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This information is intended for use by health professionals

1. Name of the medicinal product

ISOCORT ; Ketoconazole Complex Cream

2. Qualitative and quantitative composition

Composition: Each Gram Contains: Ketoconazole USP..1.0% w/w

Clobetasol Propionate USP Equivalent to Clobetasol 0.025% w/w

Neomycin Sulphate USP Equivalent to Neomycin 0.850% w/w

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Cream ; White cream

4. Clinical particulars

4.1 Therapeutic indications

For the treatment of the following mycotic infections of the skin: tinea pedis, tinea cruris and candidal intertrigo.

4.2 Posology and method of administration

ISOCORT Cream is for use in adults.

For Tinea pedis:

ISOCORT cream should be applied to the affected areas twice daily. The usual duration of treatment for mild infections is 1 week. For more severe or extensive infections (eg involving the sole or sides of the feet) treatment should be continued until a few days after all signs and symptoms have disappeared in order to prevent relapse.

For other infections:

ISOCORT cream should be applied to the affected areas once or twice daily, depending on the severity of the infection. The treatment should be continued until a few days after the disappearance of all signs and symptoms. The usual duration of treatment is: tinea versicolor 2–3 weeks, tinea corporis 3–4 weeks.

The diagnosis should be reconsidered if no clinical improvement is noted after 4 weeks. General measures in regard to hygiene should be observed to control sources of infection or reinfection. Seborrhoeic dermatitis is a chronic condition and relapse is highly likely.

Method of administration: Cutaneous administration.

There are limited data on the use of ISOCORT cream in paediatric patients. Route of

Administration: Cutaneous

Creams are especially appropriate for moist or weeping surfaces.

Adults, Elderly and Children over 1 year :

Apply thinly and gently rub in using only enough to cover the entire affected area once or twice a day until improvement occurs (in the more responsive conditions this may be within a few days), then reduce the frequency of application or change the treatment to a less potent preparation. Allow adequate time for absorption after each application before applying an emollient. Repeated short courses of ISOCORT Cream may be used to control exacerbations.

In more resistant lesions, especially where there is hyperkeratosis, the effect of clobetasol 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. If the condition worsens or does not improve within 2-4 weeks, treatment and diagnosis should be re-evaluated.
Treatment should not be continued for more than 4 weeks. If continuous treatment is necessary, a less potent preparation should be used.

Therapy with clobetasol should be gradually discontinued once control is achieved and an emollient continued as maintenance therapy. Rebound of pre-existing Clobetasol Propionate can occur with abrupt discontinuation of clobetasol.

Recalcitrant ISOCORT Cream : Patients who frequently relapse Once an acute episode has been treated effectively with a continuous course of topical corticosteroid, intermittent dosing (once daily, twice weekly, without occlusion) may be considered. This has been shown to be helpful in reducing the frequency of relapse.

Application should be continued to all previously affected sites or to known sites of potential relapse. This regimen should be combined with routine daily use of emollients. The condition and the benefits and risks of continued treatment must be re-evaluated on a regular basis.

Paediatric population:
ISOCORT Cream contraindicated in children under one year 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 cream include clobetasol propionate to ensure the amount applied is the minimum that provides therapeutic benefit.
Duration of treatment for children and infants Courses should be limited if possible to five days and reviewed weekly. Occlusion should not be used.

Application to the face Courses should be limited to five days if possible and occlusion should not be used.

Elderly Clinical studies have not identified differences in responses between the elderly and younger patients. 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 / 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.

For nasal application only. A small amount of Neomycin sulfate is placed on the little finger and applied to the inside of each nostril.

For prophylaxis: Neomycin sulfate is applied as above, twice daily, to prevent patients from becoming carriers and to inhibit the dispersion of Staphylococci.

For eradication of infection: Neomycin sulfate is applied four times daily for 10 days to eliminate organisms from the nares.

Children and elderly patients: There are no special dosage recommendations for either children or elderly patients.

4.3 Contraindications

ISOCORT cream is contra-indicated in patients with a known hypersensitivity to any of the ingredients or to ketoconazole itself.

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

ISOCORT cream is contraindicated in children under one year of age, including dermatitis and nappy eruptions.

Patients who have previously shown a hypersensitivity reaction to neomycin or chlorhexidine, although such reactions are extremely rare.

4.4 Special warnings and precautions for use

ISOCORT cream is not for ophthalmic use. If coadministered with a topical corticosteroid, to prevent a rebound effect after stopping a prolonged

treatment with topical corticosteroids it is recommended to continue applying a mild topical corticosteroid in the morning and to apply Ketoconazole 2% cream in the evening, and to subsequently and gradually withdraw the topical corticosteroid therapy over a period of 2-3 weeks.

ISOCORT Cream should be used with caution in patients with a history of local hypersensitivity to other corticosteroids or to any of the excipients in the preparation. Local hypersensitivity reactions (see section 4.8) may resemble symptoms of the condition under treatment.

Manifestations of hypercortisolism (Cushing's syndrome) and reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, leading to glucocorticosteroid insufficiency, can occur in some individuals as a result of increased systemic absorption of topical steroids. 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 section 4.8).

ISOCORT Cream contains:

• propylene glycol which may cause skin irritation.

• cetostearyl alcohol which may cause local skin reactions (e.g. contact dermatitis).

• chlorocresol which may cause allergic reactions.

Risk factors for increased systemic effects are:

• Potency and formulation of topical steroid

• Duration of exposure

• Application to a large surface area

• Use on occluded areas of skin (e.g. on intertriginous areas or under occlusive dressings(in infants the nappy 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

• In comparison with adults, children and infants 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.

Paediatric population

In infants and children under 12 years of age, long-term continuous topical corticosteroid therapy should be avoided where possible, as adrenal

suppression can occur

Children are more susceptible to develop atrophic changes with the use of topical corticosteroids.

Duration of treatment for children and infants

Courses should be limited if possible to five days and reviewed weekly. Occlusion should not be used.

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.

Use in Psoriasis Topical corticosteroids should be used with caution in psoriasis as rebound relapses, development of tolerances, 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. If used in psoriasis careful patient supervision is important.

Concomitant infection :

Appropriate antimicrobial therapy should be used whenever treating inflammatory lesions which have become infected. Any spread of infection requires withdrawal of topical corticosteroid therapy and administration of appropriate antimicrobial therapy.

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.

Application to the face If used on the face, treatment should be limited to 5 days.

Application to the 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. If ISOCORT does enter the eye, the affected eye should be bathed in copious amounts of water.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

For nasal application only. Keep out of the eyes and ears.

Neomycin sulfate contains Arachis oil (peanut oil) and should not be taken/applied by patients known to be allergic to peanut. As there is a possible relationship between allergy to peanut and allergy to Soya, patients with Soya allergy should also avoid Neomycin sulfate.

Irritative skin reactions can occasionally occur. Prolonged use of neomycin can lead to skin sensitisation, ototoxicity and nephrotoxicity. Use with caution in children, elderly patients and patients with impaired hearing (see Section 4.8 'Undesirable effects').

4.5 Interaction with other medicinal products and other forms of interaction

Drugs known to prolong QT interval

No interaction studies have been performed. Co-administered drugs that can inhibit CYP3A4 (eg 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 None known.

4.6 Fertility, pregnancy and lactation

There are no adequate and well-controlled studies in pregnant or lactating women. Data on a limited number of exposed pregnancies indicate no adverse effects of topical ketoconazole on pregnancy or on the health of the foetus/newborn child. Animal studies have shown reproductive toxicity at doses that are not relevant to the topical administration of ketoconazole.

Plasma concentrations of ketoconazole are not detectable after topical application of ISOCORT Cream to the skin of non-pregnant humans. (See

Pharmacokinetic properties, section 5.2) There are no known risks associated with the use of ISOCORT Cream in pregnancy or lactation.

Pregnancy

There are limited data from the use of ISOCORTcream in pregnant women. Topical administration of cream include corticosteroids to pregnant animals can cause abnormalities of foetal development (see section 5.3)

The relevance of this finding to humans has not been established. Administration of ISOCORT cream during pregnancy should only be considered if the expected benefit to the mother outweighs the risk to the foetus. The minimum quantity should be used for the minimum duration. Breast-feeding The safe use of topical corticosteroids 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. Administration of ISOCORT cream during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant. If used during lactation, ISOCORT cream should not be applied to the breasts to avoid accidental ingestion by the infant.

Fertility

There are no data in humans to evaluate the effect of topical corticosteroids on fertility Clobetasol administered subcutaneously to rats had no effect upon mating performance; however, fertility was decreased at the highest dose (see section 5.3). Neomycin cannot be detected in the blood following application of Neomycin sulfate and its use is unlikely to have any effect on the foetus or on breast feeding.

4.7 Effects on ability to drive and use machines

ISOCORT cream has no influence on the ability to drive and use machines. There have been no studies to investigate the effect of clobetasol 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 using cream include Clobetasol. None known.

4.8 Undesirable effects

The safety of ISOCORT cream was evaluated in 1079 subjects who participated in 30 clinical trials. ISOCORT cream was applied topically to the skin. Based on pooled safety data from these clinical trials, the most commonly reported (≥1% incidence) adverse reactions were (with % incidence): application site pruritus (2%), skin burning sensation (1.9%), and application site erythema (1%).

Including the above-mentioned adverse reactions, the following table displays adverse reactions that have been reported with the use of ketoconazole cream from either clinical trial or postmarketing experiences. The displayed frequency categories use the following convention:

Very common (≥1/10) Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not Known (cannot be estimated from the available clinical trial data)

	Adverse Reactions		
	Frequency Category		
	Common (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Not Known**
Immune System Disorders		Hypersensitivity	
Skin and Subcutaneous Tissue Disorders	Skin burning sensation	Bullous eruption Dermatitis contact Rash Skin exfoliation Sticky skin	Urticaria
General Disorders and Administration Site Conditions	Application site erythema Application site pruritus	Application site bleeding Application site discomfort Application site dryness Application site inflammation Application site irritation Application site paresthesia Application site reaction	

4.9 Overdose

Excessive topical application may lead to erythema, oedema and a burning sensation, which will disappear upon discontinuation of the treatment.

Ingestion In the event of accidental ingestion, supportive and symptomatic measures should be carried out.

Topically applied cream include clobetasol 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 (see section 4.8).

Management

In the event of overdose, ISOCORT cream should be withdrawn gradually by reducing the frequency of application or by substituting a less potent corticosteroid because of the risk of glucocorticosteroid insufficiency. Further management should be as clinically indicated or as recommended by the national poisons center, where available.

Accidental ingestion of the contents of a Neomycin sulphate is unlikely to have any adverse effects on the patient.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Usually ketoconazole cream acts rapidly on pruritus, which is commonly seen in dermatophyte and yeast infections, as well as skin conditions associated with the presence of Malassezia spp. This symptomatic improvement is observed before the first signs of healing are observed.

Ketoconazole, a synthetic imidazole dioxolane derivative, has a potent antimycotic activity against dermatophytes such as Trichophyton spp., *Epidermophyton floccosum* and Microsporum spp. and against yeasts, including Malassezia spp. and Candida spp. The effect on Malassezia spp. is particularly pronounced.

A study in 250 patients has shown that application twice daily for 7 days of ketoconazole 2% cream vs clotrimazole 1% cream for 4 weeks on both feet demonstrated efficacy in patients with tinea pedis (athlete's foot) presenting lesions between the toes. The primary efficacy endpoint was negative microscopic KOH examination at 4 weeks. Ketoconazole 2% treatment showed equivalent efficacy to 4 weeks clotrimazole 1% treatment. There was no evidence of relapse following treatment with ketoconazole cream at 8 weeks.

Clobetasol Propionate is Corticosteroids, very potent (group IV) Pharmacotherapeutic group: ATC code: D07AD

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.

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

Neomycin is a rapidly bactericidal aminoglycoside antibiotic effective against Gram positive organisms including staphylococci and a wide range of Gram negative organisms. Strains of Pseudomonas aeruginosa are resistant to neomycin, as are fungi and viruses.

5.2 Pharmacokinetic properties

Plasma concentrations of ketoconazole were not detectable after topical administration of ISOCORT cream in adults on the skin. In one study in infants with seborrhoeic dermatitis (n = 19), where approximately 40 g of Ketoconazole 2% cream was applied daily on 40% of the body surface area, plasma levels of ketoconazole were detected in 5 infants, ranging from 32 to 133 ng/mL.

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.

Mean peak plasma clobetasol propionate concentrations of 0.63 ng/ml occurred in one study eight 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 three hours after a single application of 25 g clobetasol propionate 0.05% ointment.

Distribution

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.

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.

Neomycin is either not absorbed or is absorbed only minimally through intact skin. Any neomycin which is absorbed will be rapidly excreted by the kidneys in an unchanged state.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Carcinogenesis / Mutagenesis

Carcinogenesis
Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate. Genotoxicity Clobetasol propionate was not mutagenic in a range of in vitro bacterial cell assays. Reproductive Toxicology Fertility In fertility studies, subcutaneous administration of clobetasol propionate to rats at doses of
6.25 to 50 micrograms/kg/day produced no effects on mating, and fertility was only decreased at 50 micrograms/kg/day.

Pregnancy Subcutaneous administration of Clobetasol propionate to mice (≥100 micrograms/kg/day), rats (400 micrograms/kg/day) or rabbits (1 to 10 micrograms/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 micrograms/kg/day and survival was reduced at 400 micrograms/kg/day. No treatment-related effects were observed in F1 reproductive

performance or in the F2 generation. There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics.

5.3 Preclinical safety data
None stated.

6. Pharmaceutical particulars

6.1 List of excipients
Cetostearyl ; Alcohol ;Ceto Mecrogol 1000 ;White Soft paraffin; Heavy Liquid Paraffin; Methyl paraben; Propyl Paraben

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Should be protected from light. Do not store above 25°C

6.5 Nature and contents of container
15gm or 20gm cream in collapsible Aluminum tube. Such 1 tube packed in a carton such 30 carton packed in a shipper .

6.6 Special precautions for disposal and other handling
No special requirements.

7. Marketing authorisation holder

Ningbo Voice Biochemic Co., Ltd.
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