Clotrimazole Vaginal Tablets IP
Canesten® V6
Clotrimazole Cream IP 2%
Canesten® Vaginal Cream

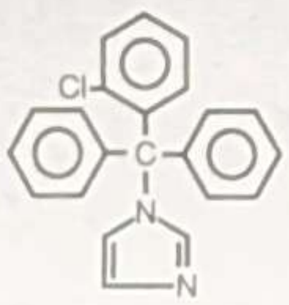
COMPOSITION

a. **Canesten® V6 Tablets**
Each tablet contains :
Clotrimazole IP ..... 100 mg
Excipients ..... q.s

b. **Canesten® Vaginal Cream**
Each gram contains:
Clotrimazole IP ..... 20 mg
Benzyl Alcohol IP ..... 1% w/w
(Preservative)
Water miscible base ..... q.s

DESCRIPTION

Canesten®contains clotrimazole, an imidazole derivative with a broad spectrum of antimycotic activity. It is approved for the treatment of variety of fungal infections. Its chemical name is 1-[(2-chlorophenyl)-di(phenyl)methyl]imidazole ($C_{22}H_{17}ClN_2$) and structural formula is as follows:



INDICATION AND USAGE

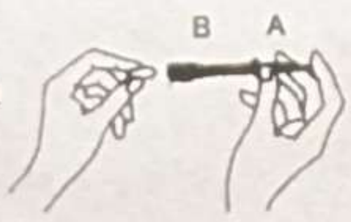
Infections of the genital regions (vaginitis) caused by fungi (usually Candida) trichomonads, and superinfections caused by Clotrimazole sensitive bacteria. For the reliable elimination of infections positively diagnosed as due to trichomonas vaginalis an oral trichomonacide must be additionally prescribed by the doctor.

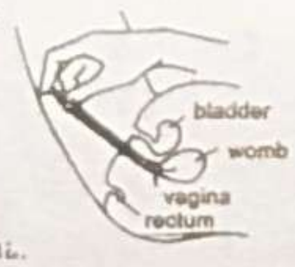
Additionally: Infections of labia and adjacent areas as well as inflammation of glans and prepuce of the sexual partner caused by yeast fungi (candidal vulvitis and candidal balanitis).

DIRECTIONS FOR USING THE APPLICATOR

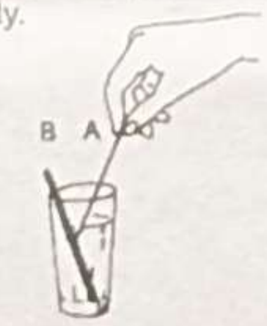
A. Canesten® V6 Tablet

1. Pull out plunger A until it stops. Place one Vaginal Tabl into the applicator B
2. Insert applicator containing the tablet carefully as deep as possible into the vagina (this is done best by lying on the back)
3. Push plunger A until it stops, thereby depositing the Tablet into the vagina. Withdraw the applicator.





4. After use, remove plunger A completely by pulling it out of the applicator B. Thereafter wash both in warm (not boiling) soapy water, and dry completely.



Note : Pregnant women should strictly follow the instructions of their physicians.

B. Canesten® Vaginal Cream

1. First pull out plunger of applicator until stops.
2. Open tube. Attach the applicator to the tube and, holding them firmly together, fill the applicator by carefully squeezing the tube
3. Disconnect the applicator from the tube. Introduce applicator as deeply as possible into the vagina (this is best done with the patient lying on her back) and empty its contents into the vagina by pushing the plunger.
4. After use, withdraw applicator, there after wash in warm soapy water and dry completely.

Note : Pregnant women should strictly follow the instructions of their physician.

Generally:

- If symptoms persist for more than 7 days or do not improve within 4 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, including diabetes or HIV infection.
- Patients should seek medical advice if they have had 3 or more infections within 6 months. If the labia and adjacent areas are simultaneously infected, local treatment with an external cream should also be given in addition to the intravaginal treatment (combination treatment).
- The sexual partner should also undergo local treatment if symptoms e.g. pruritis, inflammation, etc. are present. Treatment during the menstrual period should not be performed. 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 and while using this product as the partner could become infected.
- During pregnancy, the vaginal pessaries should be used and should be inserted without using an applicator.
- Canesten® vaginal products are for use by adults and children 18 years of age and over, unless use is advised by a doctor.

DOSAGE AND ADMINISTRATION

The vaginal tablets or vaginal cream should be inserted as deeply as possible into vagina in the evening. Insertion is best achieved when lying back with the legs slightly drawn up. Clotrimazole tablets need moisture in the vagina to dissolve completely, otherwise undissolved pieces of the vaginal tablet might crumble out of the vagina. To prevent this it is important to insert the medication as deeply as possible into the vagina at bedtime. Should the vaginal tablet not dissolve completely within one night the use of a vaginal cream should be considered.

For Treatment of Vaginal Infections:
1 vaginal tablet or contents of 1 applicator of vaginal cream (5 gm) to be introduced each evening for 6 successive days.

For treatment of Candida vulvitis or Candida balanitis:
Clotrimazole vaginal cream or cutaneous cream is applied thinly to the affected area (from external genital organs to the anus in women; glans and prepuce in men) 2-3 times a day and rubbed in. The normal period of treatment is 1-2 weeks.

CONTRAINDICATIONS

Possible hypersensitivity to clotrimazole or to other components of the product.

WARNINGS AND PRECAUTIONS

If the patient has a fever (temperature of 38°C or above), lower abdominal pain, back pain, foul smelling vaginal discharge, nausea, vaginal hemorrhage, and/or associated shoulder pain, the patient should consult a doctor.
Treatment during the menstrual period should not be performed. 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 and while using this product as the partner could become infected. The sexual partner should also undergo local treatment if symptoms, e.g. pruritus, inflammation, etc. are present.
When used in pregnancy, the vaginal tablets / vaginal soft capsule should be inserted without using an applicator (see "Pregnancy").
Clotrimazole cream may reduce the effectiveness and safety of latex products such as condoms and diaphragms when applied on the genital area (women: intravaginally, labia and adjacent area of the vulva; men: prepuce and glans of the penis).

Generally : Keep medicines out of reach of children. Avoid contact with eyes. Do not swallow.

ADVERSE REACTIONS

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
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.

DRUG INTERACTIONS

Concomitant medication with vaginal Clotrimazole and oral tacrolimus (FK-506, immunosuppressant) might lead to increased tacrolimus plasma levels, similarly with sirolimus. Patients should thus be thoroughly monitored for symptoms of tacrolimus or sirolimus overdosage, if necessary by determination of the respective plasma levels.

USE IN SPECIAL POPULATIONS

Pregnancy

While controlled clinical studies in pregnant women is limited, epidemiological investigations give no indication that harmful effect on the mother and child should be anticipated when clotrimazole is used during pregnancy. However, as with all medicine in the first trimester of pregnancy, clotrimazole should only be used after first consulting a doctor. Sanitation of the birth canal should be ensured particularly during the last 4-6 weeks of pregnancy. During pregnancy the treatment should be carried out with clotrimazole vaginal tablets, since these can 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

OVERDOSAGE

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.

CLINICAL PHARMACOLOGY

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 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 region of less than 0.062-8.0 mcg/mL substrate. The mode of action of clotrimazole is primarily fungistatic or fungicidal depending on the concentration of the clotrimazole at the site of infections. *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 trichomonas vaginalis, gram-positive microorganisms (streptococci / staphylococci), and gram-negative microorganisms (bacteroides / gardnerella vaginalis). *In-vitro* clotrimazole inhibits the multiplication of cornybacterium and gram positive cocci with exception of enterococci in concentrations of 0.5-10 mcg/mL substrate and exerts a trichomonacidal action at 100 mcg/mL.

Primarily resistant variants are 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.

Pharmacokinetics

Pharmacokinetic investigations after vaginal application have shown that only a small amount of clotrimazole (3-10%) is absorbed. Due to the rapid hepatic metabolization of absorbed clotrimazole in to pharmacologically inactive metabolites the resulting peak plasma concentrations of clotrimazole after vaginal applications of a 500 mg dose were less than 10 ng/ml, suggesting that clotrimazole applied intravaginally is unlikely to lead to measurable systematic effects or side effects.

PRECLINICAL SAFETY DATA (Carcinogenesis, Mutagenesis, Impairment of fertility)

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 slight-to-moderately toxic in experimental animals, with LD_{50} 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. Clotrimazole has been extensively studied in *in-vitro* and *in-vivo* mutagenicity assays, and no evidence of mutagenic potential was found. 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 medicine was 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. Given the limited absorption of clotrimazole after vaginal application (estimated to be 3%-10%) no hazard is expected from the use of vaginal clotrimazole.

PRESENTATION/PACK

a. **Canesten® V6** Tablets : Strip of 6's

b. **Canesten®** Vaginal Cream : Aluminium tube of 30 g

STORAGE CONDITION

a. **Canesten® V6** Tablets
Store below 30°C, protected from moisture and crushing

b. **Canesten®** Vaginal Cream
Store at a temperature not exceeding 30°C

Keep out of reach of children

SHELF LIFE

Please refer outer carton for expiry date.

LIST OF EXCIPIENTS, INACTIVE INGREDIENTS

a. **Canesten® V6** Tablets
Colloidal Silicon Dioxide, Starch, Adipic Acid, Lactose, Polysorbate 80, Sodium Bicarbonate, Stearic Acid, Magnesium Stearate

b. **Canesten®** Vaginal Cream
Octyldodecanol, Polysorbate 60, Sorbitan stearate, Cetyl Palmitate, Cetostearyl Alcohol, Benzyl Alcohol

Special Precaution For Canesten® V6 : For Vaginal insertion only. Not for oral use.

For manufacturing and marketed by information, refer to the product pack.

For feedback/queries, contact Bayer India, call 1800-22-2296, or email on ch.customercare@bayer.com

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