings. Due to the known ototoxic and nephrotoxic potential of neomycin sulphate, the use of SONADERM-NM cream in large quantities, or on large areas for prolonged periods of time is not recommended in circumstances where significant systemic absorption may occur.

Clobetasol Propionate

Use of potent topical corticosteroids, including clobetasol propionate, should be avoided on areas with thin and sensitive skin, such as on the face, groin or in the skin folds. As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. Long-term continuous therapy should be avoided. Because of a higher ratio of skin surface area to body mass, children are at a greater risk than adults for HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency after withdrawal of treatment, and of Cushing's syndrome while on treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

Neomycin Sulphate

Neomycin can induce permanent sensorineural hearing loss due to cochlear damage, mainly destruction of hair cells in the organ of Corti (spiral organ - for hearing). The risk of ototoxicity is greater with prolonged use. Neomycin sulphate may cause cutaneous sensitization. A precise incidence of hypersensitivity reactions (primarily skin rash) due to topical neomycin is not known. Discontinue promptly if sensitization or irritation occurs.

Serious adverse reactions including neurotoxicity, ototoxicity, and nephrotoxicity have occurred in patients receiving systemic aminoglycoside therapy. Although these effects have not been reported following topical use of aminoglycosides, caution is advised when used concomitantly with systemic aminoglycosides.

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.

Miconazole Nitrate

Severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported during treatment with miconazole topical formulations. If a reaction suggesting hypersensitivity or irritation should occur, the treatment should be discontinued.

4.5Drug Interactions

Clobetasol Propionate

CYP3A4 inhibitor drugs such as ritonavir and itraconazole, when coadministered with corticosteroids 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 cytochrome P450 enzyme (CYP) 3A4 inhibitor.

Neomycin Sulphate

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 is expected to be minimal and drug interactions are unlikely to be significant. Concurrent use with other potentially nephrotoxic or ototoxic drugs should be avoided unless considered essential by the physician.

Miconazole Nitrate

Miconazole administered systemically is known to inhibit CYP 3A4/2C9. 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.

4.6Use in Special Populations

Pregnant Women

Safety for use of SONADERM-NM Cream in pregnancy has not been established. It should only be used during pregnancy when considered mandatory by the physician, after careful assessment of the potential risks to the fetus.

Lactating Women

It is not known whether the components of SONADERM-NM Cream excrete in the breast milk after topical use. Nevertheless, caution should be executed when this medication is administered to lactating women.

Paediatric Patients

Safety and effectiveness of this formulation has not been established in children below 2 years of age. Due to safety concerns, SONADERM-NM Cream is not recommended in paediatric patients aged less than 2 years.

Geriatric Patients

Generally, no adjustment of dosage is required in the geriatric population. However, greater sensitivity of some older individuals cannot be ruled out.

4.7Effect on Ability to Drive and Use Machines

There have been no studies to investigate the effect of SONADERM-NM Cream on driving performance or the ability to operate machinery. From the adverse reaction profile of this product, effect on ability to drive and use machines is not expected with topical use of SONADERM-NM Cream.

4.8Undesirable Effects

SONADERM-NM cream is generally well tolerated. Following side effects may occur occasionally with the individual components of SONADERM-NM Cream.

Clobetasol Propionate

The following adverse reactions have been reported with use of clobetasol propionate. The frequency of these adverse events is unknown.

Immune System Disorders - Hypersensitivity: Local hypersensitivity reactions such as erythema, rash, pruritus, urticaria and allergic contact dermatitis may occur at the site of application and may resemble symptoms of the condition under treatment. If signs of hypersensitivity appear, application should be stopped immediately.

Endocrine Disorders - Features of Cushing's Syndrome: As with other topical corticosteroids, prolonged use especially of large amounts, or treatment of extensive areas can lead to sufficient systemic absorption to produce the features of Cushing's syndrome. This effect is more likely to occur in infants and children, and if occlusive dressings are used. In infants, the nappy may act as an occlusive dressing. Provided the weekly dosage is less than 50 gram in adults, any suppression of the HPA axis is likely to be transient with a rapid return to normal values once the short course of steroid therapy has ceased. The same applies to children given proportionate dosage.

Vascular Disorders - Dilatation of the Superficial Blood Vessels: Prolonged and intensive treatment with potent corticosteroid preparations may cause dilatation of the superficial blood vessels, particularly when occlusive dressings are used, or when skin folds are involved.

Skin and Subcutaneous Tissue Disorders: Local skin burning, local atrophy, striae, thinning, pigmentation changes, hypertrichosis, exacerbation of underlying symptoms, pustular psoriasis. Prolonged and intensive treatment with potent corticosteroid (clobetasol) preparations may cause local atrophic changes, such as thinning and striae.

Neomycin Sulphate

Neomycin occasionally causes skin sensitization. Ototoxicity and nephrotoxicity have also been reported with use of neomycin in large quantities and/or for prolonged periods.

Miconazole Nitrate

Local side effects such as itching, burning, rash, and contact dermatitis have been reported with topical miconazole therapy.

4.9Overdose

Clobetasol Propionate

Acute overdose is very unlikely to occur, however, in the case of chronic overdose or misuse, the features of hypercortisolism may appear and in this situation topical steroids should be reduced or discontinued gradually, under medical supervision.

Neomycin Sulphate

If systemic absorption of neomycin sulphate 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.

Miconazole Nitrate

Excessive cutaneous use can result in skin irritation, which usually disappears after discontinuation of therapy. If accidental ingestion of large quantities of the product occurs, an appropriate method of gastric emptying may be used if considered necessary.

5. Pharmacological Properties

5.1 Mechanism of Action

Clobetasol Propionate

The mechanism of anti-inflammatory activity of the topical corticosteroids involves induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

Clobetasol propionate also produces anti-inflammatory response, partially due to vasoconstriction and decrease in collagen synthesis.

Neomycin Sulphate

Neomycin exerts its bactericidal effect by interfering with the protein synthesis of susceptible organisms. Neomycin is rapidly acting bactericidal agent; after diffusing through the bacterial cell membrane it binds polysomes to affect protein synthesis. Neomycin disrupts the normal cycle of ribosomal function by interfering, at least in part, with the first step of protein synthesis. Neomycin also causes a misreading of the genetic code of the mRNA template and this causes incorrect amino acids to be incorporated into the growing polypeptide chain, producing nonsense proteins.

Miconazole Nitrate

Miconazole is an imidazole antifungal agent that acts by interfering with the permeability of the fungal cell membrane. Miconazole inhibits biosynthesis of ergosterol, damaging the fungal cell wall, which increases permeability causing leakage of nutrients.

5.2Pharmacodynamic Properties

Clobetasol Propionate

Like other topical corticosteroids, clobetasol propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The major effect of clobetasol propionate on skin is a non-specific anti-inflammatory response, partially due to vasoconstriction and decrease in collagen synthesis.

Neomycin Sulphate

Neomycin sulphate is bactericidal against a wide range of Gram-positive and Gram-negative bacterial pathogens including *Staphylococci, Streptococci, Escherichia, Enterobacter, Klebsiella, Hemophilus, Proteus, Salmonella* and *Shigella* species. It is also active against some strains of *Pseudomonas aeruginosa*, and against *Mycobacterium tuberculosis* and *Neisseria gonorrhea*.

Miconazole Nitrate

Miconazole possesses a wide antifungal spectrum and has some antibacterial activity. Miconazole inhibits the growth of the common dermatophytes such as *Trichophyton rubrum, Trichophyton mentagrophytes,* and *Epidermophyton floccosum*, and the yeast-like fungi such as *Candida albicans*. Also many Gram-positive bacteria including most strains of *Streptococcus* and *Staphylococcus* are susceptible to miconazole.

5.3Pharmacokinetic Properties

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. Following percutaneous absorption of clobetasol propionate, the drug probably follows the metabolic pathway of systemically administered corticosteroids i.e., metabolized primarily by the liver and then excreted by the kidneys. However, systemic metabolism of clobetasol has never been fully characterized or quantified.

Neomycin Sulphate

Although not absorbed through intact skin, topical neomycin is readily absorbed from large denuded, burned, or granulating areas. Plasma concentrations following topical application to open wounds, burns, or granulating surfaces are comparable to, or higher than, those achieved following oral preparation. Once neomycin is absorbed, it is rapidly excreted by the kidneys in active form. It has been reported to have a half-life of 2 to 3 hours.

Miconazole Nitrate

There is little absorption through skin or mucous membranes when miconazole nitrate is applied topically. Absorbed miconazole is bound to plasma proteins (88.2%) and red blood cells – RBCs (10.6%). The small amount of miconazole that is absorbed is eliminated predominantly in faeces as both unchanged drug and metabolites.

6. Nonclinical Properties

6.1 Animal Toxicology

Clobetasol Propionate

In a 4-week dermal toxicity study in rats conducted with clobetasol propionate cream (0.025%) significant immunosuppression was observed when tested at a dose level of 0.1 mg clobetasol/kg body weight per day.

In a 13-week repeat dose toxicity study in rats, topical administration of clobetasol propionate cream, 0.001, 0.005 and 0.025% at corresponding doses of 0.004, 0.02 and 0.1 mg/kg/day resulted in corticosteroid class-related systemic effects such as reductions in body weight gain, reductions in total leukocytes and individual white cells, decrease in weight of adrenals, thymus, spleen, liver and lung. Histologically, there were decreased hematopoiesis in the bone marrow, thymic atrophy and mast cell infiltration of the mesenteric lymph nodes. All these effects were indicative of severe immune suppression consistent with long-term exposure to corticosteroids. A no observable adverse effect level (NOAEL) was determined to be clobetasol propionate cream, 0.001% (0.004 mg/kg/day) in male rats while a NOAEL could not be determined in females.

In minipigs, daily dermal administration of clobetasol propionate cream at concentrations up to 0.05% (1.0 mg/kg/day clobetasol propionate) for 28 days resulted in test article-related changes in body weight, clinical pathology, histopathology, and organ weights. Based on lower adrenal weights in both males and females treated with the lowest dose tested (0.1 mg/kg as 0.005% cream), a NOAEL could not be determined in this study. These findings are consistent with topical exposure to corticosteroids.

Clobetasol propionate was not mutagenic in three different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test.

Fertility studies conducted in the rat following subcutaneous administration of clobetasol propionate at dosage levels up to 0.05 mg/kg/day revealed that females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

Neomycin Sulphate

Neomycin has low acute toxicity (LD50 values in excess of 2000 mg/kg body weight) after oral administration but it is more toxic after intravenous dosing (LD50 values in mice around 100 mg/kg body weight per day).

After repeated parenteral administration, nephrotoxic effects were noted in mice (administered 30 to 300 mg/kg body weight per day, subcutaneously), guinea pigs (administered 10 to 60 mg/kg body weight per day, subcutaneously) and in dogs (administered 24 to 96 mg/kg body weight per day, intramuscularly). Ototoxicity as noted in guinea pigs given repeated parenteral doses of neomycin, but not following oral dosing.

Neomycin gave positive results in some old and poorly reported non-GLP-compliant mutagenicity tests. A further battery of genotoxicity tests were performed under GLP conditions including a *Salmonella* microsomal assay, a AS52/XPRT Chinese hamster ovary (CHO) cell mutation assay and an *in vivo* chromosome aberration assay in CD1 mouse bone marrow cells. All tests gave negative results. Although neomycin gave positive results in 2 inadequate *in vivo* and *in vitro* mutagenicity tests, these findings could not be confirmed in a battery of well conducted genotoxicity tests. It was concluded that neomycin is unlikely to be genotoxic.

There was no increased tumour incidence in a 2-year oral carcinogenicity study in rats treated with 0, 6.5, 12.5, and 25 mg neomycin sulphate/kg body weight per day. However, hearing was impaired in several rats administered 25 mg/kg body weight per day by end of the study.
In multigeneration study in rats, no adverse effects on reproduction parameters were noted following administration of oral (dietary) doses of up to 25 mg/kg body weight per day, the highest dose used.
A teratogenicity study was conducted with the F2b females. Neomycin was administered in feed at doses equivalent to 0, 6.25, 12.5, or 25 mg/kg body weight per day from days 0 to 6 and 16 to 20 of gestation. The doses were increased to 0, 62.5, 125, or 250 mg/kg body weight per day from days 16 to 20. There was no evidence of teratogenic effects in this study.

Miconazole Nitrate

The animal studies consisted of two hamster studies and a mouse local lymph node assay (LLNA) to assess local toxicity.
In the hamster studies, a paste of miconazole nitrate (1000 mg/kg) was placed into the buccal area (pouch) of animals. The intent was to evaluate the animals over 2 weeks. But in the first study, serious adverse clinical signs were noted by Day 4 (including hypoactivity and reduced food and water consumption), and 5/10 treated animals died on Days 5 and 6. The study was terminated on Day 6. Animal deaths were attributed to swallowing the paste and possible systemic exposure to levels of miconazole exceeding LD50 values. A repeat study in hamsters was begun in which a mouth rinse was planned at 4 hours, but this study, too, resulted in early animal deaths and was terminated. Histopathologic examination of animal cheek pouches revealed thickness of the epithelium, inflammation, and dilated blood vessels. The LLNA was conducted in mice as per the standard protocol, and the result was that miconazole did not produce local irritation.
Miconazole nitrate was not genotoxic when tested *in vitro* in a bacterial reverse mutation (Ames) assay or in an *in vivo* mouse bone marrow micronucleus test. Intraperitoneal injections of miconazole to mice induced chromosomal aberrations in spermatocytes and bone marrow cells, and morphologic abnormalities in sperm at doses similar to or below clinical doses. However, no impairment of fertility was observed in intravenous studies with miconazole at 40 mg/kg/day in rats or 20 mg/kg/day in rabbits.
Miconazole nitrate administered orally at doses of 80 mg/kg/day or higher to pregnant rats or rabbits crossed the placenta and resulted in embryo- and fetotoxicity, including increased fetal resorptions. These doses also resulted in prolonged gestation and dystocia in rats, but not in rabbits. Embryofetotoxicity was not observed in intravenous studies with miconazole at lower doses of 40 mg/kg/day in rats and 20 mg/kg/day in rabbits. Teratogenicity was not reported in any animal study with miconazole.

7. Description

SONADDRM-NM Cream is a white to almost white smooth cream.

Each gram of SONADERM-NM Cream contain 0.5 mg of clobetasol propionate, 5 mg of neomycin sulphate, and 20 mg of miconazole nitrate for topical administration on intact skin.

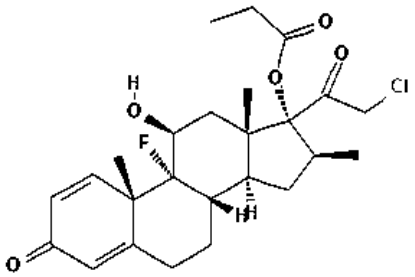
Clobetasol Propionate

Molecular Weight: 467 g/mol.

Molecular Formula: C25H32ClFO5.

Chemical Name: [(8S,9R,10S,11S,13S,14S,16S,17R)-17-(2-chloroacetyl)-9-fluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl] propanoate.

Structural Formula:



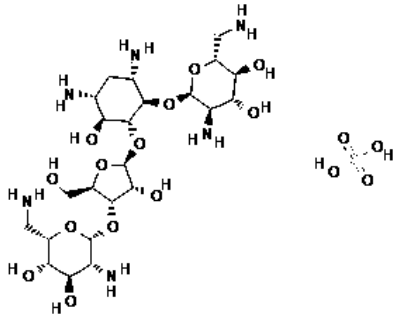
Neomycin Sulphate

Molecular Weight: 712.7 g/mol.

Molecular Formula: C23H8N6O17S.

Chemical Name: (2R,3S,4R,5R,6R)-5-amino-2-(aminomethyl)-6-[(1R,2R,3S,4R,6S)-4,6-diamino-2-[(2S,3R,4S,5R)-4-[(2R,3R,4R,5S,6S)-3-amino-6-(aminomethyl)-4,5-dihydroxyoxan-2-yl]oxy-3-hydroxy-5-(hydroxymethyl)oxolan-2-yl]oxy-3-hydroxycyclohexyl]oxyoxane-3,4-diol;sulfuric acid.

Structural Formula:



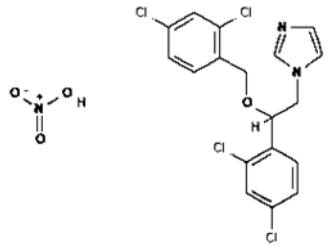
Miconazole Nitrate

Molecular Weight: 479.1 g/mol.

Molecular Formula: C18H15Cl4N3O4.

Chemical Name: 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl] imidazole; nitric acid.

Structural Formula:



Inactive ingredients (excipients) of SONADERM-NM Cream contain Sodium Acid Phosphate, Purified Water, Cetomacrogol 1000, Cetostearyl Alcohol, Liquid Paraffin, White Soft Paraffin, Chlorocresol, and Propylene Glycol.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2 Shelf-life

24 months.

8.3 Packaging Information

15 gram lami tube.

8.4 Storage and Handling Instructions

Store at temperature below 25°C. Do not freeze.
Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions

- Instruct patients to use SONADERM-NM Cream exactly as prescribed and advised by the doctor.
- Use this medicine only on intact skin and not to apply on broken or damaged skin; also avoid contact with the eyes.
- During pregnancy and lactation, instruct patients to use this medicine with caution and after consultation with the doctor.
- Not to use this medicine in children below 2 years of age.
- Instruct patients not to apply this cream on their face, armpits, or groin areas as the skin on these areas thins easily with the use of this medicine (clobetasol propionate).

10. Details of Manufacturer

M/s. Blue Cross Laboratories Pvt. Ltd.,
L-17, Verna Industrial Estate, Verna, Goa – 403 722. India

11. Details of Permission or License Number with Date

DCG(I) NOC Date: 15th March 2016.
Manufacturing License No.395. Date of Product Permission – 15th December 2005.

12. Date of Revision

January 2021.

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