SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Canesten Thrush Duo Oral Capsule & External Cream 150mg / 2% w/w capsule & cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule of Canesten Thrush Oral Capsule contains 150 mg fluconazole.

Canesten Thrush External Cream contains Clotrimazole 2% w/w.

Excipients with known effects:
Capsule: lactose
Cream: cetostearyl alcohol

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard capsule.

Opaque light blue capsule (size 1) with "Canesten®" printed in black between two black lines.

Cream.

White cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Canesten Thrush Oral Capsule is indicated for the treatment of candidal vaginitis, acute or recurrent. It should also be used for the treatment of partners with associated candidal balanitis.

Canesten Thrush External Cream is indicated for the treatment of candida vulvitis.

It should be used as an adjunct to treatment of candidal vaginitis.

It can also be used for treatment of the sexual partner's penis to prevent re-infection.

4.2 Posology and method of administration

Adults (16 to 60):

One capsule should be swallowed whole.

The cream should be applied thinly two or three times daily to the vulva and surrounding area and rubbed in gently.

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

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

Children (under 16):

Paediatric use is not recommended.

Elderly:

Not recommended in patients over 60.

Renal Impairment:

There is no separate dosage schedule in patients with renal impairment for single dose therapy.

4.3 Contraindications

Hypersensitivity to the active substances (fluconazole and clotrimazole), related azole substances or to any of the excipients listed in section 6.1.

Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozide, quinidine and erythromycin are contraindicated in patients receiving fluconazole (see sections 4.4 and 4.5).

Coadministration of terfenadine is contraindicated based upon results of a multiple dose interaction study.

4.4 Special warnings and precautions for use

Medical advice should be sought if this is the first time the patient has experienced symptoms of candidal vaginitis.

The product is available from pharmacies without prescription and includes a leaflet that advises the patient - *Do not use* Canesten Thrush Duo Oral Capsule & External Cream *without first consulting your doctor:*

If you are under 16 or over 60 years of age
If you are allergic to any of the ingredients in Canesten Thrush Duo Oral Capsule & External Cream or other antifungals and other thrush treatments
If you are taking any other medicine other than the Pill.
If you are taking the antihistamine terfenadine or the prescription medicine cisapride
If you have had thrush more than twice in the last six months
If you have any disease or illness affecting your liver or kidneys or have had unexplained jaundice.
If you suffer from any other chronic disease or illness.
If you or your partner have had exposure to a sexually transmitted disease.
If you are unsure of the cause of your symptoms.

Women only:
If you are pregnant, suspect you might be pregnant or are breast-feeding.
If you have any abnormal or irregular vaginal bleeding or a blood stained discharge
If you have vulval or vaginal sores, ulcers or blisters.
If you are experiencing lower abdominal pain or burning sensation on passing water.
If you are experiencing any adverse events such as redness, irritation or swelling associated with the treatment.
If you are experiencing fever or chills, nausea, vomiting or diarrhoea.
If you have foul smelling vaginal discharge.

Men only:
If your sexual partner does <u>not</u> have thrush.
If you have penile sores, ulcers or blisters.
If you have an abnormal penile discharge (leakage).
If your penis has started to smell.
If you have pain on passing urine.

Recurrent use (men and women): patients should be advised to consult their physician if the symptoms have not been relieved within one week of taking Canesten Oral Capsule. Canesten Oral Capsule can be used if the candidal infection returns after 7 days. However, if the candidal infection recurs more

than twice within six months, patients should be advised to consult their physician.

Renal system
Fluconazole should be administered with caution to patients with renal dysfunction (see section 4.2).

Adrenal insufficiency
Ketoconazole is known to cause adrenal insufficiency and this could also, although rarely seen, be applicable to fluconazole.

Hepatobiliary system
Fluconazole should be administered with caution to patients with liver dysfunction.
Fluconazole has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions.
The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice) and be advised to consult a doctor.

Cardiovascular system
Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram.
The QT prolongation caused by other medicinal products may be amplified via the inhibition of cytochrome P450(CYP)3A4 (see sections 4.3 and 4.5).
Patients with hypokalaemia and advanced cardiac failure are at an increased risk for the occurrence of life threatening ventricular arrhythmias and torsades de pointes.
Fluconazole must be administered with caution in patients with congenital or acquired QT prolongation, known cardiomyopathy, sinus bradycardia, cardiac arrhythmia, or history of torsades de pointes or other proarrhythmic conditions.

Dermatological reactions
Patients have rarely developed exfoliative cutaneous reactions such as Stevens Johnson syndrome and toxic epidermal necrolysis during treatment with fluconazole. The patient should be advised to consult a doctor if a rash, which is considered attributable to fluconazole, develops.

Hypersensitivity
The product should never be used again if the patient experiences a rash or anaphylaxis following the use of the drug.

Cytochrome P450
Fluconazole should be administered with caution to patients who are taking medicinal products with a narrow therapeutic window metabolized through CYP2C9, CYP2C19 and CYP3A4 (see section 4.5).

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The cream contains cetostearyl alcohol, which may cause local skin reactions (e.g. contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction

Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Fluconazole is also an inhibitor of the isozyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9, CYP2C19 and CYP3A4 coadministered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored.
The vast majority of formal interaction studies and case reports are related to multiple dose fluconazole use, therefore, the magnitude of the effect of this inhibition on an individual patient after a single dose of fluconazole is hard to predict, particularly in light of the individual variability in the activity of the isoenzymes. Nonetheless, single dose pharmacokinetic studies have demonstrated that the inhibitory action of fluconazole is immediate and leads, dose-dependently, to increased plasma concentrations of the interacting agents.
The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to fluconazole's long plasma elimination half-life of approximately 30 hours and substantially longer tissue bioavailability (see section 5.2 Pharmacokinetic Properties), therefore these interactions may be clinically relevant following coadministration with drugs that have both a narrow therapeutic window and also act on vital organ systems like the heart and brain or are involved with glucose metabolism.

Oral Anticoagulants (Coumarin-type / Warfarin, Indanedione):
Bleeding events (bruising, epistaxis, gastro-intestinal bleeding, haematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type or indanedione anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of the anticoagulant may be necessary.

Sulphonylureas (Chlorpropamide, Glibenclamide, Glipizide, Tolbutamide):
Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (e.g. chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers.
Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dose is recommended during coadministration.

Diuretics (Hydrochlorothiazide):
Co-administration of fluconazole and multiple dose hydrochlorothiazide to healthy volunteers during a kinetic interaction study, increased plasma concentrations of fluconazole by 40%. However, although the prescriber should bear this in mind, the fluconazole dose in patients receiving concomitant diuretics should not need to be altered.

Pimozide, Quinidine, Erythromycin:
Coadministration of fluconazole and other drugs such as pimozide, quinidine and erythromycin is contraindicated. Fluconazole can cause changes in the metabolism of these drugs, which can lead to increased plasma levels with potential risk of cardiotoxicity (QT prolongation and torsades de pointes).

Antiarrhythmics (Amiodarone):
Concomitant administration of fluconazole with amiodarone may increase QT prolongation. Therefore, caution should be taken when both drugs are combined, notably with high doses fluconazole (800 mg).

Antimalarials (Halofantrine):
Fluconazole can also lead to increased levels of halofantrine (via inhibitory effect on CYP3A4) with potential risk of cardiotoxicity. This combination should be avoided (see section 4.4).

Benzodiazepines (Midazolam, Triazolam):
Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole.
If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.

Cystic fibrosis transmembrane conductance regulator (CFTR) potentiator (Ivacaftor):
A reduction of the ivacaftor dose to 150 mg once daily is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole, due to increased exposure.

HMG CoA reductase inhibitors (Atorvastatin, Simvastatin, Fluvastatin):
The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked

increase in creatine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.

Antiepileptics (Phenytoin, Carbamazepine):
Levels of phenytoin may increase to a clinically significant degree during co-administration with fluconazole. Phenytoin levels should be monitored and the phenytoin dose adjusted to maintain therapeutic levels if co-administration is necessary.
Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity, therefore dose adjustment of carbamazepine may be necessary.

Oral Contraceptives (*Ethinylestradiol, Levonorgestrel):*
Studies on the use of combined oral contraceptives with multiple doses of fluconazole have been performed. No relevant effects on hormone levels occurred during a study with fluconazole 50mg, whilst the AUCs of ethinylestradiol and levonorgestrel were increased by 40% and 24% respectively during a study with fluconazole 200mg. It is therefore considered that multiple dose fluconazole is unlikely to affect the efficacy of the combined oral contraceptive.

Anti-infectives (Rifampicin, Rifabutin):
A 25% decrease in the AUC and 20% shorter half-life of fluconazole occurred when fluconazole and rifampicin were administered concomitantly. An increase in the fluconazole dose should be considered in patients receiving concomitant rifampicin.
Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.

Angiotensin II Antagonists (Losartan):
CYP2C9 and CYP3A4 are involved in the metabolism of losartan to its active carboxylic acid metabolite E-3174 that is responsible for most of the angiotensin II receptor antagonism that occurs with losartan therapy. Fluconazole was shown to significantly inhibit the conversion of losartan to this metabolite. Monitoring of patients for continued control of their hypertension is recommended.

Antidepressants (Amitriptyline and Nortriptyline):
Fluconazole increases the effect of amitriptyline and nortriptyline. Dose of amitriptyline/ nortriptyline should be adjusted, if necessary.

Analgesics/Anaesthetics (Alfentanil, Fentanyl, Methadone):
Coadministration of fluconazole may cause decreased clearance of alfentanil, fentanyl or methadone and subsequent increased or prolonged opioid effects (CNS depression, respiratory depression). Dose adjustment may be required.

Xanthines (Theophylline):

Use of fluconazole 200mg for 14 days showed an 18% decrease in the mean plasma clearance of theophylline. Patients who require high doses of theophylline or who may be at increased risk of theophylline toxicity should be monitored for signs of theophylline toxicity when fluconazole is co-administered. The therapy should be modified if signs of toxicity occur.

Antihistamines (Terfenadine, Astemizole):
One study with terfenadine and fluconazole 200mg daily did not show a prolongation in the QTc interval. Use of fluconazole (taken in multiple doses of 400mg and 800mg per day) and terfenadine concomitantly, significantly increased plasma levels of terfenadine. Spontaneous reports of palpitations, tachycardia, dizziness and chest pains have occurred in patients taking fluconazole and terfenadine concomitantly where the relationship of the reported adverse events to drug therapy or underlying medical condition is uncertain. It is recommended that terfenadine and fluconazole should not be administered concomitantly due to the potential seriousness of such an interaction (see section 4.3).
Astemizole taken concomitantly with fluconazole may be associated with elevations in serum levels of this drug in patients, which can lead to QT prolongation and torsades de pointes. Coadministration of fluconazole and astemizole is contraindicated (see section 4.3).

Propulsives (Cisapride):
Cardiac events including torsades de pointes have been reported in patients receiving fluconazole and cisapride concomitantly. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Co-administration of cisapride is contra-indicated in patients receiving fluconazole (see section 4.3).

Antivirals (Zidovudine, Saquinavir):
Fluconazole increases Cmax and AUC of zidovudine by 84% and 74%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.
Fluconazole increases the AUC and Cmax of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein.
Dose adjustment of these drugs may be required.

Non-Steroidal Anti-inflammatory drugs (Celecoxib, Flurbiprofen, Ibuprofen, Naproxen, Lornoxicam, Meloxicam, Diclofenac):
Fluconazole may increase the systemic exposure of non-steroidal anti-inflammatory drugs. Adjustment of dose during concomitant treatment may be required.

Immuno-suppressants (Ciclosporin, Tacrolimus, Sirolimus):

Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8 fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.
Increased serum levels of tacrolimus (when orally administered) and sirolimus have been reported in patients receiving fluconazole and these drugs concomitantly, potentially due to inhibition of their metabolism. Increased levels of tacrolimus have been associated with nephrotoxicity. Dose of tacrolimus or sirolimus should be adjusted.

Studies show that when fluconazole is taken orally with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, the absorption of fluconazole is not significantly impaired.

Laboratory tests have suggested that, when used together, the cream may cause damage to latex contraceptives. Consequently the effectiveness of such contraceptives may be reduced. Patients should be advised to use alternative precautions for at least five days after using this product.

4.6 Fertility, pregnancy and lactation

An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester.

Canesten Thrush Duo Oral Capsule and External Cream should not be used during pregnancy or in women of childbearing potential unless clearly necessary or as recommended by a doctor.
Fluconazole is found in breast milk so it should not be used whilst breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, undesirable effects such as dizziness have been observed. If dizziness occurs, patients should not drive or operate machines.

4.8 Undesirable effects

The listed undesirable effects are based on spontaneous reports, thus assigning accurate frequency of occurrence for each is not possible.

Canesten Thrush Oral Capsule

The most frequently (>1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase

increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash.
The following adverse reactions have been observed and reported during treatment with Fluconazole with the following frequencies: Common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Uncommon: Anaemia.
Rare: Agranulocytosis, leukopenia, thrombocytopenia, neutropenia.

Immune System Disorders
Rare: Anaphylaxis.
Not known: Hypersensitivity.

Metabolism and nutrition disorders
Uncommon: Decreased appetite.
Rare: Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

Psychiatric disorders
Uncommon: Somnolence, insomnia.

Nervous system disorders
Common: Headache.
Uncommon: Seizures, paraesthesia, dizziness, dysgeusia.
Rare: Tremor.

Ear and labyrinth disorders
Uncommon: Vertigo.

Cardiac disorders
Rare: Torsades de pointes (see section 4.4), QT prolongation (see section 4.4).

Gastrointestinal disorders
Common: Abdominal pain, vomiting, diarrhoea, nausea.
Uncommon: Constipation, dyspepsia, flatulence, dry mouth.

Hepatobiliary disorders
Common: Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased (see section 4.4).
Uncommon: Jaundice, cholestasis, bilirubin increased.
Rare: Hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage (see section 4.4).

Skin and subcutaneous tissue disorders
Common: Rash (see section 4.4).
Uncommon: Drug eruption* (see section 4.4), urticaria (see section 4.4), pruritus, hyperhidrosis.

Rare: Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous-pustulosis, dermatitis exfoliative, angioedema, face oedema, alopecia.
Not Known: Drug reaction with eosinophilia and systemic symptoms (DRESS).
. *including Fixed Drug Eruption.

Musculoskeletal and connective tissue disorders
Uncommon: Myalgia.

General disorders and administration site conditions
Uncommon: Fatigue, malaise, asthenia, pyrexia.

Canesten Thrush External Cream
Immune System Disorders
Allergic reaction (syncope, hypotension, dyspnea, urticaria).

Skin and subcutaneous tissue disorders
Blisters, discomfort/pain, oedema, erythema, irritation, peeling/exfoliation, pruritus, rash, stinging/burning.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Canesten Thrush Oral Capsule
There have been reports of overdose with fluconazole and hallucination and paranoid behaviour have been concomitantly reported.
In the event of overdose, supportive measures and symptomatic treatment, with gastric lavage if necessary, may be adequate.

Fluconazole is largely excreted in the urine and therefore, forced volume diuresis would probably increase the elimination rate. Plasma levels are decreased by approximately 50% during a 3-hour haemodialysis session.

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

However, in the event of accidental oral ingestion, routine measures such as gastric lavage should be performed only if clinical symptoms of overdose become apparent (e.g. dizziness, nausea or vomiting). Gastric lavage should be carried out only if the airway can be protected adequately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Canesten Thrush Oral Capsule

Pharmacotherapeutic group: Fluconazole is a triazole antifungal

ATC-Code: J02AC01

Fluconazole is a triazole antifungal. It is a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol.

Fluconazole shows little pharmacological activity in a wide range of animal studies. Some prolongation of pentabarbitone sleeping times in mice (p.o.), increased mean arterial and left ventricular blood pressure and increased heart rate in anaesthetised cats (i.v.) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

Fluconazole was active in a variety of animal fungal infection models. Activity has been demonstrated against opportunistic mycoses, such as infections with *Candida* spp. including systemic candidiasis in immuno-compromised animals; with *Cryptococcus neoformans*, including intracranial infections; with *Microsporum* spp. and with *Trichophyton* spp. Fluconazole has also been shown to be active in animal models of endemic mycoses, including infections with *Blastomyces dermatitides*; with *Coccidoides immitis*, including intracranial infection and with *Histoplasma capsulatum* in normal and immuno-compromised animals.

There have been reports of cases of superinfection with *Candida* species other than *C. albicans*, which are often inherently not susceptible to fluconazole (e.g. *Candida krusei*). Such cases may require alternative antifungal therapy.

Fluconazole is highly specific for fungal cytochrome P-450 dependent enzymes. Fluconazole has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of childbearing age when given 50mg daily for up to 28 days. No clinically significant effect has been seen on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers taking fluconazole 200 – 400mg daily. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50mg do not affect its metabolism.

Canesten Thrush External Cream

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 microorganisms (Streptococci / Staphylococci / Gardnerella vaginalis), and gram-negative microorganisms (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.

5.2 Pharmacokinetic properties

Canesten Thrush Oral Capsule

The pharmacokinetic properties of fluconazole are similar whether administered orally or by the intravenous route. After oral administration, fluconazole is well absorbed and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Concomitant food intake does not affect oral absorption. In the fasting state peak plasma concentrations occur between 0.5 and 1.5 hours post-dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety- percent steady state levels are reached by day 4 to 5 with multiple once daily dosing.

Administration of a loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady state levels by day 2. The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%).

Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% of the corresponding plasma levels.

High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73 mg/g and 7 days after cessation of treatment the concentration was still 5.8 mg/g.

Excretion is mainly renal, with approximately 80% of the administered dose appearing in the urine as unchanged drug. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

The long plasma elimination half-life provides the basis for single dose therapy for genital candidiasis.

A study compared the saliva and plasma concentrations of a single fluconazole 100mg dose administration in a capsule or in an oral suspension by rinsing and retaining in the mouth for 2 minutes and swallowing. The maximum concentration of fluconazole in saliva after the suspension was observed five minutes after ingestion and was 182 times higher than maximum saliva concentration after the capsule which occurred four hours after ingestion. After about four hours, the saliva concentrations of fluconazole were similar. The mean AUC (0-96) in saliva was significantly greater after the suspension compared to the capsule. There was no significant difference in the elimination rate from the saliva or the plasma pharmacokinetic parameters for the two formulations.

Canesten Thrush External Cream

Pharmacokinetic investigations after dermal application have shown that clotrimazole is minimally absorbed from the intact or inflamed skin into the human blood circulation. The resulting peak serum concentrations of clotrimazole were below the detection limit of 0.001 mcg/ml, suggesting that clotrimazole applied topically is unlikely to lead to measurable systemic effects or side effects.

5.3 Preclinical safety data

Canesten Thrush Oral Capsule

Reproductive Toxicity:

At 25 and 50mg/kg and higher doses, increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed. At doses ranging from 80mg/kg to 320mg/kg embryolethality in rats was increased and foetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. This may be a result of known effects of lowered oestrogen on pregnancy, organogenesis and parturition as it is consistent with the inhibition of oestrogen synthesis in rats.

Carcinogenesis:

No evidence of carcinogenic potential was observed in mice and rats treated orally with fluconazole for 24 months at doses of 2.5, 5 or 10mg/kg/day. The incidence of hepatocellular adenomas was increased in male rats treated with 5 and 10mg/kg/day.

Mutagenesis:

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *S. typhimurium* and in the mouse lymphoma L5178Y system. No evidence of chromosomal mutations was observed in cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole). Data derived from *in vitro* studies (human lymphocytes exposed to fluconazole) are not consistent.

Impairment of Fertility:

The fertility of male or female rats treated orally with daily doses of fluconazole at doses of 5, 10 or 20mg/kg or with parenteral doses of 5, 25 or 75mg/kg was not affected, although the onset of parturition was slightly delayed at 20mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20mg/kg and 40mg/kg, but not at 5mg/kg. The disturbances in parturition were reflected by a slight increase in the number of stillborn pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

Canesten Thrush External Cream

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity, genotoxicity and carcinogenicity.

Clotrimazole was not teratogenic in reproductive toxicity studies in mice, rats and rabbits. In rats high oral doses were associated with maternal toxicity, embryotoxicity, reduced fetal weights and decreased pup survival.

In rats clotrimazole and/or its metabolites were secreted into milk at levels higher than in plasma by a factor of 10 to 20 at 4 hrs after administration, followed by a decline to a factor of 0.4 by 24 hrs

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Canesten Thrush Oral Capsule

Lactose monohydrate
Maize starch
Colloidal silicon dioxide
Magnesium stearate
Sodium lauryl sulphate

Capsule shells contain:
Brilliant blue FCF (E133)
Titanium dioxide (E171)
Gelatine
Printing ink contains:
Shellac
Black iron oxide (E172)
Propylene glycol

Canesten Thrush External Cream

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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Canesten Thrush Oral Capsule - No special precautions for storage

Canesten Thrush External Cream - Do not store above 25°C.

6.5 Nature and contents of container

Canesten Thrush Oral Capsule - Opaque, white PVC/PVdC (60g/m^2) blister with 20µm aluminium foil backing containing one capsule.

Canesten Thrush External Cream - 10 g aluminium tube with internal lacquer coating, latex stopper and HDPE screw top.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bayer plc
400 South Oak Way
Reading
RG2 6AD

8 MARKETING AUTHORISATION NUMBER(S)

PL 00010/0652

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/06/2015

10 DATE OF REVISION OF THE TEXT

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