Summary of product characteristics

1 .Name of the medicinal product

Agisten V 2% Vaginal Cream

2 .Qualitative and quantitative composition

Cltorimazole 2%

Excipient with known effect: Cetostearyl alcohol, Benzyl alcohol

For full list of excipients, see section 6.1

3 .Pharmaceutical form

Vaginal cream

4 .Clinical particulars

4.1 Therapeutic Indications

Broad spectrum antimycotic with fungicidal action

4.2 Posology and Method of administration

One applicator charge daily (approximately 5 g) should be introduced as deep as possible into the vagina before retiring for 3 consecutive days. This is best achieved when lying on the back.

Male Partner

The vaginal cream should be applied 2-3 times a day in a thin layer on the penis for balanitis (whether symptomatic or asymptomatic). The normal period of treatment is 1-2 weeks.

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
- Treatment during the menstrual period should not be performed. The treatment should be finished before the onset of menstruation
- 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, spermicidies or other vaginal products while using this product.

- Avoidance of vaginal intercourse is recommended 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 candida vaginitis.

Before using Agisten V 2% vaginal cream, medical advice must be sought if any of the following are applicable:

- more than two infections of candida vaginitis in the last 6 months.
- previous history of sexsually 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 2% vaginal cream 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.

Patients should be advised to consult their physician if the symptoms have not been relieved within one week of using Agisten cream. The cream can be used again if the candidal infection returns after 7 days. However, if the candidal infection occurs 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 medication 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 overdosage, 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 treatment should be carried out with Agisten vaginal tablets, since these can be inserted without using an applicator

Lactation:
Available pharmacodynamic/toxicological data in animals have shown excretion of clotrimazole/metabolites in milk after intravenous administration (see section 5.3). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from clotrimazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable Effects

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

Immune system disorders: allergic reaction (syncope, hypotension, dyspnea, urticaria,)

Reproductive system and breast disorders:
genital peeling, pruritus, rash, oedema, erythema, discomfort, burning, irritation, pelvic pain, vaginal haemorrhage.
Gastrointestinal disorders:
abdominal 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 according to the National Regulation by using an online form /https://sideeffects.health.gov.il
Additionally, you can 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 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

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

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 metabolization 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 dose 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

2-Octyldodecanol, Cetostearyl Alcohol, Cetyl Esters Wax, Sorbitan Monostearate, Polysorbate 60, Benzyl Alcohol, Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Shelf life after first opening: 6 months

6.4 Special precautions for storage

Store in a cool place, below 25°C

6.5 Nature and contents of the container

An aluminum tube contains 20 gr white cream, turban shape cup and
3 applications. The tube and the applicators are enclosed in a cardboard carton

6.6 special precautions for disposal and other handling

No special requirements

7. Manufacturer and marketing authorization holder:

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

8. Registration number

048-56-23822

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