New Zealand Data Sheet

CANESORAL® DUO

Fluconazole Oral Capsule 150 mg

Clotrimazole Topical Cream 10 mg/g

1. Name of the Medicinal Product

Canesoral Duo

A powder-filled capsule containing 150 mg fluconazole and a topical cream containing 10 mg/g clotrimazole.

2. Qualitative and Quantitative Composition

Each capsule contains 150 mg fluconazole. Each gram of cream contains 10 mg clotrimazole (10 mg/g, 1% w/w).

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

Hard gelatine capsule**,** powder-filled and topical cream in a vanishing cream base.

4. Clinical Particulars

4.1 Therapeutic Indications

Canesoral Duo is indicated for vaginal candidiasis.

The cream can also be used for relief of external itching/irritation and the management of Candida vulvovaginitis or infection of the peri-anal area.

4.2 Dose and Method of Administration

The fluconazole capsule must be used as a single dose treatment only.

The clotrimazole cream should be used in conjunction with the fluconazole capsule for relief of external itching/irritation and the management of Candida vulvovaginitis or infection of the peri-anal area.

Adults

One fluconazole 150 mg capsule, swallowed whole, in a single dose. Consult a healthcare professional if over 60 years of age.

Apply the cream thinly to the affected areas and rub in gently, two or three times daily.

Paediatric Population

Canesoral Duo should not be taken by children under 18 years of age unless directed by their physician.

Patients with Impaired Renal Function

There is no separate dosage schedule in patients with renal impairment for the single dose fluconazole treatment.

4.3 Contraindications

Canesoral Duo should not be used in patients with known sensitivity to fluconazole; clotrimazole; to related azole compounds; or to any of the excipients listed in section 6.1.

Coadministration of other medicines known to prolong the QT interval and which are metabolised via the enzyme CYP3A4 such as cisapride, astemizole, erythromycin, pimozide and quinidine are contraindicated (see section 4.4 Special Warnings and Precautions for Use).

4.4 Special Warnings and Precautions for Use

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. In cases of fluconazole-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed. Canesoral Fluconazole capsule should not be used again if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole (see section 4.8 Undesirable Effects).

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson Syndrome and toxic epidermal necrolysis, during treatment with fluconazole. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported. AIDS patients are more prone to the development of serious cutaneous reactions to many medicines. Fluconazole should not be used again if a rash develops which is attributable to fluconazole.

In rare cases, as with other azoles, anaphylaxis has been reported.

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and *torsades de pointes* in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medications that may have been contributory. Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions (see section 4.8 Undesirable Effects)

The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole treated patients who are concomitantly treated with medicines with a narrow therapeutic window metabolised through CYP2C9 and CYP3A4 should be monitored.

Canesoral Fluconazole capsule contains lactose and should not be given to patients with the rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

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

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

Candidiasis

Studies have shown an increasing prevalence of infections with *Candida* species other than *C. albicans*. These are often inherently resistant (e.g., *C. krusei* and *C. auris*) or show reduced susceptibility to fluconazole (*C. glabrata*). Such infections may require alternative antifungal therapy secondary to treatment failure. Therefore, prescribers are advised to take into account the prevalence of resistance in various *Candida* species to fluconazole (see section 5.1 Pharmacodynamic properties).

4.5 Interactions with Other Medicines and Other Forms of Interaction

Fluconazole

The relevance of the following medicine interactions to single-dose fluconazole is unknown. Patients on other medications should be advised to consult their doctor or pharmacist before starting fluconazole.

Fluconazole is an inhibitor of the cytochrome P450 system, particularly the CYP 2C and to a lesser extent the CYP 3A isoforms. There are possibilities that other medicines may affect the metabolism of fluconazole and that fluconazole may affect the metabolism of other medicines. In vitro studies conducted in human hepatic microsomes demonstrate that the extent of inhibition of CYP 3A isoforms is lowest with fluconazole, when compared with ketoconazole and itraconazole.

Alfentanil

A study observed a reduction in clearance and distribution volume as well as prolongation of T½ of alfentanil following concomitant treatment with fluconazole. A possible mechanism of action is fluconazole's inhibition of CYP3A4. Dosage adjustment of alfentanil may be necessary.

Amitriptyline, Nortriptyline

Fluconazole increases the effect of amitriptyline and nortriptyline. 5-nortriptyline and/or S-amitriptyline may be measured at initiation of the combination therapy and after one week. Dosage of amitriptyline /nortriptyline should be adjusted, if necessary.

Amphotericin B

Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoforms*, and antagonism of the two medicines in systemic infection with *A. fumigatus*. The clinical significance of results obtained in these studies is unknown.

Anticoagulants

In an interaction study, fluconazole increased the prothrombin time (12%) after warfarin administration in healthy males. In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Prothrombin time in patients receiving coumarin-type anticoagulants should be carefully monitored. Dose adjustment of warfarin may be necessary.

Astemizole

Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and astemizole is contraindicated (see section 4.3 Contraindications).

Azithromycin

An open-label, randomised, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant interaction between fluconazole and azithromycin.

Carbamazepine

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. Dosage adjustment of carbamazepine may be necessary depending on concentration measurements/effect.

Calcium Channel Blockers

Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolised by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

Celecoxib

During concomitant treatment with fluconazole (200 mg daily) and celecoxib (200 mg) the celecoxib C_{max} and AUC increased by 68% and 134% respectively. Half the celecoxib dose may be necessary when combined with fluconazole.

Cisapride

Cardiac events including *torsades de pointes* have been reported in patients receiving fluconazole and cisapride concomitantly. In most of these cases, the patients appear to have been predisposed to arrhythmias or had serious underlying illness. 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. Coadministration of cisapride is contraindicated in patients receiving fluconazole (see section 4.3 Contraindications).

Cyclophosphamide

Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Cyclosporin

A kinetic study in renal transplant patients found fluconazole 200 mg daily to slowly increase cyclosporin concentrations. However, in another multiple dose study with 100 mg daily, fluconazole did not affect cyclosporin levels in patients with bone marrow transplants. Cyclosporin plasma concentration monitoring in patients, with or without impaired renal function, receiving fluconazole is recommended.

Erythromycin

Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de points*) and consequently sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated (see section 4.3 Contraindications).

Everolimus

Although not studied *in vivo* or *in vitro*, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.

Fentanyl

One fatal case of possible fentanyl-fluconazole interaction was reported. The author judged that the patient died from fentanyl intoxication. Furthermore, in a randomised crossover study with 12 healthy volunteers it was shown that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression.

Halofantrine

Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4.

HMG-CoA Reductase Inhibitors

The risk of myopathy and rhabdomyolysis increases (dose-dependent) when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin (decreased hepatic metabolism of the statin). If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis, and creatinine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected. Lower doses of HMG-CoA reductase inhibitors may be necessary as instructed in the statins prescribing information.

Hydrochlorothiazide

Concomitant oral administration of 100 mg fluconazole and 50 mg hydrochlorothiazide for 10 days in normal volunteers resulted in an increase of 41% in C_{max} and an increase of 43% in AUC of fluconazole, compared to fluconazole given alone. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving diuretics, although the prescriber should bear it in mind.

Ibrutinib

Moderate inhibitors of CYP3A4 such as fluconazole increase plasma ibrutinib concentrations and may increase risk of toxicity. If the combination cannot be avoided, reduce the dose of ibrutinib as instructed in ibrutinib prescribing information and provide close clinical monitoring.

Ivacaftor (alone or combined with drugs in the same therapeutic class)

Coadministration with ivacaftor increased ivacaftor exposure by 3-fold and hydroxymethyl-ivacaftor (M1) exposure by 1.9-fold. A reduction of the ivacaftor (alone or combined) dose is necessary as instructed in the ivacaftor (alone or combined) prescribing information.

Lemborexant

Concomitant administration of fluconazole increased lemborexant Cmax and AUC by approximately 1.6- and 4.2-fold, respectively which is expected to increase risk of adverse reactions, such as somnolence. Avoid concomitant use of lemborexant.

Losartan

Fluconazole inhibits the metabolism of losartan to its active metabolite (E-3174) which is responsible for most of the angiotensin II-receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.

Lurasidone

Moderate inhibitors of CYP3A4 such as fluconazole may increase lurasidone plasma concentrations. If concomitant use cannot be avoided, reduce the dose of lurasidone as instructed in the lurasidone prescribing information.

Methadone

Fluconazole may enhance the serum concentration of methadone. Dosage adjustment of methadone may be necessary.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The C_{max} and AUC of flurbiprofen were increased by 23% and 81% respectively when coadministered with fluconazole, compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] were increased by 15% and 82% respectively when fluconazole was coadministered with racemic ibuprofen (400 mg), compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolised by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for

adverse events and toxicity related to NSAIDs is recommended. Adjustment of dosage of NSAIDs may be needed.

Olaparib: Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations. Concomitant use is not recommended. If the combination cannot be avoided, limit the dose of olaparib to 200 mg twice daily.

Oral Contraceptives

Three kinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relevant effects on either hormone level in the 50 mg fluconazole study, while at 200 mg daily the AUCs of ethinyl estradiol and levonorgestrel were increased 40% and 24% respectively. In a 300 mg once weekly fluconazole study, the AUCs of ethinyl estradiol and norethindrone were increased by 24% and 13% respectively. Thus, multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

Oral Hypoglycaemic Agents

The effects of fluconazole on the pharmacokinetics of the sulphonylurea oral hypoglycaemic agents tolbutamide, glipizide and glibenclamide were examined in three placebo-controlled crossover studies in normal volunteers. All subjects received the sulphonylurea alone and following treatment with 100mg of fluconazole as a single daily oral dose for 7 days. Fluconazole administration resulted in significant increases in C_{max} and AUC of the sulphonylurea. Several subjects in these three studies experienced symptoms consistent with hypoglycaemia. In the glibenclamide study, several volunteers required oral glucose treatment. As fluconazole is a potent inhibitor of CYP2C8 and CYP2C9, it may also interact with other sulphonylureas (eg. glimepiride and gliclazide) and the thiazolidinediones (eg. pioglitazone and rosiglitazone), which are metabolised by these enzymes. When fluconazole and sulphonylureas or thiazolidinediones are coadministered, blood glucose concentrations should be monitored carefully. The possibility of a hypoglycaemic episode should be borne in mind.

Phenytoin

Concomitant administration of oral fluconazole (200 mg) with phenytoin at steady state resulted in an average increase of 75% of phenytoin AUC values in normal volunteers. Careful monitoring of phenytoin concentrations in patients receiving fluconazole and phenytoin is recommended.

Rifampicin

Administration of a single oral 200 mg dose of fluconazole after chronic rifampicin administration resulted in a 25% decrease in AUC and a 20% shorter half-life of fluconazole in normal volunteers. Depending on clinical circumstances, an increase of the dose of fluconazole should be considered when it is administered with rifampicin.

Pimozide

Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of *torsade de pointes*. Coadministration of fluconazole and pimozide is contraindicated.

Prednisone

There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Quinidine

Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of *torsades de points*. Coadministration of fluconazole and quinidine is contraindicated (see section 4.3 Contraindications).

Short Acting Benzodiazepines

Studies in human subjects have reported changes in midazolam pharmacokinetics and clinical effects that are dependent on dosage and route of administration. Single doses of fluconazole 150 mg resulted in modest increases in midazolam concentrations and psychomotor effects following oral administration of 10 mg that may not be clinically significant. At doses used to treat systemic mycoses, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects following oral administration of midazolam 7.5 mg, but only modest increases that are not likely to be clinically significant following intravenous infusion of midazolam 0.05 mg/kg. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored.

Rifabutin

There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored.

Saquinavir

Fluconazole increases the AUC of saquinavir by approximately 50%, increases C_{max} by approximately 55% and decreases clearance of saquinavir by approximately 50% due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Dosage adjustments of saquinavir may be necessary.

Sirolimus

Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dosage adjustment of sirolimus depending on the effect/concentration measurements.

Sulfonylureas

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

Tacrolimus

There have been reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. There have been reports of nephrotoxicity in patients to whom fluconazole and tacrolimus were coadministered. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored.

Terfenadine

Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated. The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Theophylline

In a placebo controlled interaction study, the administration of fluconazole 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk of theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole, and therapy modified appropriately if signs of toxicity develop.

Tofacitinib

Exposure is increased when tofacitinib is coadministered with medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g. fluconazole). Dosage adjustment of tofacitinib may be necessary..

Tolvaptan

Exposure to tolvaptan is significantly increased (200% in AUC; 80% in Cmax) when tolvaptan, a CYP3A4 substrate, is co-administered with fluconazole, a moderate CYP3A4 inhibitor, with risk of significant increase in adverse reactions particularly significant diuresis, dehydration and acute renal failure. In case of concomitant use, the tolvaptan dose should be reduced as instructed in the tolvaptan prescribing information and the patient should be frequently monitored for any adverse reactions associated with tolvaptan.

Triazolam

Fluconazole increases the AUC of triazolam (single dose) by approximately 50%, C_{max} by 20% - 32% and increases $t_{½}$ by 25% - 50% due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam may be necessary.

Vinca Alkaloids

Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Vitamin A

Based on a case report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS-related undesirable effects have developed in the form of pseudotumour cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS-related undesirable effects should be borne in mind.

Voriconazole

CYP2C9, CYP2C19 and CYP3A4 inhibitor: Concurrent administration of oral voriconazole (400 mg every 12 h for 1 day, then 200 mg every 12 h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg every 24 h for 4 days) to 6 healthy male subjects results in an increase in C, and AUC, of voriconazole by an average of 57% (90% CI: 20%, 107%), and 79% (90% CI: 40%, 128%), respectively. In a follow-on clinical study involving 8 healthy male subjects, reduced dosing and/or frequency of voriconazole and fluconazole did not eliminate or diminish this effect. Concomitant administration of voriconazole and fluconazole at any dose is not recommended.

Warfarin

A single dose of warfarin (15 mg) given to normal volunteers, following 14 days of orally administered fluconazole (200 mg) resulted in a 12% increase in the prothrombin time response (area under the prothrombin time-time curve). One of 13 subjects experienced a 2-fold increase in his prothrombin time response. In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Careful monitoring of prothrombin time in patients receiving fluconazole and coumarin-type anticoagulants is recommended.

Zidovudine

The AUC of zidovudine significantly increased (74%) during coadministration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

Gastrointestinal Medicines

In fasted normal volunteers, absorption of orally administered fluconazole does not appear to be affected by agents that increase gastric pH. Single dose administration of fluconazole (100 mg) with cimetidine (400 mg) resulted in a 13% reduction in AUC and 21% reduction in C_{max} of fluconazole. Administration of an antacid

containing aluminium and magnesium hydroxides immediately prior to a single dose of fluconazole (100 mg) had no effect on the absorption or elimination of fluconazole.

Physicians should be alert to the potential for interactions with other medicines for which pharmacokinetic interaction studies have not been conducted.

Clotrimazole Cream

There are no reported medicinal interactions with topical clotrimazole cream.

4.6 Fertility, Pregnancy and Lactation

Pregnancy (Category D)

There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 - 800 mg/day) fluconazole therapy for coccidiomycosis. The relationship between fluconazole use and these events is unclear. A study found any maternal exposure to fluconazole during pregnancy may increase the risk of spontaneous abortion and that doses higher than 150 mg during the first trimester may increase the risk of cardiac septal closure anomalies.

In one large observational cohort study, first trimester exposure to oral fluconazole was associated with a small increased risk of musculoskeletal malformations, corresponding to approximately 1 additional case per 1000 women treated with cumulative doses ≤ 450 mg compared with women treated with topical azoles and to approximately 4 additional cases per 1000 women treated with cumulative doses over 450 mg. The adjusted relative risk was 1.29 (95% CI 1.05 to 1.58) for 150 mg oral fluconazole and 1.98 (95% CI 1.23 to 3.17) for doses over 450 mg fluconazole.

Adverse foetal effects have been seen in animals only at high dose levels associated with maternal toxicity.

Canesoral Duo should not be used in women who are pregnant, or in women of childbearing potential unless adequate contraception is employed (see section 4.4 Special Warnings and Precautions for Use and section 4.5 Interactions with Other Medicines and Other Forms of Interaction, oral contraceptives). Effective contraceptive measures should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose.

Lactation

Fluconazole has been found in human breast milk at concentrations similar to plasma. Available pharmacodynamics/toxicological data in animals have shown excretion of clotrimazole/metabolites in milk (see section 5.3 Preclinical Safety Data). Hence the use of Canesoral Duo in nursing mothers is not recommended.

Fertility

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg, but not at 5 mg/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.

For clotrimazole, non-clinical data reveal no special hazard for humans based on conventional studies of toxicity to reproduction and development.

4.7 Effects on Ability to Drive and Use Machines

Therapy with Canesoral Duo is unlikely to impair a patient's ability to drive or use machinery.

4.8 Undesirable Effects

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment (see section 4.4 Special warnings and precautions for use).

Clotrimazole

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

Anaphylactic reaction, angioedema, hypersensitivity

Vascular disorders

Syncope, hypotension

Respiratory, thoracic and mediastinal disorders

Dyspnea

Gastrointestinal disorders

Abdominal pain, nausea

Skin and Subcutaneous Tissue Disorders

Rash, urticaria

Reproductive system and breast disorders

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

General disorders and administration site conditions

Application site irritation, oedema, pain

Fluconazole

Fluconazole is generally well tolerated.

The most common undesirable effects observed during vaginal candidiasis clinical trials and associated with fluconazole with an incidence > 1% are:

Nervous System Disorders

Headache

Gastrointestinal Disorders

Nausea, abdominal pain, diarrhoea, dyspepsia

In addition, the uncommon undesirable effects observed during vaginal candidiasis clinical trials associated with fluconazole are:

Dermatological

Pruritus, genital pruritus, rash, erythematous rash, dry skin, abnormal skin odour, urticaria

Nervous System Disorders

Dizziness, flushing, dry mouth, vertigo, hyperkinesia, hypertonia, taste perversion

Gastrointestinal Disorders

Vomiting, anorexia, flatulence, constipation, loose stools

Metabolic

Thirst

Psychiatric

Insomnia, nervousness, female sexual dysfunction

Reproductive

Intermenstrual bleeding, dysmenorrhoea, leucorrhoea, menorrhagia, uterine spasm, vaginal disorder

Respiratory

Pharyngitis

Special Senses

Taste perversion, abnormal vision, visual field defect

Urinary

Polyuria, renal pain

General

Fatigue, hot flushes, malaise, back pain, herpes simplex, pain, rigors

The following adverse events have occurred during experience with overall fluconazole use:

Blood and Lymphatic System Disorders

Leukopenia including neutropenia and agranulocytosis, thrombocytopenia

Cardiovascular Disorders

QT prolongation, *torsades de pointes* (see section 4.4 Special Warnings and Precautions for Use)

Nervous System Disorders

Seizures

Immune System Disorders

Anaphylaxis (including face oedema, angioedema, urticaria and pruritus)

Metabolic and Nutritional Disorders

Hypercholesterolaemia, hypertriglyceridaemia and hypokalaemia

Hepatobiliary Disorders

Hepatic failure, hepatitis, hepatocellular necrosis, jaundice

Skin and Subcutaneous Tissue Disorders

Alopecia, exfoliative skin disorders including Stevens-Johnson Syndrome and toxic epidermal necrolysis, drug reaction with Eosinophilia and systemic symptoms (DRESS)

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Fluconazole

There have been reports of overdosage with fluconazole, and in one case a 42-year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behaviour after reportedly ingesting 8,200 mg of fluconazole. The patient was admitted to hospital, and his condition resolved within 48 hours.

In the event of overdosage, symptomatic treatment (with supportive measures and gastric lavage if necessary) should be undertaken.

Fluconazole is largely excreted in the urine; forced volume diuresis would probably increase the elimination rate. A three-hour haemodialysis session decreases plasma levels by approximately 50%.

Clotrimazole

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic Group

Fluconazole: Antimycotics for systemic use – triazole derivatives. ATC Code: J02A C01

Clotrimazole: Antifungals for topical use – imidazole and triazole derivatives. ATC Code: D01A C01

Mechanism of Action

Fluconazole is a member of the bis-triazole class of antifungal agents. Fluconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14 alpha demethylation. Mammalian cell demethylation is much less sensitive to fluconazole inhibition. The subsequent loss of normal sterols correlates with the accumulation of 14 alpha-methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

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

Clotrimazole has a broad antimycotic spectrum of action *in vitro* and *in vivo*, which includes dermatophytes, yeasts, moulds, etc.

Under appropriate test conditions, the MIC values for these types of fungi are in 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.

Susceptibility in vitro

In vitro, fluconazole displays antifungal activity against clinically common Candida species (including *C. albicans, C. parapsilosis, C. tropicalis). C. glabrata* shows reduced susceptibility to fluconazole while *C. krusei* and *C. auris* are resistant to fluconazole. The minimum inhibitory concentrations (MICs) and epidemiological cut-off value (ECOFF) of fluconazole for *C. guilliermondii* are higher than for *C. albicans.*

Fluconazole also exhibits activity in vitro against *Cryptococcus neoformans* and *Cryptococcus gattii* as well as the endemic moulds *Blastomyces dermatiditis*, *Coccidioides immitis*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis.*

Pharmacokinetic/pharmacodynamic relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to *Candida* spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly cure is less likely for infections caused by strains with a higher fluconazole MIC.

Mechanisms of resistance

Candida spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high MICs to fluconazole which impacts adversely efficacy *in vivo* and clinically.

In usually susceptible species of Candida, the most commonly encountered mechanism of resistance development involves the target enzymes of the azoles, which are responsible for the biosynthesis of ergosterol. Resistance may be caused by mutation, increased production of an enzyme, drug efflux mechanisms, or the development of compensatory pathways.

There have been reports of superinfection with *Candida* species other than *C. albicans,* which often have reduced susceptibility (*C. glabrata*) or resistance to fluconazole (e.g., *C. krusei*, *C. auris*). Such infections may require alternative antifungal therapy. The resistance mechanisms have not been completely elucidated in some intrinsically resistant (*C. krusei*) or emerging (*C. auris*) species of Candida.

Susceptibility testing breakpoints

Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility *in vitro* and clinical response EUCAST-AFST (European Committee on Antimicrobial susceptibility Testing-subcommittee on

Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for *Candida* species (EUCAST Fluconazole rationale document (2020)-version 3; European Committee on Antimicrobial Susceptibility Testing, Antifungal Agents, Breakpoint tables for interpretation of MICs, Version 10.0, valid from 2020-02-04). These have been divided into non-species related breakpoints; which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:

Antifungal	**Species-related breakpoints (S≤/R>) in mg/L**						**Non-species related breakpoints[A] S≤/R> in mg/L**
	Candida albicans	*Candida dubliniensis*	*Candida glabrata*	*Candida krusei*	*Candida parapsilosis*	*Candida tropicalis*	
Fluconazole	2/4	2/4	0.001*/16	--	2/4	2/4	2/4

S = Susceptible, R = Resistant

A = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

* = The entire *C. glabrata* is in the I category. MICs against *C. glabrata* should be interpreted as resistant when above 16 mg/L. Susceptible category (≤0.001 mg/L) is simply to avoid misclassification of "I" strains as "S" strains. I - Susceptible, increased exposure: A microorganism is categorised as Susceptible, increased exposure when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.

For the most recent susceptibility testing interpretation according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), Antifungal agents, please see (https://www.eucast.org/).

Microbiology

Fluconazole administered orally or intravenously was active in a variety of animal models of fungal infections using standard laboratory strains of fungi.

Fluconazole exhibits *in vitro* activity against *Cryptococcus neoformans* and *Candida* spp. Activity has been demonstrated *in vivo* in normal and immunocompromised animals against infections with *Candida* spp, including systemic candidiasis and in normal animals with *C. neoformans*, including intracranial infections. One case of cross-resistance of *Candida* to fluconazole in a patient (non-HIV) previously treated with ketoconazole has been reported. The efficacy of fluconazole *in vivo* is greater than would be apparent from *in vitro* testing against the above-mentioned fungi.

Concurrent administration of fluconazole and amphotericin B in infected normal and immuno-compromised mice showed antagonism of the two medicines in systemic infection with *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.

5.2 Pharmacokinetic Properties

In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. Oral administration is not affected by concomitant food intake. In fasted normal volunteers, peak plasma concentrations occur between 1 and 2 hours post dose with a terminal plasma elimination half-life of approximately 30 hours (range 20 - 50 hours). The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11 - 12%).

Fluconazole has been found to achieve good penetration into all tissues and body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels.

The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged medicine. About 11% of the dose is excreted in the urine as metabolites. The pharmacokinetics of fluconazole are markedly affected by reduction in renal function, however, no adjustments in single-dose therapy are necessary. There is an inverse relationship between the elimination half-life and creatinine clearance.

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

There are differences in the pharmacokinetics between adults and children, with children after the neonatal period generally having a faster elimination rate and larger volume of distribution than adults.

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 µg/mL, suggesting that clotrimazole applied topically on the skin is unlikely to lead to measurable systemic effects or side effects.

5.3 Preclinical Safety Data

Carcinogenesis and Mutagenesis

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10 mg/kg/day (approximately 2 - 7 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *Salmonella typhimurium* and in the mouse lymphoma system. Cytogenetic studies *in vivo* and *in vitro* showed no evidence of chromosomal mutations.

For clotrimazole, 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.

6. Pharmaceutical Particulars

6.1 List of Excipients

Fluconazole Capsule

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

Capsule shells contain:
Titanium dioxide (E171)

Gelatin
Water

Printing ink contains:
Black iron oxide (E712), N-butyl alcohol, propylene glycol, ethanol, isopropyl alcohol, shellac glaze (esterified), ammonium hydroxide.

Clotrimazole Cream

Sorbitan stearate
Polysorbate 60
Cetyl palmitate
Cetostearyl alcohol
Octyldodecanol
Benzyl alcohol (2% w/w)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months (3 years) from date of manufacture

6.4 Special Precautions for Storage

Store at or below 25ºC.

6.5 Nature and Contents of Container

Canesoral Duo contains a blister pack of 1 fluconazole 150 mg capsule and one 10 g tube of clotrimazole 10 mg/g (1% w/w) cream.

6.6 Special Precautions for Disposal

No special requirements.

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.

7. Medicine Schedule

Pharmacist Only Medicine

8. Sponsor

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9. Date of First Approval

30 April 2015

10. Date of Revision of the Text

1 May 2023

Section changed	**Summary of new information**
4.4 Special Warnings and Precautions for Use	Candidiasis update
4.5 Interactions with Other Medicines and Other Forms of Interaction	Interaction information added for: • Everolimus • HMG-CoA reductase inhibitors • Ivacaftor • Lemborexant • Lurasidone
4.6 Fertility, Pregnancy and Lactation	Safety related change: pregnancy
4.8 Undesirable Effects	Information regarding Fluconazole and DRESS, and update to Clotrimazole cream undesirable effects
5.1 Pharmacological Properties	New information added: • Susceptibility in vitro • Pharmacokinetic/ pharmacodynamic relationship, • Mechanisms of resistance • Susceptibility testing breakpoints