
1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1.0 Name of the medicinal product

MISONE-N (Beclomethasone Dipropionate, Miconazole Nitrate & Neomycin Sulphate Cream)

2.0 Qualitative and quantitative composition

Composition:

Beclomethasone dipropionate BP	0.025%
Miconazole nitrate BP	2.0% w/w
Neomycin sulphate BP	0.5% w/w
Chlorocresol USP	0.1% w/w
Water Miscible Base	q.s

3.0 Pharmaceutical form

Ointment in a collapsible tube

4.0 Clinical Particulars

4.1 Therapeutic Indications:

It is indicated in patients 17 years and older for the topical treatment of symptomatic inflammatory tinea pedis, tinea curis and tinea corporis

4.2 Posology and Method of Administration

MISONE-N Ointment is should not be used continuously for more than one week without reevaluation by the physician. Adults and adolescents Apply thinly and gently rub in using only enough to cover the entire affected area twice daily for up to seven days. Allow adequate time for absorption after each application before applying an emollient. 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: MISONE-N 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, MISONE-N Ointment is contraindicated in children under 2 years of age. 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. Care should be taken when using MISONE-N Ointment to ensure the amount applied is the minimum that provides therapeutic benefit. Elderly, MISONE-N Ointment is suitable for use in the elderly. However, the greater frequency of decreased hepatic and 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.

4.3 Contraindications:

MISONE-N Ointment is contraindicated in children under 2 years of age. Due to the known ototoxic and nephrotoxic potential of neomycin sulphate, the use of MISONE-N Ointment in

large quantities or on large areas for prolonged periods of time is contraindicated in circumstances where significant systemic absorption may occur.

4.4 Special Warnings and Precautions for Use Hypersensitivity:

MISONE-N Ointment should be used with caution in patients with a history of local hypersensitivity to betamethasone, neomycin, miconazole or to any of the excipients in the preparation. Local hypersensitivity reactions may resemble symptoms of the condition under treatment. Application to open wounds should be avoided. 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 MISONE-N Ointment. 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. Risk factors for increased corticosteroid 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. 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.

Prolonged application to the face is undesirable as this area is more susceptible to atrophic changes. 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. In case of accidental contact with the eyes or mucous membranes, rinse with water.

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 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

Topically applied betamethasone valerate 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 occur.

Treatment

In the event of overdose, betamethasone dipropionate should be withdrawn gradually by reducing the frequency of application, or by substituting a less potent corticosteroid because of the risk of glucocorticosteroid insufficiency.

5. Pharmacological properties

5.1 Pharmacodynamic:

Mechanism of action

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.

Pharmacodynamic effects

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

5.2 Pharmacokinetic properties

Absorption

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.

Distribution

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

Metabolism

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

Elimination

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

5.3 Preclinical safety data

Reproductive toxicity

Subcutaneous administration of betamethasone dipropionate to mice or rats at doses ≥ 0.1 mg/kg/day or rabbits at doses ≥ 12 micrograms/kg/day during pregnancy produced foetal abnormalities including cleft palate and intrauterine growth retardation.

The effect on fertility of betamethasone dipropionate has not been evaluated in animals.

4.7 Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of betamethasone dipropionate with neomycin on driving performance or the ability to operate machinery. Miconazole is not known to exert an effect on the central nervous system following topical application. A detrimental effect on such activities would not be anticipated from the adverse reaction profile of BETNOVATE-GM.

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 ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1,000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1,000$) and very rare ($< 1/10,000$), including isolated reports.

Post-marketing data

Infections and Infestations

Very rare Opportunistic infection

Immune System Disorders

Very rare Hypersensitivity, generalised rash

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, alopecia, trichorrhexis

Skin and Subcutaneous Tissue Disorders

Common Pruritus, local skin burning /skin pain

Very rare Allergic contact dermatitis /dermatitis, erythema, rash, urticaria, pustular psoriasis, skin thinning* / skin atrophy*, skin wrinkling*, skin dryness*, striae*, telangiectasias*, pigmentation changes*, hypertrichosis, exacerbation of underlying symptoms

General Disorders and Administration Site Conditions

Very rare Application site irritation/pain

*Skin features secondary to local and/or systemic effects of hypothalamic-pituitary adrenal (HPA) axis suppression.

Eye disorders

Not known Vision, blurred.

Reporting of suspected reactions:

Reporting 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 suspected adverse reactions to NAFDAC.

4.9 Overdose

Symptoms and signs

hypersensitivity reactions and an increased risk of local infection. Flammability risk Product contains paraffin. Instruct patients not to smoke or go near naked flames due to the 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.

4.5 Interaction with other medicinal products and other forms of interaction:

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. Following significant systemic absorption, gentamicin 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. It is known that systemically administered miconazole nitrate inhibits CYP3A4/2C9. As there is limited percutaneous absorption of miconazole, topical application is not expected to result in systemic exposure of clinical significance. However, as there have been case reports of topical or intravaginal miconazole cream potentiating the anticoagulant effects of coumarins in adults, caution should be exercised with concomitant use and anticoagulant effect monitored.

4.6 Fertility, pregnancy and lactation:

Fertility: There are no data in humans to evaluate the effect of topical betamethasone dipropionate with neomycin on fertility. No fertility studies in animals have been performed with topical miconazole. Animal studies indicate no effects of oral miconazole on male or female fertility. As there is limited percutaneous absorption of miconazole following topical application, impact on fertility is not expected.

Pregnancy: There are limited data from the use of topical betamethasone dipropionate with neomycin in pregnant women. There are no adequate and well-controlled studies of topical miconazole in pregnant women. Oral miconazole has been shown to be embryotoxic in the rat at high doses. No reproductive studies in animals have been performed with topical miconazole. Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development. The relevance of this finding to humans has not been established. However, neomycin present in maternal blood can cross the placenta and may give rise to a theoretical risk of foetal toxicity. Thus the use of MISONE-N Ointment is not recommended in pregnancy.

Lactation: Percutaneous absorption of miconazole is limited, however, it is not known whether miconazole is excreted in human milk after topical application. The safe use of betamethasone dipropionate with neomycin and miconazole during lactation has not been established. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable amounts in breast milk. Thus, use of MISONE-N Ointment is not recommended in lactation.

6. Pharmaceutical particulars

6.1 List of excipients

Chlorocresol	BP
White Soft Paraffin	BP
Liquid Paraffin	BP
Sodium Acid Phosphate	BP
Phosphoric Acid	BP
Sodium Hydroxide	BP
Purified Water	BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Pack sizes:

15gm tube packed in carton. Such 10 carton packed in an outer carton along with an insert.

6.6 Special precautions for disposal and other handling

No special requirements

Manufactured By:

CURIS LIFESCIENCES PVT LTD

Plot No. 23, GIDC Industrial Estate,
Sanand-II, Dist. Ahmedabad- 382110,
Gujarat, India.