

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of medicinal product

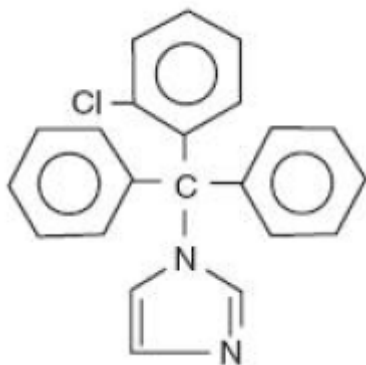
Agisten Lozenges

2. Qualitative and quantitative composition

Each Agisten Lozenge contains 10 mg clotrimazole [1-(o-chloro- α,α -diphenylbenzyl)imidazole], a synthetic antifungal agent, for topical use in the mouth.

For the full list of excipients, see section 6.1.

Structural Formula:



Chemical Formula: $C_{22}H_{17}ClN_2$

3. Pharmaceutical form

For topical oral administration.

The lozenge dosage form is a large, slowly dissolving tablet (troche), round, flat, bevel-edged white to off-white compressed lozenge, debossed with PAD 0107.

4. Clinical particulars

4.1 Therapeutic indications

Agisten Lozenges are indicated for the local treatment of oropharyngeal candidiasis. The diagnosis should be confirmed by a KOH smear and/or culture prior to treatment.

Agisten Lozenges are also indicated prophylactically to reduce the incidence of oropharyngeal candidiasis in patients immunocompromised by conditions that include chemotherapy, radiotherapy, or steroid therapy utilized in the treatment of leukemia, solid tumors, or renal transplantation.

There are no data from adequate and well-controlled trials to establish the safety and efficacy of this product for prophylactic use in patients immunocompromised by etiologies other than those listed in the previous sentence. (See DOSAGE AND ADMINISTRATION).

4.2 Posology and method of administration

Agisten Lozenge must be slowly dissolved in the mouth. The recommended dose is one lozenge five times a day for fourteen consecutive days. Only limited data are available on the safety and effectiveness of the Agisten Lozenge after prolonged administration; therefore, therapy should be limited to short term use, if possible.

For prophylaxis, to reduce the incidence of oropharyngeal candidiasis in patients immunocompromised by conditions that include chemotherapy, radiotherapy, or steroid therapy utilized in the treatment of leukemia, solid tumors, or renal transplantation, the recommended dose is one troche three times daily for the duration of chemotherapy or until steroids are reduced to maintenance levels.

4.3 Contraindications

Agisten Lozenges are contraindicated in patients who are hypersensitive to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

- Agisten Lozenges are not indicated for the treatment of systemic mycoses including systemic candidiasis.
- Abnormal liver function tests have been reported in patients treated with Agisten Lozenge; elevated SGOT levels were reported in about 15% of patients in the clinical trials. In most cases the elevations were minimal and it was often impossible to distinguish effects of clotrimazole from those of other therapy and the underlying disease (malignancy in most cases). Periodic assessment of hepatic function is advisable particularly in patients with pre-existing hepatic impairment.

Since patients must be instructed to allow each lozenge to dissolve slowly in the mouth in order to achieve maximum effect of the medication, they must be of such an age and physical and/or mental condition to comprehend such instructions.

Carcinogenesis: An 18 month dosing study with clotrimazole in rats has not revealed any carcinogenic effect.

Pediatric Use

Safety and effectiveness of clotrimazole in children below the age of 3 years have not been established; therefore, its use in such patients is not recommended.

The safety and efficacy of the prophylactic use of Agisten Lozenge in children have not been established.

Geriatric Use

Clinical studies of clotrimazole did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

DRUG ABUSE AND DEPENDENCE

No data available.

Important information about some of the ingredients of the medicine

Patients with rare glucose-galactose malabsorption should not take this medicine. Agisten lozenges contains 888 mg dextrose per lozenge.

4.5 Interaction with other medicinal products and other forms of interaction

Not known

4.6 Fertility, pregnancy and lactation

Usage in Pregnancy: Pregnancy Category C

Clotrimazole has been shown to be embryotoxic in rats and mice when given in doses 100 times the adult human dose (in mg/kg), possibly secondary to maternal toxicity. The drug was not teratogenic in mice, rabbits, and rats when given in doses up to 200, 180 and 100 times the human dose.

Clotrimazole given orally to mice from nine weeks before mating through weaning at a dose 120 times the human dose was associated with impairment of mating, decreased number of viable young, and decreased survival to weaning. No effects were observed at 60 times the human dose. When the drug was given to rats during a similar time period at 50 times the human dose, there was a slight decrease in the number of pups per litter and decreased pup viability.

There are no adequate and well controlled studies in pregnant women. Agisten Lozenges should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

Abnormal liver function tests have been reported in patients treated with Agisten Lozenges; elevated SGOT levels were reported in about 15% of patients in the clinical trials (See PRECAUTIONS section).

Nausea, vomiting, unpleasant mouth sensations and pruritus have also been reported with the use of the lozenge.

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 <https://sideeffects.health.gov.il>

Additionally, you may also report to [Padagis.co.il](https://www.padagis.co.il).

4.9 Overdosage

No data available.

5. Pharmacological properties

Clotrimazole is a broad-spectrum antifungal agent that inhibits the growth of pathogenic yeasts by altering the permeability of cell membranes. The action of clotrimazole is fungistatic at concentrations of drug up to 20 mcg/mL and may be fungicidal *in vitro* against *Candida albicans* and other species of the genus *Candida* at higher concentrations. No single-step or multiple-step resistance to clotrimazole has developed during successive passages of *Candida albicans* in the laboratory; however, individual organism tolerance has been observed during successive passages in the laboratory. Such *in vitro* tolerance has resolved once the organism has been removed from the antifungal environment.

After oral administration of a 10 mg clotrimazole lozenge to healthy volunteers, concentrations sufficient to inhibit most species of *Candida* persist in saliva for up to three hours following the approximately 30 minutes needed for a lozenge to dissolve. The long term persistence of drug in saliva appears to be related to the slow release of clotrimazole from the oral mucosa to which the drug is apparently bound. Repetitive dosing at three hour intervals maintains salivary levels above the minimum inhibitory concentrations of most strains of *Candida*; however, the relationship between *in vitro* susceptibility of pathogenic fungi to clotrimazole and prophylaxis or cure of infections in humans has not been established.

In another study, the mean serum concentrations were 4.98 ± 3.7 and 3.23 ± 1.4 nanograms/ml of clotrimazole at 30 and 60 minutes respectively, after administration as a lozenge.

6. Pharmaceutical particulars

6.1 List of excipients

Dextrose, microcrystalline cellulose, povidone, magnesium stearate.

6.2 Incompatibilities

No data available

6.3 Shelf life

The expiry date is indicated on the packaging materials.

Shelf life after first opening: Agisten lozenges can be used until the end of shelf life, as indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

Agisten Lozenges are supplied in a bottle of 70 lozenges.

7. Marketing Authorization Holder and importer: Padagis Israel Agencies, Ltd., 1 Rakefet st., Shoham

8. Registration number: 159 13 34540

Revised on May 2023 according to MOHs guidelines