2 September 2011
EMA/888361/2011
Patient Health Protection

Assessment report pursuant to Article 30 of Directive 2001/83/EC, as amended

Diflucan and associated names

INN of the active substance: fluconazole

Marketing authorisation holder: Pfizer group of companies and associated companies

Procedure no: EMEA/H/A-30/1156

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Background information on the basis of the grounds for referral

On 11 February 2010 the European Commission presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, as amended, in order to harmonise the national summary of product characteristics (SmPC), labelling and package leaflet (PL) of the medicinal products:

Diflucan and associated names (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the February 2010 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Dr Martina Weise as rapporteur and Prof Piotr Fiedor as co-rapporteur.

Diflucan medicinal products are registered in all EU Members States and also in Iceland and Norway.

2. Scientific discussion during the referral procedure

2.1. Introduction

Fluconazole is a substance belonging to the chemical class of triazole derivatives. Fluconazole specifically inhibits the fungal ergosterol synthesis and the mycotic cytochrome P-450 mediated enzymes. It is used in the systemic and topical treatment of fungal infections. Fluconazole displays antifungal activity against most clinically common *Candida* species. Fluconazole also exhibits activity *in vitro* against *Cryptococcus* species and the endemic moulds *Blastomyces dermatiditis*, *Coccidioides immitis*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis*. *Aspergillus* spp. is resistant against fluconazole. Fluconazole, a third generation azole, is characterised by high oral bioavailability, widespread distribution into body fluids and tissues, predictable renal clearance, and once-daily administration. The solubility characteristic allows oral as well as intravenous administration. Since the pharmacokinetic properties of orally and intravenously administered fluconazole are similar and fluconazole has good bioavailability, results obtained with oral dosing are also applicable to the intravenous formulation.

Fluconazole received first regulatory approval in France on 8 March 1988. Currently fluconazole is marketed in 130 countries world-wide and is approved but not marketed in further two countries.

Fluconazole is available for oral use in the 50 mg, 100 mg, 150 mg and 200 mg capsule formulation, in the 5 mg/ml syrup (oral solution) formulation, and in the 10 mg/ml or 40 mg/ml powder for oral suspension on reconstitution with water formulation.

A presentation of a single 150 mg capsule packaging is available in some Member States (MSs) which is indicated only for the genital candidiasis in adults

Fluconazole is available also for intravenous (IV) use in the 2 mg/ml saline solution formulation. It was already known that the oral absorption is rapid and almost complete so the recommended daily dose of fluconazole is the same for oral (capsules, oral suspension and syrup) and IV administration.

Furthermore, fluconazole was also available for topical use in the 0.5% gel formulation. This formulation was only approved in Italy and was indicated for the treatment of dermatomycoses due to dermatophytes, yeasts and moulds; in particular *Tinea pedis*, *Tinea corporis*, *Tinea cruris*, *Tinea*

versicolor and *Candida* infections. During the time of the evaluation of the referral procedure the Marketing Authorisation Holder (MAH) voluntarily withdrew the gel formulation from the European Market. Thus the outcome of this referral procedure does not include any evaluation of the gel formulation.

Diflucan has been included in the list of products for Product Information (PI) harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended. Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product (and its associated names), the European Commission notified the CHMP/EMA Secretariat of an official referral under Article 30 of Directive 2001/83/EC as amended in order to resolve divergences amongst the nationally authorised PIs and thus to harmonise its divergent PIs across the European Union.

2.2. Critical Evaluation

2.2.1 Quality aspects

The MAH took also the opportunity to harmonise the Quality dossier for Diflucan and associated names as part of the Article 30 referral procedure.

The harmonised dossiers were provided for the drug substance (fluconazole) and for products containing this substance, including: Diflucan 50 mg, 100 mg, 150 mg and 200 mg capsules, Diflucan 10 mg/ml and 40 mg/ml powder for oral suspension, Diflucan syrup 5 mg/ml and Diflucan 2 mg/ml solution for infusion.

Drug Substance

Sufficient information was provided on the manufacturing process of the drug substance, including description of the synthesis, purification, amounts of raw materials and yields.

The structure of the substance, including information about polymorphic properties, was adequately characterised. Fluconazole exists in 3 polymorphic forms (I, II and III) and only the polymorph III is used for manufacturing of Diflucan. The commercially utilized manufacturing process is designed to produce the desired polymorph.

The drug substance specification complies with the Ph. Eur. Monograph for Fluconazole. It contains additional tests for residual solvents and particle size. Potential impurities (related substances and residual solvents) arising from the manufacturing process have been identified and are controlled using suitably validated analytical methods.

Batch analysis results proved the compliance with the drug substance specification.

The provided stability results support the proposed re-test period and storing conditions.

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics.

Drug Product

Capsules, hard 50 mg, 100 mg, 150 mg and 200 mg

The provided dossier describes sufficiently the composition, manufacture and control of the product.

The shelf life of the capsules of five years is supported by the stability data given. The storage precaution "Do not store above 30°C" is included in the product information.

Powder for oral suspension 10 mg/ml and 40 mg/ml

The provided dossier describes sufficiently composition, manufacture, and control of the product. The shelf life has been reduced to 24 months. The storage precaution "Do not store above 25°C" is included in the product information. The shelf-life after reconstitution of 28 days with the storage precautions "Store below 30°C, do not freeze" were supported by stability data.

Syrup 5 mg/ml

The provided dossier describes sufficiently composition, manufacture, and control of the product at issue. The approved shelf life of five years without a requirement for special storage conditions has been sufficiently justified. An in-use stability of 30 days was claimed.

Solution for infusion 2 mg/ml (glass vials)

The drug product is presented as glass vials containing 25 ml, 50 ml, 100 ml or 200 ml or solution for infusion.

The pharmaceutical development and the manufacturing process including batch formula, flow chart and in-process controls were adequately described. Satisfactorily process validation data were provided.

The release and shelf life specifications contain all relevant test parameters for this pharmaceutical form. Method descriptions and the provided validation data are satisfactorily. Batch analysis data are given showing compliance with the specifications.

The shelf life of five years for all packaging sizes, if stored not frozen, is sufficiently supported by the stability data given.

Solution for infusion 2 mg/ml (flexbags)

The product is presented as plasticized polyvinyl chloride bags (plasticized PVC) overpackaged in a complex made of a 115 µm-thick film of polyamide/polyolefine/ethylene-propylene copolymer and of a 150 µm-thick peelable film of polypropylene/polyolefine/ethylene-propylene copolymer, Bags contain 100 ml or 200 ml of solution for infusion.

The manufacturing process including flow chart is adequately described. The provided process validation data for each of the packaging sizes are acceptable.

The release and shelf life specifications contain all relevant test parameters for this pharmaceutical form. The analytical methods are adequately described. Satisfactorily validation data are presented.

Batch analysis data are given showing compliance with the specifications.

Based on the provided stability data the proposed shelf life of 18 months, if stored below 30°C, can be accepted for the 100 and 200 ml packaging volume. The product should not be frozen.

Conclusions

Information on development, manufacture and control of capsules, powder for oral suspension, syrup and solution for infusion has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these

in turn lead to the conclusion that the products should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were minor unresolved quality issues which have no impact on the Benefit/Risk ratio of the products. The MAH will resolve these issues after the opinion, and implement them in the ongoing development of the medicinal product.

The issues identified are listed below.

Capsules 50 mg, 100 mg, 150 mg and 200 mg

Validation data for two additional batches of registered blend size will be provided. The specification limit for a known impurity will be reviewed when sufficient batch and stability data are collected. If necessary, updated release and shelf life specifications will be provided.

Powder for oral suspension 10 mg/ml and 40 mg/ml

The specification limit for a known impurity will be reviewed when sufficient batch and stability data are collected. If necessary, updated release and shelf life specifications will be provided.

Syrup 5 mg/ml

In May 2011, the MAH submitted a validated test method for impurities in the syrup formulation. The finished product specification will be updated once adequate information on impurities from batch release data have been obtained. The MAH will perform an in-use stability study to investigate microbiological purity. The MAH will monitor microbiological and chemical purity in parallel in this in-use stability study.

Solution for infusion 2 mg/ml (glass vial and flex bag)

The specification limit for a known impurity will be reviewed once sufficient batch and stability data are collected. If necessary, updated release and shelf life specifications will be provided.

2.2.2 Clinical aspects

In line with the Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease CHMP/EWP/1343/01 Rev.1 it is recommended to distinguish clearly in the SmPC whether there is an indication for treatment, for maintenance treatment or for prophylaxis. In that respect the MAH was requested during this regulatory procedure to work towards the distinction between the Therapeutic indications (section 4.1 of the SmPC) according to this guideline. This approach is followed also in different sections of the SPC, where applicable, e.g. in the section 4.2, Posology and Method of administration and where the doses for prophylaxis are listed separately.

In that particular section the MAH was requested firstly to clarify and justify the posology to adults, children and immunocompromised patients and in a second step to present more concisely the different doses in the treatment, maintenance and/or prevention of the different indications including the paediatric population.

The major clarifications in the different sections of the Product Information are highlighted below.

Section 4.1 – Therapeutic Indications

The structure of the text for the indications after consultation with the IDWP is based on the agreement that some indications should be strengthened, some indications should be separated from each other and that the indications should be divided into treatment and prophylaxis. Below there is an overview of the therapeutic indications as they are finally formulated and the justification on the occurring changes.

Mucosal Candidiasis

Candida species can cause a variety of clinical syndromes that are generically termed candidiasis and are usually categorised by the site of involvement. One of the most common syndromes is mucocutaneous candidiasis which includes oropharyngeal, oesophageal, candiduria, mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth). Both normal hosts and patients with compromised immune function due to cancer chemotherapy, AIDS or genetic predisposition are susceptible to such infections.

Fluconazole was formulated for oral use and approved in Europe for the treatment of mucosal candidiasis in 1988. A review of all EU SPCs including Iceland (IS) and Norway (NO) has revealed that mucosal candidiasis indications have been approved in all MSs including IS and NO in European Union.

Oropharyngeal candidiasis

Oropharyngeal candidiasis is a frequent infection in immunocompromised hosts and is particularly common among cancer and HIV infected patients (*Laudenbach and Epstein, 2009*). This infection is painful, impairs quality of life and may result in reduction of food and fluid intake. In addition, extension of oropharyngeal candidiasis to the oesophagus is a common complication, occasionally leading to fungaemia and disseminated candidiasis.

Fluconazole at 100 to 200 mg/day as capsules, and 2 to 6 mg/Kg as oral solution, was well tolerated and was efficacious in treating oropharyngeal candidiasis in immunocompromised adult and paediatric patients. It was equivalent to, or more effective than, the various comparator agents.

Oesophageal Candidiasis

Oesophageal candidiasis is a severe infection which can lead to candidaemia if untreated. Like oropharyngeal infection it occurs most frequently in immunocompromised patients. The recommended dose of fluconazole to treat this infection is 200 to 400 mg/day depending on its severity.

Fluconazole at doses from 100 mg/day to 200 mg/day, or 400 mg/day in severe cases, was well tolerated and was efficacious in immunocompromised patients with oesophageal candidiasis. It was as effective as or superior to the azole comparators.

Candiduria

Candiduria is rare in normal individuals but increasingly common in hospitalised patients. In tertiary care facilities some 10% of positive urine cultures yield a fungal pathogen (*Sobel et al 2000*). In addition, the incidence of nosocomial *Candida* urinary tract infections have increased due to

predisposing factors such as urinary tract instrumentation, the use of broad spectrum antibiotics and an increasing number of high risk patients in intensive care (*Hollenbach 2008*). The most recently recommended fluconazole dose for this indication is 200 mg (3 mg/Kg) per day (*Pappas et al 2009*).

The patients studied are hospitalised cases in general wards or in the Intensive Care Unit (ICU) and thus, had a wide range of predisposing underlying conditions including catherisation, broad spectrum antibiotic use, diabetes, surgery, gastrointestinal, renal or infectious disease and other critical illness requiring ICU residence.

The fluconazole doses used in the studies varied from 25 mg/day to 800 mg/day, although the comparative studies used 100 mg/day to 200 mg/day. The higher doses were employed for critically ill patients who were considered to be at significant risk of developing candidaemia.

In conclusion, fluconazole at 100 mg/day to 200 mg/day for 14 days was well tolerated and showed efficacy equivalent to that of amphotericin B bladder irrigation. At 800 mg/day, in high-risk ICU patients, it gave similar mycological cure rates and appeared to prevent the subsequent development of candidaemia. However, reversible elevations of hepatic transaminases were observed in some patients.

Chronic Oral Atrophic Candidiasis

Candida-associated denture stomatitis is characterised by general inflammation of that area of the palatal mucosa covered by the denture (*von Fraunhofer and Loewy 2009*). It is a very common, if relatively harmless form of oral candidiasis and may affect up to 50% of denture wearers at some time (*Cross et al 1998*). If uncontrolled it may spread to other areas including the angles of the mouth, the tongue, the pharynx and even the alimentary and respiratory tracts. It may also cause severe itching and burning sensations on the mucosa. Treatment usually involves a combination of advice on improving denture hygiene plus topical therapy with hexitidine or various antifungal agents such as amphotericin or miconazole as well as oral azoles.

In all studies fluconazole was given at a dose of 50 mg/day for 14 or 15 days and it also showed similar mycological efficacy. In conclusion, fluconazole at 50 mg/day for 14 days was well tolerated and showed efficacy similar to the active comparator agents. The CHMP agreed that fluconazole should be indicated for the treatment for chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene or topical treatment are insufficient.

Chronic Mucocutaneous Candidiasis

Chronic mucocutaneous candidiasis is a rare disorder characterised by persistent or recurrent candidal infections of the skin, nails and mucous membranes or by a variable combination of endocrine failure as well as immunodeficiency (*Eyerich et al 2010*). Clinically, the main complications are debilitating infection of the hands (*Candida* granuloma), nails (*Candida* pyronichia), mouth and oesophagus. Resulting oesophageal stricture may cause maldigestion and/or mal-absorption. Furthermore, the chronic infections may be a risk factor for the development of squamous cell carcinoma of the oral cavity and oesophagus (*Rosa et al 2008; Eyerich et al 2010*). Resistance to antifungal drugs is common on long term therapy and consequently, a flexible therapeutic management scheme is essential for these patients.

A range of antifungal agents including amphotericin B, 5-flucytosine, ketoconazole, fluconazole and itraconazole have all been shown to be effective as initial therapy and in keeping patients in remission for variable periods. The number of patients with this pathology is small but ketoconazole (at 100 mg

to 200 mg/day) has been studied in small formal clinical trials (*Petersen et al, 1980; Horsburgh et al, 1983; Mobacken et al, 1986*) in a total of 46 patients. In these studies most patients responded to initial, long term therapy (up to 14 months depending on the site and severity of infection) but some subsequently relapsed.

Fluconazole was administered at 25 mg to 100 mg/day for up to four weeks or longer in some individuals. Both clinical and mycological remissions were achieved despite most patients having received prior therapy with other azole antifungal agents. Fluconazole was effective and well tolerated in adults and children. However, as with other antifungal agents, a few patients eventually relapsed but responded to a second course of fluconazole.

Mucosal Candidiasis Overall Conclusions

In all of these studies fluconazole was efficacious and equivalent or superior to the standard agents in both adults and paediatric patients. It was also generally well tolerated and there were no changes of clinical significance, either biochemically or haematologically, at doses of up to and including 400 mg/day. A dose of 800 mg/day, in ICU patients with candiduria, resulted in reversible elevations of transaminase enzymes in some patients. Patient compliance was also good. The results are supportive of fluconazole as an appropriate treatment for mucosal candidiasis in both patients with and without AIDS. These indications are appropriate for the capsules, IV infusion, powder for oral suspension and the syrup. The CHMP noted all the data presented by the MAH and is in agreement for these indications.

Prevention of Relapse of Oropharyngeal Candidiasis

The MAH presented four studies on prevention of relapse. All studies were randomised and comparative, including both oropharyngeal and oesophageal candidiasis prevention and two were double blind. The four studies included 1268 patients; fluconazole 626 patients and placebo 642 patients.

Relapse prevention in both AIDS and cancer patients was investigated. Several different dosing regimens were employed, 100 mg/day, 200 mg/day and 200 mg three times/week. They examined relapse compared with placebo or no treatment observation. In all studies fluconazole was as or more effective than placebo/observation in preventing clinical relapse. In cancer patients it was superior to placebo in preventing mycological relapse.

The MAH concluded that continuous therapy with fluconazole at 100 mg/day and continuous or intermittent therapy at 200 mg/day are effective in preventing relapse of oropharyngeal or oesophageal candidiasis in patients with underlying AIDS or cancer and are well tolerated. These indications are appropriate for the capsules, IV infusion, powder for oral suspension and the syrup. The CHMP is in agreement in separating the treatment from the prophylaxis of the relapse on Oropharyngeal Candidiasis.

Genital Candidiasis

Infection of male and female genital areas is relatively common and responds well to an oral administration of fluconazole. Fluconazole is approved to treat acute or recurrent vulvovaginal candidiasis in women and candidal balanitis in men. Fluconazole is also used as maintenance therapy (prophylaxis) for prevention of the recurrence of vaginal candidiasis.

A review of all EU SPCs including IS and NO has revealed that vaginal candidiasis indication has been approved in all MSs.

Vulvovaginal Candidiasis and Acute vulvovaginal candidiasis

Vulvovaginitis is inflammation or infection of the vulva and vagina. Acute vulvovaginal candidiasis (VVC) is the second commonest cause of infective vaginal discharge and is caused by overgrowth within the vagina of yeasts [usually *C. albicans* (80–95% of cases) or *C. glabrata* (5%)]. An estimated 75% of women will have at least one episode of VVC, and 40%-45% will have two or more episodes, however, recurrent VVC, usually defined as 4 or more episodes of symptomatic VVC each year, affects a small percentage of women (<5%).

Fluconazole was formulated for oral use and approved in Europe for the treatment of vulvovaginal candidiasis in 1988. The original application contained information from 8 studies. These included 3 pivotal studies evaluating the efficacy of a single 150 mg dose of fluconazole which consisted of one non-comparative study and comparative studies versus clotrimazole and ketoconazole.

The pharmacokinetic profile of fluconazole enables its use as a single agent due to its prolonged elimination half-life of approximately 36 hours and its distribution into vaginal tissues and secretions, with concentrations above the minimum inhibitory concentration for *C. albicans* persisting for at least 72 hours.

Fluconazole (as a single dose) is recommended as the oral agent of choice for uncomplicated vulvovaginal candidiasis (*Pappas et al, 2009; Workowski & Berman, 2006*). For complicated vulvovaginal candidiasis, topical therapy for at least 7 days or multiple doses of fluconazole are recommended. Azole therapy is frequently unsuccessful for VVC due to *C. glabrata* (*Pappas et al, 2009*).

Recurrent vulvovaginal candidiasis and maintenance therapy

Recurrent vulvovaginal candidiasis (RVVC), usually defined as four or more episodes of symptomatic VVC each year, affects a small percentage of women (<5%). The pathogenesis of RVVC is poorly understood, and most women who have RVVC have no apparent predisposing or underlying conditions. Each individual episode of RVVC caused by *C. albicans* responds well to short duration oral or topical azole therapy. However, to maintain clinical and mycologic control, a longer duration of initial therapy (e.g., 7-14 days of topical therapy or a 150 mg, oral dose of fluconazole repeated 3 days later) to achieve mycologic remission before initiating a maintenance antifungal regimen.

Fluconazole is recommended as chronic suppressive therapy in adult patients with human immunodeficiency virus (HIV) who have frequent or severe recurrences of vulvovaginal candidiasis (*Centers for Disease Control and Prevention et al, 2009*). Severe vulvovaginitis (i.e., extensive vulvar erythema, edema, excoriation, and fissure formation) has lower clinical response rates in patients treated with short courses of topical or oral therapy. Either 7-14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended. For recurrent vulvovaginal candidiasis (greater than 4 episodes within 1 year), a suppressive regimen with fluconazole is recommended for at least 6 months. The suppressive regimen should be preceded by induction therapy with 10 to 14 days of a topical or oral azole. Fluconazole is a well-tolerated therapy (*Pappas et al, 2009*).

Candidal Balanitis

Candidal balanitis is inflammation of the penis gland caused by infection with *Candida* spp. The approval of the candidal balanitis indication was based on a single study of single dose fluconazole 150 mg in comparison to twice daily clotrimazole cream given for 7 days.

As with the local treatment of vaginal candidiasis, a high degree of effectiveness coupled with convenience of an oral dose contributes to improved patient acceptability and compliance.

Genital Candidiasis - Overall Conclusions

Oral single-dose therapy with fluconazole in vaginal candidiasis and candidal balanitis has been a treatment option for around 30 years. The evidence is based on a clinical trial programme of three studies in vulvovaginal candidiasis and one in candidal balanitis. In addition, the pharmacokinetic profile of fluconazole enables its use as a single agent due to its prolonged elimination half-life of approximately 36 hours and its distribution into vaginal tissues and secretions, with concentrations above the minimum inhibitory concentration for *C. albicans* persisting for at least 72 hours. Overall, therefore, a single 150 mg dose of fluconazole provides a safe and effective treatment for vulvovaginal candidiasis in adult women or candidal balanitis in adult men. Fluconazole with its marked activity against *Candida* species and favourable pharmacokinetics offers a safe, effective, and convenient alternative to topical therapy in a single-dose regimen for both candidal vaginitis and candidal balanitis. These indications are appropriate for the capsules, IV infusion, powder for oral suspension and the syrup. The CHMP accepted that the data presented by the MAH was satisfactory for these indications. More specifically the one 150 mg capsule presentation authorised in some MS is specifically indicated for the above genital candidiasis indications in adults when local therapy is not appropriate.

Deep endemic mycoses- coccidioidomycosis

Fluconazole was formulated for oral use and approved in Europe for the treatment of deep endemic mycoses in 16 MSs.

Certain mycoses are common and major causes of morbidity in patients with AIDS who have lived in the areas where these mycoses are endemic because of its low incidence in the European continent, the diseases are not well known. They are most often acquired through contact with nature and rarely with infected humans and animals. Most endemic mycoses occur after inhalation of conidia, while subcutaneous mycoses are caused by the inoculation of vegetable matter or soil. The frequency of AIDS- associated histoplasmosis and coccidioidomycosis is now increasing with the spread of HIV infection, other endemic mycoses are less frequently associated with HIV infection (*Lortholary et al, 1999*).

For coccidioidomycosis, azole antifungals, primarily fluconazole and itraconazole, have replaced amphotericin B as initial therapy for most chronic pulmonary or disseminated infections. Therapy with oral fluconazole is currently preferred by most physicians and some begin with doses of 800-1000 mg per day.

Coccidioidomycosis

Coccidioidomycosis is a disease with protean manifestations. Coccidioidomycosis is less common than histoplasmosis but may be seen in patients with AIDS who reside in or have visited the southwestern United States and parts of Latin America (*Wheat 1995*). This poses a real risk also for residents in Europe, as people travel across borders, though the incidence maybe rare.

The Diaz et al (1992) study included fourteen of 16 patients with coccidioidomycosis who responded to therapy with fluconazole.

Fluconazole and itraconazole have primarily replaced amphotericin B as initial therapy for most chronic pulmonary or disseminated coccidioidomycosis infections (*Gagliani et al 2005*).

Endemic mycoses remain a major public health problem in several countries and they are becoming increasingly frequent with the spread of HIV infection. The incidences in the endemic areas of these fungal infections are increasing and the population travelling toward its specific endemic regions in the United States and Southern America is growing. Fluconazole therapy is efficacious for several deep mycoses and is supported by clinical trial data as well as guidelines. When higher doses are used, some deep diseases are responsive. No substantial toxicity has been observed at higher doses.

Endemic Mycoses - Coccidioidomycosis *Conclusions*

The MAH was in addition requested to discuss the clinical benefits and safety as a primary therapy in coccidioidomycosis at 400 mg to 800 mg daily (particularly in CNS infection) compared with conventional amphotericin B or itraconazole (Galgiani et al 2007). In conclusion, the fluconazole, at 400 mg to 800 mg daily is a safe and effective primary treatment for coccidioidomycosis. The MAH provided sufficient data on the relative efficacy and safety of fluconazole in invasive fungal infections (Cryptococcosis, invasive candidiasis, deep endemic mycosis) as compared to other therapeutic options and demonstrated a favourable benefit/risk ratio. The use of fluconazole for the above indications is also supported by the IDSA guidelines. These indications are appropriate for the capsules, IV infusion, powder for oral suspension and the syrup.

For the indications of paracoccidioidomycosis, histoplasmosis, lymphocutaneous sporotrichosis, where other agents have failed or are not tolerated, it was deemed by the CHMP during the assessment that the submitted data on efficacy was not adequate. So these indications are no longer referred to in section 4.1 of the SPC and a warning has been added in the corresponding section. The CHMP is in agreement of the proposed changes.

Dermatomycosis

Dermatomycoses include Tinea pedis, Tinea corporis, Tinea cruris, Tinea versicolor, Tinea unguinium (onychomycosis) and dermal *Candida* infections. The use of fluconazole for the treatment of fungal skin infections was examined in several comparative and non-comparative studies. These studies demonstrated that oral fluconazole is an effective and well-tolerated treatment for superficial fungal skin infections.

Tinea corporis, tinea cruris, tinea pedis and cutaneous candidiasis

Superficial skin infections due to dermatophytes are widespread. Factors that determine treatment selection include spectrum of activity, pharmacokinetics, efficacy, safety and duration of therapy. Generally 2 to 6 weeks of treatment is necessary to cure skin infections. Efficacy of treatment is judged by clinical criteria (disappearance or alleviation of signs and symptoms). The use of fluconazole for the treatment of fungal skin infections was examined in several comparative and non-comparative

studies. These studies demonstrated that oral fluconazole is an effective and well-tolerated treatment for superficial fungal skin infections.

Tinea versicolor

The MAH has submitted published studies for this indication. Here below are the results of some indicative ones.

Amer et al (*1997*) conducted a randomised, open-label, multicenter study to investigate 3 regimens of fluconazole in 603 patients with tinea versicolor. The authors concluded that clinical and mycological efficacy results indicated that the Group fluconazole 300 mg weekly for 4 weeks and fluconazole 300 mg in a single dose that could be repeated 2 weeks later were the most effective, but that the difference between the groups was not clinically significant enough to warrant the use of the higher total dose. In addition, the prolonged therapeutic efficacy of fluconazole was demonstrated in this study by the maintenance of response 4 weeks after discontinuation of the drug.

Montero-Gei et al (*1999*) conducted a randomised, open-label, multicenter study evaluating 90 patients with tinea versicolor. The conclusion was that fluconazole administered as two 300 mg doses given 1 week apart was more effective than a single 450 mg dose of fluconazole and at least as effective as a 7-day regimen of itraconazole 200 mg daily.

Faegerman (*1992*) investigated 24 patients with extensive or recurrent pityriasis versicolor who were treated with a single 400 mg oral dose of fluconazole. The authors concluded that a single dose of fluconazole is a safe and effective alternative to topical treatment of pityriasis versicolor.

Onychomycosis - Tinea unguinium

Onychomycosis is difficult to treat, and often exerts a significant negative impact on quality of life. It is responsible for some 50% of all consultations for nail disorders. The prevalence of onychomycosis could be as high as 10% in certain countries, and is even higher in patients with diabetes mellitus or human immunodeficiency virus (HIV) infection. Onychomycosis is far more common on the toenail than it is on the fingernail. In fingernails, paronychia infections are common and are often caused by *C. albicans*. This may predispose patients to subsequent invasion of the remainder of the nail plate. Patients with diabetes mellitus have an increased susceptibility to candidal infections of the nails. Both sexes appear to be equally affected. Onychomycosis may occur at any age, but is unusual prior to puberty.

Although onychomycosis causes pain and discomfort, for decades, until new antifungal drugs became available it had been considered incurable. One of the earliest treatments was surgical removal of the infected nail plate, or matrixectomy. This drastic therapy was often refused by patients. It caused temporary disablement or even permanent deformation and is now not often used. Topical therapy alone is a very long treatment, with 1 or 2 applications per day for at least 6 months, and requires perfect patient compliance. Topical therapies may produce some clinical response but are not considered extremely effective, especially if a significant proportion of the nail matrix is involved (*Hettinger, 1991*).

New developments in systemic antifungal therapy included the allylamines and azole derivatives, the triazoles. Oral antifungal agents, such as itraconazole, terbinafine and fluconazole, appear to be effective. These antifungal drugs achieve high mycological and clinical cure rates in onychomycosis of the toes.

Several studies were summarised by Brown (*2009*). One study used daily dosing and the rest used once-weekly dosing. Treatment doses ranged from 100 to 450 mg weekly and 150 mg daily, and

durations ranged from 12 weeks to 12 months. Most of the studies evaluated the efficacy of fluconazole in patients with toenail onychomycosis due to dermatophyte infection. The author concluded that fluconazole was less effective than terbinafine and itraconazole in the treatment of onychomycosis. However, fluconazole may be preferred in patients unable to tolerate other oral antifungal agents due to the dosing regimen, adverse effect profile, and drug interactions.

Conclusions on Dermatomycosis

The studies submitted by the MAH confirm that fluconazole is an effective, well tolerated antimycotic agent active against Tinea corporis, Tinea cruris, Tinea pedis, Tinea versicolor and onychomycosis.

While both the once weekly and once daily regimens are effective the advantages of the once weekly regimen relative to once daily therapy include a potentially better patient compliance and lower treatment costs. Many topical antifungal agents may not penetrate keratinous tissues where fungi reside and therefore relapses occur after apparently successful treatment.

Oral agents offer advantages over topical agents in this regard, as well as in patient compliance. Use of oral agents has been limited in the past by concerns over their safety profiles. Fluconazole has a favourable safety profile and has demonstrated efficacy in the treatment of fungal skin infections. It is a good alternative to topical agents and is better tolerated by patients than the older oral antifungal drugs.

For Tinea unguinium (onychomycosis) the CHMP concluded that fluconazole is indicated only when other agents are not considered appropriate.

These indications are appropriate for the capsules, IV infusion, powder for oral suspension and the syrup. The CHMP is in agreement on the final wording of these indications.

Cryptococcosis - Cryptococcal meningitis

Fluconazole is indicated in the treatment of cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g., pulmonary, cutaneous). Fluconazole can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with HIV infection. Patients with malignancy, in intensive care units, receiving cytotoxic or immunosuppressive therapy, or with other factors predisposing to candidal infection may be treated. Many patients treated with fluconazole are severely ill and have serious background conditions including malignancies and HIV infection.

Cryptococcal meningitis is caused by the fungus *Cryptococcus neoformans*. This microorganism is found in soil contaminated by bird feces. The port of entry into the body is generally through inhalation. Cryptococcal meningitis is an opportunistic infection and AIDS-defining illness that usually occurs in patients with CD4 count <100 cells/mm^3. Although *C. neoformans* typically infects immunocompromised persons, patients with no apparent immune system problems develop cryptococcosis. In order to properly diagnose cryptococcal meningitis, a lumbar puncture must be performed. This test involves taking a sample of cerebrospinal fluid from the spinal column. Prompt diagnosis and treatment are crucial as cryptococcal meningitis can be fatal if untreated. Reported mortality rate of meningitis is 6-25%.

The MAH argued that clinical trials have demonstrated fluconazole's efficacy, its pharmacokinetics and its safety profile. Earlier clinical trials included patients with cryptococcal meningitis who received low doses of fluconazole (50-100 mg). These clinical trials supported a change in future study design which resulted in a dosage increase for patients with cryptococcosis. In general a loading dose of twice the

daily dose (400 mg) is recommended on the first day of therapy to result in plasma concentrations close to the steady-state by the second day of therapy. This is followed by 200 mg once daily. A dose of 400 mg once daily may be used based on medical judgment and the patient's response to therapy. Since oral absorption is rapid and almost complete, the daily dose of fluconazole is the same for oral (tablets and suspension) and IV administration. Pharmacokinetics studies demonstrate that fluconazole penetrates well into the aqueous humor of the cerebrospinal fluid.

In a randomised multicentre trial, Saag et al (*1992*) compared intravenous amphotericin B (0.3 mg/Kg/day) with oral fluconazole (200 mg per day) as primary therapy for AIDS-associated acute cryptococcal meningitis. Treatment was successful in 25 of the 63 amphotericin B recipients and in 44 of the 131 fluconazole recipients. There was no significant difference between the groups in overall mortality due to cryptococcosis (amphotericin B vs. fluconazole, 9 of 63 vs. 24 of 131). The authors concluded that fluconazole is an effective alternative to amphotericin B as primary treatment of cryptococcal meningitis in patients with AIDS.

In patients with AIDS, the rate of relapse after primary treatment for cryptococcal meningitis remains high. Bozzette et al (*1991*) conducted a controlled, double-blind trial to evaluate the efficacy of maintenance therapy with fluconazole. The dose of fluconazole was 100 mg daily in the first phase of study and 200 mg daily in the second phase. In patients with AIDS, silent persistent infection is common after clinically successful treatment for cryptococcal meningitis. Maintenance therapy with fluconazole is highly effective in preventing recurrent cryptococcal infection.

A subcommittee of the National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group evaluated available data on the treatment of cryptococcal disease (*Saag et al 2000*). The relative strength of each recommendation was graded according to the type and degree of evidence available to support the recommendation, in keeping with previously published guidelines by the Infectious Diseases Society of America (IDSA). The choice of treatment for the disease caused by *Cryptococcus neoformans* depends on both the anatomic sites of involvement and the host's immune status.

Cryptococcal disease that develops in patients with HIV infection always warrants therapy. For those patients with HIV who present with isolated pulmonary or urinary tract disease, fluconazole at 200-400 mg/day is indicated. It is recommended that all HIV-infected individuals continue maintenance therapy for life. Among those individuals who are unable to tolerate fluconazole, itraconazole (200-400 mg/day) is an acceptable alternative. For patients with more severe disease, a combination of fluconazole (400 mg/day) plus flucytosine (100-150 mg/day) may be used for 10 weeks, followed by fluconazole maintenance therapy. Among patients with HIV infection and cryptococcal meningitis, induction therapy with amphotericin B (0.7-1 mg/Kg/day) plus flucytosine (100 mg/Kg/day for 2 weeks) followed by fluconazole (400 mg/day) for a minimum of 10 weeks is the treatment of choice. After 10 weeks of therapy, the fluconazole dosage may be reduced to 200 mg/day, depending on the patient's clinical status. Fluconazole should be continued for life.

The MAH also presented data on alternative regimens. An alternative regimen for AIDS-associated cryptococcal meningitis is amphotericin B (0.7-1 mg/Kg/day) plus 5-flucytosine (100 mg/Kg/day) for 6-10 weeks, followed by fluconazole maintenance therapy. Lipid formulations of amphotericin B can be substituted for amphotericin B for patients whose renal function is impaired. Fluconazole (400-800 mg/day) plus flucytosine (100-150 mg/Kg/day) for 6 weeks is an alternative to the use of amphotericin B, although toxicity with this regimen is high. In all cases of cryptococcal meningitis, careful attention to the management of intracranial pressure is imperative. In summary, fluconazole 200-400 mg/day is the preferred drug of choice for patients with symptomatic infection. Patients who have completed initial therapy for cryptococcosis should be administered lifelong suppressive treatment with

fluconazole. The guidelines also indicate that fluconazole is superior to itraconazole in preventing relapse of cryptococcal disease.

For many years amphotericin B was the only fungal agent available for serious fungal infections. Fluconazole has demonstrated *in vitro* and *in vivo* efficacy against *Cryptococcus neoformans* thus providing clinicians with a treatment option that is less toxic than amphotericin B. Fluconazole has been established as a safe and effective antifungal therapy in healthy and immunocompromised patients with cryptococcal meningitis. The CHMP concluded that there is enough clinical data supporting fluconazole as treatment of cryptococcal meningitis in children and adults as well as in preventing the relapse in patients with high risk of recurrence. The CHMP accepted that there is supporting data only for the indication of cryptococcal meningitis which is implemented in the SPC. These indications are appropriate for the capsules, IV infusion, powder for oral suspension and the syrup. The infections of other sites (e.g. pulmonary, cutaneous) are not supported by the submitted data and the CHMP agreed that they are no longer mentioned in the section 4.1 of the PI.

Invasive Candidiasis

Systemic candidiasis is a *Candida* infection that spreads throughout the body. If it invades major organs such as the brain and heart, death may result. It is rare in healthy individuals and tends to occur in immunocompromised individuals. The disorder is difficult to diagnose as the fungus can invade almost any organ of the body and hence the symptoms are hugely variable.

The incidence of systemic candidal infections has increased significantly in recent years. Factors recognised as increasing the risk of developing fungal infection include the use of immunosuppressive therapy, cytotoxic chemotherapy, corticosteroids, cyclosporine, ablative radiation therapy, extended-spectrum antibiotic therapy, organ transplantation, major surgery, long-term indwelling central catheter, bladder catheter, and haemodialysis. Other risk factors include diarrhoea, neutropenia, acquired immunodeficiency syndrome, hospital transfer, and hospitalisation in an intensive care unit (*Eggimann et al 1999*). Treatment of these infections poses a challenge to clinicians.

Candida species are an increasing cause of sepsis among non-neutropenic patients receiving intensive care; one-half to two thirds of all episodes of candidemia occur in an ICU or surgical ward. *Candida* colonisation, severity of illness, number of broad-spectrum antibiotic agents used and duration of use, previous surgery (especially bowel surgery), receipt of dialysis, use of central venous catheters, receipt of parenteral nutrition, and length of ICU stay are important risk factors for invasive candidiasis. Few clinical studies have carefully examined the impact of empirical or pre-emptive treatment strategies. In one study, pre-emptive therapy with fluconazole in selected colonised patients in a surgical ICU was associated with reduced incidence of proven candidiasis.

Fluconazole has proven to be safe and efficacious for systemic candidiasis. Fluconazole and amphotericin B were associated with similar clinical response rates and survival in the treatment of candidemia; however, drug-related adverse events were more frequent with amphotericin B. Higher loading doses of fluconazole have proven to be effective.

The safety of fluconazole in prophylaxis of invasive candidiasis at doses ranging from 1.0 mg/kg/day to 12.0 mg/kg/day in 562 paediatric patients was considered to be excellent when compared with various antifungal agents. Fluconazole prophylaxis in adults at 400 mg daily has also been shown to have an excellent efficacy and safety record in comparison with itraconazole oral solution and superior safety to posaconazole.

Fluconazole at 400 mg to 800 mg daily certainly shows efficacy and safety equivalent to that of anidulafungin and voriconazole in the treatment of non-neutropenic patients with invasive candidiasis.

The CHMP concluded that fluconazole is a safe and effective medicinal product in prophylaxis or treatment for invasive candidiasis compared to other therapies. This indication does not make any more reference to individual forms of invasive candidal infections. Moreover, it is appropriate for the capsules, IV infusion, powder for oral suspension and the syrup.

Prevention of Fungal Infections in Immunocompromised Patients

Candida infections

Invasive *Candida* infections have become common and life threatening complications in patients with leukaemia, cancer, hematologic malignancies and patients with bone marrow transplantation. Neutropenic patients are at especially high risk for candidemia. Antifungal agents are being used in many prophylactic settings, but only a few studies have adequately evaluated their efficacy.

The original applications for the prevention of fungal infections indication included seven comparative clinical studies in which 755 patients received oral fluconazole, 383 patients placebo and 374 patients oral comparative agents. The majority of patients began antifungal prophylaxis prior to undergoing a period of induced neutropenia through chemo- or radiotherapy for malignant disease or bone marrow transplantation.

In a study by Bodey et al (*1994*) adults with acute leukaemia undergoing remission induction chemotherapy randomly were assigned to receive antifungal prophylaxis with amphotericin B (0.5 mg/Kg three times weekly) or fluconazole 400 mg daily. Trimethoprim-sulfamethoxazole was administered as an antibacterial prophylaxis. The authors concluded that at the dose used in this study amphotericin B was not more effective and was more toxic than fluconazole for the prophylaxis of fungal infections in patients undergoing remission induction chemotherapy for acute leukaemia.

More recently, a meta-analysis of randomised, placebo-controlled trials in neutropenic chemotherapy recipients has shown that systemically active antifungal agents can reduce the number of superficial and invasive *Candida* infections (*Bow et al 2002*).

Overall, the use of fluconazole as a prophylaxis agent to prevent breakthrough fungal infections in neutropenic patients was established in the original application and has been supported by its continuing use. Moreover, since the original application, fluconazole has become established as a standard treatment for the prevention of breakthrough infections in neutropenic patients. Recently, the Infectious Diseases Society of America (IDSA: *Pappas et al 2009*) published updated guidance for use of antifungal agents included the prevention indication where fluconazole is recommended for.

The strongest evidence for the effectiveness of fluconazole comes from the major double-blind, placebo-controlled studies described above, which utilized the dose of 400 mg/day. This is also the dose recommended by the IDSA guidance (*Pappas et al 2009*). The original market authorisation application for this indication suggested that the patients that were more likely to develop deep and prolonged neutropenia (bone marrow transplant patients) should be given the higher dose of 400 mg/day and that the other doses may also be relevant for less profound neutropenia, where there is some help from the host. The MAH considers this is still appropriate given the effectiveness demonstrated in the active comparator studies and proposes that the original dosage recommendations containing a range of doses from 50 to 400 mg/day still apply. The optimal duration of prophylaxis is not known but should, at a minimum, include the period of risk of neutropenia, as stated in the dosage text and cover a period after recovery from neutropenia to ensure adequate host defence.

The CHMP accepted that fluconazole is efficient for the prevention of candical infections in patients with prolonged neutropenia and the indication was reworded to specify that point. Also a cross reference to section 5.1 was included to the indication, as it is known that the epidemiology of invasive fungal diseases (IFDs) has changed substantially in recent years and infections due to *Candida* species are no longer the majority in many institutions. The CHMP concluded that this indication is appropriate for the capsules, IV infusion, powder for oral suspension and the syrup.

Paediatric Use

An EU work sharing project-Assessment of Paediatric data took place in 2005-2006. The proposed text for the pharmacokinetics in children is the wording that was agreed during that EU work sharing project. The text was implemented in 24 MSs via a Type II variation before the start of this referral procedure. Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single-doses studies, 2 multiple-dose studies, and a study in premature neonates. Data from one study were not interpretable due to changes in formulation pathway through the study. Additional data were available from a compassionate use study (*EU, 2006*). From the results of these studies is shown that after administration of 2-8 mg/Kg fluconazole to children between the ages of 9 months to 15 years, a steady state AUC of about 38 µg.h/mL was found per 1 mg/Kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 20 hours and the distribution volume was approximately 880 mL/Kg. A higher fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/Kg intravenously to children of 11 days – 11 months old. The distribution volume in this age group was about 950 mL/Kg.

Initial doses of fluconazole in early paediatric therapeutic studies were based on comparison with a small adult with a weight of 50 Kg and therefore a paediatric dose of 1 mg/Kg was taken as being the equivalent of a 50 mg daily dose in adults. However in one large pharmacokinetic study in 100 paediatric patients *(Brammer and Coates, 1994*), the volume of distribution varied with age, being greatest during the neonatal period (1.18 to 2.25 L/Kg) and decreasing by young adulthood to a value similar to that reported for adults (0.7 L/Kg). With the exception of neonates, fluconazole clearance was generally more rapid in children, with a mean plasma elimination half-life of just over 20 h for all paediatric age groups, compared with adults (30 hours).

The review of the SPCs (including IS and NO) has revealed that in a minority of MSs, some paediatric indications are listed under Section 4.1. In the paediatric population fluconazole is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), systemic candidiasis and cryptococcal infections and the prevention of fungal infection in at-risk immunocompromised children following cytotoxic chemotherapy or radiotherapy. Recently, recommendations from a review of treatment infection in HIV infected children by the Centres for Disease Control, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Paediatric Infectious Diseases Society, and the American Academy of Paediatrics were published. These included the management of fungal diseases.

Oropharyngeal and oesophageal candidiasis in children

Acute oral candidiasis may occur in up to 5% of newborn infants. It is most often associated with severe immunological impairment due to diabetes mellitus, leukaemia, lymphoma, malignancy, neutropenia and HIV infection where it presents as a predictor of clinical progression to AIDS. The use of broad-spectrum antibiotics, corticosteroids, cytotoxic drugs, and radiation therapy are also predisposing factors. Oropharyngeal candidiasis (OPC) continues to be one of the most frequent

opportunistic infections in HIV-infected children during the Highly Active Anti-Retroviral Therapy (HAART) era (28% of children), with an incidence rate of 0.93 per 100 child-years. Systemic therapy with fluconazole is effective for initial treatment of OPC. Oral fluconazole is more effective than nystatin suspension for initial treatment of OPC in infants; is easier to administer to children than the topical therapies; and is the recommended treatment if systemic therapy is used. The dose of fluconazole recommended for OPC in adults is 100 mg and using the algorithm above results in a dose recommendation in children of 3 mg/Kg.

Oesophageal candidiasis is primarily associated with HIV infection or other forms of immunosuppression in children. The incidence of oesophageal candidiasis is around 0.08 per 100 child-years after introduction of HAART in around 2001. *Candida* oesophagitis continues to be seen in children who are not responding to antiretroviral therapy. Risk factors for oesophageal candidiasis in children with HIV infection include low CD4 count (<100 cells/mm^3), high viral load, and neutropenia (<500 cells/mm^3).

Systemic therapy is essential for oesophageal disease and should be initiated empirically among HIV-infected children who have OPC and oesophageal symptoms. In most patients, symptoms should resolve within days after the start of effective therapy. Oral or IV fluconazole solutions, administered for 14–21 days, are highly effective for treatment of *Candida* oesophagitis.

The dose of fluconazole recommended for oesophageal candidiasis in adults is 200 mg and using the algorithm above results in a dose recommendation in children of 6 mg/Kg.

The CHMP concluded that fluconazole indication for the treatment of mucosal candidiasis (oropharyngeal, oesophageal) in children is acceptable.

Invasive candidiasis

Disseminated candidiasis is infrequent among HIV-infected children, but *Candida* can disseminate from the oesophagus particularly when co-infection with herpes simplex virus (HSV) or cytomegalovirus (CMV) is present. Candidemia occurs in up to 12% of HIV-infected children with chronically indwelling central venous catheters for total parental nutrition or intravenous antibiotics.

Fluconazole has been used to treat invasive candida infections in children. Treatment of invasive candidiasis requires higher doses of fluconazole than are used for mucocutaneous disease. Alternatively, an initial course of amphotericin B therapy can be administered and then carefully followed by completion of a course of fluconazole therapy.

The maintenance dose of fluconazole recommended for systemic candidiasis in adults is 400 mg and using the algorithm above results in a dose recommendation in children of 12 mg/Kg. Fluconazole administered to children at 12 mg/Kg/day provides exposure similar to standard 400 mg daily dosing in adults and higher doses are not recommended in children. The CHMP considered that the treatment of invasive candidiasis in children is sufficiently demonstrated and considered this indication to be approvable.

Cryptococcal infections in children

Cryptococcosis is a defining opportunistic infection for AIDS. Other conditions which pose an increased risk include certain lymphomas (e.g. Hodgkin's lymphoma), sarcoidosis, and patients on long-term corticosteroid therapy. Cryptococcal infections are more likely to occur in association with HIV disease, however, cryptococcal infections occur much less frequently among HIV-infected children than among adults. Fluconazole is used to treat paediatric patients with cryptococcal disease. The dose of

fluconazole recommended for cryptococcus in adults is 200-40 mg and using the algorithm above results in a dose recommendation in children of 6-12 mg/Kg. The CHMP considered that the efficacy and safety in the treatment as well in the prophylaxis of cryptococcal meningitis in children is sufficiently demonstrated and considered these indications to be approvable.

Prophylaxis of candidal infections in immunocompromised paediatric patients

The recommended dose for the prevention of fungal infections in immunocompromised adults is given as range 400 mg once daily, depending on the patient's risk of developing an infection. Data supporting the indication for fluconazole prevention of fungal infection in immunocompromised patients in the paediatric International Registration Dossier (1993) were derived from three studies in children; one study determined the efficacy of fluconazole versus nystatin therapy alone, one study versus oral polyenes (nystatin or amphotericin B) and the third study versus ketoconazole. Fluconazole, administered at doses of 1 mg/Kg/day and 3 mg/Kg/day was more effective than the active comparator at preventing fungal infections. The dose of fluconazole recommended for prevention of fungal infections in adults is 50-400 mg and using the algorithm above results in a dose recommendation in children of 3-12 mg/Kg. The CHMP considered that the prophylaxis of fungal infections in immunocompromised children is sufficiently demonstrated and that this indication is approvable.

Tinea capitis

Fluconazole is not indicated for *tinea capitis* in adults. Following the worksharing procedure on the paediatric population in 2006 it was agreed that in the indication section for the paediatric population a phrase non indicating fluconazole to children regarding *tinea capitis* is inserted with a cross reference to section 4.4 of Special Warnings and precaution for use. However as fluconazole was studied in children but it was not found superior to griseofulvin, the CHMP concluded that it should not be used for treatment of *tinea capitis.* In that respect *tinea capitis* is no longer mentioned in section 4.1 of the PI; the relevant warning is inserted in the section 4.4 of the PI.

Section 4.2 - Posology and method of administration

In different Member States there were differences in the posology of various infections, e.g., for individual mucosal candida infections the recommended dose is from 50 to 100 mg. The same situation appeared for cryptococcosis/prevention of cryptococcal infections, for invasive candidiasis or vaginal candidiasis. There were also differences in the wording on the dosage recommendation for adolescents and children regarding all indications.

In order to harmonise the posology the MAH was requested to include in the posology section a table with the recommended doses regarding each indication and to distinguish between treatment and prevention.

Since oral absorption is rapid and almost complete, the doses of fluconazole recommended for the treatment and/or the prophylaxis of the different indications are the same for oral (capsules, oral suspension and syrup) and IV administration. Based on the submitted data the CHMP agreed on the dosing recommendations for each indication.

Paediatric population

The pharmacokinetic profile of fluconazole in children has a well understood relationship to that in adults when volume of distribution and clearance are taken into account. This result in dosing regimen in children is equivalent to that in adults. Doses of 3 mg/Kg in children have proved effective against fungal infections in immunocompromised children and also for the treatment of paediatric patients with serious fungal infections, such as cryptococcal meningitis. The CHMP noted that the MAH will implement the results and the conclusions of the TINN (Treat Infections in Neonates) EU project when the results are available.

In addition adolescent posology had been omitted. None of the national SPCs describe the posology for this age group. Following questions raised during the CHMP discussions, the MAH decided to provide a posology for this specific age group based on the Guideline on the role of pharmacokinetics in the development of medicinal product in the paediatric population (2006).

Moreover discussions between the CHMP and the MAH regarding the possible use of fluconazole in the treatment of genital candidiasis took place. During those discussions it was clarified that in adolescents these candida infections are usually treated locally. Thus, all available safety data in children and adolescents are from other studies than genital candidiasis. Systemic treatment of genital candidiasis is normally after some history of local treatment. The CHMP is of the opinion, that the safety and efficacy for this specific indication has not been established in the paediatric population. However, a contraindication was not appropriate as the safety data available from other indications do not exclude the use of fluconazole in children in general. In very rare cases treatment in adolescents in genital candidiasis is imperative (i.e. no other (especially local) treatment option is appropriate); these cases should not be totally excluded from treatment and adaption of the adult dose is recommended.

In the final wording the doses in the paediatric population have been divided in age groups of Infant, toddler and children (28 days to 11 years old), adolescents (12 years to 17 years old) and term newborn infants (0 to 27 days old).

The doses have been also presented in a tabulated format for the corresponding indications together with recommendations.

Section 4.4 - Special warnings and precaution for use

There are differences between all Member States concerning the individual paragraphs in this section. In general, the Core Safety Profile dated 2 April 2009 of the PSUR worksharing program was considered. The main differences in this section accepted by the CHMP are listed below.

A warning on tinea capitis and the fact that should not be used in children has been added.

Regarding cryptococcosis the evidence for efficacy of fluconazole in the treatment of cryptococcosis of other sites (e.g. pulmonary and cutaneous cryptococcosis) is limited. In the case of deep endemic mycoses the CHMP concluded that the evidence for efficacy of fluconazole in the treatment of other forms of endemic mycoses such as *paracoccidioidomycosis*, *lymphocutaneous sporotrichosis* and *histoplasmosis* was limited and these indications are no longer mentioned in section 4.1 of the PI. So a warning has been added in this section.

For patients with renal impairment a warning has been added with a cross reference to the posology section of 4.2 in this patient population.

The warning on the effect on the cardiovascular system and the association with prolongation of the QT interval on the electrocardiogram has been reinforced. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are

contraindicated. Moreover halofantrine has been shown to prolong QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is therefore not recommended. More extensive information has been added in section 4.5 of the SPC.

A warning on hypersensitivity reactions has been added as per other azoles.

As fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor and fluconazole is also an inhibitor of CYP2C19. Fluconazole treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored.

All the above changes were accepted by the CHMP and apply to all formulations and presentations.

Section 4.5 - Interaction with other medicinal products and other forms of interaction

There were differences between Member States in this section with regard to the combination with halofantrine due to the interaction with CYP3A4 and additive negative effects on QT interval prolongation. This interaction is included in some Member States but not in others. The MAH took the opportunity to answer the question raised for Section 4.5 regarding halofantrine. In addition the CHMP noted that the MAH will implement the results of the scientific discussions on the medicinal products affecting the QT when these discussions conclude at European level.

The paragraph of this section containing the information of benzodiazepines has been also altered to include information of the pharmacokinetics of the interaction between fluconazole and benzodiazepines and to restrict it to midazolam and triazolam, since their metabolism depends exclusively on CYP3A4.

The paragraph regarding the potential interaction with hydrochlorothiazide was deleted as there is no evidence that the increase of plasma concentration by 40% is of clinical significance. This issue was also not discussed during the PSUR WSP DK/H/PSUR/008/001. This is in line with the SPC guideline not to confuse prescriber with useless information regarding this interaction.

In addition, the wording on the interaction of itraconazole in the PI of saquinavir and taking into account the recent labelling changes for saquinavir (contraindication for concomitant administration with other QTc interval prolonging drugs) was amended. Concomitant use of fluconazole with saquinavir was contraindicated accordingly with a cross reference to section 4.3 of the PI.

Information on the interaction of fluconazole with voriconazole which is a CYP2C9 and CYP3A4 inhibitor was added. Coadministration of oral voriconazole and oral fluconazole to 8 healthy male subjects resulted in an increase in C_{max} and AUC_{τ} of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. However it has not been established the reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect. So the CHMP recommended the monitoring for voriconazole associated adverse events in the cases of co-administration of voriconazole following the use of fluconazole.

All the above changes were accepted by the CHMP and apply to all formulations and presentations.

Section 4.8 - Undesirable effects

The CHMP noted the MAH proposal and adopted a harmonised text for this section, applicable to all Diflucan formulations. The Core Safety Profile was considered when harmonising the listed adverse reactions between national SPCs of Diflucan. The general text of frequencies classification, and the

adverse reaction obtained from post-marketing experience were clarified, and the frequency of a number of events was revised. The method and the statistical approach together with the data provided were reviewed and the CHMP considered the estimated frequency to be appropriate.

Section 5.1 - Pharmacodynamic properties

This section was partly restructured according to guidelines. Subheadings like Mode of action, PK/PD relationship, Mechanism(s) of resistance and Breakpoints (according to EUCAST) were implemented.

Other Sections of the SPC

The MAH was asked to evaluate all other sections of the nationally approved SPCs and suggest appropriate changes in the text where divergences exist. The QRD guideline was implemented in changing the wording where necessary. In addition minor typographic errors were corrected. All these changes were accepted by the CHMP.

Package Leaflet

Following all the changes in the SPC there are several corresponding changes to the Package Leaflet After the corrections were implemented a Readability Testing was performed which was submitted and assessed during the referral procedure. The final PL wording was adopted by the CHMP.

2.3 Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan

2.4 Recommendation

Regarding the Product Information, the harmonisation procedure led to the adoption by the CHMP of a harmonised set of SPCs for all fluconazole formulations included in the scope of the procedure. In summary, the CHMP adopted the following sets of indications for Diflucan and associated names:

For Capsules (50mg, 100mg, 150mg, 200mg), Solution for infusion (IV), Syrup, Powder for Oral Suspension (where applicable, see the relevant PI)

Diflucan (fluconazole) 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, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis.*
- *Chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene or topical treatment are insufficient.*

- *Vaginal candidiasis, acute or recurrent; when local therapy is not appropriate.*
- *Candidal balanitis when local therapy is not appropriate.*
- *Dermatomycosis including tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal candida infections when systemic therapy is indicated.*
- *Tinea unguinium (onychomycosis) when other agents are not considered appropriate.*

Diflucan is indicated in adults for the prophylaxis of:

- *Relapse of cryptococcal meningitis in patients with high risk of recurrence.*
- *Relapse of oropharyngeal or oesophageal candidiasis in patients infected with HIV who are at high risk of experiencing relapse.*
- *To reduce the incidence of recurrent vaginal candidiasis (4 or more episodes a year).*
- *Prophylaxis of candidal infections in patients with prolonged neutropenia (such as patients with haematological malignancies receiving chemotherapy or patients receiving Hematopoietic Stem Cell Transplantation (see section 5.1)).*

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

Diflucan is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. Diflucan can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of reoccurrence (see section 4.4).
Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Consideration should be given to official guidance on the appropriate use of antifungals.

<u>For the one 150 mg capsule presentation</u>

Diflucan (fluconazole) is indicated in the following fungal infections in adults (see section 5.1):

- *Acute vaginal candidiasis when local therapy is not appropriate.*
- *Candidal balanitis when local therapy is not appropriate.*

Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Consideration should be given to official guidance on the appropriate use of antifungals.

2.3. Conclusions

The basis for this referral procedure was a harmonisation of the SPC, labelling and package leaflet.

The CHMP having considered:

- the rapporteur and co-rapporteur assessment reports,

- scientific discussion within the Committee,
- comments from the marketing authorisation holders,

was of the opinion that the benefit/risk ratio of Diflucan and associated names is considered to be favourable. The CHMP adopted a positive opinion recommending the harmonisation of the SPC, labelling and package leaflet as set out in Annex III of the CHMP opinion for Diflucan and associated names (see Annex I).