Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT
AGISPOR® SHAMPOO

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1. Preparations

Qualitative composition in terms of the active ingredient(s) (INN):

Bifonazole

Quantitative composition in terms of the active ingredient(s) per dosage form

1 g shampoo contains 10 mg bifonazole

3. PHARMACEUTICAL FORM

3.1. Preparations

Pharmaceutical formulation in accordance with standardized terminology:

Shampoo

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Pityriorisis versicolor and Seborrhoeic dermatitis of the scalp caused by pityrosporum.

4.2. Posology and Method of Administration

Posology:

Indication	Duration of treatment
Pityriorisis versicolor Seborrhoeic dermatitis of the scalp caused by pityrosporum	4 weeks

Method of administration:

Patients should be instructed to shake the bottle well and apply Agispor shampoo to the hair or affected areas of the skin.
The recommended dose is one scalp wash three times a week, with two applications of the shampoo each time. The shampoo should be left on the scalp for 5 minutes before rinsing. Sufficient shampoo should be used to ensure a good lathering of the scalp.

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 infants and toddlers, the medicinal product should only be used under medical supervision.

4.3. Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

4.4. Special Warnings and Precautions for Use

If unsure of diagnosis, the patient should seek the advice of a doctor or pharmacist before using this product.

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

This medicine contains 338 mg Sodium lauryl sulfate in each gram . Sodium lauryl sulfate may cause local skin reactions (such as stinging or burning sensation) or increase skin reactions caused by other products when applied on the same area.

4.5. Interactions with Other Medicinal Products and Other Forms of Interaction

Limited data suggest that an interaction between topical bifonazole and warfarin may be possible, leading to increases in INR. If bifonazole is used in a patient on warfarin therapy, they should be appropriately monitored.

4.6. Fertility, Pregnancy and Lactation

Fertility
Preclinical studies gave no evidence that bifonazole can impair male or female fertility (see section 5.3).

Pregnancy
There are no clinical data from the use of bifonazole in pregnant women. Studies in animals have shown reproductive toxicity at high oral doses (see section 5.3) however these effects should not be anticipated at the low systemic exposures observed following topical bifonazole administration .
Bifonazole should only be used during pregnancy after an evaluation by a doctor of the benefit to the patient and the risk to the fetus.

Lactation
It is unknown whether bifonazole is excreted in human breast milk after topical application..
Bifonazole is excreted in milk after intravenous administration in animals (see section 5.3).
A decision must be made whether to
discontinue breast-feeding or to discontinue bifonazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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4.7. Effects on Ability to Drive and Use Machines

The medication has no or negligible influence on the ability to drive or use machinery.

4.8. Undesirable Effects

Immune system disorders

- Very rarely, systemic hypersensitivity reactions may occur.

The following adverse drug reactions are based on spontaneous reports, thus the frequency of individual events is not known (cannot be estimated from data).

• 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.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at https://sideeffects.health.gov.il.
In addition, you can report to Padagis via the following address: Padagis.co.il

4.9. Overdose

No risk of acute intoxication is seen as it is unlikely to occur following a single dermal application of an overdose (application over a large area under conditions favorable to absorption) or inadvertent oral ingestion.
However, in the event of accidental oral ingestion, routine measures such as gastric lavage should be performed only if clinical symptoms of overdose become apparent (e.g. dizziness, nausea or vomiting). Gastric lavage should be carried out only if the airway can be protected adequately.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Anti-fungals for dermatological use – Bifonazole

ATC Code: D01AC10

Bifonazole is an imidazole derivative with a broad antimycotic spectrum, which includes dermatophytes, yeasts, moulds and other fungi such as Malassezia furfur. It is also effective against Corynebacterium minutissimum.

Bifonazole exerts its anti-fungal action by inhibiting the biosynthesis of ergosterol on two different levels. Inhibition of ergosterol synthesis leads to structural and functional impairment of the cytoplasmic membrane.

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.

5.2. Pharmacokinetic Properties

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

After a single application (topical) of 15.2mg [^{14}C] bifonazole cream, and subsequent occlusion for six hours, 0.6±0.3% of the dose was absorbed. The absorption rate was approximately 0.008mg/100cm^2 per hour. In inflamed skin these values were higher by a factor of four. Similar results were obtained after the application of bifonazole as a 1% solution.
After intravenous administration of 0.016mg/kg [^{14}C] bifonazole, tissue uptake was rapid. Bifonazole is, however, rapidly metabolised with only 30% of an intravenous dose remaining unaltered 30 minutes post-dose.

Elimination
Elimination of the metabolites is biphasic ($T_{½}$ of eight and 50 hours). Within five days of administration 45% of the administered dose has been excreted renally, with 40% being eliminated via the liver and bile (faeces).

5.3. Preclinical Safety Data

Toxicological studies showed good local tolerability of topical formulations.

There were no indications of changes caused specifically by the active substance, and no signs of any systemic effects were observed.
Preclinical data on oral dosage forms reveal no special 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 resulted in embryotoxicity including lethality. In the rats, bifonazole at oral doses up to 100 mg/kg body weight was not embryotoxic, but a retarded skeletal development in the fetuses was observed at the dose of 100 mg/kg. This fetal effect on the skeletal development can be considered as a secondary effect resulting from the maternal toxicity (a reduction in body weight).

Given the low absorption of the active ingredient via the skin these results have

little relevance to clinical use. In a study of lactating rats treated with radioactively labelled bifonazole (10 mg/kg body weight intravenous), approximately 3.2% of the dose was excreted in the milk. In another study of radioactively labelled bifonazole, it was found that intravenously administered bifonazole (10mg/kg body weight) passes through the placental barrier in rats.

No impairment of male or female fertility was observed in rats at oral doses up to 40 mg/kg body weight.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Sodium lauryl sulfate, Sodium laureth sulfate, Ethyl alcohol, Cocamidopropylamine oxide, Cocamide diethanolamine, Lactic acid, Jessica MOD 1, Purified water.

6.2. Incompatibilities

Not known

6.3. Shelf Life

The expiry date of the product is indicated on the packaging materials

6.4. Special Precautions for Storage

Store in a cool place, below 25°C.

Can be used for 6 months after first opening, but no later than the expiration date.

6.5. Nature and Contents of Container

HDPE Bottle, 100 ml.

6.6. Special Precautions for Disposal and Other Handling

None

7. MANUFACTURER AND MARKETING AUTHORISATION HOLDER

Padagis Israel Pharmaceuticals LTD Israel, 1Rakefet st, Shoham, Israel

8. MARKETING AUTHORISATION NUMBER

126 23 26745 00

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