The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it: July 2017

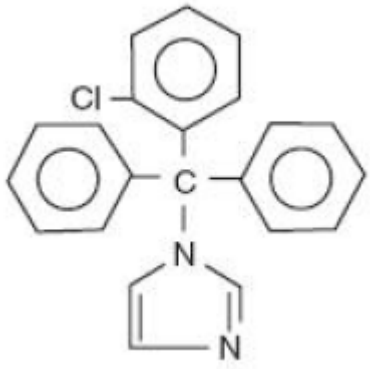
PRESCRIBING INFORMATION

Agisten Lozenges

For topical oral administration

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

Structural Formula:



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

The lozenge dosage form is a large, slowly dissolving tablet (troche) containing 10 mg of clotrimazole dispersed in dextrose, microcrystalline cellulose, povidone and magnesium stearate.

CLINICAL PHARMACOLOGY
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 concentration 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.

INDICATIONS AND USAGE

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**)

CONTRAINDICATIONS

Agisten Lozenges are contraindicated in patients who are hypersensitive to any of its components.

WARNING

Agisten Lozenges are not indicated for the treatment of systemic mycoses including systemic candidiasis.

PRECAUTIONS

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. 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.

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.

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

The safety and efficacy of the prophylactic use of Agisten Lozenges 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.

ADVERSE REACTIONS
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 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://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

Additionally, you may also report to www.perrigo-pharma.co.il.

OVERDOSAGE
No data available.

DRUG ABUSE AND DEPENDENCE
No data available.

DOSAGE AND ADMINISTRATION
Agisten Lozenges 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.

HOW SUPPLIED
Agisten Lozenges are supplied in bottle of 70 lozenges.
Shelf life: 24 months
Shelf life after first opening: 4 weeks

Store below 25°C

Manufacturer:
Paddock Laboratories, LLC, USA

Marketing Authorization Holder:
Perrigo Israel Agencies, Ltd.