SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ketoplus Shampoo

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ketoconazole BP…….2% w/v
Zinc Pyrithione (ZPTO)……..1% w/v
Shampoo base……. q.s.

3. PHARMACEUTICAL FORM

Shampoo

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ketoplus Shampoo is indicated for the prevention and treatment of dandruff and seborrhoic dermatitis.

4.2 Posology and Method of Administration

For topical administration only.
Ketoplus Shampoo is for use in adolescents and adults:

<u>For treatment of dandruff and seborrhoeic dermatitis</u>
Wash affected areas and leave for 3-5 minutes before rinsing.
Use on scalp twice a week for 4 weeks. Give at least 3 day gap between each application.

<u>For prevention of dandruff and seborrhoeic dermatitis</u>
Use on scalp once a week for prevention of dandruff and seborrhoeic dermatitis.

4.3 Contraindications

Hypersensitivity to the active substance, Ketoconazole, Zinc Pyrithione or to any of the excipients listed in section 6.1. List of excipients

4.4 Special Warnings and Precautions for Use

FOR EXTERNAL USE ONLY.
KEEP OUT OF REACH OF CHILDREN. If swallowed get medical help.
Avoid contact with eyes. Rinse eyes thoroughly with water in case contact occurs.

In patients who have been on prolonged treatment with topical corticosteroids, it is recommended that the steroid therapy be gradually withdrawn over a period of 2 to 3 weeks, while using Ketoplus Shampoo, to prevent any potential rebound effect.
Discontinue use and consult your physician if irritation develops.
If condition worsens or does not improve after regular use of this product as directed, consult a physician.
Consult a physician prior to use in children under 2 years of age.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, Pregnancy and lactation

Ketoconazole
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. No effects on the breastfed newborn/infant are anticipated.

Plasma concentrations of ketoconazole were not detectable after topical administration of ketoconazole shampoo 2% w/v to the scalp of non-pregnant humans. Plasma levels were detected after topical administration of Ketoconazole Shampoo 2% on the whole body. There are no known risks associated with the use of Ketoconazole Shampoo 2% in pregnancy or lactation.

Zinc Pyrithione
Zinc Pyrithione (ZPT) administered orally to pregnant rabbits from day 6 through day 18 of pregnancy was lethal to 6/15 at the 5 mg/kg level, 10/15 at the 19 mg/kg level and 15/15 at the 20 mg/kg level. The surviving animals lost weight and had significantly higher incidences of embryonic resorption. However, there was no evidence of teratogenicity.

In GLP- and guideline-preceding study, fertility effects of ZPT after dermal administration were investigated in Sprague-Dawley rats. Animals were treated with a 48% ZPT slurry at doses of 1.2, 7.5 and 15.0 mg/kg/day for 8 weeks (grooming not prevented) or only on days 6-15 of gestation (grooming prevented). ZPT dosed rats from the 8-week treatment scheme did not differ significantly from vehicle controls in either growth or reproductive characteristics except a statistically significantly lower lactation index in females of the highest dose group. No toxic signs such as paralysis and no test-related histopathology was seen in the males. Further, neither reproduction nor neonatal viability was affected after topical administration of ZPT on gestation days (GD) 6-15. A NOAEL of 7.5 mg/kg/day can be derived from this dermal study.

4.7 Effects on ability to drive and use machines

No studies have been performed on the influence on the ability to drive and use machines.

4.8 Undesirable effects

Ketoconazole 2% shampoo

The safety of ketoconazole 2% shampoo was evaluated in 2890 subjects who participated in 22 clinical trials. Ketoconazole 2% shampoo was administered topically to the scalp and/or skin. Based on pooled safety data from these clinical trials, there were no ADRs reported with an incidence ≥1%.
The following table displays ADRs that have been reported with the use of ketoconazole 2% shampoo from either clinical trial or post-marketing 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 form the available clinical trial data)

System Organ Class	**Adverse Drug Reactions**		
	Frequency Category		
	Uncommon (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 and <1/1,000)	**Not Known**
Immune System disorders		Hypersensitivity	
Nervous System Disorders		Dysgeusia	
Infections and Infestations	Folliculitis		
Eye Disorders	Increased lacrimation	Eye irritation	
Skin and Subcutaneous Tissue Disorders	Alopecia Dry skin Hair texture abnormal Rash Skin burning sensation	Acne Dermatitis contact Skin disorder Skin exfoliation	Angioedema Urticaria Hair colour changes
General Disorders and Administration Site Conditions	Application site erythema Application site irritation Application site pruritus Application site reaction	Application site hypersensitivity Application site pustules	

Possible side effects of pyrithione zinc shampoo
All medicines may cause side effects, but many people have no, or minor, side effects. No COMMON side effects have been reported with pyrithione zinc shampoo. Seek medical attention right away if any of these SEVERE side effects occur:

Severe allergic reactions (rash; hives; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); skin irritation. Rarely photosensitivity.

Peripheral neuritis with parasthesia and muscle weakness in one patient was associated with the prolonged use of a shampoo containing pyrithione zinc 2%. The muscle weakness had disappeared 3 months after stopping the shampoo and 2 years later the paraesthesia had improved by about 75%.

4.9 Overdose

In the event of accidental ingestion of ketoconazole, supportive and symptomatic measures should be carried out. In order to avoid aspiration, neither emesis nor gastric lavage should be instigated.

Pyrithione Zinc Shampoo may be harmful if swallowed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Imidazole and triazole derivatives
ATC Code: D01AC08

Ketoconazole is an imidazole-dioxolane antimycotic, active against yeasts, including Malassezia and dermatophytes. Its broad spectrum of activity is already well known.

Pyrithione zinc has bacteriostatic and fungistatic properties. It is used in the control of seborrhoeic dermatitis and dandruff.

Zinc Pyrithione (ZPT) (CAS 13463-41-7; EU 236-671-3) with the chemical name: Bis[(2-pyridyl-1-oxo)-thio]zinc was introduced into the Cosmetics Directive as a preservative by Directive 82/368/EEC. ZPT is currently regulated as a preservative in rinse-off products (excluding oral hygiene products) in a concentration up to 0.5% in general and up to 1.0% in hair products. Pyrithione zinc shampoo is an antiseborrheic. It works by slowing the production of skin cells, which helps to reduce flakiness.

In cultured human primary keratinocytes, ZPT caused an upregulation of heat shock proteins and other stress response genes, depletion of cellular ATP levels, formation of poly (ADP-ribose) polymers and impairment of zinc homeostasis. Further, ZPT induced DNA damage in keratinocytes and melanocytes as shown by single cell gel electrophoresis.

5.2 Pharmacokinetic properties

Ketoconazole
Plasma concentrations of ketoconazole were not detectable after topical administration of ketoconazole 2% shampoo on the scalp. Plasma levels were detected after topical administration of ketoconazole 2% shampoo on the whole body**.**

Zinc Pyrithione
A clinical pharmacokinetic study has investigated deposition, absorption and excretion of ^{14}C radiolabelled ZPT resulting from the use of a ZPT containing shampoo alone (1% ZPT) and in combination with a ZPT containing leave on hair tonic (0.1% ZPT). This study demonstrated that systemic loading of ZPT was increased significantly less than could be expected from the corresponding skin deposition in those subjects using the shampoo/tonic combination compared with those using the shampoo alone. Additionally, absorption of ZPT in patients with compromised scalps was not found to be statistically different to normal scalps patients.

Deposition, absorption and excretion parameters were measured in 20 volunteers (patients using ZPT containing shampoo alone and using the ZPT containing shampoo and ZPT containing tonic combination) over a 4 day treatment period. Each treatment group was comprised of patients with healthy scalps and patients with compromised scalps with either severe dandruff or seborrheic dermatitis. Measurements of ZPT deposition and excretion were made by analysis of clipped hair, tape stripping areas of the scalp and hands and urinalysis respectively.

Preclinical studies have demonstrated that ≥ 90% of absorbed ZPT is excreted in the urine within 24 hours, thus for the purposes of this study the level of ZPT excreted was taken to represent the level of ZPT absorbed (i.e. systemic dose).
Mean ^{14}C-ZPT Systemic Load results are shown in table below.

Table: Mean ^{14}C-ZPT Skin Deposition Measurements (Scalp and Hands)

Day	1% ^{14}C-ZPT Shampoo		1% ^{14}C-ZPT Shampoo + 0.1% ^{14}CZPT Tonic	
	LSM systemic load (µg/kg/d)#	SEM	LSM systemic load (µg/kg/d)#	SEM
1	1.02	0.14	1.39	0.14
2	2.54	0.33	3.31	0.33
3	2.73	0.32	3.32	0.32
4	2.76	0.35	3.43	0.35
5	1.96	0.32	2.29	0.32

LSM = Least Squares Mean
SEM = Standard Error of the Mean
# Average body weight per group used for calculation of µg/kg/d values

Analysis of individual subject absorption data indicated that individuals with compromised scalps demonstrated no greater absorption than individuals with normal scalps. Analysis of the urinary excretion curves indicates that steady state conditions were reached within the day treatment period of this study. Statistical analysis indicated that the amount of ZPT excreted in the urine (indicative of systemic exposure) was significantly higher in the shampoo + tonic group compared with the shampoo only group throughout the study. However the increase was less than what would have been expected from the increase in skin deposition. This suggests that a rate limiting mechanism exists for the absorption of ZPT across the skin.
The systemic exposure to ZPT increases with increasing amount of ZPT applied. Systemic exposure loads up to 3.43 µg/kg/d were obtained from the study.

5.3 Preclinical safety data

Ketoconazole
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.

Zinc Pyrithione
Acute toxicity
LD_{50} values for zinc pyrithione (ZPT) have been determined in various species after oral administration. The values in the rat ranged from 92 to 266 mg/kg and in the mouse from 160 to 1000 mg/kg. Six hundred mg/kg was found to be the LD_{50} when administered orally to dogs.

The oral LD_{50} values for shampoo formulations containing zinc pyrithione have been established in rats as 2.5 g/kg for a cream shampoo and 3.0 ml/kg for a lotion shampoo. In addition, the acute oral toxicity of the cream shampoo product with higher levels of ZPT has been studied and estimated the LD_{50}. The results showed that increasing the level of ZPT increases acute oral toxicity.

Emetic studies in dogs and pigeons showed that zinc pyrithione in a cream shampoo product is a potent emetic (ED_{50} app. 0.05 g/kg). In the emetic studies with dogs, the emesis typically occurred within 60 minutes of dosing, the average being 30 minutes, and involved two to four episodes. Occasional bloody vomitus was seen, indicating gastric

irritation. The ratios of ED_{50} to LD_{50} for both forms of the product are 1:125 for the cream shampoo and 1:42 for the lotion shampoo.

A shampoo containing 2% ZPT at levels of 2.5, 5.0, 10.0, and 20.0 g/kg was tested on rabbits. The shampoo was occluded with a rubber sleeve and left in place for 24 hours. There were no observable systemic effects in animals treated with 2.5, 5.0, or 10.0 g/kg. Two of the four animals dosed with 20 g/kg showed a slight temporary depression. There were no deaths at any level. These data are in line with a study on ZPT alone indicating that its incorporation into a shampoo formulation does not significantly enhance penetration.

Chronic toxicity
A NOAEL of 500 µg/kg/d obtained from a chronic oral study performed with ZPT based on paralysis/hind-limb weakness. In a combined chronic toxicity/carcinogenicity study the dose of 500 µg/kg bw/d is considered as LOAEL by the SCCS (Scientific Committee on Consumer Safety).

Irritation and sensitisation
From the description of skin irritation studies performed with ZPT and from human HRIPT test it can be inferred that ZPT is – at least - a mild skin irritant. The irritation potential of shampoo in rabbit eyes was not increased by the incorporation of ZPT. Zinc pyrithione was considered as a severe eye irritant in an eye irritation study of powdered ZPT (95.6 %) into the conjunctival sac of 6 New Zealand White rabbits. No reactions indicative of contact hypersensitivity were seen in any of the animals at challenge.

ZPT is not sensitising in animal studies. Concerning human data, ZPT has a low potential to induce contact hypersensitivity when tested per se or as part of a cosmetic formulation. However, in some human HRIPT studies, evaluation was partly hindered by the erythematous reactions observed.

Carcinogenicity
Signs of toxicity such as ataxia, decrease muscle tone and emaciation were observed in animals of both sexes. Lower body weight was noted in low and high dose males and in mid- and high dose females. Low dose males were sacrificed on week 97 due to high mortality compared to controls, mortality in mid- and high dose females was higher compared to controls. However, there were no indications of significant different incidences of predominant pathology between control and treated animals.
There were no incidences of neoplasia with NaPT up to 2.8 mg/kg/day. There were treatment related degenerative changes of the sciatic nerve and skeletal muscle in all treatment groups and gastric reactive change at 2.8 mg/kg/day in male rats only.

Mutagenicity / Genotoxicity
Based on an Ames test, an *in vitro* CHO/HGPRT gene mutation assay, an *in vivo* mouse bone marrow micronucleus test and an UDS-Assay, the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP/0671/03) concluded that ZPT has shown no mutagenic effect in any of the *in vitro* and *in vivo* studies conducted.

Teratogenicity/ reproductive studies
Several teratology/reproduction studies have been conducted using rats and rabbits, in which ZPT was either applied topically or given orally. Topical application (with ingestion during grooming) of levels up to 15 mg/kg/day did not adversely affect reproduction in rats.

When pregnant rats were gavaged with 15 mg/kg/day of ZPT, there was an increase in the incidence of forked and fused ribs in the neonates. A dose level of 2.5 mg/kg/day given orally is a no-effect level for teratogenicity/embryotoxicity. No material toxicity was observed in these studies.

No reproductive or teratogenic effects have been observed in rabbits and pigs following topical application of shampoo formulations containing 50 and 400 mg ZPT/kg/day respectively.

Based on the scientific data provided, the SCCS considers that ZPT, when used in a concentration up to 2.0% as an anti-dandruff agent in rinse-off hair care products, is safe for the consumer.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Aluminium Magnesium Silicate
- Colloidal Silicon Dioxide
- Hydrochloric Acid
- Hypromellose 2910, 50mPa.s.
- Imidurea
- Colour Erythrosin Supra
- Swiss Bouquet P3043
- Plain Pearly Shampoo Base
- Propylene Glycol
- Purified Water

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

HDPE bottle of 60ml.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER:
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8. MARKETING AUTHORISATION NUMBER(S): NKD/803

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:
27 Oct 2004

10. DATE OF REVISION OF THE TEXT
November 2017