SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[Invented name], 500 mg vaginal tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vaginal tablet contains 500 mg of clotrimazole *(Clotrimazolum).*
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vaginal tablet

White, biconvex, elongated tablet, rounded on one side, straight beveled on the other.
Tablet dimensions: 24.5 mm (length) x 10.0 mm (width).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of the infections of the vagina and vulva (female external genitalia) caused by microorganisms, such as fungi (usually *Candida*), sensitive to clotrimazole.

4.2 Posology and method of administration

Posology
Adults and adolescents aged 16 years and more
One vaginal tablet, deep intravaginal use, in a single dose, before bedtime.
If there is no improvement after 7 days from application, the doctor should be consulted. The treatment may be repeated. However, recurrent infections may indicate another condition that causes complaints. In case of repeated symptoms, the doctor should be consulted.

Adolescents aged 12 to 15 years
In adolescents under 16 years of age, [Invented name] can only be used after consulting a doctor. When used in this patient group (after first menstruation), the recommended dose is the same as in adults.

Children
The safety and efficacy of [Invented name] in children under 12 years of age have not been established.

Method of administration
One vaginal tablet, deep intravaginal use, in a single dose, before bedtime. The vaginal tablet should be inserted into the vagina as deep as possible.
Provide a moist environment of the vagina so that the tablet is completely dissolved. If not dissolved, some of the tablet may leak out of the vagina. To avoid this, it is recommended to insert the tablet into the vagina as deep as possible, before going to bed.

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

Before using [Invented name], medical advice must be sought if any of the following are applicable:
- when the vaginal infection occurred for the first time,
- in case of a vaginal infection in the first trimester of pregnancy,
- when there have been 4 or more infections in the past year,
- in the case of fever (≥38°C),
- in the case of pain in the lower abdomen, back pain,
- in the case of fetid vaginal discharges,
- in the case of nausea,
- in the case of vaginal bleeding and/or pain in arms.

[Invented name] should not be used during menstruation. The use of this medicinal product should be discontinued before the onset of menstruation.

Tampons, vaginal lavage, spermicides or other vaginal products should not be used concomitantly with this medicinal product.

Sexual intercourse should be avoided while using [Invented name], as the infection can be passed on to the sexual partner.

The sexual partner should receive simultaneous topical treatment if he has symptoms such as itching and inflammation. Treatment of sexual partners can help prevent reinfection.

The reliability and contraceptive efficacy of contraceptives, such as latex condoms and vaginal rings, may be reduced.

The tablets should not be swallowed.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of vaginal clotrimazole and oral tacrolimus or sirolimus (FK-506, immunosuppressants) may lead to increased tacrolimus or sirolimus plasma concentrations. Patients should be carefully monitored for signs of tacrolimus or sirolimus overdose and plasma concentrations of these medicines should be determined, if necessary.
Clotrimazole is a moderate CYP3A4 inhibitor and a weak CYP2C9 inhibitor in liver microsomes. 3–10% of the intravaginal dose of clotrimazole is absorbed into the systemic circulation, which may affect plasma concentrations of other medicinal products.
In particular, medicinal products metabolised by CYP3A4, potentially increasing plasma levels of these medicines when co-administered. Since the effect on CYP2C9 is low and only a small fraction of topical administration of clotrimazole is absorbed into the systemic circulation, the effect of clotrimazole on the CYP2C9 isoenzyme is negligible. Therefore, due to the very low absorption of clotrimazole after vaginal administration, in particular of a single dose of 500 mg, it is unlikely that clotrimazole administered intravaginally showed any clinically relevant drug interactions (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited amounts of data from the use of clotrimazole in pregnant women. Animal studies have not shown any direct or indirect toxic effects on reproduction (see section 5.3).
Clotrimazole can be used during pregnancy.
However, treatment should only be started under medical supervision during the first trimester of pregnancy. In the last 4-6 weeks of pregnancy, intimate hygiene of the genital tract should be carefully maintained.

Breast-feeding
It is not known whether clotrimazole is excreted into human milk. As systemic absorption is minimal after administration, it is unlikely to produce systemic effects. Clotrimazole can be used during lactation.

Fertility
No studies on the effect of clotrimazole on human fertility have been performed. Animal studies have not shown any effect of clotrimazole on fertility.

4.7 Effects on ability to drive and use machines

[Invented name] has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

System Organ Classification	Common (≥ 1/100 to < 1/10)	Uncommon (≥1/1 000 to <1/100)	Rare (≥ 1/10 000 to < 1/1 000)
Gastrointestinal disorders		abdominal pain	
Immune system disorders			allergic reactions
Skin and subcutaneous tissue disorders			skin rash
Reproductive system and breast disorders	burning sensation in the vagina and vulva	itching in the vulva and vagina, erythema of the vulva and vagina	vaginal bleeding
General disorders and administration site conditions		irritation in the application site	oedema

Side effects identified from post-marketing experience with clotrimazole
Since these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency, i.e. frequency not known (cannot be estimated from the available data):

Immune system disorders: anaphylactic reaction, angioedema, hypersensitivity;
Vascular disorders: syncope, hypotension;
Respiratory, thoracic and mediastinal disorders: dyspnoea;
Gastrointestinal disorders: nausea;
Skin and subcutaneous tissue disorders: urticaria;
Reproductive system and breast disorders: vaginal exfoliation, vaginal discharge, vaginal discomfort, vaginal pain;
General disorders and administration site conditions: 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 national reporting system listed in Appendix V.*

4.9 Overdose

There is no risk of acute intoxication as it is unlikely to occur after a single intravaginal administration of an overdose of the medicinal product or accidental oral ingestion. There is no specific antidote.

The following adverse reactions have been reported during acute overdose of clotrimazole: abdominal pain, upper abdominal pain, diarrhoea, indisposition, nausea and vomiting.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-infectives and disinfectants used in gynaecology; imidazole derivatives, ATC code: G01AF02

[Invented name] contains clotrimazole, which belongs to the group of imidazoles with a broad spectrum of antifungal activity. [Invented name] is intended for topical treatment of gynaecological fungal infections.

Mechanism of action
Clotrimazole inhibits the synthesis of ergosterol in fungi, resulting in structural and functional disturbances of cell membranes (permeability increases).

A wide range of *in vitro* and *in vivo* antifungal activity of clotrimazole includes dermatophytes (Epidermophyton floccosum, Microsporum canis, Trichophyton mentagrophytes, Trichophyton rubrum, Aspergilli), yeasts (e.g. Candida spp.), moulds and other fungi (e.g. Coccidioides immitis, Histoplasma capsulatum).

Under appropriate conditions, the MICs for these fungi are within the area below 0.062–8.0 µg/ml of the substrate. Clotrimazole is mainly fungistatic or fungicidal, depending on the concentration of clotrimazole at the site of infection. *In vitro* activity is limited to proliferating parts of the fungus; spores are only slightly sensitive.

In addition to antifungal action, clotrimazole also affects Gram-positive microorganisms *(Streptococcus, Staphylococcus, Gardnerella vaginalis)* and Gram-negative microorganisms *(Bacteroides)* and protozoa *(Trichomonas vaginalis)*.

Clotrimazole inhibits *in vitro* multiplication of *Corynebacterium* and Gram-positive cocci (excluding enterococci) at concentrations of 0.5–10 µg/ml of the substrate.

Among susceptible species of fungi, strains originally resistant to clotrimazole are very rare. Development of secondary resistance in therapeutic settings has so far been observed in isolated cases in the therapeutic dose range.

5.2 Pharmacokinetic properties

Absorption
Skin and vaginal pharmacokinetic studies have shown that only a very small amount of clotrimazole is absorbed (3–10% of the vaginal dose).

Metabolism
Due to the rapid hepatic metabolism of absorbed clotrimazole to pharmacologically inactive metabolites, the maximum plasma concentrations of clotrimazole observed after intravaginal administration of a 500 mg dose remained below 0.01 µg/ml. Such concentration is unlikely to result in noticeable systemic effects or adverse reactions.
In *in vitro* setting, clotrimazole is a moderate inhibitor of CYP3A4 and CYP2C9 in liver microsomes and 3–10% of the intravaginal dose of clotrimazole is absorbed into the systemic circulation. Since only a small portion of topical clotrimazole is absorbed into the systemic circulation, the effect of a single dose of 500 mg of clotrimazole on the levels of medicines metabolised by CYP3A4 and CYP2C9 is low and is unlikely to cause clinically significant drug interactions.

Elimination
Following oral and vaginal administration, clotrimazole is extensively metabolised in the liver to inactive metabolite: 2-chlorophenyl-4-hydroxyphenylmethane. Following oral administration, 10% of the administered medicinal products is excreted in the urine on the first day, 25% for 6 days, but only 1% remains unchanged.

Distribution
Distribution of clotrimazole to individual organs is unknown.
Clotrimazole is rapidly metabolized, therefore there are only traces of the unchanged substance in the circulating blood.

5.3 Preclinical safety data

Intravaginal or topical toxicology studies in various animal species showed good vaginal and local tolerance to clotrimazole.
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, toxicity to reproduction and development.
A study in which 3 female rats were given intravenous clotrimazole at a dose of 30 mg/kg demonstrated that 4 hours after administration the concentration of this medicinal product in milk was 10 to 20 times higher than the plasma concentration; after 24 hours, the milk and plasma concentrations decreased to 0.4.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Adipic acid
Sodium Hydrogen Carbonate
Magnesium stearate
Silica, colloidal anhydrous
Sodium laurilsulfate
Potato starch
Maize starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

OPA/Aluminium/PVC/Aluminium blister in a cardboard box.

1 vaginal tablet.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT