

SPACE FOR PHARMACODE

For the use of Registered Medical Practitioners or a Hospital or a Laboratory

Keto Plus[™]
Shampoo

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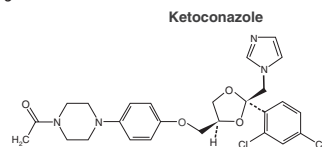
COMPOSITION

KETOPLUS shampoo contains:
Ketoconazole BP 2%
Zinc Pyrithione (ZPTO) 1%
Shampoo base q.s.

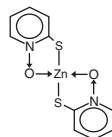
DESCRIPTION

KETOPLUS Shampoo contains:

1. Ketoconazole, a synthetic, broad-spectrum imidazole antifungal agent in a concentration of 2%. It has a chemical name of (+/-)-cis-1-Acetyl-4-[4-[2-(2,4-dichlorophenyl)-2-imidazol-1-ylmethyl-1,3-dioxolan-4-ylmethoxy]phenyl]piperazine with a molecular formula of C₂₈H₃₅Cl₂N₃O₂ and a molecular weight of 531.4. The chemical structure of Ketoconazole is:



2. Zinc pyrithione, a keratolytic, bacteriostatic and fungistatic agent in a concentration of 1%. Its Chemical Name is Bis[1-hydroxypyridine-2(1H)thionato]zinc. It has a molecular formula of C₈H₈N₂O₄S₂Zn and a molecular weight of 317.7. The chemical structure of Zinc pyrithione is:



CLINICAL PHARMACOLOGY

Pharmacodynamics

Ketoconazole:

Ketoconazole is an imidazole antifungal agent. Ketoconazole exhibits antifungal activity, similar to its predecessors, clotrimazole and miconazole, by inhibition of uptake of precursors of RNA and DNA, synthesis of oxidative and peroxidative enzymes and increasing membrane permeability. Interpretations of *in vivo* studies suggest that Ketoconazole impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes. Ketoconazole inhibits the enzyme 14- α demethylase, responsible for ergosterol synthesis. It is postulated that the therapeutic effect of ketoconazole in dandruff is due to the reduction of *Pityrosporum ovale* (*Malassezia ovale*) and this has been evidenced in clinical trials. At higher concentrations, it is fungicidal and causes direct damage to the cell membrane.

Anti-microbial spectrum of activity:

Ketoconazole is a broad-spectrum synthetic antifungal agent which inhibits the growth of the following common dermatophytes and yeasts by altering the permeability of the cell membrane:

Dermatophytes: *Trichophyton rubrum*, *T. mentagrophytes*, *T. tonsurans*, *Microsporum canis*, *M. audouinii*, *M. gypseum* and *Epidermophyton floccosum*.

Yeasts: *Candida albicans*, *C. tropicalis*, *Pityrosporum ovale* (*Malassezia ovale*) and *Pityrosporum orbiculare* (*M. furfur*).

Development of resistance by these microorganisms to ketoconazole has not been reported. MIC values of ketoconazole against *P. ovale* range from 0.001-0.1 μ g/ml.

Zinc Pyrithione:

Zinc Pyrithione has bacteriostatic and fungistatic properties. It is used similar to selenium sulfide in usual concentrations of 1 to 2% in the control of seborrheic dermatitis and dandruff. It has also been used in the treatment of pityriasis versicolor.

The MIC values of zinc pyrithione against *P.ovale* range from 0.12-8 μ g/ml.

Zinc pyrithione inhibits the membrane transport and decreases the membrane electrical potential by causing a depolarizing type of blockade in the fungal cell. The site of action is the proton pump, which is intracellular rather than extracellular. Thus, it interferes with the cellular function and produces fungistatic action. It is also an anti-biosynthetic agent and reduces the epidermal turnover. It acts directly on the DNA of the fungal cell.

Effects of the combination:

In dandruff and seborrheic dermatitis, clearing off the accumulated flakes of scales or preventing the formation of excessive scales alone will not be a sufficient treatment. This will not give immediate relief to the symptom of itching as itching is primarily caused by *P. ovale*. So, the flakes are to be cleared off. More than this, abnormal formation of flakes is to be prevented and the organism *P.ovale* has to be killed. The combination of Ketoconazole and Zinc Pyrithione exerts a synergistic action, acting on the DNA as well as the cell membrane of the fungi. Thus this combination of ketoconazole and zinc pyrithione will offer antifungal, keratolytic and antiproliferative actions relieving both the itching and scaling associated with dandruff and seborrheic dermatitis along with treatment of the fungal causative agent.

Pharmacokinetics:

Ketoconazole:

No detectable plasma ketoconazole levels were found in plasma of rabbits that were measured, using an assay method having a lower detection limit of 5 ng/ml, at doses upto 50 mg/kg given for 28 days. Ketoconazole was not detected in plasma in 39 patients who shampooed 4-10 times per week for 6 months or in 33 patients who shampooed 2-3 times per week for 3-26 months (mean:16 months). High amounts of ketoconazole were present on the hair 12 hours after a single shampoo in 6 patients but only about 5% had penetrated into the hair keratin. Chronic shampooing (twice weekly for two months) increased the ketoconazole levels in the hair keratin to 20%, but did not increase levels on the hair. There were no detectable plasma levels.

Zinc Pyrithione:

After topical application, < 1% of zinc pyrithione is absorbed in the systemic circulation.

INDICATIONS

Ketoplus shampoo is indicated in the management of Dandruff and Seborrheic Dermatitis of the scalp.

DOSAGE AND ADMINISTRATION

SHAKE WELL BEFORE USE.

Directions for use

1. Moisten hair and scalp thoroughly with water.
2. Apply sufficient shampoo to produce enough lather to wash scalp and hair.
3. Gently massage it over the entire scalp for approximately one minute.
4. Rinse the hair thoroughly with warm water. Repeat, leaving the shampoo on the scalp for an additional 3 minutes.
5. Rinse with warm water, dry hair with towel or warm air flow. Shampoo twice a week for 4 weeks with at least 3 days between each shampooing followed by once weekly shampooing as a maintenance therapy.

USE IN SPECIAL POPULATIONS

Pregnancy and Lactation

Since Ketoconazole and Zinc Pyrithione are not absorbed through the skin after topical application, pregnancy and lactation are not a contraindication for the use of KETOPLUS. But it should be used only if clearly indicated and if the potential benefit outweighs the potential risk.

Ketoconazole: Pregnancy Category C

There are no adequate and well controlled studies in pregnant women. Ketoconazole should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. However, Ketoconazole shampoo is not detected in plasma after chronic shampooing.

Caution should be exercised when ketoconazole 2% shampoo is administered to a nursing woman.

Zinc Pyrithione:

Zinc Pyrithione has not been shown to cause birth defects or other problems in humans. Pyrithione has not been reported to cause problems in nursing babies.

Paediatric Use

Safety and efficacy in children have not been established.

CONTRAINDICATIONS

KETOPLUS shampoo is contraindicated in persons showing hypersensitivity to ketoconazole, other azole derivatives, zinc pyrithione or the excipients.

WARNINGS AND PRECAUTIONS

- **KEEP OUT OF REACH OF CHILDREN.**
- **FOR EXTERNAL USE ONLY.**
- Avoid contact with eyes. If contact occurs, rinse thoroughly with water.
- If condition worsens or does not improve after regular use of this product as directed, physician should be consulted.
- There have been reports that use of the shampoo may result in removal of the curls from permanently waved hair.
- If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued.
- Physician should be informed in case of history of unusual or allergic reaction to pyrithione or history of allergy to preservatives or dyes.

ADVERSE REACTIONS

Topical treatment with KETOPLUS shampoo is well tolerated. In rare instances, discoloration of hair has been observed. Increase in normal hair loss, irritation (< 1%), abnormal hair texture, mild dryness of skin, itching, oiliness / dryness of hair and scalp have also been noted. Peripheral neuritis can be seen with zinc pyrithione, although rarely.

An exaggerated use washing test on the sensitive ante-cubital skin of 10 subjects twice daily for five consecutive days showed that the irritancy potential of ketoconazole 2% shampoo was significantly less than that of 2.5% selenium sulfide shampoo.

A human sensitization test, a phototoxicity study, and a photo allergy study conducted in 38 male and 22 female volunteers showed no contact sensitization of the delayed hypersensitivity type, no phototoxicity and no photoallergic potential due to ketoconazole 2% shampoo.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

No evidence of carcinogenicity, mutagenicity and impairment of fertility has been reported with topical use of this preparation.

Toxicology data

The oral LD50 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. Hind-limb weakness or paralysis which occurred in rats and rabbits within 8 to 14 days when ZPTO was administered in the diet at levels from 165 ppm to 330 ppm (8-16 mg/kg/day).

There is no elaborate data available on toxicology of topical ketoconazole.

OVERDOSAGE

In the event of accidental ingestion, supportive measures including gastric lavage should be carried out.

STORAGE

Store below 30°C. Protect from light.

PRESENTATION Bottle of 30 ml, 60 ml, 100 ml and 120 ml.


Keep all Medicines out of reach of children.

Reg. No. :

Manufactured By:
glenmark PHARMACEUTICALS LTD.
B/2, Mahalaxmi Chambers,
22, Bhulabhai Desai Road,
Mumbai - 400 026, (India).
At: Plot No. E-37, 39, D-Road,
MIDC, Satpur, Nashik - 422 007,
Maharashtra State, India.
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PE00000 RW

ICONGRAPHICS CODE:

PANTONE SHADE
 PANTONE BLACK PROCESS C
Supersedes Artwork Code

PHARMACODE :