PRESCRIBING INFORMATION

1 NAME OF THE MEDICINAL PRODUCT

Agisten® Paste

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clotrimazole 1.0% w/w.
Excipients with known effect: Wool fat, butyl hydroxy toluene, propyl parahydroxybenzoate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Almost white paste for topical use.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For treatment of abrasions and skin infections caused by species of fungi sensitive to clotrimazole

4.2 Posology and method of administration

To ensure complete healing, treatment should be continued for about 2 weeks after the disappearance of the subjective symptoms. The following are the usual periods of treatment:

Dermatomycoses	3-4 weeks
Erythrasma	2-4 weeks
Pityriasis versicolor	1-3 weeks
Candida vulvitis and balanitis	1-2 weeks

A thin layer should be applied to the affected sites and gently rubbed in 2-3 times daily. A

strip of paste ½ cm long is sufficient to treat an area about the size of a hand.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Do not use to treat nail or scalp infections.

4.4 Special warnings and precautions for use

Avoid contact with the eyes.
This product contains:
Wool fat that may cause local skin reactions (e.g. contact dermatitis).
Butyl hydroxy toluene that may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.
Propyl parahydroxybenzoate that may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Laboratory tests have suggested that, when Clotrimazole paste is used together, this product may cause damage to latex contraceptives. Consequently the effectiveness of such contraceptives may be reduced. Patients should be advised to use alternative precautions for at least five days after using this product.

4.6 Fertility , Pregnancy and lactation

Fertility:
No human studies of the effects of clotrimazole on fertility have been performed; however, animal studies have not demonstrated any effects of the drug on fertility.

Pregnancy:
There is a limited amount of data from the use of clotrimazole in pregnant women. Animal studies with clotrimazole have shown reproductive toxicity at high oral doses (see section 5.3). At the low systemic exposures of clotrimazole following topical treatment, harmful effects with respect to reproductive toxicity are not predicted.Clotrimazole can be used during pregnancy, but only under the supervision of a physician.

Lactation:
There are no data on the excretion of clotrimazole into human milk. However, systemic absorption is minimal after administration and is unlikely to lead to

systemic effects. Clotrimazole may be used during lactation. If used topically on the nipple area, wash breasts before feeding child.

4.7 Effects on ability to drive and use machines

Clotrimazole has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

As the listed undesirable effects are based on spontaneous reports, assigning an accurate frequency of occurrence for each is not possible.

Immune system disorders: anaphylactic reaction, angioedema, hypersensitivity.

Vascular disorders: syncope, hypotension.

Respiratory, thoracic and mediastinal disorders: dyspnoea.

Skin and subcutaneous tissue disorders: blisters, contact dermatitis, erythema, paraesthesia, skin exfoliation, pruritus, rash, urticaria' stinging/burning sensation of the skin.

General disorders and administration site conditions: application site irritation, application site reaction, oedema, pain

Reporting of suspected adverse reactions
Reporting of 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 can also report to Padagis via the following address: Padagis.co.ilOverdose

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 favourable to absorption) or inadvertent oral ingestion. There is no specific antidote. However, in the event of accidental oral ingestion, gastric lavage is rarely required and should be considered only if a life-threatening amount of Clotrimazole has been ingested within the preceding hour or 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: Antifungals for topical use – imidazole and triazole derivatives

ATC Code: D01A C01

Mechanism of Action
Clotrimazole acts against fungi by inhibiting ergosterol synthesis. Inhibition of ergosterol synthesis leads to structural and functional impairment of the cytoplasmic membrane.

Clotrimazole has a broad antimycotic spectrum of action *in vitro* and *in vivo,* which includes dermatophytes, yeasts, moulds, etc.

Under appropriate test conditions, the MIC values for these types of fungi are in the region of less than 0.062-8.0 µg/ml substrate. The mode of action of clotrimazole is primarily fungistatic or fungicidal depending on the concentration of clotrimazole at the site of infection. In vitro activity is limited to proliferating fungal elements; fungal spores are only slightly sensitive.

In addition to its antimycotic action, clotrimazole also acts on gram-positive microorganisms (Streptococci / Staphylococci / Gardnerella vaginalis), and gram-negative microorganisms (Bacteroides).
In vitro clotrimazole inhibits the multiplication of Corynebacteria and gram-positive cocci - with the exception of Enterococci – in concentrations of 0.5-10 µg/ml substrate.
Primarily resistant variants of sensitive fungal species are very rare; the development of secondary resistance by sensitive fungi has so far only been observed in very isolated cases under therapeutic conditions.

5.2 Pharmacokinetic properties

Pharmacokinetic investigations after dermal application have shown that clotrimazole is minimally absorbed from the intact or inflamed skin into the human blood circulation. The resulting peak serum concentrations of clotrimazole were below the detection limit of 0.001 mcg/ml, suggesting that clotrimazole applied topically is unlikely to lead to measurable systemic effects or side effects.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity, genotoxicity and carcinogenicity.

Clotrimazole was not teratogenic in reproductive toxicity studies in mice, rats and rabbits. In rats high oral doses were associated with maternal toxicity, embryotoxicity, reduced fetal weights and decreased pup survival.
In rats clotrimazole and/or its metabolites were secreted into milk at levels higher than in plasma by a factor of 10 to 20 at 4 hrs after administration, followed by a decline to a factor of 0.4 by 24 hrs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Wool fat, kaolin, paraffin white soft, isopropyl myristate, zinc oxide, titanium dioxide, heavy liquid paraffin, dimethicone, sequalane, propyl parahydroxybenzoate, butyl hydroxy toluene.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Use within 6 months since first opening.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

Agisten paste: Aluminium tube, 30 g.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Padagis Israel Pharmaceuticals Ltd.

Rekefet 1 st, Shoham

8 MARKETING AUTHORISATION NUMBERS

Agisten paste: 147-39-33586

Agisten® is a registered sign of Padagis Israel Pharmaceuticals LTD

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