Cream base.....Q.S.

1.3 Pharmaceutical Dosage Form

Topical Semi-solid cream

2. QUALITATIVE & QUANTITATIVE COMPOSITION 2.1 Qualitative Declaration

Composition:

Each Gram Contains:

Ketoconazole USP ..... 2.0 %

Betamethasone Dipropionate BP

Eq.to Betamethasone.....0.05 %

Cream base.....Q.S.

2.2 Quantitative Declaration

Batch Formula:

Batch Size: 300 Kg

Sr. No	Ingredients	Grade	Rationale	Label Claim	Quantity per Unit (mg)	Quantity per Batch (Actual-Kg)
PREPARATION OF OIL PHASE						
1	White Soft Paraffin	BP	Moisturizer	-----	4500	45
2	Cetostearyl Alcohol	BP	Opacifying Agent	-----	2400	24
3	Cetomacragol 1000	IH	Solubilize & emulsifying Agent	-----	600	6
PREPARATION OF AQUOUS BASE						
4	Sodium Methyl Paraben	BP	Preservative	-----	30	0.3
5	Sodium Propyl Paraben	BP	Preservative	-----	30	0.3
6	Di Sodium Edetate	BP	Chelating Agent	-----	30	0.3
7	Para Chloro Meta Cresol	BP	Preservative	-----	30	0.3
MIXING						

8	Ketoconazole	BP	Active	20 mg	600	6
9	Betamethasone Dipropionate	USP	Active	500 mcg	15	0.15
10	Mono Propylene Glycol	USP	Vehicle	-----	2400	24

3. PHARMACEUTICAL DOSAGE FORM

Topical Semi-solid

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

For topical application in the treatment of dermatophyte infections of the skin such as tinea corporis, tinea cruris, tinea manus and tinea pedis infections due to Trichophyton spp, Microsporon spp and Epidermophyton spp. Ketoconazole cream is also indicated for the treatment of cutaneous candidosis (including vulvitis), tinea (pityriasis) versicolor and seborrhoeic dermatitis caused by Malassezia (previously called Pityrosporum) spp.

Betamethasone Dipropionate is a synthetic fluorinated corticosteroid. It is active topically and produces a rapid and sustained response in eczema and dermatitis of all types, including atopic eczema, photodermatitis, lichen planus, lichen simplex, prurigo nodularis, discoid lupus erythematosus, necrobiosis lipoidica, pretibial myxodemea and erythroderma. It is also effective in the less responsive conditions such as psoriasis of the scalp and chronic plaque psoriasis of the hands and feet, but excluding widespread plaque psoriasis.

4.2 Posology and Method of Administration

Ketoconazole cream is for use in adults.

Cutaneous candidosis, tinea corporis, tinea cruris, tinea manus, tinea pedis and tinea (pityriasis)

versicolor:

It is recommended that Ketoconazole cream be applied once or twice daily to cover the affected and immediate surrounding area.

The usual duration of treatment is: tinea versicolor 2–3 weeks, yeast infections 2-3 weeks, tinea cruris 2-4 weeks, tinea corporis 3–4 weeks, tinea pedis 4-6 weeks. Seborrheic dermatitis:

Ketoconazole cream should be applied to the affected areas once or twice daily.

The usual initial duration of treatment in seborrheic dermatitis is 2 to 4 weeks. Maintenance therapy can be applied intermittently (once weekly) in seborrheic dermatitis.
Treatment should be continued until a few days after the disappearance of all symptoms. The diagnosis should be reconsidered if no clinical improvement is noted after 4 weeks of treatment. 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.

Paediatrics patients

The safety and efficacy of Ketoconazole cream in children (17 years of age and younger) has not

been established.

Adults and Children:

Once to twice daily. In most cases a thin film of Betamethasone dipropionate Cream should be applied to cover the affected area twice daily. For some patients adequate maintenance therapy may be achieved with less frequent application.

Betamethasone dipropionate Cream is especially appropriate for moist or weeping surfaces and the ointment for dry, lichenifield or scaly lesions but this is not invariably so.

Control over the dosage regimen may be achieved during intermittent and maintenance therapy by using Diprobase Cream or Ointment, the base vehicles of Betamethasone dipropionate Cream and Ointment. Such control may be necessary in mild and improving dry skin conditions requiring low dose steroid treatment.

4.3 Contraindications

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

Rosacea, acne, perioral dermatitis, perianal and genital pruritus. Hypersensitivity to any of the ingredients of the Betamethasone dipropionate presentations contra-indicates their use as does tuberculous and most viral lesions of the skin, particularly herpes simplex, vacinia, varicella. Betamethasone dipropionate should not be used in napkin eruptions, fungal or bacterial skin infections without suitable concomitant anti-infective therapy.

4.4 Special Warnings and Precautions for Use

Ketoconazole 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 cream in the evening, and to subsequently and gradually withdraw the topical corticosteroid therapy over a period of 2-3 weeks.

Local and systemic toxicity is common, especially following long continuous use on large areas of damaged skin, in flexures or with polythene occlusion. If used in children or on the face courses should be limited to 5 days. Long term continuous therapy should be avoided in all patients irrespective of age.

Occlusion must not be used.

Topical corticosteroids may be hazardous in psoriasis for a number of reasons, including rebound relapses following development of tolerance, risk of generalised pustular psoriasis and local systemic toxicity due to impaired barrier function of the skin. Careful patient supervision is important.

General: Systemic absorption of topical corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome also can be produced in some patients by systemic absorption of topical corticosteroids while on treatment. Patients receiving a large dose of a potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.
Any of the side effects that are reported following systemic use of corticosteroids, including adrenal suppression, may also occur with topical corticosteroids, especially in infants and children.

Paediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios.

If irritation develops, treatment should be discontinued and appropriate therapy instituted.

Betamethasone dipropionate is not for ophthalmic use.

Visual disturbance may be reported with systemic and topical (including, intranasal, inhaled and intraocular) 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 of visual disturbances 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.

Paediatric population:

Paediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and to exogenous corticosteroid-induced HPA axis suppression and to exogenous corticosteroid effects than adult patients because of greater absorption due to a larger skin surface area to body weight ratio. HPA axis suppression, Cushing's syndrome and intracranial hypertension have been reported in paediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in paediatric patients include linear growth retardation, delayed weight gain, low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include a bulging fontanelle, headaches and bilateral papilledema.

Instruct patients not to smoke or go near naked flames - 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

No interaction studies have been performed.

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 Ketoconazole Cream to the skin of non-pregnant humans. (See Pharmacokinetic properties, section 5.2) There are no known risks associated with the use of Ketoconazole Cream in pregnancy or lactation.

There are no adequate and well controlled studies of the teratogenic potential of topically applied corticosteroids in pregnant women. Therefore topical steroids should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether topical administration of corticosteroids would result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Ketoconazole cream has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The safety of ketoconazole cream was evaluated in 1079 subjects who participated in 30 clinical trials. Ketoconazole 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).

System Orga Class	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 Subcu taneous 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	

Betamethasone dipropionate skin preparations are generally well tolerated and side-effects are rare. The systemic absorption of betamethasone dipropionate may be increased if extensive body surface areas or skin folds are treated for prolonged periods or with excessive amounts of steroids. Suitable precautions should be taken in these circumstances, particularly with infants and children.

The following local adverse reactions that have been reported with the use of Betamethasone dipropionate include: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, striae and miliaria.

Continuous application without interruption may result in local atrophy of the skin, striae and superficial vascular dilation, particularly on the face.

Vision blurred (see also section 4.4) has been reported with corticosteroid use (frequency not known).

4.9 Overdose

Topical Application

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. Excessive prolonged use of topical corticosteroids can suppress pituitary-adrenal functions resulting in secondary adrenal insufficiency which is usually reversible. In such cases appropriate symptomatic treatment is indicated. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, reduce the frequency of application, or to substitute a less potent steroid. The steroid content of each tube is so low as to have little or no toxic effect in the unlikely event of accidental oral ingestion.

5. Pharmacological properties

5.1Pharmacodynemic property

Pharmacotherapeutic group: Antifungals for Topical Use, Imidazole and triazole derivatives

ATC Code: D01AC08

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 Ketoconazole 2% 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 Ketoconazole 2% treatment. There was no evidence of relapse following treatment with ketoconazole cream at 8 weeks.

Betamethasone dipropionate preparations contain the dipropionate ester of betamethasone which is a glucocorticoid exhibiting the general properties of corticosteroids.

In pharmacological doses, corticosteroids are used primarily for their anti-inflammatory and/or immune suppressive effects.

Topical corticosteroids such as betamethasone dipropionate are effective in the treatment of a range of dermatoses because of their anti-inflammatory, anti-pruritic and vasoconstrictive actions. However, while the physiologic, pharmacologic and clinical effects of the corticosteroids are well known, the exact mechanisms of their action in each disease are uncertain.

5.2 Pharmacokinetic properties

Plasma concentrations of ketoconazole were not detectable after topical administration of Ketoconazole in adults on the skin. In one study in infants with seborrhoeic dermatitis (n = 19), where approximately 40 g of Ketoconazole 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.

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including vehicle, integrity of the epidermal barrier and the use of occlusive dressings.

Topical corticosteroids can be absorbed through intact, normal skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Once absorbed through the skin, topical corticosteroids enter pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in
varying degrees, are metabolised primarily in the liver and excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted in the bile.

5.3 Pre-clinical safety data

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.

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical particulars

6.1 List of excipients

White Soft Paraffin

Cetostearyl Alcohol

Cetomacragol 1000

Sodium Methyl Paraben

Sodium Propyl Paraben

Di Sodium Edetate

Para Chloro Meta Cresol

Mono Propylene Glycol

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

24 months from the date of manufacture.

6.3 Special Precautions for Storage

Do not store above 25°C.

6.4 Nature and Contents of Container

30 gm cream in collapsible lami tube. Such 1 tube packed in a carton such 25 carton packed in a shipper. White Colour Smooth Cream.

7. Manufacturer / Applicant

ASTAMED HEALTHCARE (I) PVT. LTD.

114, Reena Complex,
Opposite Neelkanth Business Park,
Vidyavihar (West), Mumbai - 400 086. Maharashtra, India.

8. Marketing authorisation number(s)

9. Date of first authorisation/renewal of the authorisation

10. Date of revision of the text