

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Canesten Cream Combi Internal & External Creams

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Canesten Combi 10 % Internal Cream contains Clotrimazole 100 mg/g

Canesten Combi 2% External Cream contains Clotrimazole 20 mg/g

Excipients with known effect:

The 10% cream contains Cetostearyl alcohol 35mg in each gram of cream and Benzyl alcohol 10mg in each gram of cream

The 2% cream also contains Cetostearyl alcohol 100mg in each gram of cream and Benzyl alcohol 20mg in each gram of cream

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Vaginal Cream.

Canesten 10 % Internal Cream contains a soft, white cream in a prefilled applicator

Canesten 2% External Cream contains white oil in water type cream

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The internal cream is recommended for the treatment of candidal vaginitis.

The external cream is recommended for the treatment of candidal vulvitis. It should be used as an adjunct to treatment of candidal vaginitis. It can also be used for treatment of the sexual partner's penis to prevent re-infection.

4.2 Posology and method of administration

Adults and children of 12 years of age and older:

Canesten Internal Cream should be administered intravaginally using the applicator supplied. The contents of the filled applicator (5g) should be inserted as deeply as possible into the vagina, preferably at night, before going to bed.

If symptoms persist for more than 7 days the patient may have a medical condition that requires treatment by a doctor.

The treatment can be repeated if necessary, however, recurrent infections may indicate an underlying medical cause. Patient should seek medical advice if symptoms return within 2 months.

Canesten External Cream should be applied thinly to the vulva and surrounding area, two or three times daily and rubbed in gently.

If the cream is being used for treatment of the sexual partner's penis it should be applied two or three times daily for up to two weeks.

Treatment with the external cream should be continued until symptoms of the infection disappear. However, if after concomitant treatment of the vaginitis, the symptoms do not improve within seven days, the patient should consult a doctor.

1. Remove applicator from package. Insert plunger into applicator.
2. Remove cap by turning.
3. Introduce applicator as deeply as possible into the vagina (this is best done with the patient lying on her back with the knees bent up) and empty its contents into the vagina by pushing the plunger.
4. Remove the applicator and dispose of it.

Canesten Combi 2% External Cream:

There are no special instructions for use of the cream.

Children:

Not for use in children under 12.

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 Canesten Cream Combi Internal & External Creams 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 a sexually transmitted disease or exposure to partner with sexually transmitted disease
- pregnancy or suspected pregnancy
- aged under 12 or over 60 years
- known hypersensitivity to imidazoles or other vaginal antifungal products

The creams 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 (vaginal haemorrhage) 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 (temperature of 38°C or above) or chills
- nausea or vomiting
- diarrhoea
- foul smelling vaginal discharge
- back pain.
- associated shoulder pain.

Treatment during the menstrual period should not be performed due to the risk of the cream 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.

Avoidance of vaginal intercourse is recommended in case of vaginal infection while using this product because your partner could become infected.

Avoid contact with eyes and do not swallow.

Patients should be advised to consult their physician if the symptoms have not been relieved within one week of using Canesten Internal Cream. Canesten Internal Cream 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.

This product contains cetostearyl alcohol, which may cause local skin reactions (e.g. contact dermatitis). The product also contains benzyl alcohol which may cause allergic reactions and mild local irritation.

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 thoroughly monitored for symptoms of tacrolimus or sirolimus overdose, if necessary by determination of the respective plasma levels.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are limited data available 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 are considered unlikely. Clotrimazole may be used during pregnancy, but only under the supervision of a doctor or midwife.

During pregnancy the treatment should be carried out with clotrimazole vaginal tablets since these can be inserted without using an applicator.

Breast-feeding:

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 under medical supervision.

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 (see Section 5.3).

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. The following adverse reactions have been identified during post-approval use of Clotrimazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Immune system disorders

Hypersensitivity, anaphylactic reactions, angioedema

Allergic reaction (ME) with symptoms such as dyspnea (PT), hypotension (PT), syncope (PT), and urticaria

Skin and subcutaneous tissue disorders

Rash

Reproductive system and breast disorders

Vulvovaginal discomfort, vulvovaginal burning sensation, vaginal exfoliation, vulvovaginal pruritus, vulvovaginal pain, vaginal haemorrhage, vulvovaginal erythema, vaginal discharge

Gastrointestinal disorders

Abdominal pain, nausea

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 HPRAs Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

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).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gynecological Antiinfectives and Antiseptics ATC Code: D01A C01

Mechanism of Action

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

Pharmacodynamic Effects

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 micrograms/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.

In addition to its antimycotic action, clotrimazole also acts on, gram-positive microorganisms (streptococci/staphylococci/Gardnerella vaginalis) and gram-negative microorganisms (Bacteroides). It has no effect on lactobacilli.

In vitro, clotrimazole inhibits the multiplication of Corynebacteria and gram-positive cocci – with the exception of enterococci – in concentrations of 0.5 – 10 micrograms/ml substrate.

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 conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

The local and systemic tolerance of clotrimazole in different dosage forms was assessed in intravaginal studies in dogs and monkeys and in subacute dermal studies in rabbits. There was no evidence of treatment-related local or systemic adverse effects in any of these studies.

The oral toxicity of clotrimazole has been well-studied.

Following a single oral administration, clotrimazole was slightly-to-moderately toxic in experimental animals, with LD50 values of 761 to 923 mg/kg bw for mice, 95 to 114 mg/kg bw for newborn rats and 114 to 718 mg/kg bw for adult rats, > 1000 mg/kg bw for rabbits, and > 2000 mg/kg bw for dogs and cats.

In repeated dose oral studies conducted in rats and dogs, the liver was found to be the primary target organ for toxicity. This was evidenced by an increase in serum transaminase activities and the appearance of liver vacuolation and fatty deposits starting at 50 mg/kg in the chronic (78-week) rat study and at 100 mg/kg in the subchronic (13-week) dog study.

Clotrimazole has been extensively studied in in vitro and in vivo mutagenicity assays, and no evidence of mutagenic potential was found. A 78-week oral dosing study of clotrimazole in rats did not show any carcinogenic effect.

In a rat fertility study, groups of FB30 rats received oral doses of clotrimazole up to 50 mg/kg bw, for 10 weeks prior to mating and either throughout a 3-week mating period (for males only) or, for females, until day 13 of gestation or 4-week postpartum. Neonatal survival was reduced in 50 mg/kg bw group. Clotrimazole at doses up to 25 mg/kg bw did not impair the development of the pups. Clotrimazole at all doses did not affect fertility.

No teratogenicity effects were demonstrated in studies in mice, rabbits, and rats, given oral doses of up to 200, 180, and 100 mg/kg, respectively.

A study with 3 lactating rats administered 30 mg/kg clotrimazole intravenously showed that the drug was 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.

Given the limited absorption of clotrimazole after vaginal application (estimated to be 3%-10%), no hazard is expected from the use of vaginal clotrimazole.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Canesten Combi 10% Internal Cream contains:

Sorbitan stearate
Polysorbate 60
Cetyl palmitate
Cetostearyl alcohol
Isopropyl myristate
Benzyl alcohol
Purified water

Canesten Combi 2% External Cream contains:

Sorbitan stearate
Polysorbate 60
Cetyl palmitate
Cetostearyl alcohol
Octyldodecanol
Benzyl alcohol
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Canesten Combi 10% Internal Cream

A single dose applicator consisting of a body of HDPE, piston of LDPE, cap of LDPE, with a separate plunger of polystyrene. One applicator is contained in a blister pack.

Canesten Combi 2% External Cream

The cream is filled into Aluminium tubes (10g) with internal lacquer coating, latex stopper and HDPE screw top.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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