# Prescribing Information

## 1. NAME OF THE MEDICINAL PRODUCT

**Agispor Solution**
**Agispor Gel**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 10 mg bifonazole
1 g gel contains 10 mg bifonazole
For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Solution
Gel

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic Indications

Broad spectrum antimycotic agent.

### 4.2. Posology and Method of Administration

**AGISPOR solution and gel:**

Posology:

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

| **Indication** | **Duration of treatment** |
|---|---|
| Foot mycoses (Tinea pedis, tinea pedum interdigitalis) | 3 weeks |
| Mycoses of the trunk, hands and skin folds (Tinea corporis, tinea manuum, tinea inguinalis) | 2-3 weeks |
| Pityriasis versicolor | 2 weeks |
| Erythrasma | 2 weeks |
| Superficial candidiasis of the skin | 2-4 weeks |

Method of administration:

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.

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.

**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, Agispor 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
Agispor solution is not suitable for use in the ear canal.

## 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) should use bifonazole containing products with caution.

Do not allow Agispor to come into contact with eyes.
Antifungal treatment of the nail bed skin with Agispor can be administered only after prior keratolytic removal of the nail substance infected with fungi.
Do not drip Agispor Solution onto flames or incandescent materials. Keep away from sources of ignition; do not smoke. The solution is highly flammable because it contains ethanol.
When Agispor Gel is used concomitantly with latex products (e.g., condoms, diaphragms), the adjuvants (stearates) can reduce their functionality, thereby decreasing the reliability of these products.
Agispor Gel contains Benzyl alcohol which can cause mild local irritation.

## 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. Therefore, if bifonazole and warfarin are used concomitantly, the patient should be appropriately monitored.

## 4.6. Fertility, Pregnancy and Lactation

**Fertility**
Preclinical studies reveal no evidence that bifonazole interferes with male or female fertility (see section 5.3).

**Pregnancy**
There is insufficient data on the use of bifonazole in pregnant women. Animal studies have shown reproductive toxicity with oral use (see section 5.3). The potential risk for humans is unknown. However, because bifonazole is an exclusively topical medication, there is no

expected risk. Nevertheless, as a precautionary measure, bifonazole should be used during pregnancy only after a careful benefit/risk assessment.
The use of bifonazole should be avoided during the first three months of pregnancy.

**Lactation**
It is unknown whether bifonazole is excreted in human breast milk.
Available pharmacodynamic/toxicological data in animals have shown excretion of bifonazole/metabolites in breast milk (see section 5.3). As a precautionary breast-feeding should be interrupted during treatment with bifonazole.

## 4.7.Effects on Ability to Drive and Use Machines

Agispor has no or negligible effect on the ability to drive or use machinery.

## 4.8.Undesirable Effects

When adverse reactions are evaluated, the following frequency categories are used:

| | |
|---|---|
| Very common | (>1/10) |
| Common | (>1/100 to <1/10) |
| Uncommon | (>1/1000 to <1/100) |
| Rare | (>1/10,000 to <1/1000) |
| Very rare | (<1/10,000) |
| Not known | (cannot be estimated from the available data) |

The following adverse reactions have been identified during post-approval use of bifonazole. Because these reactions are reported voluntarily from patient groups of unknown size, the frequency cannot be estimated from the available data.

• General disorders and administration site conditions (frequency not known):
Pain at application site, oedema peripheral (at the application site)

• Skin and subcutaneous tissue disorders (frequency not known):
Dermatitis contact, dermatitis allergic, redness, pruritus, rash, urticaria, blisters, skin exfoliation, eczema, dry skin, skin irritation, skin maceration, skin burning sensation

These side effects are reversible after discontinuation of the treatment.
Benzyl alcohol can cause allergic reactions.

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: http://sideeffects.health.gov.il
Additionally, you may also report to www.perrigo-pharma.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.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1. Pharmacodynamic Properties

**Pharmacotherapeutic group:** Antifungals for topical use – imidazole and triazole derivatives
**ATC code :** D01AC10

Bifonazole a broad-spectrum antifungal agent from the group of imidazole derivatives which act against dermatophytes, yeasts, moulds and other fungi such as Malassezia furfur. It is also effective against Corynebacterium minutissimum.
Bifonazole inhibits the biosynthesis of ergosterol at two different steps in the synthesis chain. This dual mechanism of action distinguishes bifonazole from other azole derivatives and from other antifungals agents. Inhibition of ergosterol synthesis leads to structural and functional impairment of the cytoplasmic membrane. Ergosterol is an essential component of the fungal cell membrane

Bifonazole exhibits significant fungicidal effects on dermatophytes, starting at concentrations of 5 µg/ml with an onset time of 6 hours. It is fungicidal against yeasts such as Candida species at concentrations of 20 µg/ml.
The active substance also has an inhibitory effect at concentrations 2-10 times lower than the MIC (minimum inhibitory concentration) values. The rapidly proliferating mycelium of Trichophyton mentagrophytes is inhibited even at a concentration of 3 µg/ml substrate.

The resistance situation for bifonazole is favorable. Primary resistant variants of sensitive fungal species are very rare. Thus far, studies have not shown any evidence of a development of secondary resistance in primarily sensitive fungal strains.

## 5.2. Pharmacokinetic Properties

Absorption
Bifonazole penetrates well into infected skin layers.
Six hours after application, concentrations are measured that reach the MIC levels for the fungi involved in dermatomycoses or that exceed them by several orders of magnitude: from 1000 µg/cm$^3$ in the top layer of the epidermis (stratum corneum) to 5 µg/cm$^3$ in the stratum papillare.

The retention time of bifonazole solution in the skin, measured as the protective activity against infection, is 36-48 hours in guinea pigs.

The long retention time of bifonazole in the skin at effective antifungal concentrations and consideration of the type of fungicidal activity form the basis for single-dose application in local therapy. In absorption studies after topical application to intact human skin, the serum concentrations were always below the detection limit (<1 ng/ml); mild absorption was detected only in the event of inflamed skin. These extremely low drug concentrations (generally less than 5 ng/ml) mean that any systemic effect is not expected.

## 5.3. Preclinical Safety Data

Preclinical data reveal no special hazards for humans based on conventional studies of single dose toxicity and genotoxicity (mutagenicity). While effects on the liver (enzyme induction, fatty degeneration) were observed in repeated dose toxicity studies with oral administration, these arose only in the event of exposures in excess of the maximum human exposure and therefore have 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 such oral doses resulted in delayed skeletal development in the fetuses. This fetal effect on the skeletal development can be considered as a secondary effects resulting from the maternal toxicity (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.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1. List of Excipients

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

## 6.2. Incompatibilities

Not known thus far.

## 6.3. Shelf Life

Solution: The expiry date of the product is indicated on the packaging materials
Shelf life after first opening: 3 months.
Gel: The expiry date of the product is indicated on the packaging materials.
Shelf life after first opening: 3 months.

### 6.4. Special Precautions for Storage

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

### 6.5. Nature and Contents of Container

Solution: 15 ml glass bottle, brown type III, white plastic dropper and cap.
Gel: 15 gr Aluminium tube, white plastic cap.

### 6.6. Special Precautions for Disposal and Other Handling

None

## 7. MANUFACTURER AND REGISTRATION HOLDER

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

## 8. REGISTRATION NUMBER

Agispor Solution: 036 83 25609
Agispor Gel: 036 81 25610

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