SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PROCUT

FEMYCOZ COMBI KIT, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluconazole.....150 mg For 1 fluconazole tablet

Secnidazole.....1000mg For 1 secnidazole tablet

Azithromycin dihydrate / Azithromycin equivalent ….....1000mg For 1 azithromycin tablet

Each combi-kit contains:

2 Secnidazole tablets,

1 Fluconazole tablet,

1 Azithromycin tablet

3. PHARMACEUTICAL FORM

Tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FEMYCOZ COMBI KIT tablets are a combination medicine containing three active ingredients: azithromycin, secnidazole, and fluconazole. These substances work together to treat certain infections:

- Trichomonas vaginalis urethritis and vaginitis
- bacterial vaginosis
- intestinal amebiasis
- Hepatic amebiasis
- giardiasis ,
- vaginal candidiasis
- balanitis candidiasis

Official recommendations regarding the appropriate use of antifungals and antibacterials should be taken into account.

4.2 Posology and method of administration

Posology

Adult

Swallow all 4 tablets from the combi kit in a single dose.

Specific populations

Elderly people

The recommended dosage is the same as for adult patients. Elderly patients may have pro-arrhythmic conditions; therefore, particular caution is advised due to the risk of cardiac arrhythmia and torsades de pointes (see section 4.4).

Liver failure

Data available in patients with hepatic impairment are limited; therefore, FEMYCOZ should be administered with caution in patients with impaired hepatic function (see sections 4.4 and 4.8).

Method of administration

Oral route.

This medication should be taken at the beginning of a meal, in a single dose. All 4 tablets must be taken at the same time.

4.3 Contraindications

This medication MUST NEVER BE USED in the following cases:

- Hypersensitivity to fluconazole or other azole derivatives
- Hypersensitivity to secnidazole or to the imidazole family
- Hypersensitivity to azithromycin, erythromycin, any other macrolide, or ketolide
- Hypersensitivity to the excipients listed in section 6.1.
- Association with ergot alkaloids: dihydroergotamine , ergotamine (see sections 4.4 and 4.5)
- Combination with cisapride (see section 4.5)
- Association with colchicine (see section 4.5)
- Severe hepatic impairment (see section 4.4)
- Hypersensitivity to fluconazole, other azole derivatives or to any of the excipients listed in section 6.1
- Co - administration with terfenadine is contraindicated in patients treated with repeated doses of fluconazole greater than or equal to 400 mg per day based on the results of a repeated dose interaction study.
- Co - administration with other drugs known to prolong the QT interval and metabolized by cytochrome P450 (CYP) 3A4 such as cisapride , astemizole , pimozide , quinidine and erythromycin is contraindicated in patients treated with fluconazole (see sections 4.4 and 4.5)

4.4 Special warnings and precautions for use

QT interval prolongation

Cases of prolonged cardiac repolarization and QT interval prolongation, involving a risk of cardiac arrhythmia and torsades de pointes, have been observed during treatment with macrolides, including azithromycin (see section 4.8). Since the following situations may lead to an increased risk of ventricular arrhythmia (including torsades de pointes) which can be fatal, caution should be exercised when treating patients with azithromycin:

- Presenting with congenital or documented QT interval prolongation.
- Currently receiving treatment with other active substances known to prolong the QT interval (see section 4.5).
- Presenting with an electrolyte disorder, particularly in cases of hypokalemia and hypomagnesemia.
- Presenting with clinically significant bradycardia, cardiac arrhythmia, or severe heart failure.

Women and elderly patients may also be more sensitive to treatments that prolong the QT interval

Some azole derivatives, including fluconazole, are associated with QT interval prolongation on the electrocardiogram. Fluconazole causes QT interval prolongation by inhibiting the current of the rectifying potassium channel (Ikr) . QT interval prolongation caused by other drugs (such as amiodarone) may be amplified by inhibition of cytochrome P450 (CYP) 3A4. Since marketing, very rare cases of QT interval prolongation and torsades de pointes have been observed in patients treated with fluconazole. These cases include critically ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities, and potentially contributing drug interactions. Patients with hypokalemia and advanced heart failure are at higher risk of developing life-threatening ventricular arrhythmias and torsades de pointes.

FEMYCOZ should be administered with caution in patients with potentially pro-arrhythmogenic conditions.

Co - administration with other drugs known to prolong the QT interval and metabolized by cytochrome P450 (CYP) 3A4 is contraindicated (see sections 4.3 and 4.5).

Bacterial vaginosis

The level of evidence is based on a single study comparing a single dose of secnidazole to metronidazole administered for seven days. In relation to pharmacokinetic parameters (see section 5.2), the single-dose regimen of secnidazole may be insufficient in some patients, potentially requiring the use of local vaginal treatment.

Candidiasis

Studies have shown an increasing prevalence of infections with *Candida species* other than *C. albicans* . These are often intrinsically resistant (e.g., *C. krusei* and *C. auris*) or exhibit reduced susceptibility to fluconazole (*C. glabrata*). These infections may require alternative antifungal therapy if standard treatment fails. Prescribers are therefore advised to consider the prevalence of fluconazole resistance in various *Candida species.*

Kidney failure

FEMYCOZ should be administered with caution in patients with impaired renal function (see section 4.2).

In cases of severe renal impairment (glomerular filtration rate < 10 mL /min), a 33% increase in systemic exposure to azithromycin was observed.

Dosage adjustment is not necessary in patients with mild renal impairment (creatinine clearance greater than 40 mL /min). Azithromycin should be prescribed with caution in patients with creatinine clearance less than 40 mL /min.

Adrenal insufficiency

Ketoconazole is known to cause adrenal insufficiency , which can also be seen with fluconazole, although cases are rare.

Adrenal insufficiency related to concomitant treatment with prednisone (see section 4.5 "Effect of fluconazole on other medicinal products")

Hepatotoxicity

FEMYCOZ should be administered with caution in patients with impaired liver function. Fluconazole has been associated with rare cases of severe, sometimes fatal, liver toxicity, primarily in patients with serious underlying conditions. In cases of fluconazole-associated hepatotoxicity, no relationship with the total daily dose, duration of treatment, sex, or age of the patients has been established. Fluconazole-associated hepatotoxicity is generally reversible upon discontinuation of treatment.

Patients who develop abnormal liver function tests during treatment with fluconazole should be closely monitored to prevent the development of more serious liver damage. The patient should be informed of symptoms suggestive of severe liver effects (significant fatigue, loss of appetite, persistent nausea, vomiting, and jaundice). Fluconazole treatment should be stopped immediately, and the patient should seek medical attention.

Since the liver is the main route of elimination of azithromycin, azithromycin is not recommended for patients with severe hepatic impairment or for patients with severe cholestasis.

Cases of fulminant hepatitis leading to life-threatening liver failure have been reported with azithromycin (see section 4.8). Some patients may have had pre-existing liver disease or may have been taking other hepatotoxic drugs.

Liver function tests should be performed immediately if signs or symptoms of impaired liver function occur, such as the rapid onset of fatigue associated with jaundice, dark urine, a tendency to bleed, or hepatic encephalopathy. Azithromycin should be discontinued immediately if liver dysfunction develops.

Halofantrine

Halofantrine has been shown to prolong the QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. Therefore, concomitant use of fluconazole and halofantrine is not recommended (see section 4.5).

Dermatological reactions

Rare cases of exfoliative skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), have been reported during treatment with fluconazole. A drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) has been reported. Patients with AIDS are at increased risk of developing severe skin reactions with many drugs. If a rash, considered to be caused by fluconazole, develops in a patient being treated for a superficial fungal infection, treatment should be discontinued. If patients with invasive or systemic fungal infections develop a rash, they should be closely monitored, and fluconazole should be discontinued if bullous lesions or erythema multiforme develop.

In addition, severe, life-threatening skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms), and acute generalized exanthematous pustulosis (AGEP) have been reported. Patients should be advised to monitor for skin reactions and for suggestive signs and symptoms that typically appear within the first few weeks of treatment. If suggestive symptoms occur (e.g., a progressive skin rash often associated with mucosal lesions or blisters), azithromycin should be discontinued immediately. Re-initiation of treatment is not recommended.

Hypersensitivity

As with erythromycin and other macrolides, rare but serious allergic reactions such as angioedema and anaphylactic reactions (rarely fatal) have been reported. The possibility of recurrence of symptoms after discontinuation of symptomatic treatment necessitates continued monitoring and possibly further treatment.

Allergic reactions to secnidazole can occur and may be severe (see section 4.8). In these cases, FEMYCOZ should be discontinued and appropriate medical treatment should be initiated.

In rare cases, an anaphylactic reaction to fluconazole has been reported (see section 4.3).

Bloodline

Avoid administering secnidazole to subjects with a history of blood dyscrasia.

Cytochrome P450

Fluconazole is a moderate inhibitor of CYP2C9 and CYP3A4. Fluconazole is also a strong inhibitor of CYP2C19. Patients treated concomitantly with fluconazole and drugs with a narrow therapeutic index that are metabolized by CYP2C9, CYP2C19, and CYP3A4 should be monitored (see section 4.5).

Terfenadine

Co - administration of fluconazole at doses below 400 mg per day with terfenadine should be closely monitored (see sections 4.3 and 4.5).

***Clostridium difficile* -associated diarrhea**

Cases of *Clostridium difficile -associated diarrhea* (CDAD) have been reported with the use of virtually all antibiotics, including azithromycin. Their severity can range from mild diarrhea to life-threatening pseudomembranous colitis. Antibiotic treatment alters the colonic flora, leading to an overgrowth of *C. difficile* .

C. *Covid-19* (*Covid-19*) produces toxins A and B, which contribute to the development of C. *difficile* infection (CDI). These toxin-producing strains increase morbidity and mortality, as infections may be refractory to antibiotic treatment and require colectomy. The possibility of CDI should be considered in all patients who develop diarrhea after antibiotic use. It is important to consider this diagnosis in patients who present with diarrhea during or after antibiotic treatment, as cases have been observed up to two months after discontinuation of the antibiotic.

Myasthenia

Exacerbations of myasthenia symptoms and new onsets of myasthenic syndrome have been reported in patients receiving azithromycin (see section 4.8).

Superinfection

As with all antibiotics, monitoring for signs of superinfection by non-susceptible organisms, including fungi, is recommended.

Derivatives of rye ergot

In cases of treatment with ergot derivatives, some concomitantly administered macrolide antibiotics have precipitated ergotism. There are no data regarding a possible interaction between ergot and azithromycin. However, given the theoretical risk of ergotism, ergot derivatives and azithromycin should not be administered concomitantly (see sections 4.3 and 4.5).

Hypertrophic pyloric stenosis in infants

Cases of hypertrophic pyloric stenosis in infants have been reported with the use of azithromycin in newborns (treatment up to 42 days of age). Parents and caregivers should be advised to contact a doctor if vomiting or food hyperresponsiveness occurs.

Related to excipients

This medicine contains lactose. Patients with galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption (rare hereditary disorders) should not take this medicine.

This medicine contains less than 1 mmol (23 mg) of sodium per tablet, that is to say it is essentially 'sodium free'.

isomaltase deficiency .

4.5 Interactions with other medications and other forms of interaction

Contraindicated combinations

Cisapride

Increased risk of ventricular rhythm disorders, including torsades de pointes (see section 4.3).

Cardiac events, including torsades de pointes, have been reported in patients receiving concomitant fluconazole and cisapride . A controlled study demonstrated that concomitant administration of fluconazole 200 mg once daily and cisapride 20 mg four times daily resulted in a significant increase in plasma cisapride levels and prolongation of the QTc interval . Concomitant administration of fluconazole and cisapride is contraindicated (see section 4.3).

Colchicine

Increased adverse effects of colchicine with potentially fatal consequences.

Dihydroergotamine (see section 4.4)

Ergotism with the possibility of necrosis of the extremities (inhibition of the hepatic elimination of ergot alkaloids).

Ergotamine (see section 4.4)

Ergotism with the possibility of necrosis of the extremities (decreased hepatic elimination of ergotamine alkaloids).

Terfenadine

QTc interval prolongation in patients treated with both azole antifungals and terfenadine , interaction studies were conducted.

One study showed that administration of 200 mg of fluconazole daily did not lead to QTc interval prolongation . Another study with 400 mg and 800 mg of fluconazole daily showed that a daily dose of 400 mg or more of fluconazole significantly increases the plasma concentration of terfenadine when the two drugs are taken concomitantly. The combination of terfenadine and fluconazole at doses of 400 mg or more is contraindicated (see section 4.3). For fluconazole doses below 400 mg daily, the patient should be closely monitored.

Astemizole

Concomitant administration of fluconazole and astemizole may decrease the clearance of astemizole . The resulting increase in plasma concentrations of astemizole may lead to QT prolongation and, in rare cases, torsades de pointes. Co -administration of fluconazole and astemizole is contraindicated (see section 4.3).

Pimozide :

Although not studied *in vitro* or *in vivo* , concomitant administration of fluconazole and pimozide may lead to inhibition of pimozide metabolism . Increased plasma concentrations of pimozide may result in QT prolongation and, in rare cases, torsades de pointes. Co -administration of fluconazole and pimozide is contraindicated (see section 4.3).

Quinidine

Although not studied *in vitro* or *in vivo* , concomitant administration of fluconazole and quinidine may lead to inhibition of quinidine metabolism. Quinidine use has been associated with QT prolongation and, in rare cases, with torsades de pointes. Co - administration of fluconazole and quinidine is contraindicated (see section 4.3).

Erythromycin

The concomitant use of fluconazole and erythromycin may potentially increase the risk of cardiotoxicity (QT interval prolongation, torsades de pointes) and, consequently, sudden cardiac death. Co -administration of fluconazole and erythromycin is contraindicated (see section 4.3).

Associations not recommended

Dopaminergic ergot alkaloids

(Bromocriptine, cabergoline , lisuride , pergolide)

Increased plasma concentrations of the dopaminergic agent with possible increase in its activity or appearance of signs of overdose.

Alcohol (beverage or excipient)

Antabuse-like reaction (flushing, redness, vomiting, tachycardia). Avoid consuming alcoholic beverages and medications containing alcohol. Ensure complete elimination of the medication by referring to its half-life before resuming consumption of alcoholic beverages or medications containing alcohol.

Halofantrine

Fluconazole may increase plasma concentrations of halofantrine due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine may potentially increase the risk of cardiotoxicity (QT interval prolongation, torsades de pointes) and, consequently, sudden cardiac death. This co -administration should be avoided (see section 4.4).

Associations requiring precautions for use

Atorvastatin

Increased risk of adverse effects (concentration-dependent) such as rhabdomyolysis, due to decreased hepatic metabolism of the cholesterol-lowering drug.

Use lower doses of cholesterol-lowering medication or another statin not affected by this type of interaction.

Cyclosporine

Risk of increased blood concentrations of cyclosporine and creatinine.

Monitoring of blood cyclosporine concentrations, renal function monitoring and dosage adjustment during combination therapy and after discontinuation of the macrolide.

Digoxin

digoxin levels due to increased digoxin absorption .

Clinical monitoring and possibly digoxin level monitoring during azithromycin treatment and after its discontinuation.

Ivabradine

Increased risk of ventricular rhythm disorders, particularly torsades de pointes.

Clinical and electrocardiographic monitoring during the combination.

Medications that may cause torsades de pointes

Particularly class IA antiarrhythmics (e.g., quinidine), class III antiarrhythmics (e.g., amiodarone, sotalol), antipsychotics (e.g., phenothiazines, pimozide), tricyclic antidepressants (e.g., citalopram), and certain fluoroquinolones (e.g., moxifloxacin , levofloxacin). Hypokalemia (hypokalemic drugs) is a predisposing factor, as is bradycardia (bradycardic drugs) or a pre-existing prolongation of the QT interval, whether congenital or acquired (see section 4.4).

Increased risk of ventricular rhythm disorders, particularly torsades de pointes.

Clinical and electrocardiographic monitoring during the combination.

Hydroxychloroquine

Azithromycin should be used with caution in patients receiving drugs known to prolong the QT interval and potentially induce cardiac arrhythmia (see section 4.4).

Simvastatin

Increased risk of adverse effects (concentration-dependent) such as rhabdomyolysis, due to decreased hepatic metabolism of the cholesterol-lowering drug.

Use lower doses of cholesterol-lowering medication or another statin not affected by this type of interaction.

Vitamin K antagonists

Increased effect of the vitamin K antagonist and increased risk of bleeding.

More frequent INR monitoring. Possible adjustment of the vitamin K antagonist dosage during macrolide treatment and after its discontinuation.

Amiodarone

Concomitant administration of fluconazole and amiodarone may lead to QT prolongation. Therefore, caution is advised if concomitant use of these two products is necessary, particularly with high doses of fluconazole (800 mg).

Associations requiring precautions for use and dose adjustment

Effect of other medications on fluconazole

Rifampicin : Concomitant administration of fluconazole and rifampicin results in a 25% decrease in AUC and a 20% reduction in the half-life of fluconazole. An increase in the fluconazole dosage should be considered when used concomitantly with rifampicin.

Interaction studies have shown that when fluconazole is administered orally with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant alteration in fluconazole absorption was observed.

Hydrochlorothiazide : In a pharmacokinetic interaction study, co-administration of repeated doses of hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentrations of fluconazole by 40%. An effect of this magnitude should not necessitate an adjustment of the fluconazole dosage in subjects receiving concomitant diuretics.

Effect of fluconazole on other medications

Fluconazole is a moderate inhibitor of CYP450 isoenzymes 2C9 and 3A4. Fluconazole is also a potent inhibitor of the CYP2C19 isoenzyme. In addition to the observed/documented interactions listed below, there is a risk of increased plasma concentrations of other drugs metabolized by CYP2C9, CYP2C19, and CYP3A4 when administered concomitantly with fluconazole. Therefore, these combinations should be administered with caution, and the patient should be closely monitored.

The inhibitory effect of fluconazole on enzymes may persist for 4 to 5 days after the end of treatment with fluconazole, due to the long half-life (t½) of fluconazole (see section 4.3).

Abrocitinib : Fluconazole (a CYP2C19, 2C9, 3A4 inhibitor) increased the exposure of the active fraction of abrocitinib by 155%. When administered concomitantly with fluconazole, adjust the abrocitinib dose as indicated in the abrocitinib prescribing information .

Alfentanil : During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers, the AUC10 of alfentanil was doubled, probably due to CYP3A4 inhibition. Alfentanil dosage adjustment may be necessary.

Amitriptyline , nortriptyline : Fluconazole potentiates the effect of amitriptyline and nortriptyline . 5-Nortriptyline and/or S- amitriptyline levels can be measured at the start of treatment and after one week of concomitant therapy. Dosage adjustment of amitriptyline / nortriptyline may be necessary .

Amphotericin B : Concomitant administration of fluconazole and amphotericin B in normal and immunocompromised infected mice showed the following results: a slight additive antifungal effect in systemic *C. albicans infections* , and no interaction in intracranial *Cryptococcus infections. neoformans and an antagonism of the two drugs in systemic Aspergillus fumigatus* infections . The clinical significance of the results obtained in these studies is unknown.

Anticoagulants : Since marketing, as with other azole antifungals, bleeding events (bruising, nosebleeds, gastrointestinal bleeding, hematuria, and melena) associated with decreased prothrombin levels have been reported in patients receiving concomitant fluconazole and warfarin. During concomitant treatment with fluconazole and warfarin, prothrombin levels were reduced up to 2-fold, likely due to inhibition of warfarin metabolism by CYP2C9. Prothrombin levels should be closely monitored in patients receiving coumarin or indanedione anticoagulants concomitantly with fluconazole. Anticoagulant dosage adjustment may be necessary.

Short-acting benzodiazepines, such as midazolam and triazolam : Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant oral administration of 200 mg fluconazole and 7.5 mg midazolam increased the AUC and half-life of midazolam by 3.7-fold and 2.2-fold, respectively. Concomitant oral administration of 200 mg fluconazole daily and 0.25 mg triazolam increased the AUC and half-life of triazolam by 4.4-fold and 2.3-fold, respectively. Enhanced and prolonged effects of triazolam were observed when combined with fluconazole. If concomitant treatment with a benzodiazepine is required in patients treated with fluconazole, a reduction in the benzodiazepine dose and close monitoring of the patient should be considered.

Carbamazepine : Fluconazole inhibits the metabolism of carbamazepine, and a 30% increase in serum carbamazepine has been observed. There is a risk of carbamazepine toxicity. Carbamazepine dosage adjustment may be necessary based on measurements of its concentration/effect.

Calcium channel blockers : Some calcium channel blockers (nifedipine, isradipine , amlodipine, verapamil, and felodipine) are metabolized by CYP3A4. Fluconazole may potentially increase systemic exposure to calcium channel blockers. Frequent monitoring for adverse events is recommended.

Celecoxib : When celecoxib was co-administered with fluconazole (200 mg daily) , the Cmax and AUC of celecoxib increased by 68% and 134%, respectively. A 50% dose reduction of celecoxib may be necessary in patients receiving concomitant fluconazole.

Cyclophosphamide : Treatment combining cyclophosphamide and fluconazole leads to an increase in serum bilirubin and creatinine levels. This combination can be used, taking into account the risk of increased bilirubin and creatinine levels.

Fentanyl : A fatal case of fentanyl poisoning due to a possible interaction between fentanyl and fluconazole has been reported. Furthermore, in healthy volunteers, fluconazole has been shown to significantly delay the elimination of fentanyl. Increased fentanyl concentrations may lead to respiratory depression. Patients should be closely monitored for the potential risk of respiratory depression. A fentanyl dosage adjustment may be necessary.

HMG-CoA reductase inhibitors : The risk of myopathy and rhabdomyolysis is increased (dose-dependent) when fluconazole is taken concomitantly with HMG-CoA reductase inhibitors metabolized by CYP3A4, such as atorvastatin and simvastatin, or by CYP2C9, such as fluvastatin (due to decreased hepatic metabolism of the statin). If concomitant treatment is necessary, symptoms of myopathy and rhabdomyolysis, as well as creatine kinase levels, should be monitored. Treatment with HMG-CoA reductase inhibitors should be discontinued if creatine kinase levels increase significantly or if myopathy/rhabdomyolysis is diagnosed or suspected. Lower doses of HMG-CoA reductase inhibitors may be required, as indicated in the statin prescribing information.

Ibrutinib : Moderate CYP3A4 inhibitors such as fluconazole increase ibrutinib plasma concentrations and may increase the risk of toxicity. If concomitant use cannot be avoided, reduce the ibrutinib dose to 280 mg once daily (two capsules) for the duration of inhibitor use and ensure close clinical monitoring.

Ivacaftor (alone or in combination with drugs of the same therapeutic class): Co -administration with ivacaftor , a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure 3-fold and hydroxymethyl-ivacaftor (M1) exposure 1.9-fold . A dose reduction of ivacaftor (alone or in combination) is necessary as indicated in the ivacaftor (alone or in combination) prescribing information .

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

Immunosuppressants (such as cyclosporine, everolimus , sirolimus and tacrolimus):

Cyclosporine : Fluconazole significantly increases the concentration and AUC of cyclosporine. Concomitant treatment with 200 mg daily of fluconazole and cyclosporine (2.7 mg/kg/day) results in a 1.8-fold increase in the AUC of cyclosporine. This combination can be used by reducing the cyclosporine dosage according to the cyclosporine concentration.

Everolimus : Although not studied *in vivo* or *in vitro* , fluconazole may increase serum concentrations of everolimus by inhibiting CYP3A4.

Sirolimus : Fluconazole increases plasma concentrations of sirolimus , presumably by inhibiting the metabolism of sirolimus by CYP3A4 and by inhibiting P-glycoprotein. This combination can be used with an adjustment of the sirolimus dosage according to its effect and concentration.

Tacrolimus : Fluconazole can increase serum concentrations of orally administered tacrolimus up to 5-fold by inhibiting tacrolimus metabolism by CYP3A4 in the intestines. No significant pharmacokinetic changes were observed when tacrolimus was administered intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. The dosage of orally administered tacrolimus should be reduced according to the tacrolimus concentration.

Losartan : Fluconazole inhibits the conversion of losartan to its active metabolite (E-3174), which is largely responsible for the angiotensin II receptor inhibition that occurs during losartan treatment. Continuous blood pressure monitoring is necessary in patients receiving this combination.

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

Methadone : Fluconazole may increase serum methadone concentrations. A methadone dosage adjustment may be necessary.

Non-steroidal anti-inflammatory drugs (NSAIDs): The Cmax and AUC of flurbiprofen increased by 23% and 81%, respectively, when co -administered with fluconazole versus flurbiprofen alone. Similarly, the Cmax and AUC of the pharmacologically active isomer [S-(+)- ibuprofen] increased by 15% and 82%, respectively, when co -administered with fluconazole and racemic ibuprofen (400 mg) versus racemic ibuprofen alone.

Although no specific studies have been conducted, fluconazole may potentially increase systemic exposure to other NSAIDs that are metabolized by CYP2C9 (e.g., naproxen, lornoxicam , meloxicam , diclofenac). Frequent monitoring for adverse events and NSAID-related toxicity is recommended. NSAID dosage adjustments may be necessary.

Phenytoin : Fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant and repeated intravenous administration of 200 mg of fluconazole and 250 mg of phenytoin resulted in a 75% increase in the AUC24 of phenytoin and a 128% increase in the Cmin .

In case of co -administration, serum phenytoin concentrations should be monitored to avoid phenytoin toxicity.

Prednisone : A liver transplant recipient receiving prednisone developed Addison's disease following discontinuation of a 3-month course of fluconazole. Discontinuation of fluconazole likely led to increased CYP3A4 activity, resulting in increased prednisone metabolism. Patients receiving prolonged treatment with fluconazole and prednisone should be closely monitored for signs of adrenal insufficiency upon fluconazole discontinuation.

Rifabutin : Fluconazole increases serum rifabutin concentrations, resulting in an increase in rifabutin AUC of up to 80%. Cases of uveitis have been observed in patients treated with this combination. In patients receiving concomitant fluconazole and rifabutin, symptoms of rifabutin toxicity should be monitored.

Saquinavir : Fluconazole increases the AUC and Cmax of saquinavir by approximately 50% and 55%, respectively, due to inhibition of hepatic saquinavir metabolism by CYP3A4 and P-glycoprotein inhibition. The interaction with saquinavir /ritonavir has not been studied and may be more pronounced. A dose adjustment of saquinavir may be necessary .

Sulfonylureas : Fluconazole prolongs the serum half-life of concomitantly administered oral sulfonylureas (e.g., chlorpropamide , glibenclamide, glipizide , tolbutamide) in healthy volunteers. Close monitoring of blood glucose and appropriate dose reduction of sulfonylureas are recommended in case of concomitant treatment.

Theophylline : In a placebo-controlled interaction study, administration of 200 mg of fluconazole for 14 days resulted in an 18% decrease in mean plasma theophylline clearance. Patients receiving high doses of theophylline, or otherwise at increased risk of theophylline toxicity, should be closely monitored for signs of theophylline toxicity during fluconazole treatment. Treatment should be modified if signs of toxicity occur.

Tofacitinib : Exposure to tofacitinib is increased when administered concomitantly with drugs that cause both moderate inhibition of CYP3A4 and strong inhibition of CYP2C19 (e.g., fluconazole). Therefore, it is recommended to reduce the tofacitinib dose to 5 mg once daily when used in combination with these drugs.

Tolvaptan : Tolvaptan exposure is significantly increased (200% for AUC; 80% for Cmax) when tolvaptan , a CYP3A4 substrate, is co-administered with fluconazole, a moderate CYP3A4 inhibitor, with a risk of significantly increased adverse effects, including diuresis, dehydration, and acute renal failure. When used concomitantly, the tolvaptan dose should be reduced according to the tolvaptan prescribing information , and the patient should be frequently monitored for tolvaptan -related adverse effects .

Vinca alkaloids : Although no studies have been conducted, fluconazole may increase plasma levels of vinca alkaloids (e.g., vincristine and vinblastine) and lead to neurotoxicity, which may be due to an inhibitory effect on CYP3A4.

Vitamin A : Based on an observation in a patient receiving concomitant all-trans retinoic acid (the acidic form of vitamin A) and fluconazole, neurological adverse effects appeared in the form of a cerebral pseudotumor, which resolved upon discontinuation of fluconazole treatment. This combination can be used, but the risk of neurological adverse effects must be considered.

Voriconazole (CYP2C9, CYP2C19, and CYP3A4 inhibitors): Concomitant administration of oral voriconazole (400 mg every 12 hours on day 1 , then 200 mg every 12 hours for 2.5 days) and oral fluconazole (400 mg on day 1 , then 200 mg every 24 hours for 4 days) to 8 healthy male subjects resulted in an increase in the mean Cmax and AUC_T of voriconazole of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively . A dose and/or frequency reduction of voriconazole and fluconazole that would eliminate this effect has not been established. Monitoring for adverse events associated with voriconazole is recommended if voriconazole is used sequentially after fluconazole.

Zidovudine : Fluconazole increases the Cmax and AUC of zidovudine by 84% and 74%, respectively, due to an approximately 45% decrease in the oral clearance of zidovudine. The half-life of zidovudine was also prolonged by approximately 128% following concomitant administration of fluconazole. Patients receiving this combination should be monitored for adverse reactions related to zidovudine. A dose reduction of zidovudine may be necessary.

Azithromycin : A randomized, open-label, three-phase crossover study conducted in 18 healthy subjects evaluated 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. No significant pharmacokinetic interactions were observed between fluconazole and azithromycin.

Oral contraceptives : Two pharmacokinetic studies were conducted with combined oral contraceptives and repeated doses of fluconazole. No particular effect on hormone levels was observed with the administration of 50 mg of fluconazole. However, daily administration of 200 mg of fluconazole resulted in an increase in the AUC of ethinylestradiol and levonorgestrel of 40% and 24%, respectively. Therefore, multiple doses of fluconazole at these dosages are unlikely to affect the efficacy of combined oral contraceptives.

Specific problems related to INR imbalance

Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotics. A significant infectious or inflammatory context, age, and the patient's general condition appear to be risk factors. In these circumstances, it is difficult to distinguish between the infectious disease and its treatment as the cause of the INR imbalance. However, certain classes of antibiotics are more frequently implicated: these include fluoroquinolones, macrolides, tetracyclines, cotrimoxazole, and some cephalosporins.

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing age

Before starting treatment, the patient must be informed of the potential risk to the fetus. After a single dose, a one-week washout period (corresponding to 5 to 6 half-lives) is recommended before attempting pregnancy (see section 5.2). For longer treatment cycles, contraception may be considered, if necessary, in women of childbearing potential throughout the treatment period and for one week after the last dose.

Pregnancy

AZITHROMYCIN

1st quarter :

As a precaution, it is best not to use azithromycin during the first trimester of pregnancy. Indeed, although animal data in rodents do not show any malformative effect, clinical data are insufficient.

From the second quarter onwards:

Due to the expected benefit, the use of azithromycin can be considered from the second trimester of pregnancy onwards, if needed. Indeed, although limited, clinical data are reassuring regarding its use beyond the first trimester.

SECNIDAZOLE

Animal studies have not shown any teratogenic effects.

Clinical data are limited during the first trimester of pregnancy. Consequently, as a precaution, it is best to avoid using secnidazole during the first trimester. After the first trimester, based on clinical experience, the use of secnidazole is a possibility.

FLUCONAZOLE

Observational studies suggest an increased risk of spontaneous abortion in women treated with fluconazole during the first and/or second trimester compared to women not treated with fluconazole or treated with topical azoles during the same period.

Data from several thousand pregnant women treated with a cumulative dose ≤ 150 mg of fluconazole, administered during the first trimester, showed no increase in the overall risk of fetal malformations. In a large observational cohort study, oral fluconazole exposure during the first trimester was associated with a slightly increased risk of musculoskeletal malformations , corresponding to approximately 1 additional case per 1,000 women treated with cumulative doses ≤ 450 mg compared to women treated with topical azoles, and approximately 4 additional cases per 1,000 women treated with cumulative doses greater than 450 mg. The adjusted relative risk was 1.29 (95% CI 1.05 to 1.58) for 150 mg of oral fluconazole and 1.98 (95% CI 1.23 to 3.17) for doses above 450 mg of fluconazole.

Available epidemiological studies on congenital heart defects associated with fluconazole use during pregnancy provide conflicting results. However, a meta-analysis of five observational studies involving several thousand pregnant women exposed to fluconazole during the first trimester demonstrates a 1.8- to 2-fold increased risk of congenital heart defects compared to the absence of fluconazole and/or topical azole use.

Case reports describe a pattern of congenital anomalies in infants whose mothers received high doses (400 to 800 mg/day) of fluconazole during pregnancy for 3 months or more, for the treatment of coccidioidomycosis . Congenital anomalies observed in these infants include brachycephaly, auricular dysplasia, giant anterior fontanelles, bowed femurs, and radiohumeral synostosis. A causal relationship between fluconazole use and these congenital anomalies is not certain.

Fluconazole administered at standard doses and short-term treatments should not be used during pregnancy unless absolutely necessary.

The administration of high doses of fluconazole and/or prolonged treatment during pregnancy should be reserved for cases that are potentially life-threatening.

Breastfeeding

AZITHROMYCIN

Azithromycin is excreted in breast milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue or abstain from therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

SECNIDAZOLE

There are no data regarding the passage of secnidazole into breast milk. However, passage into breast milk is documented with other imidazole derivatives, and cases of oro -anal candidiasis and diarrhea have been described in breastfed infants of mothers treated with these other imidazoles.

Therefore, it is best to avoid administering this medication while breastfeeding or to suspend breastfeeding for 24 hours in the case of a single dose.

FLUCONAZOLE

Fluconazole is excreted in breast milk at concentrations similar to those in plasma (see section 5.2). Breastfeeding can be continued after a single 150 mg dose of fluconazole. Breastfeeding is not recommended after repeated administration or high doses of fluconazole. The benefits of breastfeeding on development and health should be weighed against the clinical need for FEMYCOZ for the mother and the potential adverse effects on the breastfed infant, whether attributable to FEMYCOZ or to the mother's underlying condition.

Fertility

FLUCONAZOLE

Fluconazole does not affect fertility in male or female rats (see section 5.3).

4.7 Effects on the ability to drive vehicles and use machinery

There are no data suggesting that azithromycin affects patients' ability to drive or operate machinery. However, patients should be advised that they may experience side effects such as dizziness, drowsiness, or certain visual or auditory disturbances during treatment with azithromycin. Therefore, caution is advised when driving or operating machinery.

Patients should be warned of the potential risk of dizziness during treatment with secnidazole and advised not to drive vehicles or operate machinery if such symptoms occur.

The effects on the ability to drive and use machines have not been studied. Patients should be warned of the risk of seizures or dizziness (see section 4.8) during treatment with fluconazole and advised not to drive or operate machinery if these symptoms occur.

4.8 Undersirable effects

The table below presents the adverse reactions identified during clinical trials and post-marketing surveillance by system organ class and frequency. Frequency groups are defined according to the following convention: very common (≥ 1/10); 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); and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

	Very common (≥ 1/10)	**Frequent (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare (< 1/10,000)**	**Frequency not known**
Infections and infestations			Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory problems Rhinitis Oral candidiasis			Pseudomembranous colitis (see section 4.4)
Hematological and lymphatic system disorders			Leukopenia Neutropenia Eosinophilia Anemia	Agranulocytosis Thrombocytopenia		Hemolytic anemia
Immune system disorders			Angioedema Hypersensitivity	Immediate hypersensitivity reaction (fever, erythema, urticaria, angioedema)	Anaphylaxis	
Metabolism and nutrition disorders			Anorexia Decreased appetite.	Hypercholesterolemia Hypertriglyceridemia Hypokalemia		
Psychiatric disorders			Nervousness Insomnia Drowsiness	Hustle		Aggressiveness Anxiety Delirium Hallucination
Disorders of the nervous system		Headache	Dizziness Drowsiness Dysgeusia Paresthesia Epileptic seizures Dizziness Alteration of taste	Incoordination Ataxia Paresthesias Sensorimotor polyneuritis Tremors		Syncope, Convulsion Hypoaesthesia Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis (see section 4.4)

	Very common (≥ 1/10)	**Frequent (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare (< 1/10,000)**	**Frequency not known**
Eye conditions			Visual disturbances			
Ear and labyrinth disorders			Ear problems Dizziness			Hearing problems including deafness and/or tinnitus
Heart conditions			Palpitations	Pointe twists QT interval prolongation		Arrhythmia including ventricular tachycardia
Vascular disorders			Hot flash			Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnea Epistaxis			
Gastrointestinal disorders	Diarrhea	Vomiting Abdominal pain Nausea Epigastric pain Dysgeusia Glossites Stomatitis	Constipation Flatulence Dyspepsia Gastritis Dysphagia Abdominal distension Dry mouth Eructation Oral ulceration Ptyalism			Pancreatitis Tongue discoloration
Hepatobiliary disorders		Increased alanine aminotransferase (see section 4.4) Increased aspartate aminotransferase (see section 4.4) Increased blood alkaline phosphatase (see section 4.4)	Cholestasis (see section 4.4) Jaundice (see section 4.4) Increased bilirubin (see section 4.4)	Abnormal liver function Hepatic insufficiency (see section 4.4) Hepatocellular necrosis (see section 4.4) Hepatitis (see section 4.4) Hepatocellular injury (see section 4.4)		Liver failure (which has rarely led to death) Fulminant hepatitis Liver necrosis (see section 4.4)
Skin and subcutaneous tissue disorders		Rash (see section 4.4)	Drug reaction* (see section 4.4) Rash Itching Urticaria Dermatitis Dry skin Hyperhidrosis	Photosensitivity reaction Acute generalized exanthematous pustulosis * DRESS syndrome* (drug reaction with eosinophilia and systemic symptoms) Lyell's syndrome (toxic epidermal necrolysis) (see section 4.4) Stevens-Johnson syndrome (see section 4.4) Acute generalized exanthematous pustulosis (see section 4.4) Exfoliative dermatitis		Toxic epidermal necrolysis Erythema multiforme

	Very common (≥ 1/10)	**Frequent (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare (< 1/10,000)**	**Frequency not known**
				Angioedema Facial edema Alopecia		
Musculoskeletal and systemic disorders			Osteoarthritis Myalgia Back pain Neck pain			Arthralgia
Kidney and urinary tract disorders			Dysuria Kidney pain			Acute renal failure Interstitial nephritis
Diseases of the reproductive organs and breast			Metrorrhagia Testicular disorder			
General disorders and administration site abnormalities			Edema Asthenia Faintness Fatigue Facial edema Chest pain Fever Pain Peripheral edema			
Investigations		Decreased lymphocyte count Increase in eosinophil count Decrease in blood bicarbonate concentration Increased basophils Increased monocytes Increased neutrophils	Increased aspartate aminotransferase Increased alanine aminotransferase Increased bilirubin levels Increased blood uremia Increase in blood creatinine Abnormal potassium concentration in the blood Increased alkaline phosphatase in the blood Increase in chlorides Increase in glucose Increase in platelets Decrease in hematocrit Increase in bicarbonates			

	Very common (≥ 1/10)	Frequent (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (< 1/10,000)	Frequency not known
			Abnormal sodium levels			
Injuries and poisonings			Post-procedure complication			

* including fixed drug-induced rash

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals should report any suspected adverse reactions using the FRILAB reporting form available under the pharmacovigilance tab of the website: www.frilab.ch

4.9 Overdose

The adverse effects observed with doses higher than the recommended doses were similar to those observed at the recommended doses for azithromycin.

Action to take in case of overdose: gastric lavage and symptomatic treatment.

In case of overdose, an increase in adverse effects related to the administration of secnidazole is to be expected, in particular neurological disorders as reported for other imidazoles.

Treatment is symptomatic.

Cases of fluconazole overdose have been reported. Cases of hallucinations and paranoid behavior have also been reported. In case of overdose, appropriate management (including symptomatic treatment and gastric lavage if necessary) may be required.

Fluconazole is largely eliminated in the urine; forced diuresis would likely increase the elimination rate. A three-hour hemodialysis session reduces plasma levels by approximately 50%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic class : ANTIBACTERIALS FOR SYSTEMIC USE, ANTIFUNGALS AND ANTIPROTOZOALS, ATC code: J01RA02

AZITHROMYCIN

Antibiotic of the macrolide family.

Azithromycin is the first molecule in the class of antibiotics called azalides (macrolide family).

Azithromycin works by inhibiting bacterial protein synthesis by binding to the 50S portion of the ribosome and preventing peptide translocation.

Spectrum of antibacterial activity

The critical concentrations separate susceptible strains from strains with intermediate susceptibility, and the latter from resistant strains:

S ≤ 0.5 mg/L and R > 4 mg/L

The prevalence of acquired resistance can vary geographically and over time for certain species. Therefore, information on local resistance prevalence is useful, especially for treating severe infections. This data can only provide guidance on the likelihood of a bacterial strain's susceptibility to that antibiotic.

When the variability in resistance prevalence in France is known for a bacterial species, it is indicated in the table below:

Categories	Acquired resistance frequency in France (> 10%) (extreme values)
SENSITIVE SPECIES	
Gram- positive aerobes	
Bacillus cereus	
Corynebacterium diphtheriae	
Enterococci	50–70%
Rhodococcus horse	
Methicillin -susceptible Staphylococcus aureus (MSSA)	
Methicillin -resistant Staphylococcus aureus (MRSA)*	70-80%
Streptococcus B	
Non-groupable Streptococcus	30–40%
Streptococcus pneumoniae	35–70%
Streptococcus pyogenes	16–31%
Gram-negative aerobes	
Bordetella pertussis	
Branhamella catarrhalis	
Campylobacter	
Legionella	
Moraxella	
Anaerobes	
Actinomyces	
Bacteroides	30–60%
Eubacterium	
Mobiluncus	
Peptostreptococcus	30–40%
Porphyromonas	
Prevotella	
Propionibacterium acnes	
Others	
Borrelia burgdorferi	
Chlamydia	
Coxiella	
Leptospires	
Mycoplasma pneumoniae	
Treponema pallidum	
MODERATELY SENSITIVE SPECIES	
(intermediate sensitivity *in vitro*)	
Gram- negative aerobes	
Haemophilus	
Neisseria gonorrhoeae	
Anaerobes	
Clostridium perfringens	
Others	
Ureaplasma urealyticum	
RESISTANT SPECIES	
Gram-positive aerobes	
Corynebacterium jeikeium	
Nocardia asteroides	
Gram-negative aerobes	
Acinetobacter	
Enterobacteriaceae	
Pseudomonas	
Anaerobes	
Fusobacterium	
Others	
Mycoplasma hominis	

*Methicillin resistance occurs in approximately 30 to 50% of all staphylococci and is mainly found in hospital settings.

Cardiac electrophysiology:

QTc interval prolongation was studied in a randomized, placebo-controlled, parallel-group trial involving 116 healthy volunteers receiving chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Concomitant administration of azithromycin resulted in dose- and concentration-dependent QTc interval prolongation. When comparing the results observed between healthy volunteers receiving chloroquine combined with azithromycin and those receiving chloroquine alone, it was observed that the maximum means (upper limit of the 95% confidence interval) of the QTcF interval were increased by 5 (10) ms, 7 (12) ms and 9 (14) ms respectively with azithromycin doses of 500 mg, 1000 mg and 1500 mg.

Pediatric population

Following the evaluation of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, either as monotherapy or in combination with drugs based on chloroquine or artemisinin, because non-inferiority to antimalarial drugs recommended in the treatment of uncomplicated malaria has not been established.

SECNIDAZOLE

Secnidazole is a synthetic derivative of the 5 - nitroimidazole family.

Mechanism of action

Secnidazole has amoebicidal and antiprotozoal properties.

From a bacteriological point of view, although the species usually implicated in the occurrence of vaginosis are resistant to 5-nitroimidazoles, including secnidazole, the available data have shown activity of secnidazole in this condition without the mechanism being elucidated.

Critical concentrations

The critical concentrations separate susceptible strains from strains of intermediate susceptibility, and the latter from resistant strains.

Recommendations of the Antibiogram Committee of the French Society for Microbiology (CA-SFM) (based on the recommendations established by the CA-SFM for metronidazole):

S ≤4 mg/l and R > 4 mg/l

Spectrum of antimicrobial activity

The prevalence of acquired resistance can vary geographically and over time for certain species. Therefore, it is useful to have information on local resistance prevalence, especially for the treatment of severe infections. If necessary, expert advice should be sought, particularly when the drug's effectiveness in certain infections may be compromised by the level of local resistance.

Classification of species according to their sensitivity to anti-infectives:

Classes
SPECIES THAT ARE USUALLY SENSITIVE **Anaerobes** **Bacteroides fragile** **Bilophila wadsworthia** **Clostridium spp . including Clostridium difficile and Clostridium perfringens** **Fusobacterium** **Peptostreptococcus** **Porphyromonas** **Prevotella** **Veillonella**
SPECIES WITH VARIABLE SENSITIVITY **(ACQUIRED RESISTANCE ≥ 10%)** **Anaerobes** **Bifidobacterium (+)** **Eubacterium**
NATURALLY RESISTANT SPECIES **Aerobics** **Gardnerella vaginalis** **Anaerobes** **Atopobium** **Actinomyces** **Lactobacillus spp.** **Mobiluncus** **Propionibacterium acnes**

(+) The prevalence of bacterial resistance is > 50% in France.

Antiparasitic activity

Sensitive species

Entamoeba histolytica
Giardia intestinalis
Trichomonas vaginalis

FLUCONAZOLE

Mechanism of action

Fluconazole is a triazole antifungal agent . Its primary mechanism of action is the inhibition of cytochrome P450-mediated 14- alpha demethylation of lanosterol , a crucial step in fungal ergosterol biosynthesis. The accumulation of 14-alpha methylated sterols is correlated with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole. Fluconazole has been shown to be more selective for fungal cytochrome P450 enzymes than for various mammalian cytochrome P450 enzyme systems.

Fluconazole, administered at a dose of 50 mg daily for 28 days, showed no effect on plasma testosterone concentrations in men or steroid concentrations in women of childbearing age. Fluconazole at doses of 200 mg to 400 mg daily had no clinically significant effect on endogenous steroid levels or the ACTH-induced response in healthy male volunteers.

Interaction studies with antipyrine show that single or repeated doses of fluconazole 50 mg do not influence the metabolism of antipyrine.

in vitro sensitivity

In vitro , fluconazole demonstrates antifungal activity against the most common *Candida species* (including *C. albicans , C. parapsilosis , and C. tropicalis*). *C. glabrata* exhibits reduced susceptibility to fluconazole, while *C. krusei* and *C. auris* are resistant. The MICs and epidemiological critical concentration (ECOF) of fluconazole for *C. guilliermondii* are higher than for *C. albicans* .

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

Pharmacokinetic/Pharmacodynamic Relationship

In animal studies, a correlation was observed between minimum inhibitory concentration (MIC) values and efficacy against experimental mycoses due to *Candida spp* . In human studies, a near-linear 1:1 relationship was observed between AUC and fluconazole dose. There is also a direct, though imperfect, relationship between AUC or dose and a favorable clinical response in oral candidiasis and, to a lesser extent, in candidemia . This type of clinical success is less likely for infections due to strains with a higher MIC to fluconazole.

Resistance mechanisms

Candida species have developed several resistance mechanisms to azole antifungals. Strains that have developed one or more of these resistance mechanisms exhibit high MICs to fluconazole, which negatively impacts efficacy *in vivo* and in humans.

Candida species , the most common resistance mechanism involves the target enzymes of azole derivatives, which are responsible for ergosterol biosynthesis. Resistance can be caused by mutation, increased enzyme production, drug efflux mechanisms, or the development of compensatory pathways.

Cases of superinfection with *Candida species* other than *C. albicans* , often exhibiting intrinsically reduced susceptibility (*C. glabrata*) or resistance to fluconazole (e.g., *C. krusei* , *C. auris*), have been reported. These infections may require alternative antifungal treatment. The mechanisms of resistance have not been fully elucidated in some intrinsically resistant (*C. krusei*) or emerging (*C. auris) Candida species* .

Critical concentrations (according to EUCAST)

in vitro sensitivity and clinical response, EUCAST-AFST (European Committee on Antimicrobial Susceptibility Testing-Subcommittee on Antifungal Susceptibility Testing) has established critical concentrations of fluconazole for *Candida species* (EUCAST Fluconazole rationale document (2020-version 3); European Committee on Antimicrobial Susceptibility Testing , Antifungal Agents, Tables of Critical Concentrations for Interpreting MICs, version 10.0, valid from 04/02/2020). These critical concentrations have been divided into species-independent critical concentrations, which were determined primarily based on PK/PD data and are independent of MIC distributions for specific species, and species-independent critical concentrations for the species most frequently associated with human infections. These critical concentrations are presented in the table below:

Antifungal	Species-related critical concentrations (S) in mg/l						Critical concentrations not related to a species A S 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 = sensitive, R = resistant

A. = Species-nonspecific critical concentrations were primarily determined based on PK/PD data and are independent of MIC distributions for specific species. They are intended for use only for organisms that do not have a species-specific critical concentration.

-- = Sensitivity tests not recommended as the species is not a good target for treatment with this drug.

C. glabrata strains are classified as Category I. MICs against *C. glabrata* should be interpreted as resistant when they are greater than 16 mg/L. The Susceptible category (≤ 0.001 mg/L) simply prevents misclassification of "I" strains as "S" strains. I – Susceptible with high exposure: a microorganism is classified as Susceptible with high exposure if there is a high probability of therapeutic success due to increased exposure to the agent through dose adjustment or concentration at the site of infection.

5.2 PHARMACOKINETIC PROPERTIES

AZITHROMYCIN

Absorption – distribution

Azithromycin is rapidly absorbed after oral administration.

The absorption of the tablet is not affected by food intake.

The peak plasma concentration is reached in 2 to 3 hours.

Kinetic studies have shown tissue concentrations of azithromycin to be much higher than plasma concentrations (up to 50 times the maximum plasma concentration), reflecting the molecule's strong tissue affinity. These studies also indicate that the overall exposure to 1.5 g of azithromycin administered over 3 days or 5 days is similar.

The terminal plasma elimination half-life, a faithful reflection of the tissue depletion half-life, is 2 to 4 days.

Azithromycin is widely distributed throughout the body: after a single 500 mg dose, the concentrations observed in target tissues exceed the $_{MIC90}$ levels of the most common pathogens responsible for pulmonary, tonsillar, or prostatic infections. Macrolides penetrate and accumulate in phagocytes (neutrophils, monocytes, peritoneal and alveolar macrophages).

Intraphagocytic concentrations are high in humans. These properties explain the activity of azithromycin against intracellular bacteria.

In experimental infections, during the active phase of phagocytosis, the amounts of azithromycin released are greater than during the quiescent phase. In animals, this leads to the presence of high concentrations of azithromycin at the site of infection.

Plasma protein binding is around 20%.

Elimination

Azithromycin is found primarily in unchanged form in bile and urine.

The liver is the main site of biotransformation of azithromycin, via N-demethylation. The main route of elimination is biliary.

There is also minor urinary excretion of the product. During a 5-day treatment, the product could be detected in the urine from 24 hours up to 3 weeks after administration.

SECNIDAZOLE

Following oral administration of a single 2 g dose of secnidazole, the maximum serum concentration is reached at 5.3 ± 1.3 hours. The mean plasma half-life is 17.5 ± 4.3 hours. Elimination, primarily urinary, is slow; approximately 15% of the administered dose is recovered in urine collected up to 168 ^{hours} after administration.

In a Phase I study (IPR_CONCVAG_10 study) conducted in women (n=14 evaluable) with bacterial vaginosis , significant variability was observed, with, in some cases, a significant drop in pharmacokinetic parameters between the

48th and 72nd hours, and vaginal concentrations of secnidazole were 3.6 ± 2.8 mg/L and 1.74 ± 1.4 mg/L, respectively 48 hours and 72 hours after oral administration of a single 2 g dose of secnidazole.

As with other imidazole derivatives, secnidazole can cross the placenta and pass into breast milk.

FLUCONAZOLE

Oral and intravenous forms of fluconazole are equivalent from a pharmacokinetic point of view.

Absorption

Following oral administration, fluconazole is well absorbed, and plasma levels (and systemic bioavailability) are more than 90% of those achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak fasting plasma concentrations are reached 30 minutes to 1.5 hours after administration. Plasma concentrations are dose-proportional. Ninety percent of steady-state levels are reached 4 -to 5 days after repeated once-daily dosing. Administration of a loading dose (on day 1) equal to twice the usual dose allows plasma levels to approach 90% of steady-state levels by day 2.

Distribution

The apparent volume of distribution is close to the total body water volume. Plasma protein binding is low (11-12 -%).

Fluconazole penetrates well into all body fluids studied. Fluconazole levels in saliva and sputum are comparable to plasma levels. In patients with fungal meningitis, fluconazole levels in the cerebrospinal fluid (CSF) are approximately 80% of the corresponding plasma levels.

High concentrations of fluconazole, exceeding serum concentrations, are achieved in the stratum corneum, epidermis, dermis, and eccrine sweat glands. Fluconazole accumulates in the stratum corneum. At a dose of 50 mg once daily, the fluconazole concentration after 12 days was 73 µg/g, and 7 days after stopping treatment, the concentration was still 5.8 µg/g. At a dose of 150 mg once weekly, the fluconazole concentration in the stratum corneum on day 7 was 23.4 µg/g, and 7 days after the second dose, it was still 7.1 µg/g.

The concentration of fluconazole in the nails after 4 months of treatment with 150 mg once weekly was 4.05 µg/g in healthy nails and 1.8 µg/g in diseased nails; and fluconazole was still measurable in the nails 6 months after the end of treatment.

Biotransformation

Fluconazole is only slightly metabolized. Only 11% of a radioactive dose is eliminated in the urine as metabolites. Fluconazole is a moderate inhibitor of the CYP2C9 and CYP3A4 isoenzymes (see section 4.5). Fluconazole is also a potent inhibitor of the CYP2C19 isoenzyme.

Elimination

The plasma elimination half-life of fluconazole is approximately 30 hours. The primary route of elimination is renal, with approximately 80% of the administered dose excreted unchanged in the urine. Fluconazole clearance is proportional to creatinine clearance. No circulating metabolites have been identified.

The long plasma elimination half-life allows for single doses for the treatment of vaginal candidiasis, single daily doses and single weekly doses in other indications.

Pharmacokinetics in patients with renal insufficiency

In patients with severe renal impairment (with a glomerular filtration rate [GFR] < 20 mL/min), the half-life increased from 30 to 98 hours. Therefore, a dose reduction is necessary. Fluconazole is removed by hemodialysis and, to a lesser extent, by peritoneal dialysis. After a 3-hour hemodialysis session, approximately 50% of fluconazole is removed from the blood.

Pharmacokinetics during breastfeeding

A pharmacokinetic study in ten breastfeeding women who had partially or completely stopped breastfeeding evaluated fluconazole concentrations in plasma and breast milk for 48 hours after administration of a single 150 mg dose of fluconazole. Fluconazole was detected in breast milk at a mean concentration of approximately 98% of that in the mother's plasma.

The mean maximum concentration in milk was 2.61 mg/L, 5.2 hours after administration. The estimated mean daily intake of fluconazole by the breastfed infant (assumed mean milk consumption of 150 ml/kg/day), based on the mean maximum concentration in milk, is 0.39 mg/kg/day, which is approximately 40% of the recommended neonatal dose (infant < 2 weeks) or 13% of the recommended infant dose for mucosal candidiasis.

Pharmacokinetics in children

Pharmacokinetic data were evaluated in 113 children participating in 5 studies: 2 single-dose studies, 2 repeat-dose studies, and 1 study in preterm infants. Data from one study were uninterpretable due to formulation changes during the study. Additional data were available from a compassionate use study.

Following administration of 28 -mg/kg of fluconazole to children aged 9 months to 15 years, an AUC of approximately 38 µgh / ml was found per 1 mg/kg dose unit. The mean plasma elimination half-life of fluconazole was between 15 and 18 hours, and the volume of distribution was approximately 880 ml/kg after repeated dosing. A longer plasma elimination half-life of fluconazole, approximately 24 hours, was found after administration of a single dose. This is comparable to the plasma elimination half-life of fluconazole after administration of a single 3 mg/kg IV dose to children aged 11 days to 11 months. The volume of distribution in this age group was approximately 950 ml/kg.

Experience with fluconazole in newborns is limited to pharmacokinetic studies in preterm infants. The mean age at the time of the first dose was 24 hours (range 9–36 -hours) and the mean birth weight was 0.9 kg (range 0.75–1.10 -kg) for 12 preterm infants with a mean gestational age of approximately 28 weeks. Seven patients completed the study; a maximum of 5 intravenous infusions of 6 mg/kg of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44–185) on day 1 and decreased over time to 53 (range 30–131 -) on day 7 and to 47 (range -27–68) on day 13. The area under the curve (µg / ml) was 271 (range 173–385 -) on day 1 and increased to 490 (range 292–734 -) on day 7 and decreased to 360 (range 167–566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070–1470 -) on day 1 and increased over time to 1184 (range 510–2130 -) on day 7 and to 1328 (extreme values 1040-1680 -) on day 13.

Pharmacokinetics in the elderly

A pharmacokinetic study was conducted in 22 subjects, aged 65 years and older, treated with a single 50 mg oral dose of fluconazole. Ten of these patients were also receiving diuretics. The Cmax was 1.54 µg/ml and was reached 1.3 hours after administration. The mean AUC was 76.4 ± 20.3 µg / ml and the mean terminal elimination half-life was 46.2 hours.

These pharmacokinetic parameter values are higher than the corresponding values reported in healthy young male volunteers. Co -administration of diuretics did not significantly alter either the AUC or Cmax. Furthermore, creatinine clearance (74 mL/min), the percentage of drug recovered unchanged in the urine (0.24 -h, 22%), and renal clearance of fluconazole (0.124 mL/min/kg) were generally lower in elderly subjects than in younger volunteers. The impaired elimination of fluconazole in elderly subjects therefore appears to be related to the reduced renal function characteristic of this group.

5.3 PRECLINICAL SAFETY DATA

AZITHROMYCIN

In repeated-dose toxicity studies in rats and dogs, phospholipidosis (accumulation of intracellular phospholipids) was observed in several tissues (retina, liver, dorsal root ganglion, gallbladder, kidneys, choroid plexus, spleen, pancreas). Phospholipidosis was observed to a similar degree in the tissues of newborn rats and dogs. This effect was reversible after discontinuation of treatment. The significance of these findings in animals and humans is unknown.
Azithromycin has not been shown to be genotoxic in a battery of appropriate studies. Reproductive toxicity studies have not revealed any adverse effects on embryo -fetal development in mice and rats, nor on postnatal development in rats.

SECNIDAZOLE

Non-clinical data from conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental function revealed no special hazard for humans.

FLUCONAZOLE

Effects were observed in non-clinical studies only at exposures considered sufficiently higher than the exposure observed in humans, and are of little clinical significance.

Carcinogenesis

Fluconazole showed no 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 showed an increased incidence of hepatocellular adenomas.

Mutagenesis

Fluconazole, with or without metabolic activation, was negative in mutagenicity tests performed on four strains of *Salmonella typhimurium* and on the L5178Y mouse lymphatic system. *In vivo cytogenetic studies* (mouse bone marrow cells after oral administration of fluconazole) and *in vitro* cytogenetic studies (human lymphocytes exposed to 1000 µg/ml fluconazole) showed no evidence of chromosomal mutation.

Reproductive toxicity

Fluconazole did not affect the fertility of male or female rats treated orally at daily doses of 5, 10 or 20 mg/kg or at parenteral doses of 5, 25 or 75 mg/kg.

No effects on the fetus were observed at 5 or 10 mg/kg; increases in fetal anatomical abnormalities (supernumerary ribs, renal pelvis dilation) and delayed ossification were observed at doses of 25 and 50 mg/kg and above. At doses between 80 mg/kg and 320 mg/kg, there was an increase in embryonic mortality in rats and fetal abnormalities such as deformed ribs, cleft palate, and abnormal craniofacial ossification.

The onset of parturition was slightly delayed at 20 mg/kg orally, and dystocia and prolonged parturition were observed in some mothers at 20 mg/kg and 40 mg/kg intravenously. Parturition disorders resulted in a slight increase in the number of stillborn infants and a decrease in newborn survival at these doses. These effects on parturition are consistent with the species-specific property of decreasing estrogen levels at high doses of fluconazole. These hormonal effects were not observed in women treated with fluconazole (see section 5.1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Azithromycin

Dichloromethane , isopropyl alcohol, microcrystalline cellulose, pregelatinized starch, croscaramellose sodium, sodium lauryl sulfate, colloidal silicon dioxide , magnesium stearate , hypromellose , talc, titanium dioxide , tartrazine lake

Secnidazole

Methylene chloride, lactose monohydrate, isopropyl alcohol, sodium starch glycolate , corn starch, croscaramellose sodium, HPMCE 5, magnesium stearate, purified talc, povidone, titanium dioxide , Ponceau 4R lacquer, PEG 6000

Fluconazole

Lactose monohydrate, microcrystalline cellulose, croscaramelose sodium, povidone, lauryl sodium sulfate , magnesium stearate, anhydrous colloidal silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C and away from light.

6.5 Nature and contents of container

Box containing 2 Secnidazole tablets, 1 Fluconazole tablet and 1 Azithromycin tablet for a single dose (4 tablets in total).

6.6 Special precautions for disposal and handling

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

7 MARKETING AUTHORISATION HOLDER AND OPERATOR

FRILAB SA
17 RUE DES PIERRES DU NITON
1207 GENEVA - SWITZERLAND

8 MANUFACTURER

GLOBELA PHARMA PVT. LTD.
357-358, GIDC,
SACHIN, SURAT – 394 230,
GUJARAT, INDIA

9 DATE OF REVISION OF THE TEXT

June 2025

10 DOSIMETRY

Not applicable.

11 INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

CONDITIONS FOR PRESCRIPTION AND DISPENSING

List I.