SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Clotrimazole 100 mg pessaries
Clotrilin

2. Qualitative and quantitative composition
Each pessary contains 100 mg of clotrimazole.

Excipient with known effect
Each pessary also contains 755 mg of lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Pessary.

White to off-white coloured, almond-shaped, uncoated pessary, plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications
Clotrimazole is indicated for the relief of vaginal itching, burning & discharge associated with recurrent vaginal yeast infections (vaginal candidiasis). Vaginitis due to candida species.

4.2 Posology and method of administration
The pessaries should be inserted into the vagina, as high as possible, using the applicator provided. This is best achieved when lying back with legs bent up.

Adults
Two pessaries should be inserted daily (preferably at night) for three consecutive days.
Alternatively, one pessary may be inserted daily for six days, preferably at night. A second treatment may be carried out if necessary. There is no separate dosage schedule for the elderly.

Children
Not for use in children under 16. For instructions on handling and disposal see section 6.6.

4.3 Contraindications
Hypersensitivity to the active substance or 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, medical advice must be sought if any of the following are applicable:
- more than two infections of candidal vaginitis in the last six months.

- previous history of a sexually transmitted disease or exposure to a partner with a sexually transmitted disease.
- pregnancy or suspected pregnancy.
- aged under 16 or over 60 years.
- known hypersensitivity to imidazoles or other vaginal antifungal products.

Clotrimazole should not be used if the patient has any of the following symptoms whereupon 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 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 section 4.6).

Patients should be advised to consult their physician if the symptoms have not been relieved within one week of using clotrimazole. The pessaries 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.

Excipients
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 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 breastfeeding

Pregnancy
There is a limited amount of data on 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 concerning reproductive toxicity are not predicted. Clotrimazole can be used during pregnancy, but only under the supervision of a physician or midwife. During pregnancy, the clotrimazole should be inserted without using an applicator.

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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 the 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
The frequency is not known. As the listed undesirable effects are based on spontaneous reports, assigning an 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 authorisation 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 the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

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

Pharmacological classification: 14.17 Dermatological and topical preparations: Vaginal preparations.

Mechanism of action

Azoles (e.g., clotrimazole) are usually recommended for the local treatment of vulvovaginal candidosis which is characterised 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 and moulds. 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 500 mg 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 hours after administration, followed by a decline to a factor of 0.4 by 24 hours.

6. Pharmaceutical particulars

6.1 List of excipients
Maize starch
Lactose
Pregelatinised starch
Microcrystalline cellulose
Sodium starch glycolate
Colloidal anhydrous silica
Purified talc
Povidone
Magnesium stearate
Sodium lauryl sulphate
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 30°C. Protect from light, moisture and crushing.

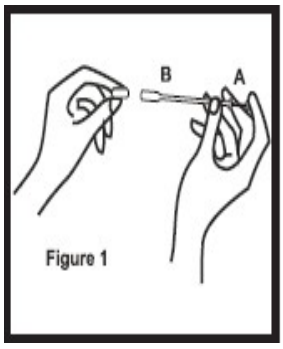
6.5 Nature and contents of the container
Six (6) pessaries are packed in an aluminium-aluminium strip pack.

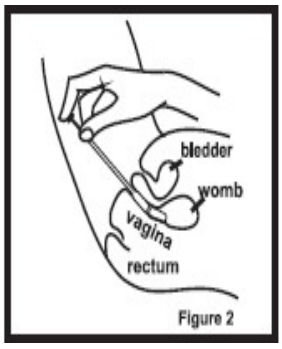
Pack size: 1 strip pack per carton.

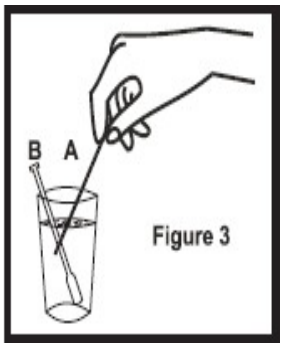
6.6 Special precautions for disposal and other handling
The following instructions for handling the product appear on the patient information leaflet.

Before handling the applicator and the foil blister pack and again afterwards (after using the applicator), the individual must wash their hands.

Directions for Insertion of pessaries using the applicator.







1. Remove one pessary from the strip pack.
2. Pull out the plunger(A) till it stops and place one tablet into the applicator (B) (See Figure-1).
3. Carefully insert the applicator containing the pessary as deeply as possible into the vagina. This is best achieved when lying on the back (See Figure-2).
4. Carefully push the plunger (A) till it stops. This pushes the pessary into the vagina. Withdraw the applicator from the vagina.
5. After use, pull out the plunger (A) completely from the applicator (B)(See Figure-3) and wash both components in warm water. Clean and dry them.
Note: Pregnant women should strictly follow the doctor's instructions.

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

7. APPLICANT
Lincoln Pharmaceuticals Limited
Lincoln House, Behind Satyam Complex, Science City Road, Sola
Ahmedabad - 380060
Gujarat
India

8. MANUFACTURER
Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Tal. Kalol
Dist. Gandhinagar
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India

9. REGISTRATION DETAILS
Zimbabwe registration number: 2023/14.17/6446
Zimbabwe category for distribution: Pharmacist Initiated Medicines (P.I.M.)

10. DATE OF REVISION OF TEXT
October 2023