SUMMRY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mycospor

2. QUALITATIVE AND QUANTITATIVE COMPOSITION IN TERMS OF THE ACTIVE SUBSTANCE(S)

Active ingredient(s)

Bifonazole

Quantitative composition

100 g cream contains;

bifonazole .....1 g

100 ml solution contains;

Bifonazole .....1 g

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream: cream

Solution: cutaneous solution

4. CLINICAL PARTICULARS

4.1 Indication(s)

Skin mycoses caused by dermatophytes, yeasts, moulds, and other fungi, e.g. Malassezia furfur, and Corynebacterium minutissimum infections: tinea pedum, tinea manuum, tinea corporis, tinea inguinalis, pityriasis versicolor, superficial candidosis and erythrasma.

4.2 Dosage and method of

administration Bifonazole cream or

solution

Bifonazole cream or solution is used once a day, preferably in the evening before retiring. It should be applied thinly to the affected skin area and rubbed in.

To achieve a lasting cure, treatment with bifonazole cream or solution, must be

carried out reliably and over an adequate period. The usual periods of treatment are :

Foot mycoses, athlete´s foot	
(Tinea pedum, tinea pedum interdigitalis)	3
weeks Mycoses of the trunk, hands and skin folds	
(Tinea corporis, tinea manuum, tinea inguinalis)	2-3 weeks
Pityriasis versicolor, erythrasma	2 weeks
Superficial candidosis of the skin	2-4 weeks

Cream: A small amount of cream is generally sufficient to treat an area of about the size of the palm of hand.

Solution: A few drops (about 3 drops) is generally sufficient to treat an area of about the size of the palm of the hand. When using the pump spray, 1 or 2 depressions of the spray head is sufficient.

Use in Children

No in-depth studies have been performed in children. From a survey of the clinical data reported there is no indication that harmful effects should be anticipated in children.

However, in babies, bifonazole should only be used under medical supervision.

4.3 Contraindications

Known hypersensitivity to bifonazole or any other ingredient in the drug product.

4.4 Special warnings and precautions for use

Patients with a history of hypersensitivity reactions to other imidazole antifungal agents (e.g. econazole, clotrimazole, miconazole) must take bifonazole containing products with caution.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Pregnancy and

lactation Pregnancy

Preclinical safety data and pharmacokinetic data in humans give no indication that harmful effects on the mother and child should be anticipated when bifonazole is used during pregnancy. However, no clinical data are available.

In the first 3 months of pregnancy bifonazole should only be used after risk:benefit ratio evaluation by a doctor.

Lactation

It is unknown whether bifonazole is excreted in human breast milk. The excretion of bifonazole in milk has been studied in animals.

Bifonazole should only be used in breast-feeding woman after risk:benefit ratio evaluation by a doctor. During lactation period bifonazole should not be applied in the chest area.

Fertility

Preclinical studies gave no evidence that bifonazole can impair male or female fertility.

4.7 Effects on ability to drive or use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

• General disorders and administration site conditions Administration site pain, oedema peripheral (at administration site)

• Skin and subcutaneous tissue disorders

Dermatitis contact, dermatitis allergic, erythema, pruritus, rash, urticaria, blister, skin exfoliation, eczema, dry skin, skin irritation, skin maceration, skin burning sensation

These side effects are reversible after discontinuation of the treatment.

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacotherapeutic group / pharmacodynamic effects

Bifonazole is an imidazole derivative (ATC Code DO 1A C10) with a broad antimycotic spectrum, which includes dermatophytes, yeasts, moulds and other fungi such as Malassezia furfur. It is also effective on Corynebacterium minutissimum.

The MIC values for the mentioned types of fungi are in the region of less than 0.062-4 (-16) g/ml substrate. Bifonazole shows a pronounced fungicidal activity

against dermatophytes, Trichophyton spp. in particular. A completely fungicidal effect is already achieved at a concentration of about 5 □g/mL and from an exposure of 6 h. On yeasts, e.g. Candida species, at concentrations of 1-4 □g/mL the effect of bifonazole is primarily fungistatic, though in concentrations of 20 □g/mL it is fungicidal.

In gram-positive cocci - excluding enterococci - bifonazole has MIC values between 4 and 16 □g/mL. In Corynebacteria, the MIC values are between 0.5 and 2 □g/mL.

The resistance situation for bifonazole is favorable. Primary resistant variants of sensitive fungal species are very rare. Investigations so far did not provide any evidence of a development of secondary resistance in primarily sensitive strains.

Mechanism of action

Bifonazole inhibits the biosynthesis of ergosterol on two different levels, distinguishing bifonazole both from other azole derivatives and from other antifungals which act only on a single level. Inhibition of ergosterol synthesis leads to structural and functional impairment of the cytoplasmic membrane.

In the special formulation of the bifonazole nail ointment (ATC Code: DO 1A C60), urea is acting as a keratoplastic.

Urea is a natural substance found e.g. in the human body. With the special formulation in the bifonazole nail ointment the infected nail keratin is softened by urea, which allows non-invasive and painless detachment of the infected nail. Moreover, it was shown by in vitro studies that in infected human toenails urea enhances the depth of penetration of bifonazole. Thus, combination of both enhances the antimycotic effect.

5.2 Pharmacokinetic

properties

Absorption

Bifonazole penetrates well into infected skin layers. 6 h after administration concentrations in the various skin layers reach from 1000 □g/cm^3 in the top layer of the epidermis (stratum corneum) to 5 □g/cm^3 in the stratum papillare. All concentrations determined are thus within a range of reliable antimycotic activity.

The skin residence time - measured by infection-protecting action in guinea pigs - is 48-72 h for bifonazole cream and 36-48 h for bifonazole solution.

Pharmacokinetic investigations after topical application to intact human skin have shown that only a small amount of bifonazole is absorbed (0.6-0.8% of the dose); the resulting serum concentrations were always below the detection limit (i.e. < 1 ng/mL). Slight absorption was observed only after application to inflamed skin (2-4% of the respective dose). In view of the extremely low plasma

concentrations (generally below 5 ng/mL) no systemic effect is likely to occur after topical application.

A multiple dose study with administration of two doses of 50 mg bifonazole (1% scalp gel) for 5 days was conducted in 8 healthy female volunteers. The geometric means of bifonazole plasma concentrations on day 1 are in a range of 0.024 – 0.062 ng/mL and on day 5 in a range 0.15 to 0.18 ng/mL. They are not higher as in all previously performed studies in healthy volunteers and patients with the 1% cream and solution formulations.

Respective plasma levels resulting from treatment with bifonazole nail ointment were always below the detection limit of bifonazole (i.e. < 1 ng/mL).

Bifonazole passes through the placental barrier in rats.

5.3 Preclinical safety data

Preclinical data reveal no spezial hazards for humans based on conventional studies of single dose toxicity and genotoxicity. Effects on the liver (enzyme induction, fatty degeneration) were observed in repeated dose toxicity studies with oral administration but only at exposures in excess of the maximum human exposure indicating little relevance to clinical use. No carcinogenicity studies were performed with bifonazole.

In reproduction toxicology studies in rats and rabbits, oral doses of 30 mg/kg body weight and higher resulted in embryo- or fetotoxicity including lethality. Given the low absorption of the active ingredient via the skin these results have little relevance to clinical use. No impairment of male or female fertility was observed in rats at oral doses up to 40 mg/kg body weight.

Acute, chronic toxicity:

The acute oral toxicity of the active substance (LD50) is higher than 2000 mg/kg body weight in mice and rats, while being higher than 500 mg/kg body weight in rabbits and dogs.

In subacute and subchronic toxicity studies with oral administration of the test substance to rats in doses up to 50 mg/kg body weight (up to 13 weeks), indications of enzyme induction were noted. However, histopathological examinations revealed no signs of damage to the liver or other parenchymal organs. In the dog, oral doses of up to and including 1 mg/kg body weight were tolerated in a 13 week study without toxicologically significant symptoms. However, application of bifonazole in doses of 3 mg/kg body weight and above caused clear dose-related organ damage. This particularly became evident in a 6 month chronic toxicity study in dogs with oral administration of bifonazole in doses of 3, 10, and 30 mg/kg body weight. Clear signs of dose-dependend fatty degeneration of the liver as well as dose-related signs of generalized maturation disturbances were observed in this study.

Investigations to assess dermal tolerability were performed in rabbits. After subacute dermal application of doses of 300 mg/kg body weight of bifonazole cream and solution (corresponding to 3 mg bifonazole/kg body weight) over 3 weeks, slight skin irritant effects (swelling, reddening) were observed which could be attributed to the additives 2-octododecanol (cream) and isopropyl myristate (solution) respectively. There were no indications of changes caused specifically by the active substance, and no signs of any systemic effects could be observed. It can therefore be assumed that only very little of the active substance is absorbed via the skin. In the primary irritation test, the cutaneous, mucosal, and ocular tolerability of the formulations was good.

The tolerability of the bifonazole nail ointment has been checked in a subacute dermal toxicity study in rabbits. Application of doses of 300 mg ointment/kg body weight (corresponding to 3 mg bifonazole and 120 mg urea/kg body weight respectively) failed to yield any evidence of substance-specific damage to the skin or to the internal organs. In particular, no ulceration occured on the treated skin areas. The local tolerability of the bifonazole nail ointment was good.

Reproduction toxicology:

Teratogenicity and embryotoxicity studies were performed in rabbits and rats with active ingredient doses of up to 30 and 100 mg/kg body weight respectively, administered by oesophageal tube. In the rats, the maternally toxic doses of 100 mg/kg body weight led to retarded skeletal maturation, which can be interpreted as a secondary effect. However, doses up to and including 30 mg/kg body weight were tolerated without damage as regards embryonal and fetal development of the embryos. In the rabbits, doses of 10 mg/kg body weight had no effect on the development of the embryos and were found to be neither embryotoxic nor specifically teratogenic. However, doses of 30 mg/kg exerted severe embryotoxic effects.

In an investigation on peri- and postnatal development in rats, the maternally toxic dose of 40 mg/kg body weight proved to be fetolethal. However, the dose of 20 mg/kg had no adverse effect on the dams or on peri-and postnatal development of the young.

Fertility investigations in rats with administration of doses up to 40 mg/kg body weight by oesophageal tube have not yielded any evidence of an influence on fertility or general reproductiveness.

Mutagenicity:

To investigate the possibility of a mutagenic potential of bifonazole, the Salmonella/microsome test for the detection of point mutagenic effects, the micronucleus test to assess chromosomal mutations, and the dominant lethal test

as an indicator of stage-specific effects on spermiogenesis were carried out. None of these investigations brought to light any mutagenic effect of bifonazole.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cream: Benzyl alcohol, cetostearyl alcohol, cetyl palmitate, 2-octyldodecanol, polysorbate 60, purified water, sorbitan monostearate.

Solution: Ethanol, isopropyl myristate.

6.2 Incompatibilities

None

6.3 Shelf life

60 months

6.4 Special precautions for storage and use

No special requirements.

6.5 Nature and contents of container

Solution

Narrow-necked glass bottle 20 mL with pump vaporizer or dropper insert and screw cap closure filled with minimum 15 mL clear, colorless to light yellowish solution

Cream

Bifonazole cream 1% is a white cream filled in aluminium tube

with inner lacquer (epoxy phenolic resin) and polyethylene (PE)

screw cap. A membrane is also included to guarantee the first

opening of the tube.

Instructions for use / handling

All: - Keep drug out of the reach of children.

Cream: -In cases of known hypersensitivity to cetostearyl alcohol, it is advisable to use a cetostearyl alcohol-free formulation (e.g. bifonazole solution) instead of the cream.

7. Marketing authorisation holder

Canespor cream

GP Grenzach Produktions GmbH

Emil-Barell-Str. 7

D-79639 Grenzach-Wyhlen

Germany

8. Marketing authorisation number(s)

3348

9. Date of first authorisation/renewal of the authorisation

16/06/2016

10. Date of revision of the text

16/06/2026