

PRODUCT MONOGRAPH

CANESTEN® 6 CREAM

1% Clotrimazole Vaginal Cream Bayer Std.

CANESTEN® 3 CREAM

2% Clotrimazole Vaginal Cream Bayer Std.

CANESTEN® 1 CREAM

10% Clotrimazole Vaginal Cream Bayer Std.

CANESTEN® 1 CREAM COMBI-PAK

CANESTEN® 1 CREAM; CANESTEN® EXTERNAL CREAM

CANESTEN® 1 COMFORTAB COMBI-PAK

CANESTEN® 500 mg Vaginal Tablets; CANESTEN® EXTERNAL CREAM

CANESTEN® 3 COMFORTAB COMBI-PAK

CANESTEN® 200 mg Vaginal Tablets; CANESTEN® EXTERNAL CREAM

CANESTEN® EXTERNAL CREAM REFILL

1% Clotrimazole Cream Bayer Std.

(Clotrimazole)

Bayer Standard

Antifungal Agent

**Bayer Inc.
77 Belfield Road
Toronto, Ontario
M9W 1G6**

Date of Preparation:

February 22, 1995

Date of Revision:

January 18, 2005

Control #094735 and 094736

PRODUCT MONOGRAPH

CANESTEN®
(Clotrimazole)
Bayer Standard

THERAPEUTIC CLASSIFICATION

Antifungal Agent

ACTION

CANESTEN® acts primarily by damaging the permeability barrier in the cell membrane of fungi. CANESTEN® brings about inhibition of ergosterol biosynthesis, an essential constituent of fungal cell membranes. If ergosterol synthesis is completely or partially inhibited, the cell is no longer able to construct an intact cell membrane. This leads to death of the fungus.

Exposure of Candida albicans to clotrimazole causes leakage of intracellular phosphorus compounds into the ambient medium with a concomitant breakdown of cellular nucleic acids and potassium efflux. The onset of these events is rapid and extensive after exposure of the organism to the drug, and causes a time-dependent and concentration-dependent inhibition of fungal growth.

INDICATIONS

CANESTEN® 6 Cream is indicated for the 6-day treatment of vaginal candidiasis.

CANESTEN® 3 Cream is indicated for the 3-day treatment of vaginal candidiasis.

CANESTEN® 200mg Vaginal Tablets are indicated for the 3-day treatment of vaginal candidiasis.

CANESTEN® 1 Cream is indicated for the 1-day treatment of vaginal candidiasis.

CANESTEN® 500 mg Vaginal Tablets are indicated for the 1-day treatment of vaginal candidiasis.

CANESTEN® Combi-Paks are indicated for either 6-Day, 3-Day or 1-Day treatment of vaginal candidiasis.

CANESTEN® External Cream Refill and CANESTEN® External Cream are indicated for the topical treatment of external irritation caused by vulvovaginal candidiasis.

CONTRAINDICATIONS

Hypersensitivity to CANESTEN®.

PRECAUTIONS

CANESTEN® Vaginal Tablets are not for oral use.

CANESTEN® External Cream and CANESTEN® Vaginal Cream are not for ophthalmic use.

As with all topical agents, skin sensitization may result. Use of CANESTEN® topical preparations should be discontinued should such reactions occur, and appropriate therapy instituted.

Use in Pregnancy

Although intravaginal application of clotrimazole has shown negligible absorption from both normal and inflamed human vaginal mucosa, CANESTEN® Vaginal Tablets and CANESTEN® Vaginal Cream should not be used in the first trimester

of pregnancy unless the physician considers it essential to the welfare of the patient.

The use of applicators may be undesirable in some pregnant patients and digital insertion of the vaginal tablets may be considered.

ADVERSE REACTIONS

Experimental, therapeutic, and large scale clinical studies have shown CANESTEN® to be well tolerated after topical application.

Erythema, stinging, blistering, peeling, edema, pruritus, urticaria, and general irritation of the skin have been reported infrequently.

Two of 419 (0.5%) patients treated with the 1% vaginal cream experienced adverse reactions judged to be possibly drug related. These were intercurrent cystitis and vaginal burning. Neither necessitated discontinuation of treatment. None were of serious consequence and no complications occurred.

The 100 mg vaginal tablets were also well tolerated. Only a few cases consisting primarily of burning sensation and mild skin reactions were reported. In studies comparing the 3- and 7-day regimen, four of 212 patients (1.9%) in the 7 day group reported adverse reactions possibly related to treatment. These included: irritation, burning, cramping, itching, redness, abdominal bloating, bleeding and rash. In an additional nine double-blind comparative studies, 5 out of 219 patients on the 7-day regimen with the 100 mg vaginal tablet experienced similar types of adverse reactions, none of which necessitated discontinuation of treatment. In a large open multicentre and two double-blind studies employing the 100 mg vaginal tablet in a 6-day regimen, 11 out of 595 (1.8%) patients complained of possible drug-related side effects. Mild burning occurred in 4 patients while other reactions such as skin rash, lower abdominal cramps, slight urinary frequency and burning or irritation in the sexual partner occurred rarely. In no case was it necessary to discontinue treatment.

In clinical trials involving 200 mg clotrimazole vaginal tablets, 24/832 patients

(2.9%) experienced an adverse reaction. 2/217 patients (0.9%) who received 2% clotrimazole vaginal cream in clinical trials experienced an adverse reaction. In clinical trials involving 500 mg clotrimazole vaginal tablets, 12/515 patients (2.3%) experienced an adverse reaction. 26/796 (3.3%) of patients in clinical trials involving 10% clotrimazole vaginal cream experienced an adverse reaction. Most adverse reactions involved local itching and burning. Only rarely was it necessary to discontinue treatment.

DOSAGE AND ADMINISTRATION

Vaginal Candidiasis

CANESTEN® 6 Cream

The recommended daily dose is ONE full applicator intravaginally for SIX consecutive days, preferably at bedtime.

CANESTEN® 3 Cream

The recommended daily dose is ONE full applicator intravaginally for THREE consecutive days, preferably at bedtime.

CANESTEN® 200mg Vaginal Tablets

The recommended daily dose is ONE vaginal tablet intravaginally for THREE consecutive days, preferably at bedtime.

CANESTEN® 3 ComforTAB Combi-Pak

The recommended dose is ONE vaginal tablet intravaginally for THREE consecutive days, preferably at bedtime. The cream should be spread onto the irritated area once or twice a day as needed, for up to seven consecutive days.

CANESTEN® 1 Cream

The recommended daily dose is ONE full applicator intravaginally (as a single dose therapy), preferably at bedtime.

CANESTEN® 500mg Vaginal Tablet

The recommended daily dose is ONE vaginal tablet intravaginally for ONE day,

preferably at bedtime.

CANESTEN® 1 ComforTAB Combi-Pak

The recommended dose is ONE vaginal tablet intravaginally for ONE day, preferably at bedtime. The cream should be spread onto the irritated area once or twice a day as needed, for up to seven consecutive days.

CANESTEN® 1 Cream Combi-Pak

The recommended dose is ONE full applicator intravaginally (as a single dose therapy) preferably at bedtime. The external cream should be spread onto the irritated area once or twice a day as needed, for up to seven consecutive days.

CANESTEN® External Cream Refill

Use only in conjunction with Canesten Vaginal Tablets or Vaginal Creams. The cream should be spread onto the irritated area once or twice daily as needed, for up to seven consecutive days.

Vaginal Candidiasis may be accompanied by irritation in the vaginal area. Therefore, concomitant local treatment with CANESTEN® Vaginal Cream (or CANESTEN® External Cream) applied to the irritated vaginal area and as far as the anal region twice a day is advisable. CANESTEN® External Cream (or CANESTEN® Vaginal Cream) applied on the glans penis may prevent re-infection by the partner.

N.B.: The cream or vaginal tablet should be inserted deep intravaginally by means of the applicator (See PRECAUTIONS). The plunger should then be depressed slowly.

CANESTEN® Vaginal 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 that the vaginal tablet is inserted deep into the vagina. If the vaginal tablet does not dissolve completely within one night, the use of a vaginal cream should be considered.

General hygienic measures such as twice daily tub baths and avoidance of tight

underclothing are important in vaginal infections.

PHARMACEUTICAL INFORMATION

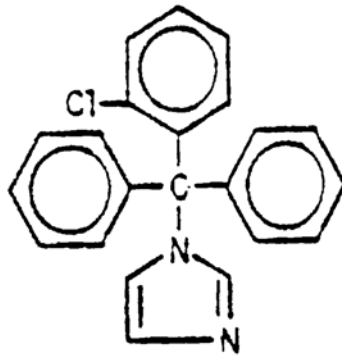
DRUG SUBSTANCE

Proper Name:

clotrimazole

Chemical Name:

1-(o-chloro- $\alpha\alpha$ -diphenylbenzyl)imidazole.



Structural Formula:

Molecular Formula: $C_{22}H_{17}ClN_2$

Molecular Weight: 344.84

Description:

Clotrimazole is a white to pale yellow, crystalline, weakly alkaline substance, M.P. $145^{\circ}C$, soluble in acetone, chloroform and ethanol, and practically insoluble in water. It forms stable salts with both inorganic and organic acids. It is not photosensitive but slightly hygroscopic and may be hydrolyzed in acid media.

Composition

CANESTEN® External Cream and CANESTEN® External Cream Refill

contains 10 mg/g of clotrimazole in a vanishing cream base of sorbitan monostearate, polysorbate 60, cetyl esters wax, cetostearyl alcohol, octyldodecanol, purified water, and benzyl alcohol 1% as preservative.

CANESTEN® 6 Cream contains 10 mg/g of clotrimazole in a vanishing cream base of sorbitan monostearate, polysorbate 60, cetyl esters wax, cetostearyl alcohol, octyldodecanol, purified water, and benzyl alcohol 1% as preservative.

CANESTEN® 3 Cream contains 20 mg/g of clotrimazole in a vanishing cream base of sorbitan monostearate, polysorbate 60, cetyl esters wax, cetostearyl alcohol, octyldodecanol, purified water, and benzyl alcohol 1% as preservative.

CANESTEN® 200mg Vaginal Tablets contains 200 mg of clotrimazole per vaginal tablet in a formulation containing lactose, maize starch, adipic acid, sodium bicarbonate, magnesium stearate, stearic acid, colloidal silicon dioxide and polysorbate 80.

CANESTEN® 3 ComforTAB Combi-Pak contains three vaginal tablets of 200 mg clotrimazole and a 10 g tube of clotrimazole 10 mg/g external cream.

CANESTEN® 1 Cream contains 100 mg/g of clotrimazole in a vanishing cream base of sorbitan monostearate, polysorbate 60, cetyl esters wax, cetostearyl alcohol, isopropyl myristate, purified water, and benzyl alcohol 1% as preservative.

CANESTEN® 500mg Vaginal Tablet contains 500 mg of clotrimazole per vaginal tablet, in a formulation containing lactose, maize starch, microcrystalline cellulose, lactic acid, crospovidone, calcium lactate, magnesium stearate, colloidal silicon dioxide and hydroxypropyl methylcellulose.

CANESTEN® 1 ComforTAB Combi-Pak contains one vaginal tablet of 500 mg clotrimazole and a 10 g tube of clotrimazole cream 10 mg/g external cream.

CANESTEN® 1 Cream Combi-Pak contains 5 g of 10% clotrimazole cream per pre-filled applicator and a 10 g tube of clotrimazole cream 10 mg/g external cream.

STABILITY AND STORAGE RECOMMENDATIONS

Store below 30°C. Avoid freezing.

AVAILABILITY OF DOSAGE FORMS

CANESTEN® 6 Cream is supplied in a 50 g tube of 1% vaginal cream in a carton containing 6 disposable plastic applicators and patient instructions. 50 g of CANESTEN® 6 Cream is sufficient for 6 intravaginal applications with additional cream for extravaginal use if required.

CANESTEN® 3 Cream is supplied in a 25 g tube of 2% vaginal cream in a carton containing 3 disposable plastic applicators and patient instructions. 25 g of CANESTEN® 3 Cream is sufficient for 3 intravaginal applications with additional cream for extravaginal use if required.

CANESTEN® 3 ComforTAB Combi-Pak is supplied in a box containing one strip of three CANESTEN® 200 mg vaginal tablets and one 10 g tube of CANESTEN® 1% External Cream.

CANESTEN® 1 Cream is supplied in a box containing one 5 g pre-filled applicator with a plunger of CANESTEN® 10% vaginal cream in a blister pack and patient instructions.

CANESTEN® 1 ComforTAB Combi-Pak is supplied in a box containing one strip of one CANESTEN® 500 mg vaginal tablet and one 10 g tube of CANESTEN® 1% External Cream.

CANESTEN® 1 Cream Combi-Pak is supplied in a box containing one 5 g pre-filled applicator with plunger of CANESTEN® 10% vaginal cream and one 10 g

tube of CANESTEN® 1% External Cream.

CANESTEN® External Cream Refill is supplied in a box containing a 15 g tube of 1% external cream as a refill.

INFORMATION FOR THE CONSUMER
EDUCATIONAL BROCHURE

CANESTEN® 6 Treatment Cream
Clotrimazole 1% vaginal cream - Antifungal

FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS
READ THIS BEFORE USING

BAYER INC.

1. What is a "yeast infection"?

A "yeast infection" may occur any time there is an overgrowth of yeast organisms in the vagina. The vagina normally has bacteria and yeast organisms present. Under some conditions, the number of yeast organisms rises, irritating the delicate tissues of the vagina and vaginal opening. Conditions that make this more likely to occur are illness and the use of antibiotics (antibiotics do not affect the yeast organism). Changes in hormone levels may also increase the risk of a yeast infection. Changes that can occur during pregnancy, with the use of oral contraceptive pills, or just before a woman's period, may all increase the risk of a vaginal yeast infection. Some diseases, such as diabetes, can also make a person more susceptible. Even such things as hot humid weather, continuous use of panty liners, or tight, non-breathing clothing may increase a woman's chances of developing a yeast infection. These infections are not usually transmitted through sexual relations, even though a small percentage of male partners do have infections at the same time.

2. How do I know if I have a "yeast infection?"

When a "yeast infection" occurs, the body responds with an increase in vaginal secretions. These secretions are generally thick and sticky, but odourless. These are often referred to as "cheesy" or "curd-like" because of their similarity to cottage cheese. These secretions are irritating to the tissues of the vaginal area, causing intense itching, redness, and swelling. Sometimes red spots or sores may develop, especially if the area has been scratched in response to the itching. Soreness in the vagina, discomfort when passing urine and pain during sexual relations is common.

Yeast infections do not cause fevers, chills, nausea, vomiting, or diarrhoea. If these symptoms are present, or if the vaginal discharge is foul-smelling, a more serious condition may be present and you should consult your physician immediately.

Even if all of your symptoms point to a yeast infection, you should not attempt to treat yourself without consulting a physician if it is your first infection. If you have a second infection in less than 2 months, or experience frequent infections, contact your physician for evaluation and advice.

3. How do I cure a "yeast infection"?

To cure a "yeast infection", it is necessary to kill the overgrowth of yeast organisms that cause the infection. CANESTEN® can cure most vaginal yeast infections. Even though the symptoms of an infection may be relieved in only a few hours or days, you should use CANESTEN® for a full 6 days. This will decrease the chance of the infection returning. If your symptoms do not disappear or improve after 3 days of treatment or disappear within 7 days, or if they get worse, discontinue treatment and contact your physician.

4. How do I use CANESTEN® 6 Cream?

CANESTEN® 6 Cream is used to treat vaginal yeast infections. CANESTEN® is inserted high into the vagina once a day (preferably at bedtime) for 6 consecutive days. Sufficient cream is provided for 6 intravaginal applications. Extra cream is supplied for use in relieving the external itching and burning sometimes associated with a vaginal yeast infection. CANESTEN® is only for use in the vagina and should never be taken by mouth. The effectiveness of CANESTEN® is not affected by menstruation. While you may have sexual relations during treatment with CANESTEN®, most couples wait until treatment has finished.

Filling the Applicator:

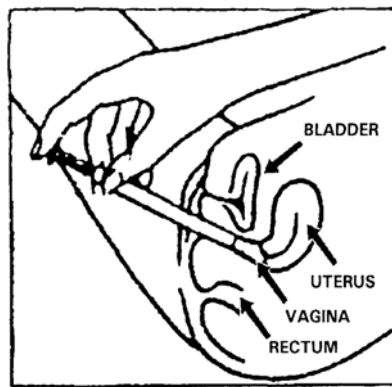
Remove the cap from the tube of CANESTEN® and reverse it to puncture the safety seal over the end of the tube. To fill the applicator, screw the open end of the applicator on the end of the tube. Gently squeeze the tube. The plunger will rise as cream enters the applicator. When the plunger stops, the proper amount of CANESTEN® has been pushed into the applicator and the applicator may be removed. Replace the cap and roll up the tube from the bottom so that the tube will be ready for the next use.

Inserting the Medication:

CANESTEN® 6 Cream is inserted into the vagina in much the same way as a tampon. Stand, squat, or lie on your back in a comfortable position. Insert the filled applicator into the vagina as far as it will comfortably go. Holding the barrel of the applicator steady, gently depress the plunger until it stops. This will release the medication high in the vagina where it will be most effective. Remove the applicator. A small additional amount of CANESTEN® cream may be applied to the opening of the vagina to help provide extra relief.

Using the Cream Externally:

A small amount of CANESTEN® cream may be applied to the opening of the vagina to help provide extra relief of external symptoms. Squeeze a small amount of cream onto your finger and gently spread over the irritated vaginal area. Use the cream once or twice a day and only during the period when external symptoms are present, to a maximum of 7 days.



Disposing of the Applicator:

The CANESTEN® vaginal applicator is recyclable where facilities exist.

5. Important Warnings

If you are at increased risk for sexually transmitted diseases, have multiple sexual partners or change partners often, consult a doctor before starting each treatment.

If this is your first yeast infection, it should be evaluated by your physician before you start any medication.

Do not use CANESTEN® if you have abdominal pain, fever or a foul-smelling vaginal discharge. If these symptoms are present, you could have a more serious condition and should consult your physician immediately.

If there is no improvement in your symptoms in 3 days or if they have not

disappeared within 7 days, you might not have a vaginal yeast infection. Consult your physician.

If you have frequent vaginal infections, or if your yeast infection returns in less than 2 months, consult your physician prior to starting treatment.

Do not use CANESTEN® if you are pregnant, think you are, or are nursing, without first consulting your physician.

If you experience a rash or new irritation while using the product, discontinue use and contact your physician.

CANESTEN® may reduce the effectiveness of some birth control methods, such as condoms, diaphragms, or vaginal spermicides. This effect is temporary and occurs only during treatment.

CANESTEN® cream is for vaginal use only. If CANESTEN® is accidentally swallowed, contact your local emergency room or Poison Control Centre immediately. Keep CANESTEN® and all other medications out of the reach of children.

CANESTEN® should not be used by girls less than 12 years of age unless advised by a physician.

If you have any questions about CANESTEN® or vaginal infections, contact your pharmacist or physician.

Medicinal Ingredient: Clotrimazole 1.0%

STORE AT ROOM TEMPERATURE BETWEEN 2°C AND 30°C

BAYER INC., Toronto, Ontario M9W 1G6

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INFORMATION FOR THE CONSUMER
EDUCATIONAL BROCHURE

CANESTEN® 3 Treatment Cream
Clotrimazole 2% vaginal cream - Antifungal

FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS
READ THIS BEFORE USING

BAYER INC.

1. What is a "yeast infection"?

A "yeast infection" may occur any time there is an overgrowth of yeast organisms in the vagina. The vagina normally has bacteria and yeast organisms present. Under some conditions, the number of yeast organisms rises, irritating the delicate tissues of the vagina and vaginal opening. Conditions that make this more likely to occur are illness and the use of antibiotics (antibiotics do not affect the yeast organism). Changes in hormone levels may also increase the risk of a yeast infection. Changes that can occur during pregnancy, with the use of oral contraceptive pills, or just before a woman's period, may all increase the risk of a vaginal yeast infection. Some diseases, such as diabetes, can also make a person more susceptible. Even such things as hot humid weather, continuous use of panty liners, or tight, non-breathing clothing may increase a woman's chances of developing a yeast infection. These infections are not usually transmitted through sexual relations, even though a small percentage of male partners do have infections at the same time.

2. How do I know if I have a "yeast infection"?

When a "yeast infection" occurs, the body responds with an increase in vaginal secretions. These secretions are generally thick and sticky, but odourless. These are often referred to as "cheesy" or "curd-like" because of their similarity to cottage cheese. These secretions are irritating to the tissues of the vaginal area, causing intense itching, redness, and swelling. Sometimes red spots or sores may develop, especially if the area has been scratched in response to the itching. Soreness in the vagina, discomfort when passing urine and pain during sexual relations is common.

Yeast infections do not cause fevers, chills, nausea, vomiting, or diarrhoea. If these symptoms are present, or if the vaginal discharge is foul-smelling, a more serious condition may be present and you should consult your physician immediately.

Even if all of your symptoms point to a yeast infection, you should not attempt to treat yourself without consulting a physician if it is your first infection. If you have a second infection in less than 2 months, or experience frequent infections, contact your physician for evaluation and advice.

3. How do I cure a "yeast infection"?

To cure a "yeast infection", it is necessary to kill the overgrowth of yeast organisms that cause the infection. CANESTEN® can cure most vaginal yeast infections. Even though the symptoms of an infection may be relieved in only a few hours or days, you should use CANESTEN® for a full 3 days. This will decrease the chance of the infection returning. If your symptoms do not improve after 3 days of treatment or disappear within 7 days, or if they get worse, discontinue treatment and contact your physician.

4. How do I use CANESTEN® 3 Cream?

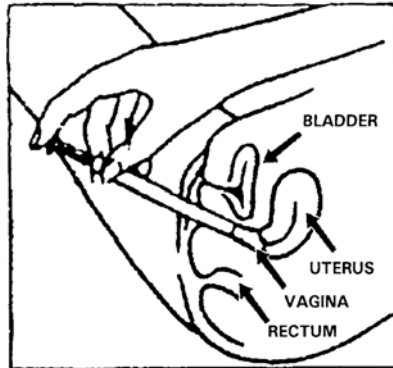
CANESTEN® 3 Cream is used to treat vaginal yeast infections. CANESTEN® cream is inserted high into the vagina once a day (preferably at bedtime) for 3 consecutive days. Sufficient cream is provided for 3 intravaginal applications. Extra cream is supplied for use in relieving the external itching and burning sometimes associated with a vaginal yeast infection. CANESTEN® is only for use in the vagina and irritated vaginal area and should never be taken by mouth. The effectiveness of CANESTEN® is not affected by menstruation. While you may have sexual relations during treatment with CANESTEN®, most couples wait until treatment has finished.

Filling the Applicator:

Remove the cap from the tube of CANESTEN® and reverse it to puncture the safety seal over the end of the tube. To fill the applicator, screw the open end of the applicator on the end of the tube. Gently squeeze the tube. The plunger will rise as cream enters the applicator. When the plunger stops, the proper amount of CANESTEN® has been pushed into the applicator and the applicator may be removed. Replace the cap and roll up the tube from the bottom so that the tube will be ready for the next use.

Inserting the Medication:

CANESTEN® cream is inserted into the vagina in much the same way as a tampon. Stand, squat, or lie on your back in a comfortable position. Insert the filled applicator into the vagina as far as it will comfortably go. Holding the barrel of the applicator steady, gently depress the plunger until it stops. This will release the medication high in the vagina where it will be most effective. Remove the applicator.



Disposing of the applicator:

The CANESTEN® vaginal applicators are recyclable where facilities exist.

Using the cream externally:

A small additional amount of CANESTEN® cream may be applied to the opening of the vagina to help provide extra relief of external symptoms. Squeeze a small amount of cream onto your finger and gently spread over the irritated vaginal area. Use the cream once or twice a day and only during the period when external symptoms are present, to a maximum of 7 days.

5.Important Warnings

If you are at increased risk for sexually transmitted diseases, have multiple sexual partners or change partners often, consult a doctor before starting each treatment.

If this is your first yeast infection, it should be evaluated by your physician before you start any medication.

Do not use CANESTEN® if you have abdominal pain, fever or a foul-smelling vaginal discharge. If these symptoms are present, you could have a more serious condition and should consult your physician immediately.

If there is no improvement in your symptoms in 3 days or if they have not disappeared within 7 days, you might not have a vaginal yeast infection. Consult

your physician.

If you have frequent vaginal infections, or if your yeast infection returns in less than 2 months, consult your physician prior to starting treatment.

Do not use CANESTEN® if you are pregnant, think you are, or are nursing, without first consulting your physician.

If you experience a rash or new irritation while using the product, discontinue use and contact your physician.

CANESTEN® may reduce the effectiveness of some birth control methods, such as condoms, diaphragms, or vaginal spermicides. This effect is temporary and occurs only during treatment.

CANESTEN® cream is for vaginal use only. If CANESTEN® is accidentally swallowed, contact your local emergency room or Poison Control Centre immediately. Keep CANESTEN® and all other medications out of the reach of children.

CANESTEN® should not be used by girls less than 12 years of age unless advised by a physician.

If you have any questions about CANESTEN® or vaginal infections, contact your pharmacist or physician.

Medicinal Ingredient: Clotrimazole 2%

STORE AT ROOM TEMPERATURE BETWEEN 2°C AND 30°C
BAYER INC., Toronto, Ontario M9W 1G6

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INFORMATION FOR THE CONSUMER
EDUCATIONAL BROCHURE

CANESTEN® 3 Treatment ComforTAB Combi-Pak
Clotrimazole 200 mg vaginal tablets + Clotrimazole 1% External Cream
- Antifungal

FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS
READ THIS BEFORE USING

BAYER INC.

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Yeast infections do not cause fevers, chills, nausea, vomiting, or diarrhoea. If these symptoms are present, or if the vaginal discharge is foul-smelling, a more serious condition may be present and you should consult your physician immediately.

Even if all of your symptoms point to a yeast infection, you should not attempt to treat yourself without consulting a physician if it is your first infection. If you have a second infection in less than 2 months, or experience frequent infections, contact your physician for evaluation and advice.

3. How do I cure a "yeast infection"?

To cure a "yeast infection", it is necessary to kill the overgrowth of yeast organisms that cause the infection. CANESTEN® can cure most vaginal yeast infections. Even though the symptoms of an infection may be relieved in only a few hours or days, you should use CANESTEN® as directed for a full 3 days. This will decrease the chance of the infection returning. If your symptoms do not improve after 3 days of treatment or disappear within 7 days, or if they get worse, discontinue treatment and contact your physician.

4. How do I use CANESTEN® 3 ComforTAB Combi-Pak?

CANESTEN® 3 vaginal tablet is used to treat the vaginal yeast infection while the CANESTEN® cream is used externally to relieve the itching associated with your vaginal yeast infection. The cream should be used only during the time when external symptoms are present and for no longer than 7 days.

One CANESTEN® vaginal tablet is placed high into the vagina once a day (preferably at bedtime) for 3 consecutive days. CANESTEN® vaginal tablets and CANESTEN® cream are only for use in the vagina and irritated vaginal area and should never be taken by mouth. The effectiveness of CANESTEN® is not affected by menstruation. While you may have sexual relations during treatment with CANESTEN®, most couples wait until treatment has finished.

Using the applicator:

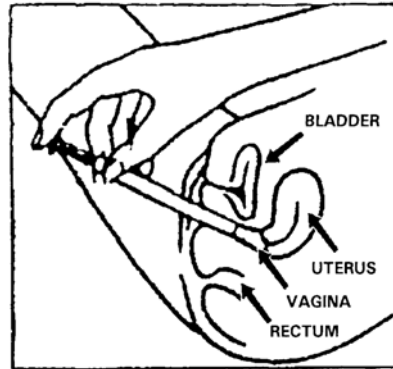
The applicator supplied with this package should be used to insure proper placement of the vaginal tablet high in the vagina, where it will provide the most benefit. To use the applicator, first remove the CANESTEN® vaginal tablet from its protective foil wrapper. Next, pull the applicator's plunger outward until it stops. The vaginal tablet is then placed into the end of the applicator and is ready for use.

Inserting the Medication:

CANESTEN® vaginal tablets are placed into the vagina in much the same way as a tampon. Stand, squat, or lie on your back in a comfortable position. Insert the loaded applicator into the vagina as far as it will comfortably go. Holding the barrel of the applicator steady, gently depress the plunger until it stops. This will release the medication high in the vagina where it will be most effective. Remove the applicator.

Using the Cream:

A small additional amount of CANESTEN® cream may be applied to the opening of the vagina to help provide extra relief of external symptoms. Squeeze a small amount of cream onto your finger and gently spread over the irritated vaginal area. Use once or twice a day and only during the period when external symptoms are present, to a maximum of 7 days.



The CANESTEN® vaginal applicator is recyclable where facilities exist.

5. Important Warnings

If you are at increased risk for sexually transmitted diseases, have multiple sexual partners or change partners often, consult a doctor before starting each treatment.

If this is your first yeast infection, it should be evaluated by your physician before you start any medication.

Do not use CANESTEN® if you have abdominal pain, fever or a foul-smelling vaginal discharge. If these symptoms are present, you could have a more serious condition and should consult your physician immediately.

If there is no improvement in your symptoms in 3 days or if they have not disappeared within 7 days, you might not have a yeast infection. Consult your physician.

If you have frequent vaginal infections or if your yeast infection returns in less than 2 months, consult your physician prior to starting treatment.

Do not use CANESTEN® if you are pregnant, think you are, or are nursing, without consulting your physician.

If you experience a rash or new irritation while using the product, discontinue use and contact your physician.

CANESTEN® may reduce the effectiveness of some birth control methods, such as condoms, diaphragms, or vaginal spermicides. This effect is temporary and occurs only during treatment.

CANESTEN® vaginal tablets are for vaginal use only. CANESTEN® cream is for external vaginal use only. If CANESTEN® is accidentally swallowed, contact your local emergency room or Poison Control Centre immediately. Keep CANESTEN® and all other medications out of the reach of children.

CANESTEN® External Cream should not be used for vaginal itching due to causes other than a yeast infection.

CANESTEN® should not be used by girls less than 12 years of age unless advised by a physician.

If you have any questions about CANESTEN® or vaginal infections, contact your pharmacist or physician.

Medicinal Ingredient: The vaginal tablet contains 200 mg clotrimazole
The tube contains clotrimazole 1% external cream

STORE AT ROOM TEMPERATURE BETWEEN 2°C AND 30°C .

BAYER INC., Toronto, Ontario, M9W 1G6

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INFORMATION FOR THE CONSUMER
EDUCATIONAL BROCHURE

CANESTEN® 1 Treatment Cream
Clotrimazole 10% vaginal cream - Antifungal

FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS
READ THIS BEFORE USING

BAYER INC.

1. What is a "yeast infection"?

A "yeast infection" may occur any time there is an overgrowth of yeast organisms in the vagina. The vagina normally has bacteria and yeast organisms present. Under some conditions, the number of yeast organisms rises, irritating the delicate tissues of the vagina and vaginal opening. Conditions that make this more likely to occur are illness and the use of antibiotics (antibiotics do not affect the yeast organism). Changes in hormone levels may also increase the risk of a yeast infection. Changes that can occur during pregnancy, with the use of oral contraceptive pills, or just before a woman's period, may all increase the risk of a vaginal yeast infection. Some diseases, such as diabetes, can also make a person more susceptible. Even such things as hot humid weather, continuous use of panty liners, or tight, non-breathing clothing may increase a woman's chances of developing a yeast infection. These infections are not usually transmitted through sexual relations, even though a small percentage of male partners do have infections at the same time.

2. How do I know if I have a "yeast infection"?

When a "yeast infection" occurs, the body responds with an increase in vaginal secretions. These secretions are generally thick and sticky, but odourless. These are often referred to as "cheesy" or "curd-like" because of their similarity to cottage cheese. These secretions are irritating to the tissues of the vaginal area, causing intense itching, redness, and swelling. Sometimes red spots or sores may develop, especially if the area has been scratched in response to the itching. Soreness in the vagina, discomfort when passing urine and pain during sexual relations is common.

Yeast infections do not cause fevers, chills, nausea, vomiting, or diarrhoea. If these symptoms are present, or if the vaginal discharge is foul-smelling, a more serious condition may be present and you should consult your physician immediately.

Even if all of your symptoms point to a yeast infection, you should not attempt to treat yourself without consulting a physician if it is your first infection. If you have a second infection in less than 2 months, or experience frequent infections, contact your physician for evaluation and advice.

3. How do I cure a "yeast infection"?

To cure a "yeast infection", it is necessary to kill the overgrowth of yeast organisms that cause the infection. CANESTEN® can cure most vaginal yeast infections and symptomatic relief can occur in a few hours or days. However, if your symptoms do not improve after 3 days of treatment or disappear within 7 days, or if they worsen, contact your physician.

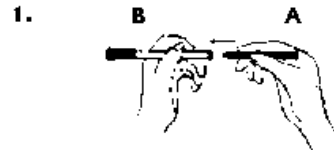
4. How do I use CANESTEN® 1 Cream?

CANESTEN® cream (pre-filled applicator) is used to treat vaginal yeast infections. CANESTEN® cream is inserted high into the vagina once (preferably at bedtime). Sufficient cream is provided for 1 intravaginal application. CANESTEN® cream is only for use in the vagina and should never be taken by mouth. The effectiveness of CANESTEN® is not affected by menstruation. While you may have sexual relations during treatment with CANESTEN®, most couples wait until treatment has finished.

Using the Applicator:

The applicator supplied with this package should be used to ensure proper placement of the vaginal cream high in the vagina preferably at bedtime, where it will provide the most benefit. To use the applicator:

1. Remove unit B from package. Insert plunger A into the barrel of the applicator B.

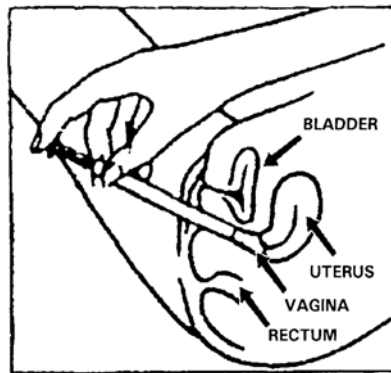


2. Detach red tip C with a twist motion.



Inserting the Medication:

CANESTEN® cream (pre-filled applicator) is inserted into the vagina in much the same way as a tampon. Stand, squat, or lie on your back in a comfortable position. Insert the pre-filled applicator into the vagina as far as it will comfortably go. Holding the barrel of the applicator steady, gently depress the plunger until it stops. This will release the medication high in the vagina where it will be most effective. Remove the applicator.



Disposing of the Applicator:

The CANESTEN® vaginal applicator is recyclable where facilities exist.

5. Important Warnings

If you are at increased risk for sexually transmitted diseases, have multiple sexual partners or change partners often, consult a doctor before starting each treatment.

If this is your first yeast infection, it should be evaluated by your physician before you start any medication.

Do not use CANESTEN® if you have abdominal pain, fever or a foul-smelling vaginal discharge. If these symptoms are present, you could have a more serious condition and should consult your physician immediately.

If there is no improvement in your symptoms in 3 days or if they have not disappeared within 7 days, you might not have a vaginal yeast infection. Consult your physician.

If you have frequent vaginal infections, or if your yeast infection returns in less than 2 months, consult your physician prior to starting treatment.

Do not use CANESTEN® if you are pregnant, think you are, or are nursing, without first consulting your physician.

If you experience a rash or new irritation after using the product, contact your physician.

CANESTEN® may reduce the effectiveness of some birth control methods, such as condoms, diaphragms, or vaginal spermicides. This effect is temporary and occurs only during treatment.

CANESTEN® Cream (pre-filled applicator) is for vaginal use only. If CANESTEN® is accidentally swallowed, contact your local emergency room or Poison Control Centre immediately. Keep CANESTEN® and all other medications out of the reach of children.

CANESTEN® should not be used by girls less than 12 years of age unless advised by a physician.

If you have any questions about CANESTEN® or vaginal infections, contact your pharmacist or physician.

Medicinal Ingredient: Clotrimazole 10.0%

STORE AT ROOM TEMPERATURE BETWEEN 2°C AND 30°C

BAYER INC., Toronto, Ontario M9W 1G6

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INFORMATION FOR THE CONSUMER
EDUCATIONAL BROCHURE

CANESTEN® 1 Treatment ComforTAB Combi-Pak
Clotrimazole 500 mg vaginal tablet + Clotrimazole 1% External Cream
- Antifungal

FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS
READ THIS BEFORE USING

BAYER INC.

1. What is a "yeast infection"?

A "yeast infection" may occur any time there is an overgrowth of yeast organisms in the vagina. The vagina normally has bacteria and yeast organisms present. Under some conditions, the number of yeast organisms rises, irritating the delicate tissues of the vagina and vaginal opening. Conditions that make this more likely to occur are illness and the use of antibiotics (antibiotics do not affect the yeast organism). Changes in hormone levels may also increase the risk of a yeast infection. Changes that can occur during pregnancy, with the use of oral contraceptive pills, or just before a woman's period, may all increase the risk of a vaginal yeast infection. Some diseases, such as diabetes, can also make a person more susceptible. Even such things as hot humid weather, continuous use of panty liners, or tight, non-breathing clothing may increase a woman's chances of developing a yeast infection. These infections are not usually transmitted through sexual relations, even though a small percentage of male partners do have infections at the same time.

2. How do I know if I have a "yeast infection"?

When a "yeast infection" occurs, the body responds with an increase in vaginal secretions. These secretions are generally thick and sticky, but odourless. These are often referred to as "cheesy" or curd-like" because of their similarity to cottage cheese. These secretions are irritating to the tissues of the vaginal area, causing intense itching, redness, and swelling. Sometimes red spots or sores may develop, especially if the area has been scratched in response to the itching. Soreness in the vagina, discomfort when passing urine and pain during sexual relations is common.

Yeast infections do not cause fevers, chills, nausea, vomiting, or diarrhoea. If these symptoms are present, or if the vaginal discharge is foul-smelling, a more serious condition may be present and you should consult your physician immediately.

Even if all of your symptoms point to a yeast infection, you should not attempt to treat yourself without consulting a physician if it is your first infection. If you have a second infection in less than 2 months, or experience frequent infections, contact your physician for evaluation and advice.

3. How do I cure a "yeast infection"?

To cure a "yeast infection", it is necessary to kill the overgrowth of yeast organisms that cause the infection. CANESTEN® can cure most vaginal yeast infections and symptomatic relief can occur in a few hours or days. However, if your symptoms do not improve after 3 days, or disappear within 7 days, or if they worsen, contact your physician.

4. How do I use CANESTEN® 1 ComforTAB Combi-Pak?

The CANESTEN® vaginal tablet is used to treat the vaginal yeast infection while the CANESTEN® cream is used externally to relieve the itching associated with your vaginal yeast infection. The cream should be used only during the time when external symptoms are present and for no longer than 7 days.

The CANESTEN® vaginal tablet is placed high into the vagina once (preferably at bedtime). CANESTEN® vaginal tablets and CANESTEN® cream are only for use in the vagina and irritated vaginal area and should never be taken by mouth. The effectiveness of CANESTEN® is not affected by menstruation. While you may have sexual relations during treatment with CANESTEN®, most couples wait until treatment has finished.

Using the applicator:

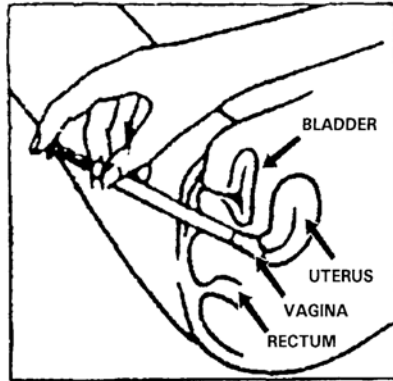
The applicator supplied with this package should be used to insure proper placement of the vaginal tablet high in the vagina, where it will provide the most benefit. To use the applicator, first remove the CANESTEN® vaginal tablet from its protective foil wrapper. Next, pull the applicator's plunger outward until it stops. The vaginal tablet is then placed into the end of the applicator and is ready for use.

Inserting the Medication:

The CANESTEN® vaginal tablet is placed into the vagina in much the same way as a tampon. Stand, squat, or lie on your back in a comfortable position. Insert the loaded applicator into the vagina as far as it will comfortably go. Holding the barrel of the applicator steady, gently depress the plunger until it stops. This will release the medication high in the vagina where it will be most effective. Remove the applicator.

Using the Cream:

A small additional amount of CANESTEN® cream may be applied to the opening of the vagina to help provide extra relief of external symptoms. Squeeze a small amount of cream onto your finger and gently spread over the irritated vaginal area. Use once or twice a day and only during the period when external symptoms are present, to a maximum of 7 days.



The CANESTEN® vaginal applicator is recyclable where facilities exist.

5. Important Warnings

If you are at increased risk for sexually transmitted diseases, have multiple sexual partners or change partners often, consult a doctor before starting each treatment.

If this is your first yeast infection, it should be evaluated by your physician before you start any medication.

Do not use CANESTEN® if you have abdominal pain, fever or a foul-smelling vaginal discharge. If these symptoms are present, you could have a more serious condition and should consult your physician immediately.

If there is no improvement in your symptoms in 3 days or if they have not disappeared within 7 days, you might not have a yeast infection. Consult your physician.

If you have frequent vaginal infections or if your yeast infection returns in less than 2 months, consult your physician prior to starting treatment.

Do not use CANESTEN® if you are pregnant, think you are, or are nursing, without consulting your physician.

If you experience a rash or new irritation while using the product, discontinue use and contact your physician.

CANESTEN® may reduce the effectiveness of some birth control methods, such as condoms, diaphragms, or vaginal spermicides. This effect is temporary and occurs only during treatment.

The CANESTEN® vaginal tablet is for vaginal use only. CANESTEN® cream is for external vaginal use only. If CANESTEN® is accidentally swallowed, contact your local emergency room or Poison Control Centre immediately. Keep CANESTEN® and all other medications out of the reach of children.

CANESTEN® External Cream should not be used for vaginal itching due to causes other than a yeast infection.

CANESTEN® should not be used by girls less than 12 years of age unless advised by a physician.

If you have any questions about CANESTEN® or vaginal infections, contact your pharmacist or physician.

Medicinal Ingredient: The vaginal tablet contains 500 mg clotrimazole.

The tube contains clotrimazole 1% external cream

STORE AT ROOM TEMPERATURE BETWEEN 2°C AND 30°C.

BAYER INC., Toronto, Ontario, M9W 1G6

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INFORMATION FOR THE CONSUMER
EDUCATIONAL BROCHURE

CANESTEN® 1 Treatment Cream Combi-Pak
Clotrimazole 10% vaginal cream + Clotrimazole 1% External Cream
- Antifungal

FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS
READ THIS BEFORE USING

BAYER INC.

1. What is a "yeast infection"?

A "yeast infection" may occur any time there is an overgrowth of yeast organisms in the vagina. The vagina normally has bacteria and yeast organisms present. Under some conditions, the number of yeast organisms rises, irritating the delicate tissues of the vagina and vaginal opening. Conditions that make this more likely to occur are illness and the use of antibiotics (antibiotics do not affect the yeast organism). Changes in hormone levels may also increase the risk of a yeast infection. Changes that can occur during pregnancy, with the use of oral contraceptive pills, or just before a woman's period, may all increase the risk of a vaginal yeast infection. Some diseases, such as diabetes, can also make a person more susceptible. Even such things as hot humid weather, continuous use of panty liners, or tight, non-breathing clothing may increase a woman's chances of developing a yeast infection. These infections are not usually transmitted through sexual relations, even though a small percentage of male partners do have infections at the same time.

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Yeast infections do not cause fevers, chills, nausea, vomiting, or diarrhoea. If these symptoms are present, or if the vaginal discharge is foul-smelling, a more serious condition may be present and you should consult your physician immediately.

Even if all of your symptoms point to a yeast infection, you should not attempt to treat yourself without consulting a physician if it is your first infection. If you have a second infection in less than 2 months, or experience frequent infections, contact your physician for evaluation and advice.

3. How do I cure a "yeast infection"?

To cure a "yeast infection", it is necessary to kill the overgrowth of yeast organisms that cause the infection. CANESTEN® can cure most vaginal yeast infections and symptomatic relief can occur in a few hours or days. However, if your symptoms do not improve after 3 days of treatment or disappear within 7 days, or if they worsen, contact your physician.

4. How do I use CANESTEN® 1 Cream Combi-Pak?

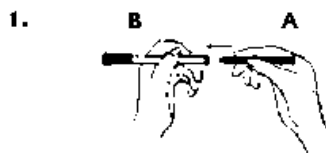
The applicator filled with CANESTEN® cream is used to treat the vaginal yeast infections while the tube of CANESTEN® cream is used externally to relieve the itching associated with your vaginal yeast infection. The external cream should only be used during the time when external symptoms are present and for no longer than 7 days.

CANESTEN® cream (pre-filled applicator) is placed high into the vagina once (preferably at bedtime). CANESTEN® vaginal and CANESTEN® external cream are only for use in the vagina and should never be taken by mouth. The effectiveness of CANESTEN® is not affected by menstruation. While you may have sexual relations during treatment with CANESTEN®, most couples wait until treatment has finished.

Using the Applicator:

The applicator supplied with this package should be used to ensure proper placement of the vaginal cream high in the vagina preferably at bedtime, where it will provide the most benefit. To use the applicator:

1. Remove unit B from package. Insert plunger A into the barrel of the applicator B.



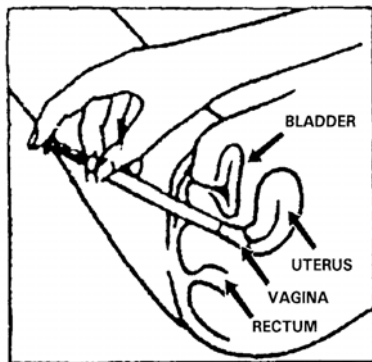
2. Detach red tip C with a twist motion.



Inserting the Medication:

CANESTEN® cream (pre-filled applicator) is inserted into the vagina in much the same way as a tampon. Stand, squat, or lie on your back in a comfortable position. Insert the pre-filled applicator into the vagina as far as it will comfortably go.

Holding the barrel of the applicator steady, gently depress the plunger until it stops. This will release the medication high in the vagina where it will be most effective. Remove the applicator.



Disposing of the Applicator:

The CANESTEN® vaginal applicator is recyclable where facilities exist.

Using the External Cream:

A small additional amount of Canesten external cream may be applied to the opening of the vagina to help provide extra relief of external symptoms. Squeeze a small amount of cream onto your finger and gently spread over the irritated area of the vulva. Use only once or twice a day and only during the period when external symptoms are present, to a maximum of 7 days.

5. Important Warnings

If you are at increased risk for sexually transmitted diseases, have multiple sexual partners or change partners often, consult a doctor before starting each treatment.

If this is your first yeast infection, it should be evaluated by your physician before you start any medication.

Do not use CANESTEN® if you have abdominal pain, fever or a foul-smelling vaginal discharge. If these symptoms are present, you could have a more serious condition and should consult your physician immediately.

If there is no improvement in your symptoms in 3 days or if they have not disappeared within 7 days, you might not have a vaginal yeast infection. Consult your physician.

If you have frequent vaginal infections, or if your yeast infection returns in less than 2 months, consult your physician prior to starting treatment.

Do not use CANESTEN® if you are pregnant, think you are, or are nursing, without first consulting your physician.

If you experience a rash or new irritation after using the product, contact your physician.

CANESTEN® may reduce the effectiveness of some birth control methods, such as condoms, diaphragms, or vaginal spermicides. This effect is temporary and occurs only during treatment.

CANESTEN® cream (pre-filled applicator) is for vaginal use only. Canesten® cream (10 g tube) is for external vaginal use only. If CANESTEN® is accidentally swallowed, contact your local emergency room or Poison Control Centre immediately. Keep CANESTEN® and all other medications out of the reach of children.

CANESTEN® should not be used by girls less than 12 years of age unless advised by a physician.

If you have any questions about CANESTEN® or vaginal infections, contact your pharmacist or physician.

Medicinal Ingredient: The pre-filled applicator contains clotrimazole 10.0%.

The tube contains clotrimazole 1% external cream.

STORE AT ROOM TEMPERATURE BETWEEN 2°C AND 30°C

BAYER INC., Toronto, Ontario M9W 1G6

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INFORMATION FOR THE CONSUMER
EDUCATIONAL BROCHURE

CANESTEN® External Cream Refill
Clotrimazole Cream 1%
- Antifungal

FOR THE TREATMENT OF EXTERNAL VAGINAL SYMPTOMS
ASSOCIATED WITH VAGINAL YEAST INFECTIONS
READ THIS BEFORE USING

BAYER INC.

1 How do I use CANESTEN® External Cream Refill?

Squeeze a small amount of cream onto your finger and gently spread over the irritated area of the vulva. Use only once or twice a day and only during the period when external symptoms are present, to a maximum of 7 days. Use only in conjunction with Canesten Vaginal Tablets or Vaginal Creams.

2. Important Warnings

If you are at increased risk for sexually transmitted diseases, have multiple sexual partners or change partners often, consult a doctor before starting treatment.

If this is your first yeast infection, it should be evaluated by your physician before you start any medication.

Do not use CANESTEN® if you have abdominal pain, fever or a foul-smelling vaginal discharge. If these symptoms are present, you could have a more serious condition and should consult your physician immediately.

If there is no improvement in your symptoms in 3 days or if they have not disappeared within 7 days, you might not have a vaginal yeast infection. Consult your physician.

If you have frequent vaginal infections, or if your yeast infection returns in less than 2 months, consult your physician prior to starting treatment.

Do not use CANESTEN® if you are pregnant, think you are, or are nursing, without first consulting your physician.

If you experience a rash or new irritation after using the product, contact your physician.

CANESTEN® may reduce the effectiveness of some birth control methods, such as condoms, diaphragms, or vaginal spermicides. This effect is temporary and occurs only during treatment.

Canesten® cream is for external vaginal use only. If CANESTEN® is accidentally swallowed, contact your local emergency room or Poison Control Centre immediately. Keep CANESTEN® and all other medications out of the reach of children.

CANESTEN® should not be used by girls less than 12 years of age unless advised by a physician.

If you have any questions about CANESTEN® or vaginal infections, contact your pharmacist or physician.

Medicinal Ingredient: Tube contains clotrimazole 1% external cream.

STORE AT ROOM TEMPERATURE BETWEEN 2°C AND 30°C

BAYER INC., Toronto, Ontario M9W 1G6

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MICROBIOLOGY

CANESTEN® is an antifungal agent with a broad spectrum of activity. In general, the in vitro activity of CANESTEN® corresponds to that of tolnaftate, griseofulvin, and pyrrolnitrin against dermatophytes (Trichophyton, Microsporum and Epidermophyton species) and to that of the polyenes, amphotericin B and nystatin, against budding fungi (Candida and Histoplasma species).

In vitro, CANESTEN® is fungistatic for most isolates of pathogenic fungi at concentrations of 0.02 to 10 µg/mL. The drug is fungicidal for many isolates of Trichophyton, Microsporum, Epidermophyton and Candida species at concentration of 0.1 to 2 µg/mL.

No one-step or multiple-step secondary resistance to CANESTEN® has developed during successive passages of C. albicans, C. krusei, C. pseudotropicalis, T. mentagrophytes, T. rubrum, Cryptococcus neoformans, Aspergillus niger, and A. nidulans. Only a few isolates have been designated as having primary resistance to CANESTEN®: a single isolate of C. guillermondii, six isolates of C. neoformans, three isolates of Paracoccidioides brasiliensis and two isolates of Blakeslea trispora.

Topical application of CANESTEN® has been effective in the treatment of skin infections experimentally induced in the guinea pig with T. mentagrophytes and T. quinckeanum.

Clinical studies conducted as double-blind trials with mycological control have shown that CANESTEN® is effective in the treatment of tinea cruris, tinea corporis, tinea pedis, tinea versicolor and cutaneous candidiasis. Mycological examinations have proven its efficacy against Trichophyton rubrum, T. mentagrophytes, Malassezia furfur and Candida albicans. Griseofulvin-resistant dermatophytes show no cross resistance to CANESTEN®. It may be assumed, therefore, that the site of action of this drug is different from that of other antimycotics. Consequently, there is no cross resistance between these agents.

Antifungal Activity in Vitro

Minimum inhibitory concentrations (MICs) of clotrimazole were determined in serial dilution in broth or agar and in agar diffusion tests using the punched hole procedure. Conventional culture substrates, incubation times, and incubation temperatures were used. At concentrations less than 2 µg/mL, clotrimazole was fungicidal for many isolates of C. albicans, Trichophyton sp., Microsporum sp., and Epidermophyton sp., tested, and at concentrations less than 5 µg/mL, Clotrimazole was fungistatic for other isolates of these species. Addition of bovine serum to the culture media at a final concentration of 30% resulted in somewhat higher MICs of clotrimazole.

The in vitro antifungal activity of clotrimazole was comparable to that of pyrrolnitrin; either compound at 0.78 µg/mL was fungicidal for most strains of Trichophyton sp., Microsporum sp. and Epidermophyton sp., tested.

The type of action of clotrimazole was determined in the Warburg apparatus by measuring the oxygen consumption of proliferating organisms exposed to varying concentrations of the drug. Additional studies were performed using a classical subculture technique with organism counts made after 16, 24 and 48 hours of exposure to the drug. These experiments showed that the primary action of clotrimazole at concentrations up to 20 µg/mL is fungistatic and affects only proliferating organisms. At concentrations greater than 20 µg/mL, clotrimazole was fungicidal for some organisms.

The determinations of MICs of clotrimazole for budding fungi and for biphasic fungi in the yeast phase have been shown to be dependent on the size of the inoculum and the length of incubation time. MICs for several isolates of Candida albicans and Torulopsis glabrata were higher when the inoculum size or incubation time or both were increased.

The effects of inoculum size has been attributed to binding of clotrimazole to the surface of the fungal cells. This was established in a study of turntable cultures of C. albicans. After 24 hours, the amount of clotrimazole in a nutrient substrate was reduced from 1 µg/mL to 0.7 µg/mL by an inoculum of 1 to 5 x 10⁵ cells/mL.

A larger inoculum, 1×10^8 cells/mL, reduced the drug concentration from 1 $\mu\text{g/mL}$ to 0.3 $\mu\text{g/mL}$. When the cultures were centrifuged and the cell sediment was washed with physiological saline solution, the wash solutions contained clotrimazole in concentrations of 0.2 $\mu\text{g/mL}$ to 0.4 $\mu\text{g/mL}$.

The effect of incubation time on the determination of MIC values is thought to be related to the mechanism of action of clotrimazole. Initial studies indicated that clotrimazole acted as an antimetabolite upon the amino acid and protein metabolism of the fungi, causing a gradual inhibition of fungal growth.

However, recent studies using C. albicans as the test organism have shown that the primary mode of action of clotrimazole is damage to the permeability of the cell membrane. Exposure of C. albicans to clotrimazole caused leakage of intracellular phosphorus compounds into the ambient medium with a concomitant breakdown of cellular nucleic acids. The onset of these events was rapid and extensive after exposure of C. albicans to the drug and caused a time-dependent and concentration-dependent inhibition of fungal growth.

Resistance Development

Only a few isolates have been designated as having primary resistance to clotrimazole; a single isolate of Candida guilliermondii, six isolates of Cryptococcus neoformans, three isolates of Paracoccidioides brasiliensis, and two isolates of Blakeslea trispora. The potential for development of secondary resistance to clotrimazole was determined for several organisms by successive passages in a liquid medium, successive passages on a solid medium, or the Warburg proliferation test. Growth of dermatophytes and yeasts on Szybalski plates was also used as a method for determining the development of secondary resistance.

No change in sensitivity was detected for C. albicans in any of the tests for secondary resistance, and no change in sensitivity was detected for Trichophyton mentagrophytes, T. rubrum, C. krusei, C. pseudotropicalis, C. neoformans, Aspergillus niger, or A. nidulans after successive passages on liquid and solid media. Possible resistance development was noted in successive passages of Torulopsis glabrata and other Torulopsis species. Data obtained from Szybalski plate growth and from other tests indicated that dermatophytes and yeasts do not develop one-step or oligo-step secondary resistance.

PHARMACOLOGY

Pharmacokinetics

Metabolism studies performed after oral or intravenous administration have shown that in most species studied, levels of clotrimazole in tissue and serum are low. The majority of the drug is excreted as metabolites in the feces, with small amounts excreted in the urine. Human studies indicate slow excretion following oral administration of ¹⁴C-labelled clotrimazole (greater than 6 days). After intraperitoneal and subcutaneous administration, very low levels have been observed in the urine. The absorption and organ distribution of the drug is very poor when administered parenterally.

The pharmacokinetics of topically applied clotrimazole in human subjects have been evaluated by Duhm et al. who reported on the penetration of radioactive clotrimazole 1% cream and 1% solution into intact and acutely inflamed skin. Six hours after application of the drug, the concentration of clotrimazole found in skin layers varied from 100 $\mu\text{g}/\text{cm}^3$ in the stratum corneum to 0.5 to 1.0 $\mu\text{g}/\text{cm}^3$ in the stratum reticulare and $<0.1 \mu\text{g}/\text{cm}^3$ in the subcutis. No measurable amount of radioactivity (0.001 $\mu\text{g}/\text{mL}$) was found in the serum within 48 hours after application of 0.5 mL of the solution or 0.8 g of the cream.

Intravaginal application of ^{14}C -labelled clotrimazole vaginal tablets containing 100 mg of active substance in human subjects has shown that the amount absorbed is less than 1/200 of that absorbed after the oral administration of 1.5 g of clotrimazole. The maximum serum concentration values were between 0.016 and 0.05 $\mu\text{g}/\text{mL}$ from one to three days after intravaginal application. Intravaginal application in human subjects of 5 mL ^{14}C -labelled clotrimazole vaginal cream containing 50 mg of active substance has shown that the systemic absorption of clotrimazole from the Vaginal Cream is quantitatively proportional to that from the Vaginal Tablets.

In animal experiments; clotrimazole exerts an in vitro and in vivo, dose-dependent, stimulating effect on certain microsomal enzyme systems which is approximately equal to that of phenobarbital in its inductive potential. However, this stimulating effect subsides rapidly when treatment is discontinued. The enzyme-inductive effect of clotrimazole has been found to be intact in adrenalectomized animals.

In 11 double-blind and one large multicentre open study, treatment of 814 patients with the 100 mg vaginal tablet for 6 to 7 days resulted in an average mycological cure rate of 79% (range of 67 - 91%). In studies comparing the 3- and 7-day regimen, 168 patients were treated with one clotrimazole vaginal tablet (100 mg) daily for 7 days. Overall and mycological cure rates were 67 and 70%, respectively.

In 8 double-blind studies and one single-blind study involving 432 patients using the 1% cream for 7 days, the average mycological cure rate was 72% with a range of 55 - 90%.

Oral contraceptives did not significantly alter mycological cure rates and overall success. In a limited number of pregnant women, both the 1% cream and the 100 mg tablet appeared to be effective, although the cure rates seemed to be somewhat lower.

In clinical trials involving 200 mg clotrimazole vaginal tablets, 498/611 patients (82%) had a negative culture for Candida sp. four weeks following treatment.

In clinical trials with clotrimazole 2% vaginal cream, 266/303 patients (88%) had a negative culture for Candida sp. four weeks following treatment.

In clinical trials with clotrimazole 500 mg vaginal tablets, 158/231 patients (68%) had a negative culture for Candida sp. four weeks following treatment.

In clinical trials with clotrimazole 10% vaginal cream, 592/726 patients (82%) had a negative culture for Candida sp. four weeks following treatment.

TOXICOLOGY
ACUTE TOXICITY (ORAL)

Animal

Species	LD ₅₀ mg/kg
Mouse	761-923
Rat	708-718
Rabbit	>1000
Cat	>1000; vomiting from 100 mg/kg
Dog	>2000; vomiting from 100 mg/kg

Multidose Local Tolerance

1. Primary skin irritation (patch test): no detectable reddening on the intact rabbit skin at either 24 or 72 hours with 1% solution or cream of clotrimazole. Very slight erythema formation after 24 hours in the scarified rabbit skin.
2. Primary irritation on conjunctival mucosa: clotrimazole solution or cream produced a transient conjunctival irritation in rabbits, consisting in low-grade reddening and a slight increase in secretion. No grossly detectable alterations were present in either the cornea or the iris of any of the treated animals. Both the cream and solution produced a transient, very slight reddening of the conjunctival mucosa. No alterations occurred on the cornea.
3. Subacute (up to 13 weeks) dermal tolerance: the application of 1% clotrimazole solution or 1% cream was systemically well tolerated; no edema was seen on the treated skin, although mild erythema was observed sporadically. The animals in all groups with abraded skin manifested a slight healing tendency.

4. Subacute (dogs: 14 days; monkeys: 13 weeks) local vaginal tolerance: the repeated application of clotrimazole vaginal tablets showed a satisfactory local and systemic tolerance. There were no detectable adverse effects, and the cytological examination in monkeys indicated variations consistent with normal estrus cycles.
5. Subacute (5 dogs: 30 days; 4 monkeys: 13 weeks; 10 healthy human volunteers: 28 days) local vaginal tolerance. The repeated application of Vaginal Cream showed a satisfactory local and systemic tolerance without adverse effects or abnormalities in vaginal cytology in all species.

REPRODUCTION AND TERATOLOGY

At dosages up to 100 mg/kg (subcutaneous), clotrimazole was well tolerated by pregnant mice, rats and rabbits, and it had no embryotoxic or teratogenic effect.

When given to pregnant rats at oral doses up to 100 mg/kg from day 6 through day 15 of gestation, the number of resorptions was higher and the fetal weights were lower than the controls, but the number of fetal malformations did not differ significantly from that of the control group.

Rats treated with clotrimazole for 10 weeks at dosage up to 50 mg/kg/day did not show any difference from the control group in the duration of estrus, fertility, duration of pregnancy, or in the number of implantations and resorptions. The dose of 50 mg/kg/day impaired the development of the young, and dams receiving this dose level raised fewer offspring.

The intravaginal administration of 100 mg/kg clotrimazole from the sixth to the fifteenth day of gestation was well tolerated by pregnant rats, and there were no harmful effects on the fertilization rate, the resorption rate, the mean fetal weight, and the frequency of stunted forms and of fetuses with slight bone alterations. No malformations were produced by this dose.

Human

In 453 cases under treatment which were evaluated with respect to photosensitivity and phototoxicity, no reactions were encountered.

Twenty normal subjects were tested in a controlled study for sensitivity to ultraviolet radiation. Areas of skin treated with clotrimazole were irradiated for 30 seconds on the first day, and for one-half minute longer each time on every second day thereafter. One of the 20 subjects was irradiated once only; 9 subjects three times, and 10 subjects four times. One subject developed papule formation after the first exposure to ultraviolet radiation.

The topical tolerance of CANESTEN® Vaginal Tablets was studied in 462 patients with Candida or Trichomonas infections of the vagina. Five patients reported irritation (itching and burning after insertion) not necessitating the treatment to be discontinued.

There were undesirable effects in three (0.5%) of 653 patients treated with CANESTEN® Vaginal Cream which were possibly related to treatment. Discontinuation of treatment was necessary in a patient with a sensation of vaginal burning and in another patient with a possible allergic reaction, manifested by vaginal burning, local irritation and erythema. Treatment was, however, continued in a patient with intercurrent cystitis.

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