BPCA Executive Summary

NDA 21-718 N 000

Division of Dermatologic and Dental Products – HFD 540

Submission date:	10/28/03
Applicant:	Pfizer Pharmaceuticals Group, 235 East 42nd Street, New York, NY 10017, USA.
Generic name:	Fluconazole
Trade name:	Diflucan®
Chemical name:	2, 4-difluoro-α, α1-bis (1H-1, 2 , 4-triazol-1-ylmethyl) benzyl alcohol
Pharmacologic category:	Anti-fungal
Indication:	Treatment of Tinea Capitis in children
Dosage form:	Suspension
Route of Administration:	Oral
Primary Reviewer:	Bindi Nikhar, M.D., Medical Officer
Date of Summary:	March 30, 2004 Revised April 20, 2004

EXECUTIVE SUMMARY

Overview

The Food and Drug Administration issued a Pediatric Written Request to Pfizer on December 31, 2001 with an amendment dated June 7, 2002, for pediatric studies using Diflucan (fluconazole). The requested studies were for two clinical safety and efficacy studies in pediatric patients with tinea capitis. The amendment to the Pediatric Written Request further defined the safety evaluations needed.

Pediatric Exclusivity was granted on January 23, 2004, because the terms of the Written Request were met. The submitted data, however, were inadequate to support the new proposed indication.

The two clinical studies submitted did not demonstrate that fluconazole at 6 mg/kg/day for 6 weeks was superior to griseofulvin at the maximum labeled dose (11 mg/kg/day) for 6 weeks for the combined clinical and mycological outcome at week 6 in the Modified Intent to Treat Population (MITT).

There were no new safety concerns raised by these new studies that were not already listed in the Diflucan product label. Thus, no new information is incorporated into the product label.

Background

This supplemental NDA has been submitted for Diflucan (Fluconazole) oral suspension for the treatment of tinea capitis in pediatric patients, in response to the Pediatric Written Request originally issued on December 31, 2001, and later revised on June 7, 2002, in order to qualify for Pediatric Exclusivity.

Fluconazole is a synthetic triazole antifungal, currently indicated for the treatment of several systemic fungal infections in the adult and pediatric population. The INDICATIONS AND USAGE section of the label for Diflucan reads as follows:

> "DIFLUCAN (fluconazole) is indicated for the treatment of:
> 1. Vaginal candidiasis (vaginal yeast infections due to *Candida*).
> 2. Oropharyngeal and esophageal candidiasis. In open noncomparative studies of relatively small numbers of patients, DIFLUCAN was also effective for the treatment of *Candida* urinary tract infections, peritonitis, and systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia.
> 3. Cryptococcal meningitis. Before prescribing DIFLUCAN (fluconazole) for AIDS patients with cryptococcal meningitis, please see **CLINICAL STUDIES** section. Studies comparing DIFLUCAN to amphotericin B in non-HIV infected patients have not been conducted.
>
> Prophylaxis. DIFLUCAN is also indicated to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy.
>
> Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. 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."

Tinea capitis is a dermatophyte infection of the scalp that primarily affects the pediatric population. Griseofulvin is currently approved for the treatment of tinea capitis. Current practice describes use of griseofulvin for the indication of tinea capitis at higher doses than currently labeled. Concerns regarding treatment failure and off-label use of

fluconazole in the pediatric population prompted the request for studies to evaluate the safety and efficacy of fluconazole in the treatment of tinea capitis in children. Griseofulvin was chosen as a comparator for study with a dosage (11 mg/kg/day) that is currently labeled, but below the dosage used in current practice among pediatricians and dermatologists. In order to demonstrate efficacy in the absence of a placebo arm both the FDA and Pfizer agreed that Diflucan would have to be superior to griseofulvin. Also, in the peer-reviewed dermatologic and pediatric literature, griseofulvin is often regarded as being only minimally effective, and there are frequent reports of improved efficacy with fluconazole at doses comparable to those studied by Pfizer when compared to griseofulvin at doses exceeding labeled dosing.[1,2,3,4]

Clinical Efficacy

There were two pivotal safety and efficacy studies conducted, A0561015 and A0561016. Study A0561015 was conducted in Guatemala, Costa Rica, Chile, India and the U.S, while Study A0561016 was conducted in Guatemala, Costa Rica, Chile and the U.S. Both studies examined the efficacy of Diflucan® (fluconazole) at doses which lead to enthusiastic efficacy accounts in the medical literature versus Grifulvin® (griseofulvin) at labeled doses which are regarded by some as minimally effective in the treatment of tinea capitis in children.

These studies were randomized, parallel, multicenter, single dummy, third party-blind, 3-arm studies of fluconazole compared to griseofulvin for the treatment of tinea capitis due to dermatophyte species in male or female children aged 3 to 12 years. Patients were randomized at baseline in a 1:1:1 ratio to receive once daily oral suspension of 1 of 3 treatment regimens: Fluconazole at 6 mg/kg day for 3 weeks duration followed by placebo for 3 weeks *or* fluconazole at 6 mg/kg/day for 6 weeks duration *or* griseofulvin at 11 mg/kg/day for 6 weeks duration.

For Protocol A0561015, 130/139/132 patients were randomized to treatment for the fluconazole 6 wk/fluconazole 3 wk/griseofulvin 6 wk groups, respectively. For Protocol A0561016, 156/163/160 patients were randomized to treatment for the fluconazole 6 wk/fluconazole 3 wk/griseofulvin 6 wk groups respectively. Clinical and mycological efficacy evaluations were made at baseline and at weeks 3, 6 and 10.

Patients of either gender, who exhibited clinical findings suggestive of inflammatory or non-inflammatory tinea capitis and had microscopy (potassium hydroxide) positive for fungal elements within or outside the hair shaft were eligible for entry in these studies.

Efficacy variables included clinical outcome based on signs and symptoms, mycological outcome based on culture results, and the combined clinical and mycological outcomes based on both.

Clinical outcome was based on the signs and symptoms of hair loss/breakage, scaling/desquamation, pustules/purulence, and/or post-auricular/cervical lymphadenopathy. Mycological outcome was recorded as positive or negative, corresponding to positive or negative culture results.

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[1] Chan and Friedlander, Curr Opin Infect Dis. 2004, 17: pp. 97-103.
[2] Chan and Friedlander, Expert Opin Pharmacother. 2004, 5: pp. 219-227.
[3] Gupta et al., Clinics in Dermatol. 2003, 21: pp. 417-425.
[4] Pomerantz and Sabnis, Paediatr Drugs. 2002, 4: pp. 779-783.

A combined outcome of clinical and mycological results was based on the following definition:

Success	culture negative and clinical cure
Partial success	culture negative and clinical improvement
Failure	all other combinations

Clinical Cure was defined as the absence of signs and symptoms of tinea capitis. Clinical improvement, which was not an acceptable endpoint per the FDA written request, was considered to be of limited value in the setting of tinea capitis where minimal signs and symptoms may signify continued disease.[5]

The *primary efficacy endpoint* was the combined outcome at Week 6 in the modified intent-to-treat (MITT) population. *Secondary efficacy endpoints* included the Week 6 clinical and mycological outcomes analyzed separately and the clinical, mycological and combined outcomes at Weeks 3 and 10. The presence/absence of burning/stinging/and pruritus was also summarized. The ITT (Intent-to-treat) population included all subjects randomized and dispensed study medication. The MITT (modified ITT) population included all ITT patients with positive baseline culture. Nested superiority hypothesis tests were used for statistical comparison of treatment groups, and all tests were at a significance level of 0.05.

Looking at individual study results, for study A0561015, the analysis of the primary efficacy endpoint, i.e. the combined outcome at week 6 showed that fluconazole administered for 6 weeks was not superior to griseofulvin administered for 6 weeks in the treatment of tinea capitis in children. The success rate for fluconazole given for 6 weeks was 17%, while the success rate for griseofulvin given for 6 weeks was 16.3%, the p-value for fluconazole given for 6 weeks versus griseofulvin given for 6 weeks was 0.8679 (not significant).

For study A0561016, the results were similar, the analysis of the primary efficacy endpoint showed that fluconazole given for 6 weeks was not superior to griseofulvin given for 6 weeks in the treatment of tinea capitis in children. The success rate for fluconazole given for 6 weeks was 19.4%, while the success rate for griseofulvin given for 6 weeks was 19.0%; the p-value for fluconazole given for 6 weeks versus griseofulvin given for 6 weeks was 0.8937.

The analyses of secondary efficacy endpoints for both studies supported the results of the primary analysis. The efficacy conclusions remained consistent across the subgroups defined by age, race, gender, baseline organisms, baseline severity, area of involvement and geographical region.

Since these studies failed to demonstrate the superiority of the higher dose fluconazole regimen over griseofulvin at labeled doses below those often recommended off-label for the indication of tinea capitis, the indication of the treatment of tinea capitis should not be added to labeling for the Diflucan (fluconazole) drug product.

Clinical Safety

The safety data were derived from the following sources:

[5] Fuller et al., BMJ 2003, 326: pp 539-541. (http://bmj.bmjjournals.com/cgi/content/full/326/7388/539) This article concludes with the following: "Scalp ringworm seems to be increasing in the United Kingdom and is reaching epidemic proportions in some areas. T. tonsurans is responsible for most of these cases. Doctors should consider scalp ringworm in any child with a scaly scalp in whom a diagnosis of dandruff or scalp eczema has been suspected."

- Data from three US-run clinical trials in pediatric patients using fluconazole 6 mg/kg/day.
- Additional data from one non-US (Egyptian) clinical trial that was performed in pediatric subjects with tinea capitis receiving fluconazole at a weekly dose of 5 mg/kg or 9mg/kg. These have not been included in the pooled analysis. (This study has been reviewed but was not included in the NDA review document, since the efficacy and safety parameters used for this study did not support the US studies).
- Serious adverse events data from all clinical trials supported by the Applicant.

Data from 3 studies (A0561015, A0561016 and A0561017) were pooled for the Summary of Clinical Safety.

A total of 1063 patients were dispensed drug, out of which, 470 received fluconazole for 6 weeks (fluconazole 6 wk group), 301 received fluconazole for 3 weeks (fluconazole 3 wk group) and 292 received griseofulvin (griseofulvin group). In all 3 treatment groups, the patients were predominantly black (>70%) and male (>64%). In the fluconazole 6 wk group, 94% of patients were from the US, 4% were from South/Central America, and 2% were from India. In the fluconazole 3 wk group, 90% of patients were from the US, 7% were from South/Central America, and 3% were from India. In the griseofulvin group, 90% were from the US, 7% were from South/Central America, and 3% were from India.

There were no deaths in any of the treatment groups. Five patients had serious adverse events, 3 of these patients received griseofulvin, and 2 received fluconazole (6 wk group). No serious adverse event was reported by more than one individual, and none of these events were considered related to the study drug.

A total of 23 patients discontinued from the pooled studies due to adverse events (adverse events were recorded up to 14 days after the last dose of study drug); 7 in the fluconazole 6 wk group, 8 in the fluconazole 3 wk group, and 8 in the griseofulvin group.

In all 3 treatment groups, adverse events related to skin and appendages were the most common reason for discontinuation, accounting for approximately 1% of the patients in each of the treatment groups. Three patients, one in each treatment group discontinued due to laboratory abnormalities (i.e., increases in either GGT or SGOT and SGPT).

The most commonly reported adverse events were respiratory tract infections, increased cough, allergic symptoms, and GI symptoms.

The most frequently reported (≥ 1%) adverse events which were treatment related in all 3 groups respectively for fluconazole 6 wk/fluconazole 3 wk/griseofulvin included: headache 0.9%/0.35/1.7%, rash 0.9%/0.0%/0.3%, abdominal pain 0.6%/1.3%/1.4%, and dyspepsia 0.4%/0.0%/1.0%. Adverse events associated with the digestive and dermatologic system (including allergic reactions) and headache are known adverse events associated with both griseofulvin and fluconazole, while those adverse events associated with the upper and lower respiratory system are not unexpected in the age groups studied.

Liver enzyme tests showed more shifts from normal baseline values to high abnormal values during treatment in the two fluconazole treatment groups than in the Griseo group. Three patients, one in each group discontinued treatment due to raised liver transaminases (SGOT/SGPT/GGT), all had maximum values which were < 3 X ULN. In

all 3 patients, the causality was attributed to the study drug, and liver enzymes returned to normal on discontinuation of treatment. One patient in the fluconazole 6 wk group had a post-treatment increase in alkaline phosphatase about one week after completion of treatment; the patient was asymptomatic, and he was referred for follow up. Elevated liver enzymes have been associated with both griseofulvin and fluconazole.

Changes in the white blood cell count were the most frequently reported changes in hematological variables. Clinically meaningful changes in hematological variables without regard to baseline values (reported in ≥ 5% of patients) were as follows for the 3 groups respectively (fluconazole 6 wk/fluconazole 3 wk/griseofulvin): lymphocytes > 1.2 x ULN 16%/18%/13%, neutrophils < 0.8 x LLN 18%/17%/16%, eosinophils > 1.2 x ULN 6%4/%/9%.

Increase in serum creatinine > 1.3 x ULN for fluconazole 6 wk/.Fluconazole 3 wk/griseofulvin respectively were as follows: 2%/3%/2%.

In summary, there was a higher frequency of shifts in LFTs from normal to high abnormal values in the fluconazole groups than in the griseofulvin group. In the fluconazole group, 1.9% discontinued due to adverse events, the majority of these were skin related adverse events. Overall, the safety conclusions remained consistent across the age and gender subgroups. Abdominal symptoms observed in the clinical studies have already been well described in the Diflucan label and the incidence of headache was 0.9% in the fluconazole 6 wk group, 0.3% in the fluconaozle 3 wk group and 1.7% in the griseofulvin group. Since this is not statistically or clinically significant, no updates in the adverse reactions in children part of the label are required for this non-approvable indication.

The 14-day cardiac contractility study in healthy male beagle dogs (also requested as part of the Written Request) showed that the QTc intervals were increased throughout the period of treatment. This study showed that the effects of Diflucan on increasing the QTc interval could be seen in healthy dogs. This finding is consistent with what is known for other imidazole anti-fungal drug products and was conveyed to and discussed with HFD-590. It was concluded that this information reaffirmed the potential for increased QTc intervals with the imidazole anti-fungal drug products as a class.

In conclusion, the administration of fluconazole 6 mg/kg/day for 3 to 6 weeks in 771 children with tinea capitis was associated with adverse events, which have already been identified in the Diflucan label.

Dosing

The dose of Diflucan (fluconazole) used in these studies, i.e. 6 mg/kg/day, was based on the results of six completed studies that were previously supplied in a supplemental NDA (filed to NDA 19-949 and NDA 19-950 on November 23, 1993) that supported this dose. Through pharmacokinetic (PK) studies conducted during the course of these submissions, it was noted that escalation of oral/intravenous doses of fluconazole from 2 to 8 mg/kg/day, resulted in increased systemic exposure.

No antifungal susceptibility testing was performed by the Applicant before commencing these studies.

At the Diflucan dose of 6 mg/kg/day for 6 weeks, the Applicant was not able to show superiority over griseofulvin at 11 mg/kg/day for 6 weeks in the combined outcome in the MITT population. The pediatric labeled dose of griseofulvin is 10 mg/kg daily;

however the label indicates that the dosage can be individualized, as with adults. In clinical practice recommendations, griseofulvin doses for pediatric tinea capitis are higher than 10 or 11 mg/kg/day, often ranging from 15 to 25 mg/kg/day with durations of 6 to 8 weeks.[6] Thus, the conducted studies failed to show superiority of Diflucan over what would be considered a lesser effective dose of griseofulvin for pediatric tinea capitis.

Although higher doses of fluconazole (i.e. > 6 mg/kg) may have trended toward greater efficacy in the 6 week duration group, the incidence of treatment emergent adverse events was higher in the fluconazole 6 week treatment group compared to the fluconazole 3 week treatment group. As some adverse events may be dose dependent, it is expected that higher doses of fluconazole may approach dosages where the safety of the pediatric patient may be at greater risk. Thus, while higher doses and longer duration of treatment of fluconazole may show greater efficacy, this will have to be balanced by the possible emergence of treatment related adverse events, especially in the younger age groups. This will be important if the Applicant is considering future trials with these modifications. At this time, no dosing modifications are recommended for the Diflucan label.

Special Populations

These studies were conducted in the pediatric population, in children 3 to 12 years of age per the Pediatric Written Request.

[6] Gupta et al, Clin Dermatol. 2003, 21: pp. 417-425. Dosage regimens for the treatment of tinea capitis were included in Table 3 (page 419) of this paper. The dosage regimens for griseofulvin and fluconazole are excerpted below:

Drug	Dosage	Duration
Griseofulvin	15-25 mg/kg/day	6-8 weeks
Fluconazole	6 mg/kg/day	3-6 weeks

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/s/

Markham Luke
4/21/04 02:00:20 PM
MEDICAL OFFICER

BPCA Executive Summary entered into DFS for Dr. Bindi Nikhar, who is the primary reviewer for this NDA, in her absence. Concur with conclusions described in summary.

Jonathan Wilkin
4/21/04 02:40:28 PM
MEDICAL OFFICER

Concur with Dr. Nikhar's review.