

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-022

MICROBIOLOGY REVIEW(S)

HFD-540
Vaughan

OCT - 1 1999

Microbiology Review

Division of Special Pathogens and Immunologic Drug Products

(HFD-590)

NDA# 21-022

Reviewer : Linda Gosey
Correspondence Date : 12-18-98
CDER Receipt Date : 12-30-98
Review Assigned Date: 01-04-99
Review Complete Date: 09-10-99

Sponsor: Hoechst Marion Roussel
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Submission Reviewed: Original NDA

Drug Category: Antifungal

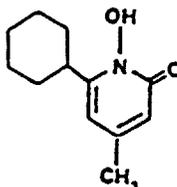
Indication: Treatment of mild to moderate onychomycosis without
lunula involvement due to *Trichophyton rubrum*.

Dosage Form: Nail lacquer, 8%

Product Names:

- a. Proprietary: Loprox
- b. Nonproprietary: Ciclopirox
- c. Chemical: 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone

Structural Formula:



Molecular weight = 207.

Supporting Documents: IND [redacted] NDA 18-748; NDA 19-824;
NDA 20-519

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Background:

Characterization of Disease:

Historically, the term onychomycosis has referred to infections of the nail caused by a mold or a yeast. However, today we know that infections produced by the dermatophytic molds are uniquely characterized and have more accurately been termed tinea unguium. As a consequence, the modern definition for onychomycosis is an infection of the nail caused by fungi other than the dermatophytes. For onychomycosis the primary invasion of the nail plate is caused by *C. albicans*, *C. parapsilosis* and *Scopulariopsis brevicaulis*. Other etiologic agents of onychomycosis are *Aspergillus flavus*, *A. candidus*, *A. fumigatus*, *A. sydowi*, *A. terreus*, other *Aspergillus* species, *Cephalosporium* species and *Fusarium oxysporum*. Onychomycosis is associated with chronic paronychia where active invasion of the nail plate is less frequent.

Tinea unguium is an invasive disease of the nail plate caused by a dermatophyte. Generally, tinea unguium is classified into 2 sub-types, leukonychia mycotica (superficial white onychomycosis, SWO) and invasive subungual onychomycosis (commonly called ringworm of the nail). In leukonychia mycotica the nail is invaded from the top exhibiting pitting or infected patches on the surface of the nail. This type of infection is almost always produced by *T. mentagrophytes*.

The most common clinical pattern of tinea unguium is distal and subungual onychomycosis (DLSO) where the distal edges of the nail plate are invaded first. The nail becomes thick and opaque in color. Almost all species of dermatophytes have been associated with ringworm of the nail. However, the major dermatophytes causing tinea unguium of the finger nail and toe nail are *Trichophyton rubrum*, *T. interdigitale* and *Trichophyton mentagrophytes*, respectively. Other dermatophytes associated with tinea unguium are *T. tonsurans*, *T. violaceum*, *E. floccosum*, *T. schoenleinii*, *T. concentricum* and rarely, *M. gypseum*, *M. canis*, *T. audouinii*, *T. soudanense* and *T. gourvilii*.

The diagnosis of subungual tinea unguium is difficult due to the low numbers of fungi present and the location of the fungi in the lowermost sections of the nail plate. In tinea unguium the nail bed is generally distorted with an accumulation of debris beneath them. However, in Candidiasis onychomycosis nails are usually not grossly distorted. With tinea unguium only one nail may be infected where as in onychomycosis several

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neighboring tissue is the reason why tinea unguium is more difficult to treat.

Treatment of tinea unguium or onychomycosis requires an understanding of the ultrastructure of the nail. Keratinocytes exist within the nail plate and are strongly linked by numerous desmosomes and phospholipid layers. The nail plate consists of 3 different layers; a thin ventral plate, a thick intermediate plate and a thin dorsal plate. The cells of the dorsal plate are very flat and lack nuclei. The cells of the intermediate plate are less flat and possess cytoplasmic portions. The ventral plate consists of 1-2 cell layers with nuclear residues. As a result of their composition and structure the three nail plates can have different drug penetration characteristics.

Antifungal Drug:

Ciclopirox olamine is the active component found in Loprox cream and lotion. However, ciclopirox free acid is the active ingredient in Loprox gel. Ciclopirox free acid is considered the active moiety in ciclopirox olamine. In an aqueous solution ciclopirox olamine dissociates to ciclopirox free acid which is also referred to as ciclopirox. Loprox nail lacquer contains 8% ciclopirox free acid with gantrez ES435 as one of the excipients. Toxicity studies in animals suggest that the free acid is less toxic than the olamine salt.

In this NDA submission the sponsor is seeking approval of ciclopirox nail lacquer, 8%, for the topical treatment of mild to moderate onychomycosis without lunula involvement due to *Trichophyton rubrum*

Summary:

Preclinical Microbiology:

The sponsor has submitted numerous published articles describing the in vitro and in vivo activity of ciclopirox against various fungi. The reviewing microbiologist will examine the results described in each article and summarize the data.

1. Ceschin-Roques, et. al., 1991. Ciclopirox nail lacquer 8%: In vivo penetration into and through nails and in vitro effect on pig skin. Skin Pharmacol. 4:89-94.

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This paper discusses several different experiments that were conducted to assess the antifungal activity of ciclopirox. In one experiment the in vitro penetration of 0.5 - 8% ciclopirox was evaluated using excised pig skin. Pig skin was kept on water agar where various concentrations of ciclopirox lacquer was applied and removed 30 minutes later. After treatment different layers of the stratum corneum were removed with adhesive tape. The layers of skin were then infected with *T. mentagrophytes* conidia. Over a 7 day period the growth of the mould was observed.

The concentration of ciclopirox in the different layers of skin was determined using the % inhibition of growth of *T. mentagrophytes*. Ciclopirox lacquer at 0.5% inhibited mould growth by 88% and 63% in the 2nd and 10th layers of skin, respectively. Total inhibition of growth at all layers of skin were noted when 4% and 8% ciclopirox nail lacquer was applied.

Comments: The ability to extrapolate the activity of ciclopirox from this in vitro study to humans is complicated by several issues. First, in this study the drug was first applied to the skin and then exposed to the mould. This design is more like a prophylactic study as opposed to an established infection study where the fungal infection would normally be present in the various levels of skin prior to exposure to drug. Second, the activity of the drug was not tested against the invasive form of the mould that would be seen in an established infection. It is well known that the activity profile of antifungal agents is different, generally less effective, when tested against the invasive form versus the saprophytic phase of mould-growth. Third, excised pig skin does not have the same physiologic characteristics as human nail. As such, it is difficult to equate the activity from this experiment to what might be found in human nail. Lastly, it is unknown how the culturing of moulds from the skin samples was conducted. It is extremely difficult to accurately determine the exact % of mould growth as stated in this study.

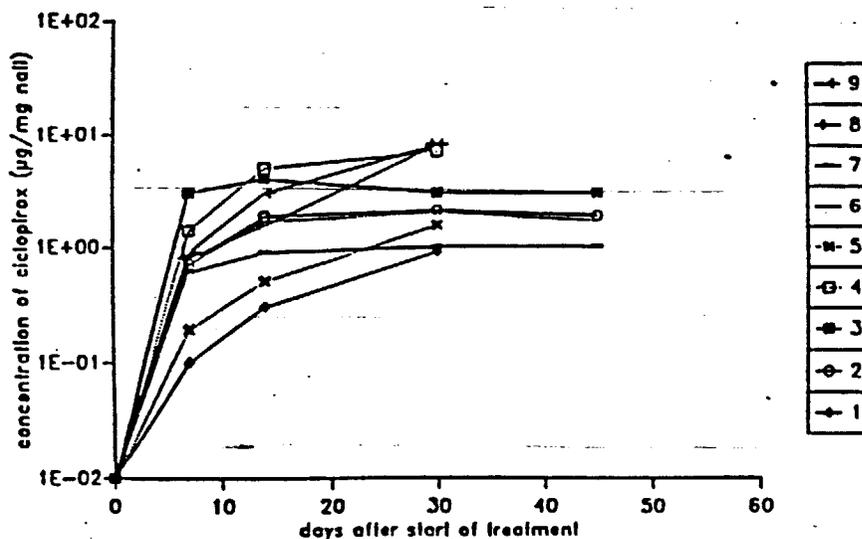
In a second experiment 8% ciclopirox lacquer was applied daily to the finger nails (approximately 5-15 mg/nail) of 9 healthy volunteers. Before each application of ciclopirox lacquer or the sampling of nail, methanol was used to remove any residual lacquer. It is well known that methanol exhibits cidal activity against fungi. Samples from distal nail were removed after 7, 14, 30 and 45 days of drug application, as well as 7 and 14 days post therapy. Various layers from each nail sample were evaluated to determine the concentration of drug present and the microbiologic effect. *C. pseudotropicalis* MICs were

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days post therapy. Various layers from each nail sample were evaluated to determine the concentration of drug present and the microbiologic effect. An MIC of 3.125 ug/ml was determined for *C. pseudotropicalis* (test organism) using a micro titer plate technique employing neopeptone glucose broth. Test microtiter plates employing yeast nitrogen broth (NYBG) were incubated at 28°C and read at 18, 24 and 48 hours. The lower limit of ciclopirox detection was estimated to be 0.04 ug/mg nail.

This study demonstrated that steady state was reached after ciclopirox nail lacquer was applied for 30 days (See Fig. 1). After 7 days of application, 51.4% of the drug was located in the first layer with progressively decreasing drug concentrations in each successive nail layer. No drug was found in the third and fourth layers in 3/9 and 4/9 patients, respectively. Table 1 shows the varying concentrations of drug found the 4 layers of nail after 30 days of treatment. The quantity of drug found in nail 7 or 14 days post therapy was at the lower level of detection in 2/4 patients and 4/4 patients, respectively, suggesting that drug disappears rapidly once therapy is stopped (See table 2).

Fig. 1



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Table 1

Table 1: Relative percentages of ciclopirox in the 4 nail layers

subject	7-day sample				14-day sample				30-day sample			
	lay. 1	lay. 2	lay. 3	lay. 4	lay. 1	lay. 2	lay. 3	lay. 4	lay. 1	lay. 2	lay. 3	lay. 4
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
mean	49.6	34.6	11.6	4.2	32	24.1	21.2	22.7	34.7	26.4	19.7	19.2
±	±	±	±	±	±	±	±	±	±	±	±	±
s.e.	2.8	2.4	2.8	1.3	1.5	1.4	1.1	2.1	1.5	2.4	1.2	1.4

lay. = layer
 s.e. = standard error
 - = below detection limit

Table 2

Table 2: Residual amounts of ciclopirox ($\mu\text{g}/\text{mg}$ nail) 7 and 14 days after the end of treatment (D45)

concentration of ciclopirox ($\mu\text{g}/\text{mg}$ nail) time after treatment

subject	D45 (end of treatment)	7 days	14 days
2	1.55	0.05	0.04
3	3.3	0.32	0.04
6	1.94	0.13	0.04
7	1.26	0.04	0.04

70.

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There are several issues regarding how this study was conducted and the interpretation of the data. First, methanol was used daily during the treatment phase of the study. It is well known that methanol inhibits the growth of fungi. To what extent the activity demonstrated in this study is due to methanol versus the drug is not known. Second, *C. pseudotropicalis* was used to determine the concentration of ciclopirox in the various layers of nail. While this method is acceptable to determine the concentration of ciclopirox in the nail it does not tell us if the various concentrations were sufficient to inhibit the relevant dermatophytes. The data from this ex vivo study also demonstrates that this agent must be applied daily and that it take approximately 14 days to obtain equal levels of drug in the lower layers of nail (i.e. approximately 20% of the drug concentration applied).

2. Hanel and Ritter. 1990. Chapter 10: Formulation. Handbook of experimental pharmacology, 96: 251-278.

In this chapter the authors discuss the various animal models that have been used to assess antifungal agents. Of note was their comment that the skin of hairy animals allows greater penetration of drugs than human skin due to the number of hair follicles present. As a result, pig skin is most similar to human skin when drug penetration properties are to be studied. They further state that normal skin should be used since mechanical damage to skin can lead to less reproducible results. Abraded skin should only be used if the influence of the inflammatory response is to be investigated.

Pig skin is also used to determine the activity of topical antifungals. In this experiment pig skin is infected with *T. mentagrophytes*. After the mould is allowed to grow for 1-2 days the infected skin is exposed to various antifungal preparations. After a specified time the skin is scraped off and washed to remove excess drug. The skin is then plated onto malt agar to determine the presence of viable fungi. Using this method ciclopirox lacquer and cream were the most active formulations (See Fig 2 and 3).

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Fig 2.

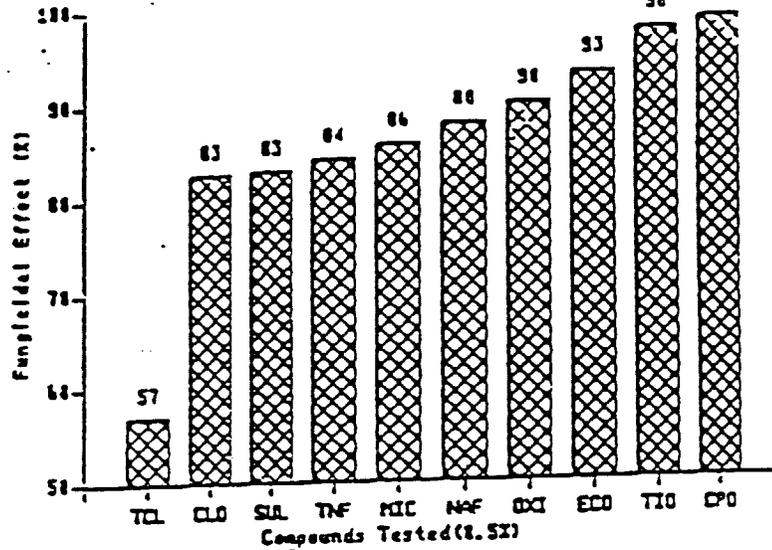


Fig. 2. Fungicidal activity of antifungals in a lacquer formulation tested against *Trichophyton mentagrophytes* on pig skin with 2 h exposure, mean of 3 experiments. TCL, tolicidate; CLO clotrimazole; SUL, sulbentine; TNF, tolnaftate; MIC, miconazole; NAF, naftifine; OXI, oxiconazole; ECO, econazole; TIO, tioconazole; CPO, ciclopirox free acid. Modified from HÄNEL et al. (1988)

Fig. 3

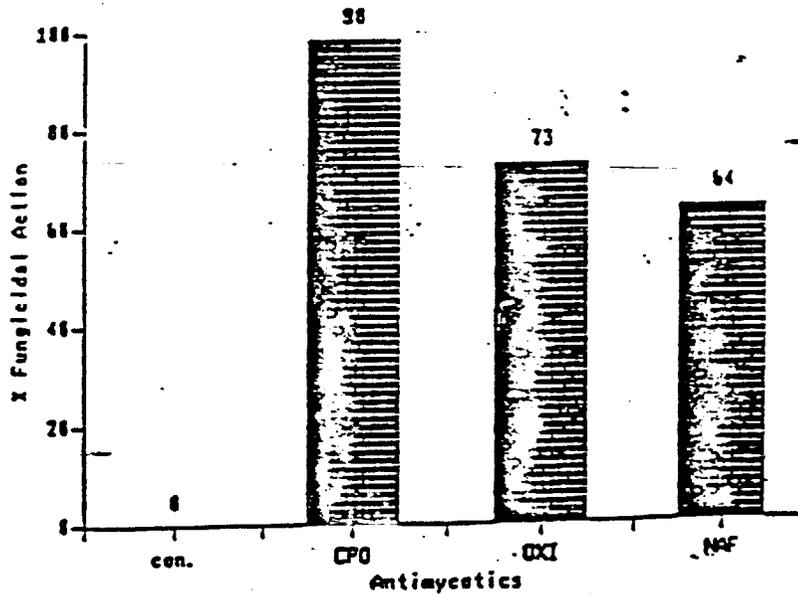


Fig. 3 Fungicidal activity of 1% cream formulations tested against *Trichophyton mentagrophytes* on pig skin with 1 h exposure, mean of 14 experiments. con, control; CPO, ciclopirox olamine; OXI, oxiconazole; NAF, naftifine. Modified from HÄNEL et al. (1988)

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This chapter also contained information regarding the evaluation of antifungal agents against fungal infections of human nail which consist of either cowhorn or excised human nails. In both cases, the water content of the nail or horn is crucial in order to extrapolate the results to human disease. In vitro studies using cowhorn generally treat the material first and then infect with the fungus. As noted previously this design is more like a prophylactic study and does not assess how the antifungal agent acts against established disease. Experiments using human nail can be problematic due to differences in nail thickness and condition or age of the donor. Table 3 shows the deposition of 8% ciclopirox free acid after a 1-10 hour exposure with 5 mg/cm² lacquer. The data show that the lowest concentration of ciclopirox was found in the deep nail plate.

Table 3

Table 3. Penetration of ciclopirox nail lacquer in human nails (µg/ml)

Nail	1	2	3	4	5	6	7	8	9	10
Incubation time	18 h	18 h	18 h	24 h	24 h	24 h	24 h	48 h	48 h	48 h
Dorsal plate (62 µm thickness)	4102	1780	4708	3639	5957	3565	9967	14245	13970	8189
Upper intermediate plate (240 µm thickness)	1079	130	844	726	538	310	157	1683	1587	1392
Lower intermediate plate-ventral plate (200-600 µm thickness)	1.4	1.3	26.6	6.7	13.7	4.1	6.6	10.1	9.4	73.6

3. In house study: Permeation of Batrafen into human toenails from nail polish (lot designation 17084a).

In this study 8% batrafen (ciclopirox) was formulated into a nail polish base with gantrez. Radio labeled batrafen was applied to extracted human toenails. Radioactive measurements were made 16, 24 and 48 hours after the polish was applied. Good penetration was observed in nails to a depth of 0.4 mm with the total nail depth being 0.8 - 2.0 mm. The investigator noted that penetration of the substance to depths greater then 0.4 mm was slow and depended on the structure of the nail (i.e. "diffusional flow owing to different partition coefficients in the various nail layers may be responsible for this phenomenon of lack of accumulation"). The investigator also noted that severely infected nails took up more of the applied antifungal due to the disruption of the nail surface. When looking at the

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raw data from 5 patients, it was noted that at 48 hours only trace amounts of drug were observed in the lower layers of the nail and at the uppermost layer of the nail the % of drug applied varied widely from 8-47% of the total amount applied. These data suggest that patients applying this agent may obtain widely variable results and that viable fungi located deep in the nail most likely will not be affected potentially producing mycologic failure and possibly relapse.

4. Mertin and Lippold. 1997. In vitro permeability of the human nail and of a keratin membrane from bovine hooves: Prediction rate of antimycotic through the nail plate and their efficacy. J. Pharm. Pharmacol. 49:866-872.

In this paper the investigators discuss how the molecular size of the drug influences the permeability of antifungal agents through human nail plates and keratin membranes from bovine hooves. Previous work suggested that drug penetration was independent of the lipophilicity of the diffusing substance.

In these experiments various drugs were prepared in 42% ethanol. However, ciclopirox was dissolved in a higher concentration of ethanol (percentage not specified). From these penetration studies the investigators surmised that drug permeability using the bovine hoof model was similar to the human nail plate model. The use of ethanol decreased the swelling of the keratin membrane from 36% to 27% thus allowing a higher sensitivity of permeability towards compounds with a smaller molecular size. In this study the sponsors observed that ciclopirox deviated from the predicted value due to the fact that approximately 50% of ciclopirox dissociated at pH 8.1 and as an anion its penetration was inhibited through the negatively charged keratin membrane. While this test system is interesting it appears that it was not an appropriate test model for assessing the penetration characteristics of ciclopirox.

5. Niewerth et. al., 1998. Antimicrobial susceptibility testing of dermatophytes: Comparison of the agar macrodilution and broth micro dilution tests. Chemotherapy 44: 31-35.

In this study in vitro susceptibility testing was performed against 50 dermatophytic strains comprising 4 different species. The species of dermatophytes were 38 *T. rubrum*, 10 *T. mentagrophytes sensu stricto*, 1 *T. mentagrophytes var. quinckeanum* and 1 *Microsporum canis*. The agar macrodilution method employing Kimmig agar and a broth microdilution method employing nutrient broth were used to determine terbinafine,

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griseofulvin MIC values. Table 4 shows the MIC values for the dermatophytes using both the agar macrodilution and broth microdilution susceptibility testing methods. Ciclopirox olamine MICs were the same for the 4 different dermatophytic species. However, the ciclopirox olamine MIC₉₀s from the agar macrodilution method (MIC 20 ug/ml) were approximately 7-10 fold higher than those obtained from the broth microdilution method (MIC 2 or 3 ug/ml). While these data are interesting there are two things that should be noted. First, the investigators did not use the proposed NCCLS susceptibility testing method for septate hyphae. This is the recommended method used in the United States. As a result, it is unknown what the MIC values would be using this preferred method. Second, without a standardized and validated susceptibility testing method the ability to correlate MIC values to clinical activity is impossible. Thus, at this time, it is unknown what concentration of ciclopirox is needed to kill dermatophytic moulds.

Table 4

Table 4. In vitro activity of griseofulvin, itraconazole, sertaconazole, terbinafine and ciclopiroxolamine against 50 dermatophytes using the agar macrodilution test and the broth microdilution test

Antifungal agent	Organism	Isolates	Agar macrodilution test, µg/ml			Broth microdilution test, µg/ml		
			MIC ₅₀	MIC ₉₀	range	MIC ₅₀	MIC ₉₀	range
Griseofulvin	<i>T. rubrum</i>	38	100	200	1-200	3	3	2-4
	<i>T. mentagrophytes</i>	10	100	200	10-200	3	3	2-3
	<i>T. quinckeanum</i> ¹	1	200	200	200	3	3	3
	<i>M. canis</i>	1	200	200	200	2	2	2
Itraconazole	<i>T. rubrum</i>	38	10	10	2-10	1	1	0.5-2
	<i>T. mentagrophytes</i>	10	10	10	5-10	1	1	0.5-1
	<i>T. quinckeanum</i> ¹	1	100	100	100	1	1	1
	<i>M. canis</i>	1	10	10	10	1	1	1
Sertaconazole	<i>T. rubrum</i>	38	10	10	5-10	3	3	2-3
	<i>T. mentagrophytes</i>	10	10	10	10	2	2	2
	<i>T. quinckeanum</i> ¹	1	10	10	10	3	3	3
	<i>M. canis</i>	1	10	10	10	3	3	3
Terbinafine	<i>T. rubrum</i>	38	0.1	0.2	0.02-0.2	0.01	0.01	0.001-0.01
	<i>T. mentagrophytes</i>	10	0.1	0.2	0.1-0.2	0.001	0.01	0.001-0.01
	<i>T. quinckeanum</i> ¹	1	0.2	0.2	0.2	0.001	0.001	0.001
	<i>M. canis</i>	1	0.2	0.2	0.2	0.001	0.001	0.001
Ciclopiroxolamine	<i>T. rubrum</i>	38	20	20	20	2	3	2-3
	<i>T. mentagrophytes</i>	10	20	20	20	2	2	2
	<i>T. quinckeanum</i> ¹	1	20	20	20	3	3	3
	<i>M. canis</i>	1	20	20	20	3	3	3

¹ *T. mentagrophytes* var. *quinckeanum*.

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Yang et. al. 1997. A new simulation model for studying in vitro topical penetration of antifungal drugs into hard keratin. J. Mycol. Med. 7:195-98.

In this experiment the investigators used infected ovine hooves to determine the penetration of 1% ciclopirox olamine, 1% sulconazole, 5% amorolfine and 8% ciclopirox. Sections of hoof were infected on the interior side for 5 days at which time antifungal agents were applied to the external side of the hoof every 2 days. Three separate experiments were performed where drug was added before, at the same time and after the hoof was infected. Drugs placed on the hoof before they were infected partially inhibited the growth of the fungus suggesting that the various test drugs did have activity. However, when the fungus was allowed to grow for 5 days prior to treatment all of the antifungal agents failed to inhibit the fungal growth showing that established disease is more difficult to treat (See table 5). Other factors that can contribute to the efficacy of an antifungal agent are the thickness and density of the hoof or nail which ultimately influences the penetrability of the antifungal agent.

Table 5

TABLE 5- Growth of dermatophytes implanted on ovine hooves

<i>Antifungal</i>	<i>T. rubrum</i>	<i>T. mentagrophytes</i>	<i>T. interdigitale</i>	<i>E. Floccosum</i>
Pretreatment				
5% amorolfine	+	+	+	+
8% ciclopirox	++	++	++	++
1% ciclopiroxolamine	++	+++	+++	++
1% sulconazole	+	+	+	+
Simultaneous treatment				
5% amorolfine	++	++	++	++
8% ciclopirox	+++	++	+++	+++
1% ciclopiroxolamine	+++	++	+++	+++
1% sulconazole	++	++	++	++
Post-treatment				
5% amorolfine	+++	+++	+++	+++
8% ciclopirox	+++	+++	+++	+++
1% ciclopiroxolamine	+++	+++	++++	++++
1% sulconazole	+++	+++	++++	++++

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7. In house study. _____ 1989. Fingernail penetration, in vivo of 8% ciclopirox nail lacquer. _____

Finger nails from 9 healthy volunteers were used to determine drug absorption from daily applications of 8% ciclopirox nail lacquer over a 45 day period. Two samples were obtained on days 7, 14, 30, and 45 as well as 7 and 14 days post therapy. Total drug absorbed and the amount of drug that penetrated 4 different layers of nail were assessed. Extracted nails were placed in a moist atmosphere and were in contact with a 10% polyethylene glycol (PEG) solution. Total drug absorbed was determined via _____

with a lower level of detection of _____ ug/ml. Relative percentages of drug were determined in the 4 layers of nail. Tables 6 and 7 show the total amount of drug (ug/mg nail) absorbed over time. One should note that there is a significant difference in drug recovered at day 30 between the two sets of patients (i.e. 3.35 ug/mg vs. 2.1 ug/mg). It is unclear why there was less drug absorbed in the second group versus the first group. It is also of interest to note that drug levels did not appear to increase after day 30 suggesting that an equilibrium was obtained at approximately 2.0 ug/mg.

Table 6

	7 days	14 days	30 days
Mean	0.89	1.72	2.35
standard error	0.25	0.41	0.82

Table II:

Mean concentrations (\pm s.e.) of ciclopirox in nail (as ug/mg nail) for the 9 subjects, after 7, 14 and 30 days of application.

Table 7

	7 days	14 days	30 days	45 days
Mean	1.16	0.84	2.1	2.01

Table III:

Mean concentrations of ciclopirox in nail (as ug/mg nail) for subjects 2, 3, 6 and 7, after 7, 14, 30 and 45 days of treatment.

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Table 8 shows the individual drug levels obtained over time in the nine patients. Of interest is the widely varying concentrations of drug absorbed per patient. At day 30 the drug concentration ranged from 0.95 - 6.5 ug/mg nail.

Table 8

Subject	7 days	14 days	30 days	45 days
1	∟			
2				
3				
4				
5				
6				
7				
8				
9				└
Mean	0.692	1.783	3.35	2.01
+/-	+/-	+/-	+/-	+/-
s.e.	0.252	0.413	0.822	0.45

Table I:
 Concentrations of ciclopirox in nail (as ug/mg nail)

∟: not determined

When drug concentration was measured in the 4 layers of nail it was noted that it took 2 weeks to reach what appears to be steady state. After 30 days of daily application 35%, 26%, 20%, and 19% of the drug was located in the 1st, 2nd, 3rd and 4th layers of nail. At day 30 the range of % drug at the 4th layer of nail still varied greatly from 10-24%. Clearly more drug accumulates on the surface layer of nail and less drug is delivered to the deep nail layers. In addition, it was observed that varying concentrations of drug absorbed were due to inter-patient variability (See table 9).

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Table 9

Table IV:
Relative percentages of ciclopirox in the 4 nail layers

Subject	7-day sample				14-day sample				30-day sample			
	Layer 1	Layer 2	Layer 3	Layer 4	Layer 1	Layer 2	Layer 3	Layer 4	Layer 1	Layer 2	Layer 3	Layer 4
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
Mean	49.6	34.6	11.6	4.2	32	24.1	21.2	22.7	34.7	26.4	19.7	19.2
s.e.	2.8	2.4	2.0	1.3	1.5	1.4	1.1	2.1	1.5	2.4	1.2	1.4

Of particular importance is the concentration of drug deposited into the various sections of nail. For example: At day 45 patient 7 had — ug/mg of ciclopirox in the nail. If the 4th layer of fingernail absorbed 24% of the drug that would calculate out to — ug/mg. Without validated in vitro susceptibility data to compare clinical efficacy to the concentration of drug available at the infection site it is impossible to determine what are relevant MICs or minimum fungicidal concentration (MFCs). Therefore these drug concentrations may be inadequate to eradicate a dermatophytic infection. Another fact that should be taken into account when correlating fingernail efficacy to toe nail efficacy is that the toe nails are generally thicker, 0.7 mm vs. 1.0 - 1.2 mm, respectively. The ability of the drug to penetrate to deeper levels in toe nails was not studied in this experiment.

A third segment of the experiment looks at the quantity of drug that remains in the nail after the drug is no longer applied.

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Table 10 shows that 7 days after the last application of nail lacquer very small quantities of drug can be found in the nail, ranging from _____ ug/mg. These results suggest that the drug breaks down rapidly and a long term post antibiotic effect is not achieved.

Table 10

	D45 (end of treatment)	P 7 days	P 14 days
Subject 2	1.55	0.05	0.04
Subject 3	3.3	0.32	0.04
Subject 6	1.94	0.13	0.04
Subject 7	1.26	0.04	0.04

Table X:
Residual amounts of ciclopirox (ug/mg nail)
7 and 14 days after the end of treatment (D45)

8. In house study, Report 1.3. _____ 1989. In vivo toe nail penetration of ciclopirox supplied as an 8% varnish.

Five healthy volunteers applied daily 8% ciclopirox nail lacquer to their toe nails for a period of 45 days. After 7, 14, 30, and 45 days of treatment distal parts of the nail were removed. Samples 7 and 14 days post therapy were also collected. Total drug absorbed and the amount of drug that penetrated 4 different layers of nail were assessed. Extracted nails were placed in a moist atmosphere and were in contact with a 10% polyethylene glycol (PEG) solution.

Total drug absorbed was determined via a _____ with a lower level of detection of _____ ug/mg nail. Relative percentages of drug were determined in the 4 layers of nail. Tables 11 shows the total amount of drug (ug/mg nail) absorbed over time. One should note that there is a significant difference in drug recovered at day 45 between the individual patients (range _____ ug/mg vs. _____ ug/mg). The data show that drug levels appear to reach equilibrium after the nail lacquer has been applied for 30 days with a mean drug level of 5.91 ug/mg.

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Table 11

Subjects	7 days	14 days	30 days	45 days	Res. 7 days	Res. 14 days
Subject 1						
Subject 2						
Subject 3						
Subject 4						
Subject 5						
Means	1.39	4.64	5.91	6.83	1.44	0.81
±	±	±	±	±	±	±
Stand. error	0.74	2.25	2.42	2.76	0.71	0.7

Table 11 Individual data and means ± SEM for ciclopirox concentrations in the nail (µg/mg nail) for the 5 subjects at the various sampling time points.

Table 12 shows the individual drug levels obtained over time in the five patients. In this experiment near equivalent drug levels were found in all 4 nail layers starting at day 7 and remaining approximately the same at day 45. The amount of drug penetrated to the various layers of nail are drastically different from those observed in the finger nail study conducted by the same investigators. In addition, inter-patient variability seen in the finger nail experiment was not seen in this toe nail study. From this toe nail study the expected concentration of ciclopirox in the 4th layer of toe nail after 45 days of treatment would be _____ ug/mg nail (i.e. _____ ug/mg _____ ug/mg x _____).

The investigator's suggest the greater drug concentration seen in the toe nail study maybe due to the fact that the toe nails grew slower or received more drug. Alternatively, finger nails were exposed to the external environment to a greater extent than the toe nails thus eliminating the drug and nail varnish. Without studies to confirm their hypothesis the reason why higher ciclopirox drug concentrations were obtained in the toe nail versus the finger nail remains unknown.

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Table 12

Subjects	Sample at time 7 days				Sample at time 14 days				Sample at time 30 days				Sample at time 45 days			
	Layer 1	Layer 2	Layer 3	Layer 4	Layer 1	Layer 2	Layer 3	Layer 4	Layer 1	Layer 2	Layer 3	Layer 4	Layer 1	Layer 2	Layer 3	Layer 4
1																
2																
3																
4																
5																
Mean	20.4	26.0	25	27.6	22.4	24.6	26.0	26.2	25.6	27.2	24	23.2	27.0	25.0	21.2	25.2
s/-	s/-	s/-	s/-	s/-	s/-	s/-	s/-	s/-	s/-	s/-	s/-	s/-	s/-	s/-	s/-	s/-
Stand. error	1.99	0.37	1.52	2.09	3.31	2.30	1.52	2.05	1.70	1.36	1.10	1.05	1.20	2.75	1.03	1.90

Comments:

The sponsor submitted several articles, published and in house, describing the in vitro and ex vivo activity of ciclopirox. The ability to characterize the pre-clinical activity of ciclopirox is complicated by several factors. First, several investigators studied the activity of ciclopirox olamine versus ciclopirox free acid. It is unknown how the activity of the two compounds are related and how they both act against the dermatophytic moulds. Second, some investigators studied the activity of ciclopirox in a nail polish or nail varnish vehicle versus the nail lacquer vehicle. Without studying the various drug products in parallel it is unknown how the different vehicles may have altered the activity profile of ciclopirox. Third, several studies evaluated the activity of ciclopirox using bovine horn or hooves. While these biological materials are similar to human nail the activity profile of ciclopirox characterized by the use of these materials may not accurately predict how ciclopirox would act against dermatophytic infections found in human nail. Fourth, some of the ex vivo studies only evaluated the penetration properties of ciclopirox and not the activity of the compound. While these investigators did not determine the activity profile of the ciclopirox nail lacquer the absorption characteristics of the drug product do help to explain what was observed in the clinical trials.

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Two ex vivo studies were conducted by Michel and Roques, Industrial Microbiology and Virology Laboratory, France which assessed the penetration characteristics of ciclopirox nail lacquer. One study assessed the activity of ciclopirox nail lacquer in excised human finger nail and a second set of experiments evaluated the penetration of ciclopirox in human toe nail. The results from the two studies showed that after 30 days of applying 8% ciclopirox nail lacquer daily a mean of 2.0 ug/mg and 5.91 ug/mg of ciclopirox was absorbed in extracted human fingernail and toenail, respectively. Penetration studies using human fingernail demonstrated that after 30 days of daily application of 8% ciclopirox nail lacquer 35%, 26%, 20%, and 19% of the drug was located in the 1st, 2nd, 3rd and 4th layers of nail. At day 30 the range of % drug at the 4th layer of nail still varied greatly from 10-24%. However, when the same experiment was conducted using toe nails near equivalent percentages of drug (approximately 20%) were found in all 4 layers of toe nail. The study results also showed that the concentration of drug absorbed varied from patient to patient.

Of particular concern is the concentration of drug deposited to the various sections of nail. From these two studies it was observed that less drug was absorbed and less penetrated into the deep layers of finger nail compared to toe nail. However, it should also be noted that only a portion of the total drug was delivered to the deep layers of either nail type. The data showing lower drug penetration suggest that 8% ciclopirox nail lacquer may be less effective against finger nail infections versus toe nail infections.

The investigator's suggest that the greater drug concentration seen in the toe nail study may be due to the fact that the toe nails grow slower, however, these studies were conducted using extracted nail. As a result their hypothesis does not hold up. In the clinical trials where intact human nail is treated, external environmental factors (i.e. hand washing, the rubbing of socks on toe nails, etc.) may have an impact on drug absorption and ultimately clinical outcome. However, the ex vivo data clearly show that the deep layers of both toe nail and finger nail only absorb a portion of the drug applied. In addition, the pre-clinical studies evaluating the activity of ciclopirox against established dermatophytic infections clearly show that 8% ciclopirox nail lacquer does not kill or significantly inhibit the growth of dermatophytes once an infection is established. As a result, the pre-clinical studies show that, without external environmental factors that could potentially attenuate the drug's activity, 8% ciclopirox nail

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lacquer is not potent enough to eliminate dermatophytic fungal infections of the nail.

Determining an effective dose of ciclopirox is complicated by the fact that there is no established or validated in vitro susceptibility method currently available to accurately measure ciclopirox MICs against dermatophytic moulds. Without an established in vitro susceptibility testing method MIC results can not be compared to nor correlated with clinical efficacy. Therefore, it is currently unknown what concentration of ciclopirox is necessary to eradicate an established dermatophytic infection of the nail.

Clinical Studies:

Phase II clinical trials:

Two phase II clinical trials, 211 and 212, were conducted to assess the clinical and microbiologic response of 8% ciclopirox nail lacquer against dermatophytic infections of the finger nail. According to the medical officer, Dr. Brenda Vaughan, clinical efficacy was not demonstrated in either of these two studies. Dr. Vaughan further stated that the sponsor concurred with this assessment in correspondences with the Division.

Phase III clinical trials:

Two phase III clinical trials were conducted to assess the activity of 8% ciclopirox nail lacquer against distal tinea unguium of the great toe nail. Immunocompetent subjects with tinea unguium were stratified 1:1 to receive either the vehicle or 8% ciclopirox nail lacquer. The products were to be applied daily for a maximum of 48 weeks. Prior to applying the nail lacquer, the nail was trimmed and unattached nail was removed. Excess horny material was filed off prior to treatment. Once a week the lacquer was to be removed with either alcohol or nail polish remover (active ingredient - acetone). Screening samples for potassium hydroxide (KOH) preparation and fungal culture were taken within 28 days of enrollment. Eligible patients had to have at baseline (i.e. just prior to initiating treatment)

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a positive KOH preparation demonstrating the presence of hyphae and a positive fungal culture due to a dermatophytic mould. Patients with a negative baseline culture were not considered evaluable. In addition to presenting with tinea unguium, eligible patients could have tinea pedis (interdigital, plantar or mossaasin). The protocol design also allowed the concomitant use of 1% topical ciclopirox cream to treat the surrounding infected skin.

In both studies four efficacy parameters were measured: fungal culture, KOH preparation, global evaluation score from 0 (cleared) to 5 (exacerbation) and planimetric measurement of the involved nail area (expressed as percent of nail involved). These parameters were used to define the following categories:

	Fungal culture	KOH examination	Global Evaluation	Affected nail area
- Treatment Success*:	negative	negative	-	≤10%
- Treatment Cure:	negative	negative	cleared	-
- Therapeutic Success:	negative	-	-	≤10%
- Clinical Success:	-	-	-	≤10%
- Clinical Cure:	-	-	cleared	-
- Therapeutic Cure:	negative	-	cleared	-
- Mycological Cure:	negative	negative	-	-
- Negative culture:	negative	-	-	-
- Negative KOH:	-	negative	-	-

* Primary efficacy variable as redefined per amendment

In the initial protocol design the primary efficacy endpoint was time to treatment cure which was defined as negative fungal culture, negative KOH and clearing of the nail. In a major protocol amendment dated May 1996 the sponsor requested that the primary endpoint be changed to "treatment success" defined as a negative fungal culture, negative KOH and <10% of the nail area infected. In this same amendment the follow-up period was shortened from 6 months to 3 months.

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If treatment success was obtained anytime during the 48 week treatment period the patient was asked to discontinue therapy and return 12 weeks later for a follow-up assessment. Subjects still exhibiting clinical signs or mycologic evidence of a fungal infection were allowed to continue for another 48 weeks of therapy in the open label clinical trial 320. During the follow-up period subjects were assessed for relapse. Re-emergence of either clinical signs, a positive KOH or positive fungal culture were indicative of relapse.

At the study centers nail specimens were collected for KOH preparation and fungal culture. Prior to collecting the sample nails were washed with isopropyl alcohol. Several samples close to the advancing proximal edge of the nail were collected using the 1.5 mm skeel curette. A KOH preparation was considered positive if the presence of hyphae was observed. Specimens for fungal culture were placed on sabouraud dextrose agar with chloramphenicol and cycloheximide and shipped to the central laboratory

Species identification was determined using gross morphology, microscopic examination and other nutritional and biochemical tests. Antifungal susceptibility testing was not conducted in any of the clinical trials.

Clinical trial 312:

In clinical trial 312 microbiologic assessments were made on 112 and 110 patients in the drug and vehicle arms, respectively. Sixteen patients were dropped because they either received no therapy or inadequate therapy. In the treatment arm of the intent to treat (ITT) population, *T. rubrum* and *T. mentagrophytes* was the pathogenic agent in 108/112 (96.4%) and 4/112 (3.6%) of the patients, respectively. Eight of the 112 (7.1%) drug treated patients were defined as a therapeutic cure or success. However, the sponsor stated that patient 05-218 was not evaluable. In addition, three subjects did not have follow up data thus leaving only 4/8 (50%) of these patients having at least 12 weeks of follow-up as required by the protocol design (See table 13).

In the vehicle arm *T. rubrum* and *T. mentagrophytes* were the pathogenic organisms in 108/110 (98.2%) and 3/110 (1.8%) of the patients, respectively. One patient obtained a therapeutic cure after 48 weeks of therapy and remained negative up to week 24. The patient's infection was due *T. rubrum*.

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Table 13

SUCCESSSES IN PATIENTS TREATED WITH 8% CICLOPIROX NAIL LACQUER
 CLINICAL TRIAL 312

	with follow-up data	with out follow-up data
Treatment Success Baseline (+)	0	1
Treatment Success Baseline (-)	0	1
Treatment Cure Baseline (+)	4	1
Treatment Cure Baseline (-)	0	0

Baseline (+) results are for fungal culture

Patients classified as a "treatment success" or "treatment cure" with follow-up data of at least 12 weeks post-therapy were further analyzed (See table 14).

Table 14

POST-THERAPY ASSESSMENT of PATIENTS in TRIAL 312

N=5	Mycological Cure	Mycological Relapse	Species Identification
	1	1	T. mentagrophytes
	1	1	T. rubrum

The data clearly show that only a few patients 4/91 (4.4%) obtained a therapeutic success after 48 weeks of therapy. Of these patients a relapse rate of 2/4 (50%) was observed 12 to 24 weeks post therapy.

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Clinical Trial 313:

In clinical trial 313, 118 and 117 patients were enrolled in the drug and vehicle arms, respectively. In the treatment arm fourteen patients were dropped because they either received no treatment or inadequate therapy. Fungal cultures and KOH preparations were obtained on each patient. In the treatment arm 113/118 (95.8%) and 5/118 (4.2%) of the infections from the ITT population were due to *T. rubrum* and *T. mentagrophytes*, respectively. Seventeen of the 118 (14.4%) drug treated patients were defined as a therapeutic cure or success. Of these 17 patients 8/17 (47%) were baseline fungal culture positive, 2/17 (11.8%) had baseline cultures overgrown with contaminating organisms and 6/17 (35.3%) had a negative baseline fungal culture. Only 8/17 (47%) of these patients had at least 12 weeks of follow-up (See table 15).

In the vehicle arm *T. rubrum* and *T. mentagrophytes* were the pathogenic organisms in 113/117 (96.6%) and 5/117 (4.4%), respectively. One patient obtained a therapeutic cure after 48 weeks of therapy. However, 12 weeks post therapy the patient relapsed with a positive fungal culture and KOH preparation. The patient's infection was due *T. rubrum*.

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Table 15

SUCSESSES IN PATIENTS TREATED WITH 8% CICLOPIROX
 CLINICAL TRIAL 313

	with follow-up data	with out follow-up data
Treatment Success Baseline (+)	2	4
Treatment Success Baseline (-)/ Overgrown	0	3
Treatment Cure Baseline (+)	3	0
Treatment Cure Baseline (-)/ Overgrown	3	2

Baseline (±) results are for fungal culture

Patients classified as a treatment success or treatment cure with follow-up data of at least 12 weeks post-therapy were further analyzed (See table 16).

Table 16

POST-THERAPY ASSESSMENT of PATIENTS in TRIAL 313

N=8	Mycological Cure	Mycological Relapse	Clinical Relapse	Species Identification
	0	0	1	T. mentagrophytes
	4	3	0	T. rubrum

The clinical data clearly show that only a few patients (8/95 or 8.4%) obtained a therapeutic success after 48 weeks of therapy and had adequate follow-up data. Of these patients a relapse rate of 4/8 (50%) was observed 12 to 24 weeks post therapy.

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Comments:

In the phase III clinical studies 312 and 313 the sponsor evaluated the activity of a 48 week daily treatment regimen of 8% ciclopirox nail lacquer against mild to moderate distal subungual Tinea unguium of one great toe nail. In the clinical trials patients were excluded if they were diabetic, HIV positive, had a history of immunosuppression or used steroids. Eligible patients could use 1% ciclopirox cream on the surrounding infected skin while applying the nail lacquer to the affected nails.

The combined microbiologic results from these clinical trials demonstrated limited efficacy against the dermatophyte *T. rubrum*. There were 10/230 (4.3%), 3/230 (1.3%) and 0 global cures (clinical and microbiologic) due to *T. rubrum*, *T. mentagrophytes* and *E. floccosum* organisms, respectively. Relapse rates of 4/8 (50%) and 2/3 (66%) were seen in patients with *T. rubrum* and *T. mentagrophytes* infections, respectively.

The ability to address the issue of drug resistance is incumbered by two facts. First, antifungal susceptibility testing was not conducted on the fungal isolates recovered from eligible patients enrolled in clinical trials 312 or 313. Comparing MIC values from fungal isolates recovered from individuals over time (i.e. before therapy is initiated and at the end of therapy) has been shown to be useful in assessing drug resistance development, as well as identifying inherently resistant fungal strains. Second, currently there are no established or validated antifungal susceptibility testing methods for testing dermatophytes against antifungal agents. As a consequence, the FDA is unable to define breakpoints for susceptible and resistant strains of dermatophytes. In the absence of established susceptibility testing methods and the ciclopirox susceptibility data obtained with clinical isolates to ciclopirox it is not possible to comment on why there was such a low cure rate obtained in the phase III clinical trials.

In the two phase II clinical trials, 211 and 212, ciclopirox 8% nail lacquer was applied to infected finger nails. After reviewing the outcome data the reviewing medical officer determined that clinical efficacy was not demonstrated in either of the two studies and the sponsor concurred. These results were not unexpected as the results from the ex vivo studies conducted by _____ suggest that drug absorption and penetration is poor in the fingernail with this drug delivery system.

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Fungal cultures were obtained from patients enrolled in these clinical trials, however, the results (including species identification) were not provided in the NDA. This information was requested from the sponsor on 8/20/99.

The sponsor has suggested that frequent hand washing may be the cause for the lack of efficacy in the finger nail trial. If this assumption is true then water exposure to the feet via daily showering or bathing should also contribute to the low efficacy rate observed in the toe nail studies. However, the high relapse rate in the few patients that did initially respond to therapy in the phase III trials suggests that the lack of efficacy may be due to inadequate drug levels reaching the nail base where the fungal growth originates. The fact that clinical evidence of disease was observed in the majority of the patients after 48 weeks of therapy further indicates that microbiologic cure (i.e. elimination of the fungal pathogen) was not obtained with this therapeutic regimen. If the activity of the drug was such that it killed the fungus, then over the 48 week treatment time the infected nail would have grown out leaving normal nail in its place.

In the two phase III clinical trials it was noted that intermittent positive/negative KOH and fungal culture results were observed over time for many of the patients. In many instances culture or KOH results were highly variable (e.g. first +, then -, then +, then -) from one visit to the next. In addition, the KOH results often did not agree with the culture results on the same specimen. These erratic test results suggest that the quality of the specimen obtained varied from week to week and that the final microbiologic test results defining the microbiologic response were subject to a great deal of variability and sampling error.

Another possible reason for culture negative and positive KOH results is the high content of isopropyl alcohol (46%) in the nail lacquer. The sponsor submitted information taken from the Martindale "Extra Pharmacopoeia" where it states that isopropyl alcohol is bactericidal and fungicidal. The microbiologic results suggests that the fungus is killed sometime after it invades the horny nail but is not killed at the base of the infection as demonstrated by the continued clinical evidence of disease and positive KOH preparations. Therefore, the nominal efficacy rate and high relapse rate seen in these phase III studies could be due at least in part to the affect of the isopropyl alcohol in lieu of the ciclopirox.

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The clinical data obtained from the phase II and III clinical trials, consisting of intermittent positive/negative test results, persistent clinical evidence of disease after 48 weeks of therapy, low microbiologic cure rates and high relapse rates do not support approval of 8% ciclopirox nail lacquer for the proposed indication. The nominal microbiologic activity seen in the clinical trials may in fact be potentially due to the affect of the isopropyl alcohol and not ciclopirox.

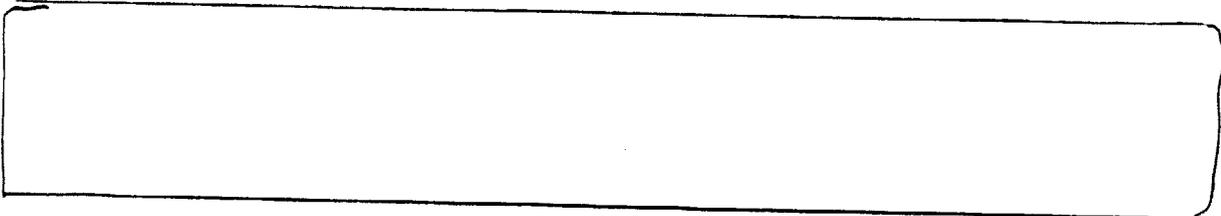
However, if this product were to be approved the clinical microbiologic data can only support the following narrow indication: treatment of mild to moderate distal subungual tinea unguium of the toe nail due to *T. rubrum* when used daily

The proposed wording is based on the following:

1. The medically correct term for the disease treated in these clinical trials is distal subungual tinea unguium. Onychomycosis is an infection of the nails due to non-dermatophytic moulds or *Candida* species. These patient populations were excluded from the clinical trials. In addition, patients with white superficial tinea unguium were not studied in these pivotal clinical trials.
2. The indication should be limited to the toe nails. The sponsor concurred with the medical officer's assessment of these data; i.e. the phase II studies of the finger nail showed no efficacy.
3. In assessing the data it was noted that approximately 70% of the intent to treat population also used 1% ciclopirox cream on the surrounding infected skin. The ability to assess the efficacy of the nail lacquer alone is confounded by the presence of the 1% ciclopirox cream. A more complete evaluation of these data can be found in the medical officer's review.
4. If approved, the product label should clearly state that this product has not been studied in immunocompromised patients (including but not limited to diabetics, HIV positive patients and subjects who are on steroid therapy) as these patient populations were excluded from the clinical trials.
5. The draft guidance entitled "Developing Antimicrobial Drugs - General considerations for Clinical Trials", dated July 1998,

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states: "In regard to microorganisms included in the INDICATIONS AND USAGE section of the label, only those considered to be an etiologic agent (pathogen) in at least 10% of the evaluable cases of the specific infection studied with the investigative agent should be included if the cure rate is acceptable. The phrase "at least 10%" means at least 10% of the evaluable cases meeting both clinical and microbiological evaluable criteria, or 10 total cases, whichever is higher".



6. The microbiologic data from the two phase III clinical trials showed nominal activity against toe nail infections due to *T. rubrum*. The combined data from clinical trials 312 and 313 demonstrated a global cure rate of 4.3% with a relapse rate of 44%.

Conclusions:

Four factors impact the potential approval of 8% ciclopirox nail lacquer: the clinical efficacy, the microbiologic activity, the risk/benefit profile and compliance.

Issues regarding the risk/benefit ratio and compliance will be discussed by the reviewing medical officer. The microbiologic activity of 8% ciclopirox nail lacquer as it pertains to the pivotal clinical trials is summarized below.

In two phase II clinical trials with 8% ciclopirox nail lacquer no efficacy could be demonstrated against finger nail infections. The results from the in vitro studies support this observation.

The microbiologic results from the two phase III clinical trials clearly demonstrated that 8% ciclopirox nail lacquer had negligible activity against mild to moderate toe nail infections due to the dermatophyte *T. rubrum*. In clinical trial 312, 4/112 (3.6%) subjects in the treatment arm obtained a global assessment of "cure" (clinical and mycologic cure) after 48 weeks of daily treatment. All 4 of these subjects had a positive fungal culture at baseline. These subjects were re-assessed at 12-24 weeks post-therapy to determine relapse

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rates. Two of the 4 patients were infected with *T. mentagrophytes*, one of which relapsed. The other 2 patients were infected with *T. rubrum*, of which, 1 relapsed. The relapse rate for responders in this study was 50% (i.e. 2/4).

In clinical trial 313, 8/118 (6.7%) ITT patients obtained a global assessment of "cure" after 48 weeks of daily therapy. Three of the 8 (37.5%) and 5/8 (62.5%) subjects were baseline fungal culture negative and positive, respectively. Of the 8 patients, 7 (87.5%) were infected with *T. rubrum* and 1 (12.5%) with *T. mentagrophytes*. At follow-up 4/8 subjects (50%) relapsed; 3 with *T. rubrum* and 1 with *T. mentagrophytes*. In this study only 5/8 subjects had a positive baseline fungal culture. An additional point of interest was patient 1219 who was stratified to the vehicle arm. This patient also meet the definition of global assessment cure, however, during follow-up he relapsed. Thus, in the vehicle arm there was a global cure rate of 1/117 (i.e. 0.8%)

The draft guidance entitled "Developing Antimicrobial Drugs - General considerations for Clinical Trials", dated July 1998, states: "In regard to microorganisms included in the INDICATIONS AND USAGE section of the label, only those considered to be an etiologic agent (pathogen) in at least 10% of the evaluable cases of the specific infection studied with the investigative agent should be included if the cure rate is acceptable. The phrase "at least 10%" means at least 10% of the evaluable cases meeting both clinical and microbiological evaluable criteria, or 10 total cases, whichever is higher. In addition to compromising at least 10% of evaluable cases or at least 10 evaluable cases which ever is greater, the eradication rate of the particular pathogen should be considered adequate and clinically acceptable for that pathogen to be included in this section of the labeling."

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[REDACTED]

Based on existing standards the sponsor did not study a sufficient number of cases due to the [REDACTED]. Therefore, these [REDACTED] should be eliminated from the INDICATIONS AND USAGE section of the label. In addition, the sponsor did not provide adequate clinical data demonstrating that 8% ciclopirox nail lacquer is effective against nail infections due to *T. rubrum* (i.e. 5.4% global cure rate with a relapse rate of 44.4%).

In conclusion, the clinical microbiologic data do not support approval of 8% ciclopirox nail lacquer for the topical treatment of mild to moderate onychomycosis without lunula involvement due to *Trichophyton rubrum*, [REDACTED].

However, if this drug were to be approved the clinical microbiology data can only support the following indication for 8% ciclopirox nail lacquer: treatment of mild to moderate distal subungual tinea unguium of the toe nail due to *T. rubrum* [REDACTED].

The data are confounded by the fact that over 70% of the subjects also used 1% ciclopirox cream while on study drug. The reader is directed to the medical officer's review for a complete assessment of the available data. Furthermore, the product label should clearly state that [REDACTED]

[REDACTED] that this product has not been studied in immunocompromised patients (including but not limited to diabetics, HIV positive patients and subjects who are on steroid therapy).

- Recommendations for the Sponsor:

At this time there are no microbiology comments to be conveyed to the sponsor.

[REDACTED] /S/ [REDACTED]
Linda L. Gosey
Microbiologist (HFD 590)

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Concurrences:

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/S/

Signature 10/13/99 Date

HFD-590/MicroTL

/S/

Signature 10/11/99 Date

CC:

HFD-540/Orig.NDA #21-022
HFD-540/Division File
HFD-540/MO:Vaughan
HFD-540/CSO:FCross
~~HFD-590/CSO:EllenFrank~~
HFD-540/Chem
HFD-540/Pharm
HFD-590/ReviewMicro:Gosey

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