**ANNEX I**

**LIST OF THE INVENTED NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANT, MARKETING AUTHORISATION HOLDER, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES**

 

| Member State | Marketing Authorisation Holder/Applicant | Invented name | Strength | Pharmaceutical Form | Route of administration | Packaging | Package-size |
|---|---|---|---|---|---|---|---|
| Germany | Alfred E. Tiefenbacher (GmbH & Co.) | Fluconazol Tiefenbacher 50 mg Hartkapseln | 50 mg | Capsule, hard | Oral use | PVC/PVdC/Alu Blister | 3, 7, 10, 14, 20, 28, 30, 42, 50, 100 |
| Germany | Alfred E. Tiefenbacher (GmbH & Co.) | Fluconazol Tiefenbacher 100 mg Hartkapseln | 100 mg | Capsule, hard | Oral use | PVC/PVdC/Alu Blister | 7, 10, 14, 20, 28, 30, 50, 60, 100 |
| Germany | Alfred E. Tiefenbacher (GmbH & Co.) | Fluconazol Tiefenbacher 150 mg Hartkapseln | 150 mg | Capsule, hard | Oral use | PVC/PVdC/Alu Blister | 1, 2, 4 ,6 10, 20 |
| Germany | Alfred E. Tiefenbacher (GmbH & Co.) | Fluconazol Tiefenbacher 200 mg Hartkapseln | 200 mg | Capsule, hard | Oral use | PVC/PVdC/Alu Blister | 7, 10 ,14, 20, 28, 30, 50, 100 |
| Sweden | Alfred E. Tiefenbacher (GmbH & Co.) | Fluconazol Tiefenbacher 50 mg kapsler, hårda | 50 mg | Capsule, hard | Oral use | PVC/PVdC/Alu Blister | 3, 7, 10, 14, 20, 28, 30, 42, 50, 100 |
| Sweden | Alfred E. Tiefenbacher (GmbH & Co.) | Fluconazol Tiefenbacher 100 mg kapsler, hårda | 100 mg | Capsule, hard | Oral use | PVC/PVdC/Alu Blister | 7, 10, 14, 20, 28, 30, 50, 60, 100 |
| Sweden | Alfred E. Tiefenbacher (GmbH & Co.) | Fluconazol Tiefenbacher 150 mg kapsler, hårda | 150 mg | Capsule, hard | Oral use | PVC/PVdC/Alu Blister | 1, 2, 4 ,6 10, 20 |
| Sweden | Alfred E. Tiefenbacher (GmbH & Co.) | Fluconazol Tiefenbacher 200 mg kapsler, hårda | 200 mg | Capsule, hard | Oral use | PVC/PVdC/Alu Blister | 7, 10 ,14, 20, 28, 30, 50, 100 |

## ANNEX II

## SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

 

## SCIENTIFIC CONCLUSIONS

## OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF Fluconazole CONTAINING MEDICINAL PRODUCTS

Fluconazole is a triazole antifungal agent used against a variety of fungal infections. Fluconazole acts by inhibition of the formation of ergosterol, an important component of the fungal cell membrane.

### ➢ Teratogenic potential of fluconazole

Fluconazole has been incriminated in four cases of malformations resembling the Antley-Bixler syndrome. These occurred under therapeutic dose regimens (mostly 400 mg fluconazole/day). Whereas the SPC proposed by the RMS requested a risk-benefit judgement with regard to pregnancy and lactation, the CMS contended that fluconazole must be contraindicated in pregnancy except for life-threatening cases.

A search of major biomedical databases (MEDLINE, TOXLINE, EMBASE, RTECS, DART, HSDB) until March 2003 identified several publications on the teratogenic potential of fluconazole.

Consistent teratogenic findings in the in-vitro mouse and rat studies were the dose-related anomalies of branchial arches. In-vivo studies have been performed in the mouse, rat and the rabbit. In mice, fluconazole at 50 mg/kg reduced embryo viability, increased incidence of rib abnormalities, and dilated renal pelvis. Maternal toxicity was not observed at this dosage. In rats, fluconazole at dosages from 25 mg/kg caused increases in foetal anatomical variants such as supernumerary ribs, renal pelvis dilation and delays in ossification. At dosages from 80 mg/kg and higher, embryo lethality increased and more foetal abnormalities, like wavy ribs, cleft palate, abnormal craniofacial ossification, were observed. These effects in the rats have been ascribed to a species-specific lowering effect of fluconazole on oestrogen synthesis and the applicant doubts the clinical relevance of these findings, since there is no evidence to date that oestrogen concentrations are decreased in the women receiving fluconazole. Fluconazole was not teratogenic in the rabbit at doses of 20 mg/kg. Spontaneous abortions were observed at 75 mg/kg. However, this dose was associated with clear signs of maternal toxicity.

More than 1000 exposed pregnancies have been studied, and the outcome does not suggest that in utero exposure to standard single or repetitive doses of fluconazole is associated with an increased risk of foetal malformations or unwanted pregnancy outcome. Five cases of high-dose treatment have been identified, resulting in malformations in 4/5 live births. The malformations in all four cases seem consistent with the pattern described as the Antley-Bixler syndrome. Antley-Bixler syndrome is a rare disorder characterized by craniosynostosis, midface hypoplasia, radiohumeral synostosis, joint contractures, arachnodactyly, and femoral bowing and fractures.

Standard doses of 200 mg daily or less of fluconazole administered as a single or repeated dose has been used during the first trimester without indication of adverse foetal effects.

Furthermore, treatment with higher doses of fluconazole should be possible in case of life-threatening infections. A label of contraindication during pregnancy is not warranted.

### ➢ QT- prolongation potential of fluconazole

Fluconazole has been reported to induce QT-prolongation in humans and is listed by the WHO as a causative agent of Torsades de Pointes. Moreover, fluconazole was claimed by the CMS to be known to strongly inhibit the HERG channel. In consequence, the CMS requested inclusion in the SPC warnings of a number of conditions increasing the risk for a QT-prolongation and potentially leading to clinically relevant adverse events.

The search of the open literature did not identify any non-clinical studies of the potential of fluconazole to induce QT-prolongation. No references to the testing of fluconazole in the HERG assay were found in search of the PubMed database.

Drug induced TdP may be mediated through a primary drug effect, by block of the repolarizing outward current $I_{Kr}$ (HERG channel). Drug induced TdP may also occur as a secondary drug effect mediated through repolarization modifying factors such as hypokalemia, bradycardia, gender, heart

 

failure or through pharmacokinetic interactions when for instance an inhibitor of a CYP450 metabolic enzyme is co-administered with a QT prolonging drug which is a substrate of this enzyme, or other metabolic factors, such as liver or renal disease.

TdP occurs with a low frequency, but is however, potentially life threatening. In the WHO list 17 reports are registered on TdP with fluconazole. Certainly, reporting rates do not correspond to the true incidence rates. There is a lack of knowledge on the predictability of TdP despite known risk factors.

Data from clinical trials on the QT prolonging potential of fluconazole or from ECG registries are not available. There are few published reports on TdP in patients treated with fluconazole all concern females. In 3 of the 4 reports either a high dose was given or plasma levels were/could be expected to be high due to conditions interfering with the excretion of the drug.

Treatment with fluconazole may be a potentially life saving treatment. For this reason it is not justified, to contraindicate it in the presence of risk factors known to increase the potential for QT prolongation. These risk factors are appropriately mentioned under the warnings section in 4.4 where it also is stated that if treatment with QT prolonging substances is considered necessary, the patient must be closely monitored including ECG monitoring. It should be up to the treating physicians to weigh the risk of treatment against the benefit of treatment.

## OVERALL CONCLUSION ON THE BENEFIT/RISK

The antifungal activity of fluconazole is well known. Fluconazole has mainly been investigated for the treatment of Cryptococcosis (meningitis), Candidiasis (systemic, oesophageal and oropharyngeal, vaginal) with oral or parental administration.

The risk/benefit ratio for Fluconazol remains positive, provided that appropriate information is included in the SPC regarding the teratogenic potential and the potential for QT-interval prolongation, since neither the teratogenic potential nor the potential for QT-interval prolongation preclude the safe use of the active substance.

## GROUNDS FOR AMENDMENT OF THE SUMMARY (IES) OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was to agree on a summary of Products Characteristics in view of the teratogenic potential and the potential for QT-interval prolongation.
- the Summary of Products Characteristic proposed by the applicant has been assessed based on the documentation submitted and the scientific discussion within the Committee.

the CPMP has recommended the granting of the Marketing Authorisation(s) with amendments of the Summary of Product Characteristics as set out in Annex III for Fluconazol Tiefenbacher 50 mg, 100 mg, 150 mg, 200 mg, capsules, hard (see Annex I).

 

**ANNEX III**

**AMENDED SUMMARY OF PRODUCT CHARACTERISTICS OF THE REFERENCE MEMBER STATE**

**NOTE: THIS SPC IS THE ONE THAT WAS ANNEXED TO THE COMMISSION DECISION CONCERNING THIS REFERRAL FOR ARBITRATION; THE TEXT WAS VALID AT THAT TIME.**

**IT IS NOT SUBSEQUENTLY MAINTAINED OR UPDATED BY THE EMEA, AND THEREFORE MAY NOT NECESSARILY REPRESENT THE CURRENT TEXT.**

 

## 1. NAME OF THE MEDICINAL PRODUCT

Fluconazol Tiefenbacher 50 mg capsule, hard
Fluconazol Tiefenbacher100 mg capsule, hard
Fluconazol Tiefenbacher 150 mg capsule, hard
Fluconazol Tiefenbacher 200 mg capsule, hard

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg, 100 mg, 150 mg, 200 mg fluconazole.
For excipients see 6.1.

## 3. PHARMACEUTICAL FORM

Capsule, hard

Fluconazol 50 mg light blue/white capsule size ‘4’
Fluconazol 100 mg deep blue/white capsule size ‘2’
Fluconazol 150 mg light blue/light blue capsule size ‘1’
Fluconazol 200 mg purple/white capsule size ‘0'

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Acute and recurrent vaginal candidiasis when systemic therapy is considered appropriate.

Fungal infections of the skin caused by tinea corporis/cruris/dermatophytes identified by direct microscopy and/or positive culture and where systemic therapy should be considered accordingly.

Mucosal candida infection. These include oropharyngeal, oesophageal, mucocutaneous and non-invasive bronchopulmonar candidiasis and candiduria in patients with compromised immune function.

Systemic candidiasis (candidaemia, disseminated deep candidiasis, peritonitis) in non-neutropenic patients.

Prevention of deep-seated candida infections (particularly Candida albicans) in connection with bone marrow transplantation.

Acute cryptococcal meningitis in adults. Normal hosts and patients with AIDS, organ transplanted or other causes of immunosuppression may be treated.

Fluconazol r can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.

Consideration should be given to official guidance on the appropriate use of antifungal agents. Not all indications are applicable for paediatric patients; see details in 4.2 Posology and method of administration.

### 4.2 Posology and method of administration

The daily dose is depending on the type and severity of the fungal infection. The treatment of infections requiring multiple dosing must be continued until clinical parameters or laboratory results

show that the active fungal infection has declined. An insufficient treatment period may lead to recurrence of the active infection.

Depending on the severity of the disease and the clinical state of the patients of the disease intravenous administration may be required. It is not necessary to change the daily dose of fluconazole when changing the route of administration from intravenous to oral.

*Adults:*
-Vaginal candidiasis: 150 mg as a single dose.

-Tinea corporis- cruris: 50 mg once daily or 150 mg once weekly for 2-4 weeks.

The effects of this dose on children have not been studied.

-Mucous membrane candidiasis:
Oropharyngeal candidiasis: Normal daily dose: 50 mg for 7-14 days. Duration of treatment depends on clinical response.
Oesophageal mucocutaneous, non-invasive bronchopulmonary candidiasis and candiduria: Normal dose is 50 mg daily for 14-30 days.
In severe and particular recurrent cases the dose can be increased to 100 mg.
*Systemic candidiasis:*
Usually, a single 400 mg loading dose should be administered on Day 1, followed by 200 mg daily, thereafter. The dose may be increased to 400 mg once daily. The duration of treatment depends on the clinical response but can often be up to several weeks.

-Prevention of candida infections in neutropenic patients:
400 mg once daily. Prophylaxis with fluconazole should begin in time before the appearance of expected neutropenia. Treatment should be continued for 7 days after the neutrophil counts have increased to > $1x10^9$/ l.

Cryptococcal meningitis in immunosuppressed patients: For infections with cryptococcal meningitis the usual dose is 400 mg on the first day followed by 200-400 mg once daily. Duration of treatment for cryptococcal infections depends on the clinical response, but is usually at least 6-8 weeks for cryptococcal meningitis.
For the prevention of relapse of cryptococcal meningitis in patients with AIDS, fluconazole may be administered at a daily dose of 100 – 200 mg.
Duration of maintenance treatment in AIDS patients should be carefully justified, because of the increased risk of resistance to fluconazole.

***Paediatric use:***
The capsules are clearly unsuitable for children younger than 5-6 years, who cannot take oral medication.
As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. The maximum daily dose of 400 mg should not be exceeded in children. Fluconazole is administered as a single daily dose each day.

Fluconazol Tiefenbacher should not be used in children and adolescents under the age of 16 years except in case of no therapeutic alternative, as efficacy and safety has not been sufficiently shown.

-Mucous membrane candidiasis: The recommended dosage of fluconazole is 3 mg/kg daily. A loading dose of 6 mg/kg may be used on the first day to achieve steady state levels more rapidly.
-Systemic candidiasis infection: Recommended dose is 6-12 mg/kg daily, depending on the severity of infection.
-Prevention of candida infections in neutropenic children: 3-12 mg/kg daily depending on the extent and duration of the neutropenia (see adult dosing).

 

*Elderly:*
Patients without impaired renal function usually receive normal dosing. The dosage to patients with impaired renal function (creatinine clearance <50 ml/min.) is given below.

*Patients (adult and paediatric) with impaired renal function:*
Fluconazole is mainly excreted unchanged in the urine. No change in the single dose treatment is required. For patients with impaired renal function the treatment with multiple doses of 50-400 mg is given initially, after which the daily dose (depending on therapeutic indication) should be based on the following table:

| Creatinine clearance (ml/min.) | Percentage of recommended dose |
|---|---|
| > 50 | 100% |
| 11-50 (no dialysis) | 50% |
| Regular dialysis | 100% after each dialysis |

*Method of Administration*
Oral use, capsules should be swallowed whole, independent of food intake.

**4.3 Contraindications**

Fluconazol should not be used in patients with known hypersensitivity to fluconazole, other azole derivatives or to any of the excipients.
Fluconazol should not be co-administered with drugs both known to prolong the QT-interval and metabolised by CYP3A4 such as cisapride, astemizole, terfenadine, pimozide and quinidine.
(see also point 4.5 „Interaction with other medicinal products and other forms of interaction").

**4.4 Special warnings and special precautions for use**

Severe hepatic toxicity, including death, has been reported in rare cases, primarily in patients suffering from serious underlying diseases. No obvious relationship between hepatotoxicity and total daily dose of fluconazole, duration of therapy, gender or age of the patient has been observed. Patients who develop abnormal liver test values or significant increases of originally abnormal levels during treatment must be monitored closely. The benefits of the treatment should be evaluated against the risks of developing serious liver damage if therapy is continued in patients whose liver enzyme values rise during fluconazole treatment. In most cases, liver toxicity has been reversible at discontinuation of the treatment.

Some azoles have been associated with QT-interval prolongation. Rare cases of Torsade de Pointes during treatment with fluconazole have been reported. And although the association of fluconazole and QT-prolongation has not been formally established, fluconazole should be used with caution in patients with potentially proarrythmic conditions such as:

- Congenital or documented acquired QT prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrythmias
- Concomitant medication not metabolised by CYP3A4 but known to prolong QT interval (see section 4.5 Interactions with other medicinal products and other forms of interaction).

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiation of fluconazole treatment.

Halofantrine has been shown to prolong $QT_c$ at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is not recommended.

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to the development of severe cutaneous reactions to many medicinal products. If a rash develops in a patient

treated for a superficial fungal infection that is considered attributable to fluconazole, further therapy with this agent should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if bullous lesions or erythema multiforme develop.

Anaphylactic reactions have in rare cases been reported (see 4.8 Undesirable effects).

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

The dose of fluconazole must be reduced when creatinine clearance is below 50 ml/min (see 4.2 Posology and method of administration).

In women of child-bearing potential, appropriate contraceptive measures should be considered in case long-term treatment is indicated (see section 4.6. Pregnancy and lactation).

## 4.5 Interaction with other medicinal products and other forms of interaction

*The following combinations are contra-indicated:*
Cisapride (CYP3A4 substrate): There have been reports about cardiac cases including torsades de pointes in patients receiving fluconazole concomitantly with cisapride. Concomitant treatment with fluconazole and cisapride is contra-indicated.

Terfenadine (with doses of 400 mg fluconazole or higher; CYP3A4 substrate): Due to occurrence of serious cardiac dysrhythmias secondarily to prolongation of the QTc-interval in patients on treatment with azole products concomitantly with terfenadine, interaction studies have been performed. One study with 200 mg fluconazole daily did not show any prolongation of the QTc-interval. Another study with 400 mg and 800 mg fluconazole daily showed that fluconazole 400 mg or more daily significantly increases the plasma level of terfenadine, if the two medicinal products are taken concomitantly. Concomitant treatment with terfenadine and fluconazole doses of 400 mg or more is contra-indicated. At fluconazole doses below 400 mg, the patient should be closely monitored.

Astemizole (CYP3A4 substrate): Astemizole overdoses have led to prolonged QT interval and severe ventricular arrhythmia, torsades de pointes and cardiac arrest. Concomitant treatment with fluconazole and astemizole is contra-indicated due to the potential for serious, even fatal, cardiac effects.

*Medicinal products affecting the metabolism of fluconazole:*
Hydrochlorothiazide: In a pharmacokinetic interaction study with healthy volunteers who concomitantly received fluconazole and multiple doses of hydrochlorothiazide the plasma concentrations of fluconazole increased with 40%. An effect of this size should not give rise to any change of the fluconazole dose in patients, who are concomitantly treated with diuretics, even though the physician should be observant on this relation.

Rifampicin (CYP450 inducer): Concomitant intake of fluconazole and rifampicin resulted in a 25% reduction of AUC and 20% shorter half-life of fluconazole. Increase of dosage should be considered in patients concomitantly receiving rifampicin.

*Effect of fluconazole on the metabolism of other medicinal products:*
Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Besides the observed/documented interactions listed below there is a risk of increased plasma concentrations of other medicinal products metabolised by CYP2C9 or CYP3A4 (e.g. ergot-alkaloids, quinidine) when co-administered with fluconazole. Therefore, care should always be taken when using these combinations and the patients should be carefully monitored. The enzyme-inhibiting effect of fluconazole may persist for 4-5 days after end of fluconazole treatment due to the long fluconazole half-life.

Alfentanil (CYP3A4 substrate): Concomitant intake of fluconazole 400 mg and alfentanil 20 µg/kg intravenously in healthy volunteers increased the alfentanil $AUC_{10}$ approximately 2-fold and decreased the clearance by 55%, probably through inhibition of CYP3A4. When using these combinations a dose adjustment may be required.

Amitriptyline: Several case reports have described the development of increased amitriptyline concentrations and signs of tricyclic toxicity when amitriptyline was used in combination with fluconazole. Coadministration of fluconazole with nortriptyline, the active metabolite of amitriptyline, has been reported to result in increased nortriptyline levels. Due to the risk of amitriptyline toxicity, consideration should be given to monitoring amitriptyline levels and making dose adjustments as may be necessary.

Anticoagulants (CYP2C9 substrate): Concomitant intake of fluconazole during warfarin treatment has been shown to prolong the prothrombin time up to 2-fold. This is likely due to an inhibition of warfarin metabolism via CYP2C9. The prothrombine time must be closely monitored in patients on treatment with coumarin derivatives.

Benzodiazepines (CYP3A4 substrate): Concomitant intake of fluconazole 400 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7- fold and 2.2-fold, respectively. Fluconazole 100 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 2.5-fold and 1.8-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If it is necessary to treat patients with a benzodiazepine concomitantly with fluconazole, a reduction of the benzodiazepine dose should be considered, and the patients should be closely monitored.

Calcium channel antagonists (CYP3A4 substrates): Some dihydropyridine calcium channel antagonists, including nifedipine, isradipine, nicardipine, amlodipine, and felodipine, are metabolised via CYP3A4. Literature reports have documented substantial peripheral oedema and/or elevated calcium antagonist serum concentrations during concurrent use of itraconazole and felodipine, isradipine, or nifedipine. An interaction might occur also with fluconazole.

Celecoxib (CYP2C9 substrate): In a clinical study, concomitant treatment with fluconazol 200 mg daily and celecoxib 200 mg resulted in an 68% and 134% increase in celecoxib $C_{max}$ and AUC, respectively. The interaction is believed to be due to inhibition of cytochrome P450 2C9 metabolism of celecoxib. Halving the Celecoxib dose is recommended to patients concurrently treated with fluconazole.

Cyclosporin (CYP 3A4 substrate): Clinically significant interactions with cyclosporin have been shown at fluconazole doses of 200 mg and higher. In a pharmacokinetic study with renal transplant patients receiving fluconazole200 mg daily and cyclosporin 2.7 mg/kg/day, there was a 1.8-fold increase in cyclosporin AUC and a 55% decrease in clearance. It is recommended to follow the cyclosporin plasma concentrations in patients on treatment with fluconazole.

Didanosine: Coadministration of didanosine and fluconazole appears to be safe and has little effect on didanosine pharmacokinetics or efficacy. However, it is important to monitor fluconazole response. It may be advantageous to stagger fluconazole dosing to a time prior to didanosine administration.

Halofantrin (CYP3A4 substrate): Drugs that inhibit CYP3A4 lead to an inhibition of halofantrine metabolism.

HMG-CoA reductase inhibitors (CYP2C9 or CYP3A4 substrates): The risk of myopathy is increased when fluconazole is administered concurrently with HMG-CoA reductase inhibitors that are metabolised via CYP3A4, such as atorvastatin and simvastatin, or via CYP2C9, such as fluvastatin. Up to 200% individual increases in the area under the curve (AUC) of fluvastatin may occur as a result of the interaction between fluvastatin and fluconazole. Caution is warranted if concurrent administration of fluconazole and HMG-CoA reductase inhibitors is deemed necessary. The combination may require a dose reduction of the HMG-CoA reductase inhibitors. Patients should be

monitored for signs and symptoms of myopathy or rhabdomyolysis and creatine kinase (CK) levels. HMG-CoA therapy should be discontinued if CK levels show a marked increase, or if myopathy or rhabdomyolysis is diagnosed or suspected.

Losartan (CYP2C9 substrate): Fluconazole inhibits the conversion of losartan to its active metabolite (E-3174), which is responsible for a large part of the angiotensin II receptor antagonism that occurs with losartan therapy. Concomitant treatment with fluconazole might lead to increased concentrations of losartan and decreased concentrations of the active metabolite. It is recommended that patients receiving the combination be monitored for continued control of their hypertension.

Oral contraceptives: Two pharmacokinetic studies have been performed with a combined oral contraceptive and multiple dosing of fluconazole. 50 mg fluconazole did not influence any of the hormone concentrations, but 200 mg daily increased AUC of ethinyloestradiol and levonorgestrel with 40 and 24%, respectively. Thus, it is hardly likely that multiple dosing of fluconazole at these doses has an influence on the effect of the combined oral contraceptive.

Phenytoin (CYP2C9 substrate): Intake of fluconazole 200 mg concomitantly with phenytoin 250 mg intravenously increased the phenytoin AUC by 75% and $C_{min}$ by 128 %. If it is necessary to administer both substances concomitantly, the phenytoin concentration must be controlled, and the phenytoin dose adjusted, in order to avoid toxic concentrations.

Prednisone (CYP3A4 substrate): A liver transplant recipient receiving prednisone experienced an Addisonian crisis when a three-month course of fluconazole was discontinued. The withdrawal of fluconazole likely caused an increase in CYP3A4 activity, leading to an increase in the degradation of prednisone. Patients receiving long-term therapy with fluconazole and prednisone should be closely monitored for signs of adrenal insufficiency when fluconazole is withdrawn.

Rifabutine (CYP3A4 substrate): Reports about interaction with administration of fluconazole concomitantly with rifabutine have appeared, leading to increased serum levels of rifabutine. Uveitis in patients treated concomitantly with fluconazole and rifabutine has been reported. Patients who receive rifabutine and fluconazole concomitantly must be closely followed.

Sulphonyl urea (CYP2C9 substrate): It has been demonstrated that fluconazole prolongs the plasma half-life of concomitantly administered sulphonyl urea (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonyl urea derivatives may be used concomitantly to diabetics, but the possibility of development of hypoglycaemia must be kept in mind and blood glucose levels closely monitored.

Tacrolimus and sirolimus (CYP3A4 substrates): Concomitant intake of fluconazole and tacrolimus 0.15 mg/kg b.i.d. increased tacrolimus $C_{min}$ 1.4 and 3.1-fold with fluconazole doses of 100 mg and 200 mg, respectively. Renal toxicity has been reported in patients concomitantly receiving fluconazole and tacrolimus. Although no interaction studies have been conducted with fluconazole and sirolimus, a similar interaction as with tacrolimus might be expected. Patients who receive tacrolimus or sirolimus and fluconazole concomitantly must be closely monitored for tacrolimus/sirolimus plasma levels and toxicity.

Theophylline: Intake of fluconazole 200 mg for 14 days resulted in 18% decrease in the mean plasma clearance of theophylline. Patients on treatment with high doses of theophylline or with other reason to be at increased risk of theophylline toxicity should be carefully observed during fluconazole therapy, and the theophylline dose should be adjusted as necessary.

Trimetrexate: Fluconazole may inhibit the metabolism of trimetrexate, leading to increased trimetrexate plasma concentrations. If the combination cannot be avoided, trimetrexate serum levels and toxicity should be closely monitored.

Zidovudine: Interaction studies showed increased zidovudine AUC by approximately 20% and 70% when taken concomitantly with fluconazole 200 mg or 400 mg daily, respectively, probably due to

 

inhibition of the glucuronidation. Patients receiving this combination must be controlled for zidovudine related side-effects.

*Pharmacodynamic interactions*
Medicinal products that prolong QT interval: Case reports indicate that fluconazole might have the potential to induce QT prolongation leading to serious cardiac arrhythmia. Patients treated concomitantly with fluconazole and other drugs that prolong QT interval should be carefully monitored, since an additive effect cannot be excluded.

Amphotericin B: In vitro and in vivo animal studies have found antagonism between amphotericin B and azole derivatives. The mechanism of action of imidazoles is to inhibit ergosterol synthesis in fungal cell membranes. Amphotericin B acts by binding to sterols in the cell membrane and changing membrane permeability. Clinical effects of this antagonism are to date unknown, and a similar effect may occur with amphotericin B cholesteryl sulfate complex.

Interaction studies have shown that no clinically significant change in absorption of fluconazole occurs with oral use together with food, cimetidine, antacids or after radiation therapy of the whole body in connection with bone marrow transplantation.

## 4.6 Pregnancy and lactation

Data from several hundred pregnant women treated with standard doses (below 200 mg/day) of fluconazole, administered as a single or repeated dose during the first trimester, do not indicate undesirable effects on the foetus.

There are reports on multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in children whose mothers were treated for 3 months or longer with high doses (400-800 mg/day) of fluconazole for coccodiodal mycosis. The relationship between these effects and fluconazole is unclear.

Studies in animals have shown teratogenic effects (see section 5.3. preclinical safety data).

Fluconazole in standard doses and short-term treatment should not be used in pregnancy unless clearly necessary. Fluconazole in high doses and/or in prolonged regimens should not be used during pregnancy except for life threatening infections.

Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high-dose fluconazole.

## 4.7 Effects on ability to drive and use machines

Fluconazole has no or negligible influence on the ability to drive and use machines
However when driving vehicles or operating machines it should be taken into account that occasionally dizziness or seizures may occur.

## 4.8 Undesirable effects

The following treatment-related undesirable effects were reported in 4,048 patients receiving fluconazole for 7 or more days in clinical trials:

 

| Organ systems | *Very common* >1/10 | *Common* >1/100, <1/10 | *Uncommon* >1/1,000, <1/100 | *Rare* >1/10,000, <1/1,000 | *Very rare* <1/10,000 |
|---|---|---|---|---|---|
| General | | | fatigue, malaise, asthenia, fever | | |
| Central and Peripheral Nervous System | | headache | convulsions, dizziness, paresthesia, tremor, vertigo | | |
| Skin and Appendages | | skin rash | pruritus | exfoliative skin disorder (Stevens-Johnson syndrome) | |
| Gastrointestinal | | nausea and vomiting abdominal pain, diarrhoea | anorexia, constipation, dyspepsia, flatulence | | |
| Musculoskeletal | | | myalgia | | |
| Autonomic Nervous System | | | dry mouth, increased sweating | | |
| Psychiatric | | | insomnia, somnolence | | |
| Liver and Biliary System | | Clinically significant increase of AST, ALT and alkaline phosphatase | cholestasis, hepatocellular damage, jaundice Clinically significant increase of total bilirubin, | hepatic necrosis | |
| Special Senses | | | taste perversion | | |
| Hematopoietic and Lymphatic | | | anaemia | | |
| Immunologic | | | | anaphylaxis | |

Adverse clinical events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%). However, the patterns of adverse events in HIV infected and non-HIV infected patients were similar.

In addition, the following adverse events have occurred under conditions where a causal association is uncertain (e.g. open trials, during post-marketing experience):

 

| Organ systems | *Very common* >1/10 | *Common* >1/100, <1/10 | *Uncommon* >1/1,000, <1/100 | *Rare* >1/10,000, <1/1,000 | *Very rare* <1/10,000 |
|---|---|---|---|---|---|
| Central and Peripheral Nervous System | | | | seizures | |
| Skin and Appendages | | | | alopecia | exfoliative skin disorder (Stevens-Johnson syndrome and toxic epidermal necrolysis), erythema exudativum multiforme |
| Liver and Biliary System | | | | hepatic failure<br>hepatitis<br>hepatic necrosis | |
| Immunologic | | | | | anaphylaxis, angiooedema, face oedema and pruritus |
| Hematopoietic and Lymphatic | | | | leukopenia, including neutropenia and agranulocytosis, thrombocytopenia | |
| Metabolic | | | | hypercholesterolemia, hypertriglyceridemia, hypokalemia | |

### 4.9 Overdose

In case of overdosing the treatment is symptomatic with supporting measures and gastric lavage, if necessary. Fluconazole is mainly excreted in the urine. Forced volume diuresis will probably increase the elimination rate. Haemodialysis for 3 hours decreases the plasma levels with approx. 50%.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

*Pharmacotherapeutic Group*
Antimycotics for systemic use, triazole derivatives
ATC code: J02AC01
Fluconazole is a triazole derivative with fungistatic effect, which specifically inhibits the synthesis of the fungi's ergosterol, which is believed to lead to defects in the cell membrane. Fluconazole is highly specific for fungal cytochrome P-450 enzymes. Doses of fluconazole 50mg daily for 28 days have not been shown to influence serum levels of testosterone in men or the steroid concentration in fertile women.
The spectrum of application includes a number of pathogens including *Candida albicans* and *non-Candida albicans species*, *Cryptococcus spp* and dermatophytes. *Candida krusei* is resistant to fluconazole. Forty percent of *Candida glabrata* are primarily resistant to fluconazole. Infections caused by *Aspergillus*-species should not be treated with fluconazole.

### 5.2 Pharmacokinetic properties

Absorption: Fluconazole is well absorbed after oral intake. The absolute bioavailability is above 90 %. The oral absorption is not affected by concomitant food intake. The maximum fasting plasma concentration is reached 0.5 – 1.5 hours after dose intake. 90% of the steady-state level is reached 4-5 days after dosing once daily.
Plasma concentration is proportional to the dose. After administration of 200 mg of fluconazole, $C_{max}$ is around 4.6 mg/l and plasma concentrations at steady-state after 15 days are around 10 mg/l. After

 

administration of 400 mg of fluconazole, $C_{max}$ is around 9 mg/l and plasma concentrations at steady-state after 15 days are around 18 mg/l.
Intake of a double dose on day 1 results in plasma concentrations of approx. 90% of steady-state on day 2.

Distribution: The volume of distribution corresponds to the total body water. The protein binding in plasma is low (11-12%).

The concentration in saliva corresponds to the plasma concentration. In patients with fungal meningitis the concentration of fluconazole in the cerebrospinal fluid is approx. 80% of the corresponding plasma concentration.

In stratum corneum, epidermis-dermis and in exocrine sweat higher concentrations of fluconazole are reached compared to those in serum. Fluconazole is accumulated in stratum corneum. At a dose of 150 mg once weekly the concentration of fluconazole in stratum corneum was after 2 doses 23.4 µg/g and 7 days after the second dosing it was still 7.1 µg/g.

Elimination: Fluconazole is mainly renally excreted. Approx. 80% of the taken dose is excreted in the urine in non-metabolized form. Fluconazole clearance is proportional to the creatinine clearance. Circulating metabolites have not been demonstrated.
The half-life in plasma is approximately 30 hours.
Children eliminate fluconazole more rapidly than adults do. The half-life in children and adolescents of 5-15 years is between 15.2-17.6 hours.

### 5.3 Preclinical safety data

Preclinical data from conventional studies on repeat-dose/general toxicity, genotoxicity or carcinogenicity indicate no special hazard for humans not already considered in other sections of the SPC.

In reproduction toxicity studies in rat an increased incidence of hydronephrosis and extension of renal pelvis was reported and embryonal lethality was increased. An increase in anatomical variations and delayed ossification was noted as well as prolonged delivery and dystocia. In reproduction toxicity studies in rabbits abortions were recorded.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Capsules content:*
maize starch
colloidal anhydrous silica
sodium laurilsulphate
magnesium stearate.

*Capsule shell:*
gelatin
patent blue V (E131)
titanium dioxide (E171)
200 mg capsules also contain azorubine (E122).

*Printing ink:*
*50mg capsules:*
shellac
carbon black E153
*100 mg and 200 mg capsules:*

shellac
carbon black E153 (only black ink)
titanium dioxide E171 (only white ink)

*150mg capsules:*
shellac
carbon black E153 (only black ink)
erythrosine E127 (only blue ink)
brilliant blue E133 (only blue ink)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf-life

2 years.

### 6.4 Special precautions for storage

Do not store above 25 °C. Store in the original container.

### 6.5 Nature and content of container

The capsules are packed in PVC/PVdC/aluminum-foil blisters.

*Pack sizes:*

*Presentation*
50 mg capsules: 3, 7, 10, 14, 20, 28, 30, 42, 50 and 100 capsules
100 mg capsules: 7, 10, 14, 20, 28, 30, 50, 60 and 100 capsules
150 mg capsules: 1, 2, 4, 6, 10 and 20 capsules.
200 mg capsules: 7, 10, 14, 20, 28, 30, 50 and 100 capsules.

Not all pack sizes may be marketed

### 6.6 Instructions for use and handling, and disposal (if appropriate)

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

ALFRED E. TIEFENBACHER (GmbH & Co.)
Van-der-Smissen-Str. 1
22067 Hamburg
Deutschland

## 8. MARKETING AUTHORISATION NUMBER

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

 