SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Clotrim 500mg vaginal tablet.

2. Qualitative and quantitative composition

Clotrimazole 500mg.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Vaginal Tablet.

White color, torpedo biconvex vaginal tablet.

4. Clinical particulars

4.1. Therapeutic indications

Clotrimazole 500mg Vaginal tablet is indicated for the treatment of candidal vaginitis.

4.2. Posology and method of administration

The vaginal tablet should be inserted into the vagina, as high as possible, using the applicator provided.

Adults: One 500mg vaginal tablet should be inserted at night. Using the applicator provided, the vaginal tablet should be inserted as high as possible into the vagina. This is best achieved when lying back with legs bent up. A second treatment may be carried out if necessary.

Clotrimazole vaginal tablet 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 vaginal tablet may be noticed by women who experience vaginal dryness. To help prevent this it is important that the vaginal tablet is inserted as high as possible into the vagina at bedtime.

Children: As the product is used with an applicator, paediatric usage is not recommended.

For instructions on handling and disposal see section 6.6.

4.3. Contraindications

Hypersensitivity to the active substance 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 Clotrimazole vaginal tablet, 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.

Clotrimazole vaginal tablet 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.

- Diarrhoea.

- Foul smelling vaginal discharge.

Treatment during the menstrual period should not be performed due to the risk of the vaginal tablet 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 vaginal tablet 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 Clotrimazole 500mg Vaginal tablet. Clotrimazole 500mg 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 overdosage, if necessary by determination of the respective plasma levels.

4.6. Fertility, pregnancy and lactation

Pregnancy:
There is 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 or midwife.
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.

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.

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. Healthcare professionals are asked to report any suspected adverse reactions via:

CIOMS form and send to rajoriver@joriver.com or rareg@ joriver.com or you can call Tel: +962-6-5320623.

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 anti-infective 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 microgram/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

Microcrystalline Cellulose pH 101
Maize starch
Lactose Monohydrate
Pregelainized Starch
Sodium Starch Glycolate
Polysorbate 80

Povidone K-30
Crospovidone
Colloidal Silicone Dioxide
Magnesium Stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store at temperature not to exceed 30ºC.

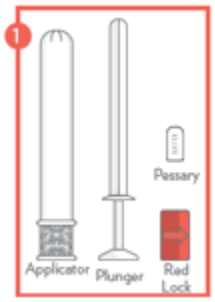
6.5. Nature and contents of container

The pack contains one Alu/Alu blister with 1 Vaginal tablet and separate applicator.

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 handling the applicator and the foil blister pack and again afterwards when you have used the applicator.



1. Image 1 shows all the components included in the Clotrimazole 500mg Vaginal tablet pack.

Remove the applicator from the packaging and pull out the plunger (with the red lock attached) from the applicator.

2. Remove the vaginal tablet from the foil blister pack and place into the open end of the applicator with the curved edge of the vaginal tablet facing down. Push the plunger and lock into the applicator until you feel a click.

3. Once you have felt the click, remove the lock from the plunger.

4. Carefully insert the applicator as deep as is comfortable into the vagina (this is easiest when lying on your back with your knees bent up) up to the patterned grip zone. Hold the applicator at the patterned grip zone. Carefully push the plunger all the way until it stops to dispense the vaginal tablet.

5. Remove the applicator. Dispose of the applicator in a safe place, out of the reach of children.

The applicator cannot be flushed down the toilet.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Jordan River Pharmaceutical industries. L.L.C

Um Za'aroora street

Mubes Al baqa'a

Amman – Jordan

8. MARKETING AUTHORISATION NUMBER(S)

07989/NMR/2019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/07/2023

10. DATE OF REVISION OF THE TEXT

27/07/2023