Diflucan 150 mg, capsules
Box of 4
Fluconazole

Date: May 2021, Version no. 8

Reference market: Morocco

West Africa

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diflucan 150 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 150 mg gel capsule contains:
Fluconazole……150.00 mg

Excipient with known effect: each capsule also contains 149.12 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

The 150 mg gel capsules have a turquoise blue body and a turquoise blue cap printed with "Pfizer" and "FLU-150" in black ink. The capsule size is no.1 and is made available in boxes of 1 and 4 capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diflucan is indicated in the following fungal infections (see section 5.1).

Diflucan is indicated in adults for the treatment of:

- Cryptococcal meningitis (see section 4.4).
- Coccidioidomycosis (see section 4.4).
- Invasive candidiasis.
- Mucosal candidiasis including oropharyngeal candidiasis, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis.
- Chronic oral atrophic candidiasis (pain resulting from wearing dentures) if dental hygiene or local treatment are insufficient.
- Vaginal candidiasis, acute or recurrent; when local treatment is not appropriate.
- Candidal balanitis when local treatment is not appropriate.
- Dermatomycosis, including *tinea pedis, tinea corporis, tinea cruris, tinea versicolor* and dermal Candida infections when systemic therapy is indicated.
- *Tinea unguium* (onychomycosis) when other agents are not appropriate.

Diflucan is indicated in adults for the prophylaxis of:

- Relapse of cryptococcal meningitis in patients with a high risk of recurrence.
- Relapse of oropharyngeal or oesophageal candidiasis in patients infected with HIV who have a high risk of recurrence.
- To reduce the incidence of recurrence of vaginal candidiasis (4 or more episodes per year).
- Prevention of *Candida* infections in patients with prolonged neutropoenia (such as patients with haematological malignancies receiving chemotherapy or patients receiving a haematopoietic stem cell transplantation (see section 5.1)).

Diflucan is indicated in term newborns, infants, toddlers, children, and adolescents aged from 0 to 17 years

Diflucan is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prevention of *Candida* infections in

immunosuppressed patients. Diflucan can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence (see section 4.4).

Treatment may be instituted before the results of cultures and other laboratory tests are known; however, once these results are available, the anti-infectious treatment should be adjusted accordingly.

Official recommendations for appropriate use of antifungal agents should be taken into account.

4.2 Posology and method of administration

Posology

The dose should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple dosing should be continued until clinical parameters or laboratory tests indicate that the active fungal infection has subsided. An inadequate treatment period may lead to recurrence of active infection.

Adults

Indications		**Posology**	**Duration of treatment**
Cryptococcosis	- Treatment for cryptococcal meningitis.	Loading dose: 400 mg the first day Subsequent dose: 200 mg to 400 mg once per day	Usually at least 6 to 8 weeks. In life-threatening infections, the daily dose can be increased to 800 mg.
	- Maintenance therapy to prevent recurrence of cryptococcal meningitis in patients with a high risk of recurrence.	200 mg once per day	Indefinitely at a daily dose of 200 mg.
Coccidioidomycosis		200 mg to 400 mg once per day	11 months up to 24 months or longer, depending on the patient. A dose of 800 mg daily may be considered for certain infections and in particular for meningeal disease.
Invasive candidiasis		Loading dose: 800 mg the first day Subsequent dose: 400 mg once per day	In general, the recommended duration of treatment for candidaemia is 2 weeks after the first negative blood culture result and after the resolution of signs and symptoms attributable to candidaemia.
Treatment of mucosal candidiasis	- Oropharyngeal candidiasis	Loading dose: 200 mg to 400 mg the first day Subsequent dose: 100 mg to 200 mg once per day	7 to 21 days (until remission of oropharyngeal candidiasis). Longer periods may be used in severely immunosuppressed patients.
	- Oesophageal candidiasis	Loading dose: 200 mg to 400 mg the first day Subsequent dose: 100 mg to 200 mg once per day	14 to 30 days (until remission of oesophageal candidiasis). Longer periods may be used in severely immunosuppressed patients.

	- Candiduria	200 mg to 400 mg once per day	7 to 21 days. Longer periods may be used in severely immunosuppressed patients.
	- Chronic atrophic candidiasis	50 mg once per day	14 days
	- Chronic mucocutaneous candidiasis	50 mg to 100 mg once per day	Up to 28 days. Longer periods depending on both the severity of infection or underlying immunosuppression and infection.
Prevention of relapse of mucosal candidiasis in patients infected with HIV who have a high risk of relapse	- Oropharyngeal candidiasis	100 mg to 200 mg once per day or 200 mg 3 times per week.	Indefinite period in patients with chronic immunosuppression.
	- Oesophageal candidiasis	100 mg to 200 mg per day or 200 mg 3 times per week.	Indefinite period in patients with chronic immunosuppression.
Genital candidiasis	- Acute vaginal candidiasis - Candidal balanitis	150 mg	Single dose.
	- Treatment and prophylaxis of recurrent vaginal candidiasis (4 episodes per year or more).	150 mg every 3 days for a total of 3 doses (D1, D4 and D7) followed by a maintenance dose of 150 mg once weekly	Maintenance dose : 6 months.
Dermatomycosis	- *tinea pedis,* - *tinea corporis,* - *tinea cruris,* - *Candida* infections	150 mg once weekly or 50 mg once daily	2 to 4 weeks, *tinea pedis* may require treatment for up to 6 weeks.
	- *tinea versicolor*	300 mg to 400 mg once weekly	1 to 3 weeks.
		50 mg once daily	2 to 4 weeks.

	- *tinea unguium* (onychomycosis)	150 mg once weekly	Treatment should be continued until replacement of the infected nail (replaced by an uninfected nail). Regrowth of fingernails and toenails normally requires 3 to 6 months and 6 to 12 months respectively. However, growth rates may vary significantly between individuals and by age. After successful treatment of long-term chronic infections, nails can occasionally remain disfigured.
Prophylaxis of *Candida* infections in patients with prolonged neutropoenia		200 mg to 400 mg once per day	Treatment should start several days before the anticipated onset of neutropoenia and continue for 7 days after resolution of the neutropoenia (neutrophil count greater than 1000 cells per mm^3).

Specific populations

Elderly patients
Dosage should be adjusted based on renal function (see "*Renal impairment"*).

Renal impairment
Diflucan is mainly excreted in urine as an unchanged active substance. In single-dose therapy, no dosage adjustment is necessary. In patients (including children) with impaired renal function who will receive repeated doses of fluconazole, an initial dose of 50 mg to 400 mg should be administered, based on the normal dosage recommended for the indication concerned. After this initial loading dose, the daily dose (according to the indication) should be based on the following table:

Creatinine clearance (ml/min)	**Percent of recommended dose**
> 50	100 %
≤50 (no dialysis)	50 %
Regular dialysis	100% after each dialysis session

Patients on regular dialysis should receive 100% of the recommended dose after each dialysis; on non-dialysis days, patients should receive a reduced dose according to their creatinine clearance.

Liver failure

Limited data are available in patients with hepatic failure; therefore, fluconazole should be administered with caution in patients with impaired liver function (see sections 4.4 and 4.8).

Paediatric population

A maximum dose of 400 mg daily should not be exceeded in the paediatric population.

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Diflucan is administered as a single daily dose.

In paediatric patients with impaired renal function, see the dosage in the section on "*Renal impairment.*" The pharmacokinetics of fluconazole have not been studied in the paediatric population with renal failure (for "neonates" who often exhibit primary renal immaturity, see below).

Infants, young children and children (aged 28 days to 11 years):

Indication	**Posology**	**Recommendations**
- Mucosal candidiasis	Initial dose: 6 mg/kg Subsequent dose: 3 mg/kg once per day	The initial dose may be used on the first day to achieve steady state levels more rapidly
- Invasive candidiasis - Cryptococcal meningitis	Dose: 6 to 12 mg/kg once per day	Depending on the severity of the disease
- Maintenance therapy to prevent recurrence of cryptococcal meningitis in children with a high risk of recurrence	Dose: 6 mg/kg once per day	Depending on the severity of the disease
- Prevention of *Candida* infections in immunosuppressed patients	Dose: 3 to 12 mg/kg once per day	Depending on the extent and duration of induced neutropoenia (see adult dosage)

Adolescents (aged 12 to 17 years):
The prescribing physician will determine the most appropriate dosage (adults or children) depending on the weight and pubertal development of the adolescent. Clinical data indicate that children have a higher fluconazole clearance than that observed in adults. A dose of 100, 200 and 400 mg in adults corresponds to a 3, 6 and 12 mg/kg dose in children to obtain comparable systemic exposure.
Safety and efficacy in the genital candidiasis indication in the paediatric population have not been established. The current available safety data for other paediatric indications are described in section 4.8. If treatment for genital candidiasis is imperative in adolescents (aged 12 to 17 years), the dosage should be the same as in adults.

Full-term neonates (aged 0 to 27 days)
Neonates excrete fluconazole slowly. Few pharmacokinetic data are available to support this dosage in full-term neonates (see section 5.2).

Age group	**Posology**	**Recommendations**
Neonates (aged 0 to 14 days)	The same mg/kg dose as for infants, young children and children should be given every 72 hours	A maximum dosage of 12 mg/kg every 72 hours should not be exceeded
Full-term neonates (aged	The same mg/kg dose as for infants, young children and	A maximum dosage of 12 mg/kg every 48 hours should not be exceeded

15 to 27 days):	children should be given every 48 hours	

Method of administration

Diflucan may be administered either orally or by intravenous infusion, the route depending on the clinical state of the patient. When changing from intravenous to oral administration, or vice versa, there is no need to change the daily dose.

The doctor should prescribe the most appropriate pharmaceutical form and dosage according to age, weight and dose. The capsule formulation is not suitable for infants and young children. Liquid oral formulations of fluconazole are available and better adapted to this population.

The capsules should be swallowed whole, with or without food.

4.3 Contraindications

Hypersensitivity to the active substance, to other azole derivatives, or to any of the excipients listed in section 2.

Combination with terfenadine is contraindicated in patients treated with Diflucan at multiple doses greater than or equal to 400 mg per day based on the results of a multiple dose interaction study. Combination with other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozide, quinidine, amiodaroneand erythromycin is contraindicated in patients treated with fluconazole (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Tinea capitis
Fluconazole has been studied for the treatment of *tinea capitis* in children. It was shown not to be superior to griseofulvin with an overall success rate less than 20%. Therefore, Diflucan should not be used to treat ringworm of the scalp (tinea capitis).

Cryptococcosis
Proof of the efficacy of fluconazole in the treatment of cryptococcosis on other sites (e.g. pulmonary and cutaneous cryptococcosis) is limited, which prevents dosing recommendations.

Deep endemic mycoses
Proof of the efficacy of fluconazole in the treatment of other forms of endemic mycoses such as paracoccidioidomycosis, sporotrichosis and lymphocutaneous histoplasmosis is limited, which prevents specific dosing recommendations.

Renal system
Diflucan should be administered with caution to patients with impaired kidney function (see section 4.2).

Adrenal insufficiency
Ketoconazole is known to cause adrenal insufficiency, and the phenomenon has also been reported with fluconazole, although cases are rare. For adrenal insufficiency associated with concomitantly administered prednisone, see section 4.5 **Interaction with other medicinal products and other forms of interaction**.

Hepatobiliary system
Diflucan should be administered with caution to patients with impaired liver function.

Diflucan has been associated with rare cases of serious and even fatal hepatic toxicity, primarily in patients with serious underlying medical conditions. In cases of fluconazole-associated hepatotoxicity, no obvious relationship with total daily dose, duration of therapy, sex or age of patient has been observed. Fluconazole-associated hepatotoxicity is usually reversible following discontinuation of treatment.

Patients who develop abnormal liver function tests during treatment with fluconazole should be monitored closely to avoid the development of a more serious hepatic injury. The patient should be informed of the symptoms suggestive of serious hepatic effects (significant asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment with fluconazole should be discontinued immediately and the patient should consult a doctor.

Cardiovascular system
Some azole derivatives, including fluconazole, are associated with prolongation of the QT interval on electrocardiogram. Fluconazole results in prolongation of the QT interval due to inhibition of the rectifier potassium channel current (I_{kr}). Prolongation of the QT interval caused by other medicinal products (such as amiodarone) may be amplified by inhibition of cytochrome P450 (CYP) 3A4. In post-marketing, very rare cases of QT prolongation and torsades de pointes have been observed in patients taking Diflucan. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medicinal treatment that may have been contributory. Patients with hypokalaemia and advanced cardiac insufficiency are at a higher risk of developing potentially fatal ventricular arrhythmias and torsades de pointes.

Diflucan should be administered with caution in patients with these potentially proarrhythmic conditions.

Combination with other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated (see sections 4.3 and 4.5).

Halofantrine
It has been shown that halofantrine prolongs the QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. Concomitant use of fluconazole and halofantrine is therefore not recommended (see section 4.5).

Dermatological reactions
Rare cases of exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), have been reported during treatment with fluconazole. Patients with AIDS are at a higher risk of developing severe cutaneous reactions to many medicinal products. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, all further treatment with this medicinal product should be discontinued. If patients with invasive or systemic fungal infections develop a rash, they should be monitored closely and fluconazole should be discontinued if bullous lesions or erythema multiforme develop.

Hypersensitivity
In rare cases anaphylactic reactions have been reported (see section 4.3).

Cytochrome P450
Fluconazole is a moderate inhibitor of CYP2C9 and of CYP3A4. Fluconazole is also a potent inhibitor of CYP2C19. Patients treated simultaneously with Triflucan and with medicinal products with a narrow therapeutic window metabolised via CYP2C9, CYP2C19 and CYP3A4 should be monitored (see section 4.5).

Terfenadine

Coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be strictly monitored (see sections 4.3 and 4.5).

Excipients
The capsules contain lactose monohydrate. The capsules are not advised in patients presenting an intolerance to galactose, Lapp lactase deficiency, or glucose or galactose malabsorption syndrome (rare hereditary diseases).

Diflucan capsules contain less than 1 mmol (23 mg) sodium per capsule, that is to say they are essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

Cisapride: Cardiac events have been reported, in particular torsades de pointes, in patients who simultaneously received fluconazole and cisapride. One controlled study demonstrated that concomitant administration of fluconazole 200 mg once daily and cisapride 20 mg four times daily led to a significant increase in the plasma levels of cisapride and a lengthening of the QTc interval. Concomitant administration of fluconazole and cisapride is contraindicated (see section 4.3).

Terfenadine: Because of the occurrence of severe cardiac arrhythmias secondary to prolongation of the QTc interval in patients treated by both azole antifungals and terfenadine, interaction studies have been conducted. One study showed that administration of 200 mg of fluconazole daily did not lead to a prolongation of the QTc interval. Another study with 400 mg and 800 mg of fluconazole daily demonstrated that a daily dose of fluconazole greater than or equal to 400 mg significantly increases plasma concentrations of Terfenadine if the two medicinal products are taken concurrently. The combination of fluconazole and terfenadine at doses greater than or equal to 400 mg is contraindicated (see section 4.3). For doses of fluconazole lower than 400 mg daily, the patient should be strictly monitored.

Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. The resulting increased plasma concentrations of astemizole can lead to QT prolongation and, in rare cases, the onset of torsades de pointes. Coadministration of fluconazole and astemizole is contraindicated (see section 4.3).

Pimozide: Although it has not been studied *in vitro* or *in vivo*, concomitant administration of fluconazole and pimozide may result in an inhibition of pimozide metabolism. The increased plasma concentrations of pimozide can lead to QT prolongation and, in rare cases, the onset of torsades de pointes. Coadministration of fluconazole and pimozide is contraindicated (see section 4.3).

Quinidine: Although it has not been studied *in vitro* or *in vivo*, concomitant administration of fluconazole and quinidine may result in an inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and, in rare cases, the onset of torsades de pointes. Coadministration of fluconazole and quinidine is contraindicated (see section 4.3).

Erythromycin: Concomitant use of fluconazole and erythromycin may potentially increase the risk of cardiotoxicity (prolongation of the QT interval, torsades de pointes), and consequently, of sudden cardiac death. Coadministration of fluconazole and erythromycin is contraindicated.
Amiodarone: Concomitant administration of fluconazole and amiodarone may result in inhibition of amiodarone metabolism. The use of amiodarone has been associated with a prolonged QT interval. Coadministration of fluconazole and amiodarone is contraindicated (see section 4.3).

Inadvisable combination:

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

Combination to be used with caution:

Amiodarone: Concomitant administration of fluconazole and amiodarone may exacerbate QT interval prolongation. Caution is required if the concomitant administration of fluconazole and amiodarone is necessary, especially with a high dose of fluconazole (800 mg).

Combinations requiring precautions for use or dosage adjustments:

Effect of other medicinal products on fluconazole

Rifampicin: Concomitant administration of fluconazole and rifampicin results in a 25% decrease in the AUC and a 20% reduction in the half-life of fluconazole. An increase in the fluconazole dose should be considered in case of concomitant use 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 impairment of fluconazole absorption was observed.

Hydrochlorothiazide: In one pharmacokinetic interaction study, co-administration of multiple doses of hydrochlorothiazide to healthy volunteers receiving fluconazole increased the plasma concentration of fluconazole by 40 %. An effect of this magnitude should not require adjustment of the dose of fluconazole in patients receiving diuretics concomitantly.

Effect of fluconazole on other medicinal products

Fluconazole is a moderate inhibitor ofCYP450 2C9 and 3A4 isoenzymes. Fluconazole is also a potent inhibitor of isoenzyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other medicinal products metabolised by CYP2C9, CYP2C19 and CYP3A4 in case of concomitant administration with fluconazole. As a result, these combinations should always be administered with caution and the patient should be closely monitored. The enzyme inhibiting effect of fluconazole persists 4 to 5 days after the end of fluconazole treatment because of the long half-life ($t_{½}$) of fluconazole (see section 4.3).

Alfentanil: During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers, the AUC_{10} of alfentanil is increased 2 fold, probably through inhibition of CYP3A4. Dose 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 treatment and after one week of treatment. It may be necessary to adjust the dosage of amitriptyline/nortriptyline.
Amphotericin B: Concomitant administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a slight additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans* and antagonism of the two medicinal products in systemic infection with Aspergillus fumigatus. The clinical significance of the results obtained in these studies is unknown.

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria and melena) in association with increases in prothrombin time have been reported in patients receiving fluconazole and warfarin concurrently. During concomitant treatment with fluconazole and warfarin, the prothrombin time

was prolonged up to 2 fold, probably due to an inhibition of the warfarin metabolism via CYP2C9. Prothrombin time should be closely monitored in patients receiving coumarin- or indanedione-type anticoagulants concurrently with fluconazole. Dose adjustment of the anticoagulant may be necessary.

Benzodiazepines (short acting), i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole led to a substantial increase in midazolam concentrations and psychomotor effects. Concomitant administration of fluconazole 200 mg and midazolam 7.5 mg orally increased the AUC and half-life of midazolam by 3.7 times and 2.2 times respectively. Fluconazole 200 mg daily administered concomitantly with triazolam 0.25 mg orally increased the AUC and half-life of triazolam 4.4 fold and 2.3 fold, respectively. Potentiated and prolonged effects of triazolam have been observed in the combination of treatment with fluconazole. If concomitant treatment by a benzodiazepine is necessary in patients treated with fluconazole, a reduction of the benzodiazepine dose and appropriate 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 developing toxicity from carbamazepine. Dose adjustment of carbamazepine may be necessary depending on measurements of its concentration/its effect.

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

Celecoxib: During concomitant treatment with fluconazole (200 mg per day) and celecoxib (200 mg), the C_{max} and AUC of celecoxib were increased by 68% and 134%, respectively. A 50% reduction in celecoxib dosage is recommended in patients also taking fluconazole.

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

Fentanyl: One fatal case of fentanyl intoxication due to possible interaction between fentanyl and fluconazole has been reported. Furthermore, it was shown in healthy volunteers that fluconazole significantly delayed the elimination of fentanyl. The increase in fentanyl concentration can lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dose adjustment of fentanyl may be necessary.

HMG-CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis is increased when fluconazole is administered simultaneously with HMG-CoA reductase inhibitors metabolised by CYP3A4, such as atorvastatin and simvastatin, or by CYP2C9, such as fluvastatin. If concomitant treatment is necessary, symptoms of myopathy and rhabdomyolysis, and creatinine kinase concentrations should be monitored. Treatment with HMG-CoA reductase inhibitors should be discontinued if creatinine kinase concentrations increase significantly or in case of diagnosis or suspicion of myopathy/rhabdomyolysis.

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

Immunosuppressants (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole at 200 mg daily and ciclosporin (2.7 mg/kg/day), there

was a 1.8-fold increase in the AUC of ciclosporin. This combination may be used by reducing the dosage of ciclosporin based on ciclosporin concentration.

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

Sirolimus: Fluconazole increases plasma concentrations of sirolimus, presumably by inhibiting the metabolism of sirolimus via CYP3A4 and by inhibiting P-glycoprotein. This combination may be used with an adjustment in the dosage of sirolimus based on its effect and its concentration.

Tacrolimus: Fluconazole may increase the serum concentrations of tacrolimus administered orally by up to 5 times through inhibition of tacrolimus metabolism via CYP3A4 in the intestines. No significant pharmacokinetic change has been observed when tacrolimus is administered intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. The orally administered dosage of tacrolimus should be reduced as a function of tacrolimus concentration.

Losartan: Fluconazole inhibits the conversion of losartan to its active metabolite (E-31 74), which is responsible for most of the angiotensin II receptor inhibition which occurs during treatment with losartan. Continuous monitoring of blood pressure is recommended in patients receiving this combination.

Methadone: Fluconazole may increase serum concentrations of methadone. Dose adjustment of methadone may be necessary.

Non-steroidal anti-inflammatories: The C_{max} and AUC of flurbiprofen were increased by 23% and 81%, respectively, in coadministration with fluconazole compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer [S--(+)-ibuprofen] increased by 15% and 82% respectively during coadministration of fluconazole and racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.

Although no specific study has been conducted, fluconazole may potentially increase systemic exposure to other NSAIAs that are metabolised by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicities related to NSAIAs is recommended. Dose adjustment of NSAIAs may be necessary.

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. Repeated concomitant administration of 200 mg of fluconazole and 250 mg of phenytoin intravenously led to a 75% increase of the AUC24 of phenytoin and a 128% increase in C_{min} In case of coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: A liver-transplanted patient receiving prednisone developed Addison's disease following discontinuation of a 3-month long treatment with fluconazole. The withdrawal from fluconazole likely led to increased CYP3A4 activity, having as a result an increased metabolism of prednisone. Patients on long-term treatment combining fluconazole with prednisone should be closely monitored for signs of adrenal cortex insufficiency after discontinuation of fluconazole.

Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to an increase in the AUC of rifabutin of up to 80%. Cases of uveitis have been reported in patients treated with this combination. In case of combination therapy, it is necessary to take into account the symptoms of rifabutin toxicity.

Saquinavir: Fluconazole increases the AUC and C_{max} of saquinavir by approximately 50% and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and may be more marked. Dose adjustment of saquinavir may be necessary.

Hypoglycaemic sulphonamides: Fluconazole prolonged the serum half-life of simultaneously administered oral hypoglycaemic sulphamides (e.g., chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers. Frequent monitoring of blood sugar and an appropriate reduction of the dosage of hypoglycaemic sulphamides are recommended in case of concomitant treatment.

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

Tofacitinib: Exposure to tofacitinib increases when co-administered with a medicine that causes a moderate inhibition of CYP3A4 and a strong inhibition of CYP2C19 (e.g. fluconazole). Therefore, a dose reduction of tofacitinib to 5 mg once daily is recommended when combined with these medicinal products.

Tolvaptan: exposure to tolvaptan is significantly increased (200% for AUC; 80% for C_{max}) when tolvaptan, a CYP3A4 substrate, is co-administered with fluconazole, a moderate CYP3A4 inhibitor, with a risk of a significant increase in adverse effects, in particular high urine output, dehydration and acute renal failure. In cases of concomitant use, the dose of tolvaptan should be reduced in accordance with the prescription information for tolvaptan and the patient should be regularly monitored for any tolvaptan-related adverse effects.

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

Vitamin A: In a case-report in one patient receiving combination therapy with all--trans-retinoic acid (an acid form of vitamin A) and fluconazole, undesirable neurological effects developed in the form of pseudotumour cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but a risk of occurrence of undesirable neurological effects should be considered.

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

Zidovudine: Zidovudine: Fluconazole increases the C_{max} and the AUC of zidovudine by 84% and 74%, respectively, due to a decrease of around 45% of clearance of oral zidovudine. The half-life of zidovudine was likewise prolonged by approximately 128% following concomitant administration with fluconazole. Patients receiving this combination should be monitored for the development of undesirable effects associated with zidovudine. Dose reduction of zidovudine may be considered.

Azithromycin: Azithromycin: An open-label, randomized, three-way crossover study 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 interaction was observed between fluconazole and azithromycin.

Oral contraceptives: Two pharmacokinetic studies have been performed with combined oral contraceptives and repeated doses of fluconazole. No particular effect on hormone level was noted with administration of 50 mg fluconazole. Taking 200 mg fluconazole daily led to an increase in the AUC of ethinyl estradiol and levonorgestrel of 40% and 24%, respectively. Therefore, it is unlikely that multiple doses of fluconazole at these dosages has an effect on the efficacy of combined oral contraceptives.

Ivacaftor: Concomitant administration of ivacaftor, a potentiator of CFTR (cystic fibrosis transmembrane conductance regulator), multiplied ivacaftor exposure by 3 times, and exposure to hydroxymethyl-ivacaftor (M1) by 1.9 times. A dose reduction of ivacaftor to 150 mg once daily is recommended in patients taking moderate CYP3A inhibitors, such as fluconazole and erythromycin

4.6 Fertility, pregnancy and lactation

Pregnancy

Multiple congenital abnormalities have been reported (including brachycephalia, ear dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were being treated for coccidioidomycosis for three or more months at high doses (400-800 mg daily) of fluconazole. The relationship between fluconazole and these effects is unclear.

Studies in animals have shown reproductive toxicity (see section 5.3).

Short-term fluconazole treatment at standard doses should not be used during pregnancy unless absolutely necessary.

Prolonged use of fluconazole and/or use at high doses should not be conducted during pregnancy except in the case of potentially life-threatening infections.

Breast-feeding

Fluconazole is excreted into the milk at concentrations similar than those in the plasma (see section 5.2).. Breast-feeding may be maintained after adose of 150 mg fluconazole. Breast-feeding is not recommended after repeated administration or after high doses of fluconazole. The health and developmental benefits of breast-feeding should be taken into consideration, as well as the maternal clinical need for Diflucan and any potential adverse effects in the breastfed child related to Diflucan intake or the underlying maternal pathology.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of Diflucan on the ability to drive vehicles or use machines. Patients should be warned about the risk of occurrence of seizures or vertigo (see section 4.8) while taking Diflucan and should be recommended not to drive or operate machines if these symptoms occur.

4.8 Undesirable effects

The most frequently reported (>1/10) side effects are headache, abdominal pain, diarrhoea, nausea, vomiting, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood alkaline phosphatase and rash.

The following adverse reactions have been observed and reported during treatment with Diflucan with the following frequencies: 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), Not known (cannot be estimated from the available data)

System organ class	Common	Uncommon	Rare	Frequency not known
Blood and lymphatic system disorders		Anaemia	Agranulocytosis, leukopoenia thrombocytopoenia. neutropoenia,	
Immune system disorders			Anaphylaxis	
Metabolic and nutritional disorders		Decreased appetite	hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia,	
Psychiatric disorders		Drowsiness, insomnia		
Nervous system disorders	Headache	Epileptic seizures paraesthesia, dizziness, altered sense of taste	Tremors	
Ear and labyrinth disorders		Dizziness		
Cardiac disorders			torsades de pointes (see section 4.4), lengthening of the QT interval (see section 4.4),	
Gastrointestinal disorders	abdominal pain, vomiting, diarrhoea, nausea	constipation. dyspepsia, flatulence, dry mouth		
Hepatobiliary disorders	increase in alanine aminotransferase* (see section 4.4), increase in aspartate aminotransferase* (see section 4.4), increase in blood alkaline phosphatase (see section 4.4)	Cholestasis (see section 4.4), jaundice (see section 4.4), increase in bilirubin levels (see section 4.4)	liver failure (see section 4.4), hepatocellular necrosis (see section 4.4), hepatitis (see section 4.4), hepatocellular damage (see section 4.4)	
Skin and subcutaneous tissue disorders	Rash (see section 4.4)	Drug eruption* (see section 4.4), urticaria (see section 4.4), pruritus, excessive sweating	Lyell's syndrome (toxic epidermal necrolysis) (see section 4.4), Stevens-Johnson syndrome (see section 4.4), acute generalised exanthematous pustulosis (see section	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

System organ class	Common	Uncommon	Rare	Frequency not known
			4.4), exfoliative dermatitis, angioedema, facial oedema alopecia.	
Musculoskeletal and connective tissue disorders		Myalgia		
General disorders and administration site conditions:		fatigue malaise asthenia, fever		

*Including fixed drug eruption

Paediatric population
The nature and incidence of undesirable effects and laboratory abnormalities observed during paediatric clinical trials, excluding the genital candidiasis indication, are comparable to those seen in adults.

Reporting of suspected undesirable effects
Reporting suspected undesirable effects after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected side effects via the national reporting system.

4.9 Overdose

Cases of overdose with Diflucan have been reported. Hallucinations associated with paranoid behaviour have been reported concomitantly.
In the event of overdose, management (with symptomatic treatment and gastric lavage if necessary) may be adequate.
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%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC01.

Mechanism of action
Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of lanosterol 14 alpha-demethylase mediated by cytochrome P 450, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole. It has been shown that fluconazole is more selective against fungal cytochrome P 450 enzymes than various cytochrome P 450 enzyme systems in mammals.

Fluconazole, administered at a dosage of 50 mg daily for up to 28 days, does not exert an effect on plasma concentrations of testosterone in men or concentrations of steroids in women of child-bearing age. Fluconazole, administered at a dosage of 200 mg to 400 mg daily, does

not have a clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers. Interaction studies with antipyrine show that single or repeated doses of 50 mg of fluconazole do not affect the metabolism of antipyrine.

In vitro susceptibility:
In vitro, fluconazole has proven antifungal activity against the majority of the most common species of *Candida* (including *C. albicans*, *C. parapsilosis*, *C. tropicalis*). *C. glabrata* shows a wide range of susceptibility while *C. krusei* is resistant to fluconazole.

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 relationships
In animal studies, a correlation was observed between minimum inhibitory concentration (MIC) values and efficacy against experimental mycoses due to *Candida* spp. In studies in human subjects, an almost 1/1 linear relationship between the AUC and the dose of fluconazole was observed. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidiasis and, to a lesser extent, candidaemia to treatment. Similarly, cure is less likely for infections caused by strains with a higher MIC to fluconazole.

Resistance mechanisms
Candida species have developed a certain number of mechanisms of resistance to azole antifungal agents. Fungal strains which have developed one or more of these mechanisms of resistance have high minimum inhibitory concentrations (MICs) to fluconazole, which adversely impacts efficacy, both *in vivo* and in humans.

Cases of superinfection with *Candida* species other than *C. albicans*, often intrinsically resistant to fluconazole (e.g., *Candida krusei*), have been reported. These cases may require alternative antifungal treatment.

Critical concentrations (according to EUCAST)
Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, *in vitro* susceptibility and clinical response, the EUCAST-AFST (European Committee on Antimicrobial Susceptibility Testing-Subcommittee on Antifungal Susceptibility Testing) has determined critical concentrations for fluconazole for *Candida* species (EUCAST Fluconazole rational document (2007-version 2). These critical concentrations have been divided into non-species-related critical concentrations, which have been determined primarily on the basis of PK/PD data and are independent of MIC distributions for specific species, and species-related critical concentrations for the species most frequently associated with human infection. These critical concentrations are presented in the table below:

Antifungal	Species-related critical concentrations (S≤ /R>)					Non-species-related critical concentrations[A] S≤ /R>
	Candida albicans	*Candida glabrata*	*Candida krusei*	*Candida parapsilosis*	*Candida tropicalis*	
Fluconazole	2/4	IE	-	2/4	2/4	2/4

S = susceptible, R = resistant
A. = non-species-related critical concentrations have been determined primarily on the basis of PK/PD data and are independent of MIC distributions for specific species. They are intended to be used only for organisms that do not have specific critical concentrations.
-- = susceptibility testing not recommended because the species is not a good target for treatment with this medicinal product.

IE = insufficient evidence that the species in question is a good target for treatment with this medicinal product.

5.2 Pharmacokinetic properties

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

Absorption

After oral administration, fluconazole is well absorbed and plasma levels (as well as systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by simultaneous food intake. Peak plasma concentrations in the fasting state are achieved 30 minutes to 1.5 hours post-dose. Plasma concentrations are proportional to dose. 90% of steady state levels are achieved 4-5 days after administration with single repeated daily dosing. Administration of a loading dose (on day 1) of twice the usual daily dose enables plasma levels to approach 90% of steady state levels by day 2.

Distribution

The apparent volume of distribution is similar to total body water. Binding to plasma proteins is low (11-12%).

Fluconazole penetrates well into all the bodily fluids studied. Fluconazole levels in the saliva and sputum are comparable to the plasma levels. In patients affected by a fungal meningitis, fluconazole levels in the CSF are about 80% of the corresponding plasma levels.

High concentration of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis and dermis and in the eccrine sweat glands. Fluconazole accumulates in the stratum corneum. At a dose of 50 mg once daily, fluconazole concentration after 12 days was 73 µg/g and, 7 days after discontinuation of treatment, the concentration was still 5.8 µg/g. At a dose of 150 mg once per week, 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; fluconazole could still be measured in nails 6 months after the end of treatment.

Biotransformation

Fluconazole is poorly metabolised. Only 11% of a radioactive dose is excreted as metabolites in the urine. Fluconazole is a moderate inhibitor of CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also a potent inhibitor of CYP2C19.

Elimination

The plasma elimination half-life of fluconazole is around 30 hours. The major route of elimination is renal, with approximately 80% of the administered dose appearing in the urine in an unchanged form. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

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

Pharmacokinetics in renal failure

In patients with severe renal failure (GFR< 20 ml/min), the half-life goes from 30 to 98 hours. A reduction of the dose is needed. Fluconazole is eliminated by haemodialysis and, to a lesser extent, by peritoneal dialysis. After a 3-hour haemodialysis session, around 50% of fluconazole is eliminated from the blood.

Pharmacokinetics during breastfeeding

A pharmacokinetic study in ten breastfeeding women who discontinued breastfeeding temporarily or permanently, assessed fluconazole concentrations in plasma and breast milk for 48 hours following administration of a single dose of 150 mg of Diflucan. Fluconazole was detected in breast milk at an average concentration of approximately 98% of that detected in maternal plasma. The mean maximum concentration in breast milk was 2.61 mg/L, 5.2 hours after dosing. The estimated daily intake of fluconazole in infants from breast milk (assuming an average milk consumption of 150 mL/kg/day) based on the mean maximum concentration in milk is 0.39 mg/kg/day, which represents approximately 40% of the recommended neonatal dose (age <2 weeks) or 13% of the recommended infant dose for mucosal candidiasis.

Pharmacokinetics in children
Pharmacokinetic data were evaluated in 113 children taking part in 5 studies; 2 single-dose studies, 2 repeated-dose studies, and 1 study in premature newborns. Data from one study were not interpretable due to changes in formulation pathway during study. Additional data were available from a compassionate use study.

After administration of 2-8 mg/kg of fluconazole to children aged 9 months to 15 years, an AUC of around 38 µg·h/mL was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the volume of distribution was around 880 mL/kg after administration of repeated doses. A higher fluconazole plasma elimination half-life of around 24 hours was found after administration of a single dose. This is comparable with the fluconazole plasma elimination half-life after administration of a single dose of 3 mg/kg IV 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 premature newborns. The mean age at the time of administration of the first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75-1.10 kg) for 12 premature newborns of mean gestation of approximately 28 weeks. Seven patients completed the study; 5 intravenous infusions of a maximum of 6 mg/kg 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·h/ml) was 271 (range 173-385) on day 1 and it 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 (range 1040-1680) on day 13.

Pharmacokinetics in elderly patients
A pharmacokinetic study was conducted in 22 subjects aged 65 years and older receiving a single 50 mg oral dose of fluconazole. Ten of these patients simultaneously received diuretics. C_{max} was 1.54 µg/ml, achieved 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 µg·h/mL and the mean elimination half-life was 46.2 hours. These pharmacokinetic parameter values are higher than the corresponding values reported in healthy young male volunteers. Coadministration of diuretics did not significantly alter either the AUC or C_{max}. In addition, values for creatinine clearance (74 mL/min), the percentage of medicinal product recovered unchanged in the urine (0-24 h, 22%) and the renal clearance of fluconazole (0.124 mL/min/kg) were generally lower in older people than in younger volunteers. The alteration of fluconazole elimination in elderly patients seems to be related to the reduced renal function characteristic of this group.

5.3 Preclinical safety data

Effects were observed in animals only at exposures considered sufficiently greater than the maximum exposure observed in humans, and have limited clinical significance.

Carcinogenicity

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

Mutagenicity
Fluconazole, with or without metabolic activation, proved to be negative in mutagenicity tests conducted on 4 strains of *S. typhimurium* and in mouse lymphoma L5178Y cells. Cytogenetic studies *in vivo* (murine bone marrow cells, after oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at concentrations of 1,000 µg/ml) did not show any sign of chromosomic mutation

Reproductive toxicity
Fluconazole did not affect fertility in male and female rats treated orally at daily doses of 5, 10 or 20 mg/kg/day, or parenterally at doses of 5, 25 or 75 mg/kg.

No foetal effects were observed at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg, there was an increase in embryonic mortality in rats and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification.
The onset of birthing was slightly delayed at 20 mg/kg orally and dystocia and prolongation of birthing were observed in some mothers at 20 mg/kg and 40 mg/kg intravenously. The birthing disorders are expressed by a slight increase in the number of stillbirths and a decrease in newborn survival at these doses. These effects on birthing are consistent with the species-specific oestrogen-lowering property produced by high doses of fluconazole. These hormonal effects have not been observed in women treated with fluconazole (see section 5.1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30° C.

6.5 Nature and contents of container
150 mg capsules: Clear PVC blister acks or white opaque PVC/PVDC blister packs with aluminium foil backing.

Diflucan 150 mg: box of 1 capsule or box of 4 capsules

All the presentations may not be registered

6.6 Special precautions for handling and disposal

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

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

Marketing Authorisation Holder:
Laboratoires Pfizer S.A.
0,5 Km, route de Oualidia
El Jadida – Maroc

Manufacturer:
Laboratoires Pfizer S.A.
km 0.5, Route de Oualidia
BP 35, 24 000
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Local representative:

Pfizer Afrique de l'Ouest

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8. GENERAL CLASSIFICATION FOR SUPPLY

List I.

9. DATE OF REVISION OF THE TEXT

11/2020