Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT
AGISPOR
Cream, solution, gel, shampoo

AGISPOR ONYCHOSET
Nail ointment

KERATOSPOR
Nail ointment

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1. Preparations

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

Cream, cutaneous solution, gel, shampoo: Bifonazole
Ointment: Bifonazole in combination with urea

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

1g cream contains 10 mg bifonazole
1 ml cutaneous solution contains 10 mg bifonazole
1 g gel contains 10 mg bifonazole
1 g shampoo contains 10 mg bifonazole
1 g nail ointment contains 10 mg bifonazole and 400 mg urea

3. PHARMACEUTICAL FORM

3.1. Preparations

Pharmaceutical formulation in accordance with standardized terminology:

Cream
Cutaneous solution
Gel
Shampoo
Ointment
4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

**AGISPOR cream, solution and gel:**
Broad spectrum antimycotic agent.

**AGISPOR shampoo:**
Pityriasis versicolor and sebarrhoeic dermatitis of the scalp caused by pityrosporum.

**AGISPOR ONYCHOSET and KERATOSPOR nail ointment:**
For nail stripping and antifungal treatment of fungal infections of the finger nails and toenails.

4.2. Posology and Method of Administration

**AGISPOR cream, solution and gel:**

**Posology:**

To achieve a lasting cure, treatment with AGISPOR cream, solution and gel must be carried out reliably and over an adequate period. The usual periods of treatment are summarized in the table below:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot mycoses (Tinea pedis, tinea pedum interdigitalis)</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Mycoses of the trunk, hands and skin folds (Tinea corporis, tinea manuum, tinea inguinalis)</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Pityriasis versicolor</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Erythrasma</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Superficial candidiasis of the skin</td>
<td>2-4 weeks</td>
</tr>
</tbody>
</table>

**Method of administration:**

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

**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.

Gel: A strip of gel (1/2 cm long) is generally sufficient to treat an area of about the size of the palm of the hand.

**AGISPOR shampoo:**

**Posology:**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seborrhoeic dermatitis of the scalp</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

**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.

**AGISPOR ONYCHOSET and KERATOSPOR nail ointments:**

**Posology:**

The nail ointment is applied in a thin layer to the infected nail once a day in a quantity sufficient to cover the entire nail surface.

The treatment with AGISPOR ONYCHOSET / KERATOSPOR nail ointment should be carried out carefully each day and should be continued until no more of the softened, fungally infected nail substance can be scraped off. This usually takes 7-14 days, depending on the extent of the infection and the thickness of the nail.

After detachment of the nail, consequent antimycotic treatment of the nail bed should be carried out with AGISPOR cream once daily for about 4 weeks.

**Method of administration:**

After application of the nail ointment the treated fingernail or toenail is covered with a plaster, and this dressing is left in place for 24 hours. The dressing should be changed daily; the finger or toe (or the hand or foot) should be bathed for about 10 minutes in warm water after removal of the plaster. After bathing in water, the softened infected nail substance is removed with the scraper. The treated nails are then dried, further AGISPOR
ONYCHOSET / KERATOSPOR nail ointment is applied as described above, and the nails are once again covered with the ready-to-use plaster.

It is not necessary to cover the skin surrounding the nail. However, if in exceptional cases irritation occurs, the edges of skin surrounding the nail should be covered with a suitable product, such as zinc paste, before fixing the plaster.

After detachment of the nail, i.e. before the start of the antifungal follow-up treatment, the treating doctor should check that onycholysis has been completed, and, if necessary, give the nail bed a final cleaning.

Nail plates that are significantly dystrophic appear to respond better to avulsion with urea.

**Cream, solution, gel, shampoo and ointment:**

**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**

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

If symptoms continue/persist after treatment, seek medical advice.

Generally:
- Keep medicine out of the reach of children. Avoid contact with eyes.
- Do not swallow.

**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).

For nail ointment only:

Preclinical studies gave no evidence that urea would raise concerns for a sperm-damaging potential (see section 5.3). No information is available on possible effects on female fertility.

**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 (see section 5.3). However, no clinical data are available. As a precautionary measure, it is preferable to avoid the use of bifonazole during the first trimester of pregnancy.

For nail ointment only:

There are no data from the use of urea in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of urea (or the nail ointment) during the first trimester of pregnancy.

**Lactation**

It is unknown whether bifonazole is excreted in human breast milk. The excretion of bifonazole in milk has been studied in animals. Available pharmacodynamic/toxicological data in animals have shown excretion of bifonazole/metabolites in milk (see section 5.3). Breast-feeding should be discontinued during treatment with bifonazole.

For nail ointment only:

It is unknown whether urea is excreted in human milk. Breast-feeding should be discontinued during treatment with urea or the nail ointment.

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

The following adverse reactions have been identified during post-approval use of bifonazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

- 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.

Nail ointment only
- Skin and subcutaneous tissue disorders
  Dermatitis contact, skin maceration, desquamation, nail disorder, nail discoloration, erythema, skin irritation, application site pain, pain in extremity, pruritus, rash

These side effects are reversible after discontinuation of the treatment.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Cream, solution, gel and shampoo:

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, thereby distinguishing bifonazole both from other azole derivatives and
from other anti-fungals which act only on a single level. 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.

**Ointment:**

**Pharmacotherapeutic group:** Anti-fungals for dermatological use – Bifonazole, combinations

**ATC Code:** D01AC60

**Mode of action:**
Bifonazole is an imidazole derivative with a broad anti-mycotic spectrum, which includes dermatophytes, yeasts, moulds and other fungi. Urea is acting as a keratoplastic.

Bifonazole exerts its anti-fungal action by inhibiting the biosynthesis of ergosterol on two different levels, thereby distinguishing bifonazole both from otherazole derivatives and from other anti-fungals which act only on a single level. 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.

Urea is a naturally occurring substance found e.g. in the human body. With the 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**

**Cream, solution, gel and shampoo:**

**Absorption**
Bifonazole penetrates well into infected skin layers. 6 hours after administration concentrations in the various skin layers reach from 1000 μg/cm³ in the top layer of the epidermis (stratum corneum) to 5 μg/cm³ in the stratum papillare. All concentrations determined are thus within a range of reliable antimycotic activity.

**Ointment:**

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

5.3. Preclinical Safety Data

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

Bifonazole passes through the placental barrier in rats. A study with lactating rats administered bifonazole intravenously showed that the drug was secreted into milk.

For nail ointment only:

Non-clinical data reveal no special hazards for humans from urea based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction and development.

Genotoxicity studies gave mixed results. The genotoxic effects reported in some studies may be related to the uncoiling DNA at highly non-physiological urea concentration, the exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Cream: 2-octyldecanol, cetyl stearyl alcohol, cetyl esters wax-NF, sorbitan stearate, polysorbate 60, benzyl alcohol, purified water.
Solution: Ethanol, isopropyl myristate.

Gel: polyoxyethylene-30-cetyl stearyl alcohol, macrogol 7 glycerol cocoate, isopropyl isostearate, ethanol, lactic acid, benzyl alcohol, purified water.

Shampoo: Sodium lauryl sulphate, sodium lauryl ether sulphate, ethyl alcohol, lactic acid, cocamide diethanolamine, cocamidopropylamine oxide, Perfume 199-95, purified water.

Nail ointment: Beeswax white, paraffin white soft, wool fat.

6.2. Incompatibilities

Not known

6.3. Shelf Life

AGISPOR
Cream: 36 months. Shelf life after first opening: 3 months.

Solution: 60 months.
Gel: 48 months. Shelf life after first opening: 3 months.

Shampoo: 24 months.

AGISPOR ONYCHOSET Nail Ointment: 36 months.

KERATOSPOR Nail Ointment: 36 months. Shelf life after first opening: 3 months.

6.4. Special Precautions for Storage

AGISPOR
Cream: store in a cool place, below 25°C.
Solution: store below 25°C.
Gel: store in a cool place, below 25°C.
Shampoo: store in a cool place, below 25°C.

AGISPOR ONYCHOSET Nail Ointment: store in a cool place, below 25°C.

KERATOSPOR Nail Ointment: store in a cool place, below 25°C.

6.5. Nature and Contents of Container

AGISPOR
Cream: Aluminium tube, 15 gr.
Solution: Brown type III glass bottle.
Gel: Aluminium tube, 15 gr.
Shampoo: HDPE Bottle, 100 ml.

AGISPOR ONYCHOSET Nail Ointment: Aluminium tube, 10 gr. Plasters, scraper and a metering dispenser.

KERATOSPOR Nail Ointment: Aluminium tube, 10 gr. and a metering dispenser.

6.6. Special Precautions for Disposal and Other Handling

Instructions for use / handling:
All: If irritation or sensitivity develops, discontinue treatment and institute appropriate therapy.

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.

Solution: The solution is flammable due to ethanol content. Keep away from ignition sources.

Nail ointment: Lasting therapeutic success depends largely on careful removal of the diseased nail areas and subsequent consequent treatment of the nail bed with bifonazole cream or other bifonazole formulations.
Allergy to the plaster is possible, though very rare. Consult your doctor if such an allergy occurs. You may switch to a different plaster or to rubber finger stalls.

7. MANUFACTURER AND MARKETING AUTHORISATION HOLDER

Perrigo Israel Pharmaceuticals, Ltd., P.O.B 16, Yeruham.

8. MARKETING AUTHORISATION NUMBER

AGISPOR
Cream: 036 82 25608 00
Solution: 036 83 25609 00
Gel: 036 81 25610 00
Shampoo: 126 23 26745 00

AGISPOR ONYCHOSET Nail Ointment: 123 58 26495 00

KERATOSPOR Nail Ointment: 105 78 26596 00
The content of this leaflet was checked and approved by the Ministry of Health in August 2014.

1.9.2014