

Summary of product characteristics

1 .Name of the medicinal product

Agisten V™ 0.5g Vaginal Tablet

2 .Qualitative and quantitative composition

Clotrimazole 500mg

For full list of excipients, see section 6.1

3 .Pharmaceutical form

Vaginal tablet.

Nearly white to slightly yellowish

4 .Clinical particulars

4.1 Therapeutic Indications

Broad spectrum antimycotic with fungicidal and trichomonacidal action (for single dose treatment).

4.2 Posology and Method of administration

One vaginal tablet to be inserted in the evening.

The vaginal tablet should be inserted into the vagina, as high as possible into the vagina, using the applicator provided. This is best achieved when lying back with the legs bent up. A second treatments can be repeated if necessary.

Agisten v 0.5 g vaginal tablets need moisture in the vagina in order to dissolve completely, otherwise undissolved pieces of the vaginal tablet might crumble out of the vagina. Pieces of undissolved tablet may be noticed by women who experience vaginal dryness. To help prevent this it is important to insert the vaginal tablet as high as possible into the vagina at bedtime.

Generally

- If symptoms persist for more than 7 days the patient may have a medical condition that requires treatment by a doctor
- The treatments can be repeated if necessary however recurrent infections may indicate an underlying medical cause, including diabetes or HIV infections. Patients should seek the medical advice if symptoms return within 2 months
- Since the vagina and vulva are usually both affected, a combination treatment (treatment of both of these areas) should be performed
- If the labia and adjacent areas are simultaneously infected, local treatment with an external cream should also be given. The sexual partner should also undergo local treatment if symptoms, e.g. pruritus, inflammation, etc. are present.

- Do not use tampons, intravaginal douches, spermicides or other vaginal products while using this product.
- Vaginal intercourse should be avoided in case of vaginal infection and while using this product because the infection could be transferred to your partner, and the effectiveness and safety of latex products such as condoms and diaphragms may be reduced.
- Intended for use by adults and children 12 years of age and older

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Medical advice should be sought if this is the first time the patient has experienced symptoms of candidal vaginitis.

Before using Agisten v 0.5 g vaginal tablets, medical advice must be sought if any of the following are applicable:

- more than two infections of candidal vaginitis in the last 6 months.
- previous history of sexually transmitted disease or exposure to partner with sexually transmitted disease.
- pregnancy or suspected pregnancy
- aged under 16 or over 60 years
- known hypersensitivity to imidazoles or other vaginal antifungal products.

Agisten v 0.5 g vaginal tablets should not be used if the patient has any of the following symptoms where upon medical advice should be sought:

- irregular vaginal bleeding
- abnormal vaginal bleeding or a blood-stained discharge
- vulval or vaginal ulcers, blisters or sores
- lower abdominal pain or dysuria
- any adverse events such as redness, irritation or swelling associated with the treatment
- fever or chills
- nausea or vomiting
- diarrhea
- foul smelling vaginal discharge

Treatment during the menstrual period should not be performed due to the risk of the pessary being washed out by the menstrual flow. The treatment should be finished before the onset of menstruation.

Do not use tampons, intravaginal douches, spermicides or other vaginal products while using this product.

Vaginal intercourse should be avoided in case of vaginal infection and while using this product because the partner could become infected.

When used in pregnancy, the pessary should be inserted without using an applicator (See Pregnancy”).

Patients should be advised to consult their physician if the symptoms have not been relieved within one week of using Agisten v 0.5 g vaginal tablets. Agisten v 0.5 g vaginal tablet can be used again if the candidal infection returns after 7 days. However, if the candidal infection recurs more than twice within six months, patients should be advised to consult their physician.

4.5 Interaction with other medicinal products and other forms of interaction

Laboratory tests have suggested that, when 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.

Concomitant treatment with vaginal clotrimazole and oral tacrolimus (FK-506; immunosuppressant) might lead to increased tacrolimus plasma levels and similarly with sirolimus. Patients should thus be closely monitored for signs and symptoms of tacrolimus or sirolimus overdose, if necessary by determination of the respective plasma levels.

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 are 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 vaginal 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.

During pregnancy the vaginal tablet should be inserted without using an applicator.

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.

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

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

Immune system disorders: Anaphylactic reaction, angioedema, hypersensitivity.

Vascular disorder: syncope, hypotension.

Respiratory, thoracic and mediastinal disorders: dyspnea.

Gastrointestinal disorders: abdominal pain, nausea

Skin and Subcutaneous Tissue Disorders: rash, urticaria, pruritus.

Reproductive system and breast disorders: vaginal exfoliation, vaginal discharge, vaginal haemorrhage, vulvovaginal discomfort, vulvovaginal erythema, vulvovaginal burning sensation, vulvovaginal pruritus, vulvovaginal pain.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 (www.Health.gov.il) according to the National Regulation by using an online form [/https://sideeffects.health.gov.il](https://sideeffects.health.gov.il) Additionally, you can also report to Padagis.co.il.

4.9 Overdose

No risk of acute intoxication is seen as it is unlikely to occur following a single vaginal or 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, routine measures such as gastric lavage should be performed only 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: Gynaecological antiinfectives and antiseptics – imidazole derivatives

ATC Code: G01A F02

Mechanism of Action

Azoles (e.g. clotrimazole) are usually recommended for the local treatment of vulvovaginal candidosis that is characterized by vulvovaginal symptoms such as itching, burning, discharge, redness, swelling and soreness.

Clotrimazole acts against fungi by inhibiting ergosterol synthesis. Inhibition of ergosterol synthesis leads to structural and functional impairment of the fungal 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 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.

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 vaginal application have shown that only a small amount of Clotrimazole (3-10% of the dose) is absorbed. Due to the rapid hepatic metabolism of absorbed clotrimazole into pharmacologically inactive metabolites the resulting peak plasma concentrations of clotrimazole after vaginal application of a 500mg dose were less than 10 ng/ml., reflecting that clotrimazole applied intravaginally does not 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

Lactose Monohydrate, Microcrystalline Cellulose, Lactic Acid, Maize Starch, Crosspovidone, Calcium Lactate, Colloidal anhydrous silica, Magnesium Stearate, Hydroxypropyl Methylcellulose.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a cool place, below 25°C

6.5 Nature and contents of the container

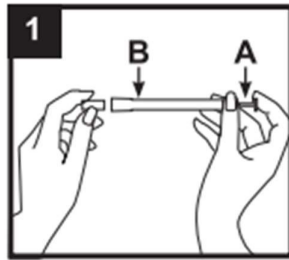
Each vaginal tablet is packed into a blister pack. The blister and the applicator are enclosed in a cardboard carton

6.6 special precautions for disposal and other handling

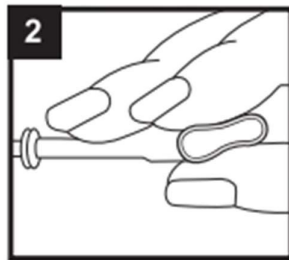
The following instructions for handling the product appear on the patient information leaflet.

Wash your hands before removing the tablet from its package and again after using the applicator.

1. Remove the applicator from the package. Pull out the plunger (A) until it stops. Remove the vaginal tablet from the aluminum blister pack and place it firmly into the wide end of the applicator (B).

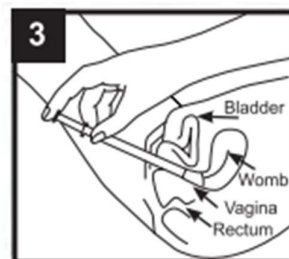


2. To fit the tablet into the applicator, squeeze the applicator end lightly on both sides. The tablet fits the applicator exactly and should be pressed to the end of the applicator up to a depth of about 1 cm.



3. Gently insert the applicator into the vagina as deeply as possible and as is comfortable, (the easiest way

to do this is while lying on your back with your knees bent upwards). Hold the applicator in place and slowly press the plunger until it stops so that the tablet is placed in the vagina.



4. Remove the applicator. Dispose of the applicator in a safe place, out of the reach of children. Do not dispose of the applicator in the toilet.

7. Manufacturer and marketing authorization holder:

Padagis Israel Pharmaceuticals Ltd. 1 Rakefet st. Shoham

8. Registration number

031-74-25210-00

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