New Zealand Data Sheet

CANESTEN™

Canesten Clotrimazole Thrush Treatment Once Cream, vaginal cream 100 mg/g (10%)

Canesten Clotrimazole Thrush Treatment 3 Day Cream, vaginal cream 20 mg/g (2%)

Canesten Clotrimazole Thrush Treatment 6 Day Cream, vaginal cream 10 mg/g (1%)

Canesten Clotrimazole Thrush Treatment 6 Day Pessary, vaginal pessary 100 mg

Canesten Clotrimazole Thrush Treatment Once Pessary, vaginal pessary 500 mg

Canesten Clotrimazole Thrush Treatment Once Pessary + Cream, vaginal pessary 500 mg + topical cream 10 mg/g (1%)

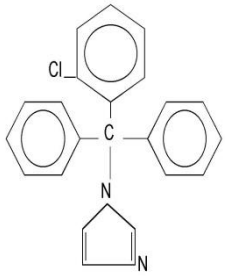
Canesten Clotrimazole Thrush Treatment Once Soft Vaginal Pessary, soft vaginal pessary 500 mg (not marketed)

Canesten Clotrimazole Thrush Treatment Once Soft Vaginal Pessary + Cream, soft vaginal pessary 500 mg + topical cream 10 mg/g (1%) (not marketed)

Name of the Medicinal Product

Clotrimazole

1-(o-chloro- α, α - diphenylbenzyl) imidazole



$C_{22}H_{17}ClN_2$

Molecular Weight 344.84

Clotrimazole is a colourless, crystalline, weakly alkaline substance, melting point 141°- 145°C, soluble in acetone, chloroform and ethanol and practically insoluble in water. It forms stable salts with both organic and inorganic acids. It is not photosensitive but is slightly hygroscopic, and may be hydrolysed in acid media.

Qualitative and Quantitative Composition

Canesten Clotrimazole Thrush Treatment Once Cream

Canesten Clotrimazole Thrush Treatment Once Cream contains 100 mg/g (10% w/w) of clotrimazole in a vanishing cream base. The cream also contains sorbitan stearate, polysorbate 60, cetyl palmitate, cetostearyl alcohol, isopropyl myristate, benzyl alcohol (1% w/w) and purified water.

Canesten Clotrimazole Thrush Treatment 3 Day Cream

Canesten Clotrimazole Thrush Treatment 3 Day Cream contains 20 mg/g (2% w/w) of clotrimazole in a vanishing cream base. The cream also contains sorbitan stearate, polysorbate 60, cetyl palmitate, cetostearyl alcohol, octyldodecanol, benzyl alcohol (2% w/w) and purified water.

Canesten Clotrimazole Thrush Treatment 6 Day Cream

Canesten Clotrimazole Thrush Treatment 6 Day Cream contains 10 mg/g (1% w/w) of clotrimazole in a vanishing cream base. The cream also contains sorbitan stearate, polysorbate 60, cetyl palmitate, cetostearyl alcohol, octyldodecanol, benzyl alcohol (2% w/w) and purified water.

Canesten Clotrimazole Thrush Treatment 6 Day Pessary

Canesten Clotrimazole Thrush Treatment 6 Day Pessary contains 100 mg of clotrimazole in each pessary. The pessaries also contain lactose, maize starch, magnesium stearate, silicon dioxide, calcium lactate pentahydrate, crospovidone, lactic acid, hypromellose, microcrystalline cellulose.

Canesten Clotrimazole Thrush Treatment Once Pessary

Canesten Clotrimazole Thrush Treatment Once Pessary contains 500 mg of clotrimazole in each pessary. The pessaries also contain lactose, microcrystalline cellulose, lactic acid, maize starch, crospovidone, calcium lactate; magnesium stearate, silicon dioxide, hypromellose.

Canesten Clotrimazole Thrush Treatment Once Pessary + Cream

Canesten Clotrimazole Thrush Treatment Once Pessary + Cream contains 500 mg of clotrimazole in each pessary and 10 mg/g clotrimazole in the cream. The pessary also contains lactose, microcrystalline cellulose, lactic acid, maize starch, crospovidone, calcium lactate; magnesium stearate, silicon dioxide, hypromellose. The cream also contains sorbitan stearate, polysorbate 60, cetyl palmitate, cetostearyl alcohol, octyldodecanol, benzyl alcohol (2% w/w) and purified water.

Canesten Clotrimazole Thrush Treatment Once Soft Vaginal Pessary (not marketed)

Canesten Clotrimazole Thrush Treatment Once Soft Vaginal Pessary contains 500 mg of clotrimazole in each soft vaginal pessary. The soft pessary also contains white, soft paraffin, liquid paraffin, gelatin, glycerol, titanium dioxide, quinoline yellow, sunset yellow, and traces of purified water, lecithin and fractionated coconut oil.

Canesten Clotrimazole Thrush Treatment Once Soft Vaginal Pessary + Cream (not marketed)

Canesten Clotrimazole Thrush Treatment Once Soft Vaginal Pessary + Cream contains 500 mg of clotrimazole in each soft vaginal pessary and 10 mg/g clotrimazole in the cream. The soft pessary also contains white, soft paraffin, liquid paraffin, gelatin, glycerol, titanium dioxide, quinoline yellow, sunset yellow, and traces of purified water, lecithin and fractionated coconut oil. The cream also contains sorbitan stearate, polysorbate 60, cetyl palmitate, cetostearyl alcohol, octyldodecanol, benzyl alcohol (2% w/w) and purified water.

Pharmaceutical Form

Canesten Clotrimazole Thrush Treatment Once Cream

Vaginal cream.

Canesten Clotrimazole Thrush Treatment 3 Day Cream

Vaginal cream.

Canesten Clotrimazole Thrush Treatment 6 Day Cream

Vaginal cream.

Canesten Clotrimazole Thrush Treatment 6 Day Pessary

Vaginal pessary.

Canesten Clotrimazole Thrush Treatment Once Pessary

Vaginal pessary.

Canesten Clotrimazole Thrush Treatment Once Pessary + Cream

Combination product – vaginal pessary and topical cream.

Canesten Clotrimazole Thrush Treatment Once Soft Vaginal Pessary (not marketed)

Vaginal soft gel pessary.

Canesten Clotrimazole Thrush Treatment Once Soft Vaginal Pessary + Cream (not marketed)

Combination product – vaginal soft gel pessary and topical cream.

Clinical Particulars

Therapeutic Indications

Canesten Clotrimazole Thrush Treatment Once, 3 Day and 6 Day creams are indicated for the topical treatment of vulvovaginal candidiasis. Canesten Clotrimazole cream may also be used in conjunction with Canesten Clotrimazole vaginal pessaries in the management of Candida vulvovaginitis or infection of the peri-anal area, while application of the cream to the glans penis of the partner may help prevent re-infection of the female.

Canesten Clotrimazole Thrush Treatment Once and 6 Day vaginal pessaries are indicated for the topical treatment of vaginal candidiasis.

Canesten Clotrimazole Thrush Treatment Once Pessary + Cream is indicated for the topical treatment of vulvovaginal candidiasis. The cream can also be used in the management of Candida vulvovaginitis or infection of the peri-anal area, while application of the cream to the glans penis of the partner may help prevent re-infection of the female.

Posology and Method of Administration

Canesten Clotrimazole Thrush Treatment 6 Day Cream

Once daily, preferably in the evening for six successive days, one applicator should be filled with cream (approx. 5 g) and inserted as deeply as possible into the vagina with the patient lying on her back. The 35 g tube of cream for vaginal use provides for six such doses.

Canesten Clotrimazole Thrush Treatment 3 Day Cream

Once daily, preferably in the evening for three successive days, one applicator should be filled with cream (approx. 5 g) and inserted as deeply as possible into the vagina with the patient lying on her back. The 20 g tube of cream for vaginal use provides for three such doses.

Canesten Clotrimazole Thrush Treatment Once Cream

The disposable applicator should be filled with Canesten Once cream, ensuring the entire contents of the tube are used (approx. 5 g). The cream is then inserted as gently and deeply as possible into the vagina with the patient lying on her back at bedtime as a single dose of treatment.

Canesten Clotrimazole Thrush Treatment Vaginal Pessaries

The pessaries should be inserted as deeply as possible into the vagina once daily, preferably in the evening before going to bed. This is best achieved using the plastic applicator provided and when lying back with the legs slightly drawn up. In pregnancy, digital insertion may be preferable to use of the applicator.

A course of treatment normally consists of either a single 500 mg pessary (Canesten Clotrimazole Thrush Treatment Once Pessary) or of six 100 mg pessaries (Canesten Clotrimazole Thrush Treatment 6 Day Pessary). The latter may be given either as two pessaries, inserted one after the other, daily for three days or as one pessary daily for six days. Clinical investigations have shown comparable efficacy from either dosage scheme. Where a first course proved unsuccessful, a second course produced success in 8 of 12 women treated.

Clotrimazole vaginal pessaries need moisture in the vagina to dissolve completely, otherwise undissolved pieces of the vaginal pessary 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 pessary not dissolve completely within one night, the use of a vaginal cream should be considered.

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.

Contraindications

Hypersensitivity to the active substance, clotrimazole, or to any of the excipients as listed under Qualitative and Quantitative Composition.

Special Warnings and Precautions for Use

If the patient has a fever (temperature of 38^{o}C or above), lower abdominal pain, back pain, foul smelling vaginal discharge, nausea, vaginal haemorrhage and/or associated shoulder pain the patient should consult a doctor.

Generally:

Keep the medicine out of reach of children.
Avoid contact with eyes.
Do not swallow.

Clotrimazole cream may reduce the effectiveness and safety of latex products such as condoms and diaphragms when applied to the genital area (women: intravaginally, labia and adjacent area of the vulva; men: prepuce and glans of the penis). The effect is temporary and occurs only during treatment.

For products containing cetostearyl alcohol i.e. the cream presentations:

Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

Interactions with Other Medicinal Products and Other Forms of Interaction

Concomitant medication 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 overdosage, if necessary by determination of the respective plasma levels.

Fertility, Pregnancy and 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 medicine on fertility.

Pregnancy (Category A)

Data from the use of clotrimazole in pregnant women is limited. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Preclinical Safety Data). As a precautionary measure, it is preferable to avoid the use of clotrimazole during the first trimester of pregnancy.

During pregnancy, the treatment should be carried out with Canesten Clotrimazole vaginal pessaries since these can be inserted without using an applicator.

Lactation

Available pharmacodynamic/toxicological data in animals have shown excretion of clotrimazole/metabolites in milk (see Preclinical Safety Data). Breast-feeding should be discontinued during treatment with clotrimazole.

Effects on Ability to Drive and Use Machines

The medication has no or negligible influence on the ability to drive or use machinery.

Undesirable Effects

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

Allergic reaction (syncope, hypotension, dyspnoea, urticaria).

Reproductive System and Breast Disorders

Genital peeling, pruritis, rash, oedema, erythema, discomfort, burning, irritation, pelvic pain, vaginal haemorrhage.

Gastrointestinal Disorders

Abdominal pain.

Overdose

No risk of acute intoxication is seen as it is unlikely to occur following a single vaginal or dermal application of an overdose (application over a large area under conditions favourable to absorption) or inadvertent oral ingestion. There is no specific antidote.

Pharmacological Properties

Pharmacotherapeutic Group

Antifungals for topical use – imidazole and triazole derivatives.

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 fungal 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 the region of less than 0.062 – 8.0 µg/mL substrate.

The mode of action of clotrimazole is primarily 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 micro-organisms (Streptococci / Staphylococci / Gardnerella vaginalis) and gram-negative micro-organisms (Bacteroides).

In vitro clotrimazole inhibits the multiplication of Corynebacteria and gram-positive cocci (with the exception of Enterococci) in concentrations of 0.5 – 10 µg/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.

Pharmacokinetic Properties

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

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 slight-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 new born 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* mutagencity 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 the 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 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.

Pharmaceutical Particulars

Incompatibilities

None known.

Special Precautions for Storage

Canesten Clotrimazole Thrush Treatment 6 Day Pessaries: Store at or below 30^{o}C.

Canesten Clotrimazole Thrush Treatment Once Soft Vaginal Pessaries (not marketed): Store at or below 30^{o}C.

All other presentations: Store at or below 25^{o}C.

Nature and Contents of Container

Canesten Clotrimazole Thrush Treatment Once Cream

One tube containing 5 g of vaginal cream, 100 mg clotrimazole per gram (10% w/w) packed with a single-use applicator and patient instruction sheet.

Canesten Clotrimazole Thrush Treatment 3 Day Cream

One tube containing 20 g of vaginal cream, 20 mg clotrimazole per gram (2% w/w) packed with three single-use disposable applicators and patient instruction sheet.

Canesten Clotrimazole Thrush Treatment 6 Day Cream

One tube containing 35 g of vaginal cream, 10 mg clotrimazole per gram (1% w/w) packed with six single-use disposable applicators and patient instruction sheet.

Canesten Clotrimazole Thrush Treatment 6 Day Pessary

Packs of six vaginal pessaries each sealed in a blister with plastic applicator and patient instruction sheet. Each pessary contains 100 mg clotrimazole per tablet.

Canesten Clotrimazole Thrush Treatment Once Pessary

One vaginal pessary sealed in a blister with plastic applicator and patient instruction sheet. Each pessary contains 500 mg clotrimazole.

Canesten Clotrimazole Thrush Treatment Once Pessary + Cream

One vaginal pessary sealed in a blister with plastic applicator, one tube containing 10 g topical cream and patient instruction sheet. Each pessary contains 500 mg clotrimazole. Each gram of cream contains 10 mg clotrimazole.

Canesten Clotrimazole Thrush Treatment Once Soft Vaginal Pessary (not marketed)

One soft vaginal pessary sealed in a blister with plastic applicator and patient instruction sheet. Each pessary contains 500 mg clotrimazole.

Canesten Clotrimazole Thrush Treatment Once Soft Vaginal Pessary + Cream (not marketed)

One soft vaginal pessary sealed in a blister with plastic applicator, one tube containing 10 g topical cream and patient instruction sheet. Each pessary contains 500 mg clotrimazole. Each gram of cream contains 10 mg clotrimazole.

Instructions for Use/Handling

Medicines should not be disposed of via wastewater or household waste. Ask a pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Medicine Classification

Pharmacist Only Medicines

Name and Address

Bayer New Zealand Limited
3 Argus Place
Hillcrest
North Shore
Auckland 0627

Freephone 0800 847 874

Date of Preparation

14 March 2013

Ref: Canesten Clotrimazole Vaginal Products Company Core Data Sheet Version 4.0, dated 1 October 2012