Member State EU/EEA	Marketing authorisation holder	Invented Name	Strength	Pharmaceutical form	Route of administration	Content (concentration)
	Kent CT13 9NJ United Kingdom					
United Kingdom	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom	Diflucan	200 mg	Capsule, Hard	Oral use	N/A
United Kingdom	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom	Diflucan	50 mg/5ml	Powder for Suspension	Oral use	10 mg/ml
United Kingdom	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom	Diflucan	200 mg/5ml	Powder for Suspension	Oral use	40 mg/ml
United Kingdom	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom	Diflucan	2 mg/ml	Solution for Infusion	Intravenous use	2 mg/ml

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Scientific conclusions

Overall summary of the scientific evaluation of Diflucan and associated names (see Annex I)

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. Fluconazole displays antifungal activity against most clinically common *Candida* species. Fluconazole also exhibits activity *in vitro* against *Cryptococcus* species. 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 is available for oral use in the 50 mg, 100 mg, 150 mg and 200 mg capsule formulation, in the 5 mg/mL syrup formulation, and in the 50 mg or 200 mg/5 mL powder for oral suspension on reconstitution with water formulation. As the treatment of genital candidiasis requires a single 150 mg dose of fluconazole, a convenient presentation containing a single 150 mg fluconazole capsule is available in some Member States (MSs) only for the indication of genital candidiasis, more specifically for the treatment of acute vaginal candidiasis and candidal balanitis.

Fluconazole is available also for intravenous (IV) use in the 2 mg/mL saline solution formulation.

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. During the time of the evaluation of the 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 Summary of Product Characteristics (SPC) harmonisation 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 products (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 SPCs and thus to harmonise its divergent SPCs across the European Union.

Section 4.1 – Therapeutic Indications

50 mg, 100 mg, 150 mg and 200 mg capsule, 5 mg/mL syrup, 50 mg/5mL or 200 mg/5 mL powder for oral suspension, 2 mg/mL solution for infusion.

The CHMP assessed the Product Information of the product taking into account the current national ones and the existing scientific knowledge and discussed the indications for each individual medical condition. The prophylactic use of Diflucan, as distinct from the treatment indications was also discussed and justified. In addition the paediatric indications have been clarified.

In all the mycosal candidiasis 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 at doses of up to and including 400 mg/day. The results are

supportive of fluconazole as an appropriate treatment for mucosal candidiasis including oropharyngeal, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis. The CHMP agreed that fluconazole should be indicated for the treatment of chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene or topical treatment are insufficient.

The indication of relapse prevention in immunocompromised (HIV and cancer) patients was investigated. Several different dosing regimens were employed, 100 mg/day, 200 mg/day and 200 mg three times/week. In all studies fluconazole was as or more effective than placebo in preventing clinical relapse. In cancer patients it was superior to placebo in preventing mycological relapse. The CHMP 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 immunocompromised patients and are well tolerated. The CHMP is in agreement in separating the treatment from the prophylaxis of the relapse on Oropharyngeal Candidiasis and presenting the posology accordingly.

Candidal 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. 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. The CHMP concluded that fluconazole with its activity against *Candida* species and its pharmacokinetics offers a safe, effective, and convenient alternative to topical therapy in a single-dose regimen for both candidal vaginitis and candidal balanitis in adults as well as for the prevention of the recurrence of vaginal candidiasis. The CHMP accepted that the data presented by the MAH was satisfactory for these indications.

Endemic mycoses remain a major public health problem in several countries and they are becoming increasingly frequent with the spread of HIV infection. Coccidioidomycosis is a disease with protean manifestations. 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 this is supported by clinical trial data and recommended by clinical guidelines. The CHMP concluded that the fluconazole, at 400 mg to 800 mg daily is a safe and effective primary treatment for coccidioidomycosis. It was also agreed by the CHMP that the MAH provided sufficient data on the efficacy and safety of fluconazole in invasive fungal infections (cryptococcosis, invasive candidiasis) 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 Infectious Diseases Society of America (IDSA) guidelines. For the indications of paracoccidioidomycosis, histoplasmosis, lymphocutaneous sporotrichosis, where other agents have failed or are not tolerated, it was deemed by the CHMP 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.

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 antimycotic agent against Tinea corporis, Tinea cruris, Tinea pedis, Tinea versicolor and onychomycosis. For Tinea unguinium

(onychomycosis) it was concluded that fluconazole is indicated only when other agents are not considered appropriate. The CHMP is in agreement on the final wording of the indication.

Cryptococcal meningitis is caused by the fungus *Cryptococcus neoformans*. Although *C. neoformans* typically infects immunocompromised persons, patients with no apparent immune system problems also develop cryptococcosis. Fluconazole has demonstrated *in vitro* and *in vivo* efficacy against *Cryptococcus neoformans* and 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 and there are clinical data supporting fluconazole as treatment in children and adults. The CHMP accepted that the supporting data were only for the indication of cryptococcal meningitis which was implemented in the SPC and not the general cryptococcosis indication.

Fluconazole has proven to be safe and efficacious for invasive 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. 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.

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. Overall, the use of fluconazole as a prophylaxis agent to prevent breakthrough fungal infections in neutropenic patients was established in the original application.

Moreover 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 including the prevention indication where fluconazole is recommended for prevention. The CHMP agreed with the submitted data and accepted that fluconazole is efficient for the prophylaxis of candidal infections in patients with prolonged neutropenia.

Paediatric Use

An EU work sharing project-Assessment of Paediatric data took place in 2005-2006. 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. Additional data were available from a compassionate use study (*EU, 2006*). The proposed text for the pharmokinetics in children is the wording that was agreed during the EU work sharing project.

Fluconazole is effective as a treatment against fungal infections in adults across the dose range recommended in national SPCs (50-400 mg daily). 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.

Mucosal candidiasis (Oropharyngeal and oesophageal) 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.

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 CHMP agreed that the data available are sufficient for the safe and efficacious use of fluconazole for the treatment and prevention of the mycosal (oropharyngeal and oesophageal) candidiasis in children.

Invasive candidiasis in children

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. 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.

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. As per the adult indication the CHMP agreed that there is sufficient evidence for the indication of treatment as well of prevention of relapse of cryptococcal meningitis in children.

Prophylaxis of candidal infections in immunocompromised children

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 agreed that fluconazole is indicated in the prophylaxis of candidal infections in immunocompromised children.

Finally and summarising here 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.

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.

For the 150 mg, one capsule presentation

The indication of the genital candidiasis and more specifically the vulvovaginal candidiasis in adult women and the candidal balanitis in adult men was authorised in some MS for the 150 mg, one capsule presentation due to the convenience of one dose treatment. The CHMP accepted that the data presented by the MAH was satisfactory for these indications. However as the first line treatment of this candidiasis is the topical application, the one 150 mg capsule presentation is specifically indicated for the above genital candidiasis indications in adults when local therapy is not appropriate.

For the one 150 mg capsule presentation the section 4.1 of the SPC is agreed by the CHMP as follows:

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.

Section 4.2 - Posology and method of administration

In Member States there were differences in the posology of various infections, e.g. for individual mucosal candida infections. 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 results in a dosing regimen in children that 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 adolescent posology had been omitted; none of the national SPCs described the posology for this age group. Following questions raised by the CHMP the MAH provided 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."

Furthermore the CHMP is of the opinion, that the safety and efficacy for indication of genital candidiasis has not been established in the paediatric population as all available data in children and adolescents are from studies in other indications rather than genital candidiasis. However in very rare

cases treatment in adolescents is imperative (i.e. no other (especially local) treatment option is appropriate) and these cases should not be totally excluded from treatment. So, the final wording in section 4.2 of the SPC regarding this indication reflects the CHMP discussion in all formulations including the 150 mg, one capsule presentation.

In the final approved text of the section 4.2 of the SPC 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).

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 was considered.

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 evidence for efficacy of fluconazole in the treatment of other forms of endemic mycoses such as *paracoccidioidomycosis, lymphocutaneous sporotrichosis* and *histoplasmosis* was limited and they are no longer mentioned in the 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, 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.

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

The CHMP noted the MAH proposal and adopted a harmonised text for this section. The inclusion of substances for which an involvement of CYP 3A4 and additive negative effects on QT interval prolongation is known (such as halofantrine, midazolam and triazolam) is justified.

The inclusion of the wording on the interaction of itraconazole (another triazole) 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. Concomitant use of fluconazole with saquinavir was contraindicated accordingly with a cross reference to section 4.3 of the PI. All the above changes were accepted by the CHMP and apply to all formulations.

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 European Committee of Antimicrobial Succeptibility Testing - 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. 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 Package Leaflet wording was adopted by the CHMP.

QUALITY – MODULE 3

The MAH submitted a proposal for harmonisation of the Quality module. 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.

Based on the review of data the CHMP adopted a harmonised Module 3.

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

In conclusion, based on the assessment of the MAH proposal and responses and following the discussions of the committee, the CHMP adopted harmonised sets of Product Information documents for the various presentations of Diflucan and associated names, taking into account the pharmaceutical forms. In particular, the indications and their associated posology recommendations were harmonised. A harmonised Module 3 was also adopted. Based on the above, the CHMP considers the benefit/risk ratio of Diflucan and associated names to be favourable and the harmonised Product Information documents to be approvable.

Whereas

- the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet
- the summary of products characteristic, labelling and package leaflet proposed by the marketing authorisation holders have been assessed based on the documentation submitted and the scientific discussion within the Committee

the CHMP has recommended the amendment of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Diflucan and associated names (see Annex I).