1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PRODUCT NAME: Ketaconazole 1%, Neomycin Sulphate 5000 IU and Clobetasol Propionate 0.25mg

BRAND NAME: Ketacon plus Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRODUCT NAME:

Each filled tube contains:
Ketaconazole ……..……1%
Neomycin Sulphate…….. 5000iu
Clobetasol Propionate……. 0.25mg
Excipients……q.s.

For complete list of excipients refer section 6.1.

3. *PHARMACEUTICAL FORM*:

Cream
White creamy and very smooth when applied to the skin

4. *CLINICAL PARTICULARS*

4.1 Therapeutic Indication:

Local therapy for mycotic infections eg, tinea manum, tinea corporis, tinea inguinalis, etc

4.2 Posology and method of administration:

Apply externally to the affected area 2 times a day.

Ordinary tinea corporis, inguinalis: 2 weeks; tinea pedis, tinea manum: 4 weeks.

For topical administration.

4.3 Contraindications:

Long-term treatment of ulcerative conditions, rosacea, pruritus, presence of acute infections. Hypersensitivity, Burning, Stinging, Itching, Skin atrophy, Irritation, Dryness, Hypopigmentation, Acneiform eruptions, Cracking and fissuring of the skin

4.4 Special warning and precautions for use

Long term continuous topical therapy should be avoided where possible, particularly in infants and children, as adrenal suppression can occur readily even without occlusion.
If used in childhood, or on the face, courses should be limited to 5 days and occlusion should not be used. It should be noted that the child's napkin may act as an occlusive dressing.

The face, more than other areas of the body, may exhibit atrophic changes after prolonged treatment with potent topical corticosteroids. This must be borne in mind when treating such conditions as psoriasis and severe eczema.
If applied to the eyelids, care is needed to ensure that the preparation does not enter the eye, as glaucoma might result. If the cream does enter the eye, it should be bathed in copious amounts of water.
Topical corticosteroids may be hazardous in psoriasis for a number of reasons, including rebound relapses, development of tolerance, risk of generalized pustular psoriasis and development of local or systemic toxicity due to impaired barrier
function of the skin. If used in psoriasis careful patient supervision is important. Extension of the infection may occur due to the masking effect of the steroid.
If infection persists, systemic chemotherapy is required. Any spread of infection requires withdrawal of topical corticosteroid therapy.
Bacterial infection is encouraged by the warm, moist conditions induced by occlusive dressings and the skin should be cleansed before a fresh dressing is applied.
Following significant systemic absorption, aminoglycosides such as neomycin can cause irreversible ototoxicity; and neomycin has nephrotoxic potential.

In renal impairment, the plasma clearance of neomycin is reduced .Extended or recurrent application may increase the risk of contact sensitization. Products which contain antimicrobial agents should not be diluted

Paediatric population

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 bodyweight ratio compared with adults.

Long term continuous topical therapy should be avoided where possible, particularly in infants and children, as adrenal suppression can occur readily even without occlusion.

If used in childhood, or on the face, courses should be limited to 5 days and occlusion should not be used. It should be noted that the child's napkin may act as an occlusive dressing.

Application to the face

Application to the face is undesirable as, more than other areas of the body, this area may exhibit atrophic changes after prolonged treatment with potent topical corticosteroids. If used on the face, treatment should be limited to only a few days. This must be borne in mind when treating such conditions as psoriasis and severe eczema.

Topical steroid withdrawal syndrome

Long term continuous or inappropriate use of topical steroids can result in the development of rebound flares after stopping treatment (topical steroid withdrawal syndrome). A severe form of rebound flare can develop which takes the form of a dermatitis with intense redness, stinging and burning that can spread beyond the initial treatment area. It is more likely to occur when delicate skin sites such as the face and flexures are treated. Should there be a reoccurrence of the condition within days to weeks after successful treatment a withdrawal reaction should be suspected. Reapplication should be with caution and specialist advise is recommended in these cases or other treatment options should be considered.

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 section 4.8). If the cream does enter the eye, it should be bathed in copious amounts of water.

Use in Psoriasis

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

Osteonecrosis, serious infections and immunosuppression

Cases of osteonecrosis serious infections (including necrotizing fasciitis) and systemic immunosuppression (sometimes resulting in reversible Kaposi's sarcoma lesions) have been reported with long-term use of clobetasol propionate beyond the recommended doses (see section 4.2). In some cases patients used concomitantly other potent oral/topical corticosteroids or immunosuppressors (e.g. methotrexate, mycophenolate mofetil). If treatment with local corticosteroids is clinically justified beyond 4 weeks, a less potent corticosteroid preparation should be considered.

Infection

Extension of the infection may occur due to the masking effect of the steroid.

If infection persists, systemic chemotherapy is required. Any spread of infection requires withdrawal of topical corticosteroid therapy.

Infection risk with occlusion

Bacterial infection is encouraged by the warm, moist conditions induced by occlusive dressings, and the skin should be cleansed before a fresh dressing is applied.

Ototoxicity and nephrotoxicity

Following significant systemic absorption, aminoglycosides such as neomycin can cause irreversible ototoxicity; and neomycin has nephrotoxic potential (see section 4.3).

Renal impairment

In renal impairment, the plasma clearance of neomycin is reduced (see section 4.2).

Contact sensitisation

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

Dilution

Products which contain antimicrobial agents should not be diluted.

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.

Fire hazard in contact with dressings, clothing and bedding

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.

Excipients:

Arachis oil: Clobetasol/neomycin/nystatin Cream contains arachis oil (peanut oil) and should not be taken/applied by patients known to be allergic to peanuts. As there is a possible relationship between allergy to peanut and allergy to soya, patients with soya allergy should also avoid this medicinal product.

4.5 Drug Interactions

Ketaconazole

None known.

Neomycin sulphate and Clobetasol propionate

CYP3A4 inhibitors

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.

Systemic aminoglycoside therapy

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

Neuromuscular blocking agents

Following significant systemic absorption neomycin sulfate can intensify and prolong the respiratory depressant effects of neuromuscular blocking agents. However, if used in accordance with the recommendations systemic exposure to neomycin sulfate is expected to be minimal and drug interactions are unlikely to be significant.

No hazardous interactions have been reported with use of clobetasol propionate

4.6 Fertility, Pregnancy & Lactation

Ketaconazole

There are no adequate and well-controlled studies in pregnant or lactating women. To date, no other relevant epidemiological data are available. Data on a limited number of exposed pregnancies indicate no adverse effects of topical Ketaconazole 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 Ketaconazole.

Neomycin sulphate and Clobetasol propionate

Pregnancy

There are limited data from the use of clobetasol propionate with neomycin sulfate and nystatin in pregnant women.

Topical administration of 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.

Breast-feeding

The safe use of clobetasol propionate with neomycin sulfate and nystatin during breast-feeding has not been established. It is not known whether the topical administration of corticosteroids could result in sufficient systemic absorption to product detectable amounts in breast milk. Thus, the use of clobetasol propionate with neomycin sulfate and nystatin is not recommended in lactation.

Fertility

There are no data in humans to evaluate the effect of topical clobetasol propionate with neomycin sulfate and nystatin on fertility.

Clobetasol propionate administered subcutaneously to rats had no effect upon mating performance; however, fertility was decreased at the highest dose (see section 5.3). The relevant of this finding to humans has not been established.

4.7 Effects on ability to drive and use machines:

This medicine has no influence on the ability to drive and use machines.

4.8 Undesirable Effects

Ketaconazole

The safety of Ketaconazole cream was evaluated in 1079 subjects who participated in 30 clinical trials. Ketaconazole cream was applied topically to the skin.

Based on pooled safety data from these clinical trials, the most commonly reported (≥1% incidence) ADRs were (with % incidence): application site pruritus (2%), skin burning sensation (1.9%), and application site erythema (1%). Including the above-mentioned adverse drug reactions (ADRs), the following table displays ADRs that have been reported with the use of Ketaconazole 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 Organ Class	**Adverse Drug 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 paraesthesia Application site reaction	

Neomycin sulphate and Clobetasol propionate

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 to <1/10); uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Clinical trial data

Skin and subcutaneous tissue disorders	
Common:	Skin atrophy*, telangiectasis*
Uncommon:	Striae*

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

Post-marketing data

Infections and infestations	
Very rare:	Opportunistic infection
Immune system disorders	
Very rare:	Allergic reactions including anaphylaxis and hypersensitivity
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
Skin and subcutaneous tissue disorders	
Very rare:	Skin thinning*, skin wrinkling*, skin dryness*, pigmentation changes*, hypertrichosis, exacerbation of underlying symptoms, allergic contact dermatitis/dermatitis, pustular psoriasis (see section 4.4), erythema, rash, urticaria, alopecia*, trichorrhexis*, pruritus, local skin burning/skin pain
Not known:	Withdrawal reactions - redness of the skin which may extend to areas beyond the initial affected area, burning or stinging sensation, itch, skin peeling, oozing pustules. (see section 4.4)

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

General disorders and administration site conditions	
Very rare:	Application site irritation/pain

Reporting of suspected adverse 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 via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Ketaconazole

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.

Neomycin sulphate and Clobetasol propionate

Symptoms and signs

Topically applied clobetasol propionate 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 section 4.4 and 4.8).

Treatment

In the event of chronic overdosage or misuse topical steroids should be withdrawn gradually under medical supervision by reducing the frequency of application or by substituting a less potent corticosteroid because of the risk of adrenal insufficiency.

Consideration should be given to significant systemic absorption of neomycin sulfate (see section 4.4 and 4.5). 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 sulfate should also be determined. Haemodialysis may reduce the serum level of neomycin sulfate.

Further management should be as clinically indicated or as recommended by the National Poisons Centre, where available.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Ketaconazole

Pharmacotherapeutic Group: Imidazole and triazole derivatives; ATC code: D01 AC08

Ketaconazole has a potent antimycotic action against dermatophytes and yeasts. Ketaconazole cream acts rapidly on the pruritus, which is commonly seen in dermatophyte and yeast infections. This symptomatic improvement often occurs before the first signs of healing are observed.

A study in 250 patients has shown that application twice daily for 7 days of Ketaconazole 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. Ketaconazole 2% treatment showed equivalent efficacy to 4 weeks clotrimazole 1% treatment. There was no evidence of relapse following treatment with Ketaconazole cream at 8 weeks.

5.2 Pharmacokinetic properties

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

5.3 Preclinical 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.

6. Pharmaceutical particulars

6.1 List of excipients

Propylene Glycol

Stearyl Alcohol

Cetyl Alcohol

Sorbitan Stearate

Polysorbate 60

Isopropyl Myristate

Sodium Sulphite Anhydrous (E221)

Polysorbate 80

Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Tube made of 99.7% aluminum, lined on inner side with heat polymerised epoxyphenol resin with a latex coldseal ring at the end of the tube. The cap is made of 60% polypropylene, 30% calcium carbonate and 10% glyceryl monostearate.

Tubes of 5, 15 and 30g.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No Special requirements.

Any unused medicinal products or waste material should be disposed of in accordance with local requirements.

Neomycin sulphate and Clobetasol propionate

5. *PHARMACOLOGICAL PROPERTIES*
5.1 Pharmacodynamic properties

Pharmacoterapeutic group: Clobetasol and antibiotics, ATC code: D07CD01

Mechanism of action

Clobetasol propionate is a highly active corticosteroid with topical anti-inflammatory activity. The major effect of clobetasol propionate on skin is a non-specific anti-inflammatory response, partially due to vasoconstriction and decrease in collagen synthesis.

The use of nystatin in the local treatment of candidal infections of the skin and of neomycin as a broad-spectrum antibiotic is well known.

The principle action of the preparation is based on the anti-inflammatory activity of the corticosteroid. The broad spectrum antibacterial and anti-candidal activity provided by the combination of neomycin and nystatin allow this effect to be utilised in the treatment of condition which are likely to become infected.

5.2 Pharmacokinetic properties

Absorption

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.

Distribution

Mean peak plasma clobetasol propionate concentrations of 0.63ng/ml occurred in one study 8 hours after the second application (13 hours after an initial application) of 30g clobetasol propionate 0.05% ointment to normal individuals with healthy skin. Following the application of a second dose of 30g of clobetasol propionate cream 0.05% mean peak plasma concentrations were slightly higher than the ointment and occurred 10 hours after application.

Biotransformation

In a separate study, mean peak plasma concentrations of approximately 2.3ng/ml and 4.6ng/ml occurred respectively in patients with psoriasis and eczema 3 hours after a single application of 25g clobetasol propionate 0.05% ointment. However, systemic metabolism of clobetasol has never been fully characterised or quantified. Following percutaneous absorption of clobetasol propionate the drug probably follows the metabolic pathway of systemically administered corticosteroids, i.e. metabolised primarily by the liver and then excreted by the kidneys.

5.3 Preclinical safety data

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.

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.

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.

6. *PHARMACEUTICAL PARTICULARS*

6.1 List of excipients

Cetomacrogol 1000 B.P,Cetostearyl Alcohol B.P,Liquid Paraffin (Light) B.P,white Paraffin soft,Sodium Methyl Paraben B.P, Sodium Propyl Paraben B.P ,Glycerin B.P,Sodium Phosphate B.P Disodium EDTA,Propylene Glycol BP, Fragrance (blue water)

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Collapsible aluminium tube, with a polypropylene cap.

Pack sizes: 15g

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not dilute.

Patients should be advised to wash their hands after applying Ketacon plus cream unless it is the hands that are being treated.

7. *APPLICANT*

Name of the Applicant:
SAGAR VITACEUTICALS NIGERIA LIMITED

Business Address:
Plot 6, New Makun City,
Along Lagos/Ibadan expressway,
K/m 53/55 Sagamu.
Ogun State,
NIGERIA

Manufactured by:

SAGAR VITACEUTICALS NIGERIA LIMITED.
Plot 6, New Makun City,
Along Lagos/Ibadan expressway,
K/m 53/55 Sagamu.
Ogun State,
NIGERIA

8. *WHO PREQUALIFICATION REFERENCE NUMBER*
Not applicable

9. *DATE OF PREQUALIFICATION / RENEWAL OF PREQUALIFICATION*
Not applicable

10. *DATE OF REVISION OF THE TEXT*
Not applicable