Rates By Body System Irrespective of Relationship To Study Drug (continued)

	HOE 296NL		Vehicle	
	No.	%	No.	%
Skin and Appendages	**46**	**38.7**	**53**	**44.9**
Fungal dermatitis	14	11.8	20	16.9
Nail disorder	6	5.0	9	7.6
Contact dermatitis	2	1.7	6	5.1
Rash	16	13.4	6	5.1
Acne	2	1.7	5	4.2
Skin hypertrophy	2	1.7	4	3.4
Maculopapular rash	1	0.8	3	2.5
Eczema	2	1.7	2	1.7
Herpes simplex	0	0.0	2	1.7
Skin benign neoplasm	4	3.4	2	1.7
Skin disorder	4	3.4	2	1.7
Skin ulcer	0	0.0	2	1.7
Alopecia	0	0.0	1	0.8
Application site reaction	0	0.0	1	0.8
Psoriasis	0	0.0	1	0.8
Seborrhea	0	0.0	1	0.8
Subcutaneous hematoma	2	1.7	1	0.8
Urticaria	0	0.0	1	0.8
Vesciculobullous rash	1	0.8	1	0.8
Furunculosis	1	0.8	0	0.0
Pruritus	1	0.8	0	0.0
Skin carcinoma	1	0.8	0	0.0
Skin discoloration	1	0.8	0	0.0
Special Senses	**4**	**3.4**	**10**	**8.5**
Blurred vision	0	0.0	2	1.7
Ear disorder	0	0.0	2	1.7
Eye disorder	0	0.0	2	1.7
Otitis media	1	0.8	2	1.7
Ear pain	1	0.8	1	0.8
Lacrimation disorder	1	0.8	0	0.0
Conjunctivitis	1	0.8	0	0.0
Retinal detachment	1	0.8	0	0.0
Urogenital System	**9**	**7.6**	**13**	**11.0**
Prostatic disorder	2	1.7	4	3.4
Epididymitis	0	0.0	2	1.7
Urinary tract infection	3	2.5	2	1.7
Abnormal ejaculation	0	0.0	1	0.8
Dysmenorrhea	0	0.0	1	0.8
Kidney calculi	0	0.0	1	0.8
Male genital pain	1	0.8	1	0.8
Metrorrhagia	0	0.0	1	0.8
Urogenital neoplasm	0	0.0	1	0.8
Hematuria	1	0.8	0	0.0
Menopause	1	0.8	0	0.0
Prostatic carcinoma	2	1.7	0	0.0
Urination impaired	1	0.8	0	0.0
Vaginal moniliasis	1	0.8	0	0.0

No deaths occurred in either group. There were no discontinuations due to TEAE in the ciclopirox group; there was one discontinuation in the vehicle group.

Reviewer's comment:

A higher incidence of rash 16 (13.4%) was reported for the active group than 6 (5.1%) in the vehicle group. In the active group, 3 of the AEs reported as rash were not confined to the foot (dermatitis of the right chest, heat rash, and rash right inner thigh).. All others, although not listed as the target toe, were mostly periungual erythema of the digits and likely related to therapy. These AEs were mild to moderate in intensity. In the vehicle group, 2 of the reported AEs were located on the digits (erythema of periungual tissues and right thumb dermatitis).

8.2.2.5 Reviewer's Comments/Conclusions of Study 313 Results

Efficacy:

1) *Efficacy of ciclopirox nail lacquer 8% over vehicle was demonstrated at Week 48, Week 48 (LOCF) for Complete Cure; however, efficacy was not demonstrated at either post-treatment follow visits.*
2) *Efficacy of ciclopirox nail lacquer 8% was demonstrated at Week 48 (LOCF) for Almost Clear/Effectively Treated/Treatment Success.*
3) *Valid conclusions can not be drawn regarding eradication of the infecting organism in the Effectively Treated nor Mycological Cure groups at the end of study because of possible inhibitory effects and presence of the active drug*
4) *As in Study 312, nail trimming was an integral part of protocol procedures and is considered as adjunctive therapy.*

Safety:

5) *Rash consisting mostly of periungual erythema at 13.4% in the active vs. 5.1% in the vehicle group was reported in Table 35, TEAE irrespective of relationship to study drug, and is significant. However, the intensity for rash was listed as mild to moderate. Although the active drug appears to be an irritant, there were no known drop-outs due to irritation.*
6) *As presented, no clinically significant differences in laboratory evaluations between the active and vehicle groups were noted.*

8.2.3 Indication #1 Dermatophytic Onychomycosis of the Fingernails

8.2.3.1 Trial #3 Sponsor's Study HOE Protocol 211

Title: A Double-Blind Study of the Safety and Efficacy of Ciclopirox (Loprox®) Nail Lacquer 8% vs. Its Lacquer Vehicle in Patients with Dermatophytic Onychomycosis of the Fingernails

Study dates: Study 211 - November 1988 to June 1989

8.2.3.1.1 Objective

This study was designed to compare the safety and efficacy of 8% ciclopirox nail lacquer with that of the vehicle in the treatment of patients with distal subungual onychomycosis of the fingernail.

8.2.3.1. 2 Study Design /Methods

This was a multicenter, randomized, double-blind, vehicle-controlled, parallel group, comparative study in a total of 110 patients from 7 centers. It was designed to compare the safety and efficacy of the 8% ciclopirox nail lacquer with that of the vehicle in the treatment of fingernail onychomycosis. The treatment was applied once daily at bedtime. Patients were treated for a maximum of 6 months; patients with clinically and mycologically documented cures could discontinue earlier. During the treatment phase the patient was seen at monthly return visits. Patients were scheduled for a post-treatment visit evaluation, 4 weeks after treatment stopped. Mycological evaluations (KOH and culture) were made at baseline, after 2 and 6 months of treatment and at the Post-Treatment Visit. Local and systemic safety assessments were made.

Investigators were instructed to trim nails back to the point of attachment to the nail bed. The efficacy endpoints were Complete Cure(no visible sign of fungal infection) , Improvement (50% to <100% of previously affected nail is cleared of signs of fungal infection) and Poor/no improvement (less than 50% of previously affected nail is cleared of signs of fungal infection).

Reviewer's comments:

The sponsor submitted Study 211 to the NDA as a Phase II Study in support of safety. Protocol 211 was conducted under IND [redacted] According to the sponsor, IND [redacted]

8.2.3.1.4 Study Results

Eighty-six male and female patients with stable or exacerbating distal subungual onychomycosis of the fingernail were recruited from the following seven centers in the US.

Investigator Number Previously Used	Investigator/ Number	Patient Numbers
001	C. Ralph Daniel, MD / 034	101 - 120
002	Vincent Falanga, MD. / 029	201 - 220
003	Robert E. Kalb, MD / 037	301 - 320
004	Lawrence Norton, MD / 044	401 - 420
005	O. Fred Miller, MD /042	501 - 520
006	Larry E. Millikan, MD/043	601 - 620
007	Richard Scher, MD / 046	710 – 720

Reviewer's comment: *Ronald Savin, MD was listed as Investigator 18 for Center #3 in a response for information request received 09-03-99.*

One patient from Center 6 did not receive treatment and was dropped. Patients were randomized as follows: 42 to the ciclopirox lacquer 8% treatment group and 43 to the lacquer vehicle treatment group.

8.2.3.1.4.1 Demographics, Evaluability

Table 41 Demographics (Partial Extraction Sponsor's Table 3)

Characteristic	Ciclopirox lacquer 8% (N = 42)	Lacquer vehicle (N = 43)
Sex		
Male	33 (79%)	40 (93%)
Female	9 (21 %)	3 (7%)
Age (Yrs.)		
Mean	58.0	52.7
Std	13.3	14.8
Minimum	30.0	18.0
Maximum	76	79
Race		
White	41 (98%)	42 (98%)
Hispanic	1 (2%)	1 (2%)

Both the active and vehicle groups were similar. According to the sponsor, demographic data was also comparable across center.

Study Completion Status

Table 42 Completion Status (Study 211)

	Intent to Treat Subjects	
	HOE 29NL	Vehicle
No. of subjects treated	42	43
Completed Study	36	33
Did not complete Study	6	10
Entered Post-treatment Observation	30	27
Entered Open-label Extension Study*	6	6
Reason for not completing study		
Protocol violation	1	0
Abnormal Safety	1	1
Lost to follow-up	0	5
Lack of efficacy	1	1
Subject request	2	1
Other	1	2

Abnormal safety was listed as the reason for discontinuation for one patient in each group from Center 1.

The AEs listed as abnormal safety for the active and vehicle groups were as follows:

Active Group
Center 1 reported Pt. 7, a 72 y.o. male with swelling and rash on right palm. This AE was reclassified as probably related to drug therapy.

Vehicle Group
Center 1 reported Pt. 6, a 74 y/o/ male with anemia due to chronic renal disease.

Reviewer's comment:
The open-label extension study to which 16 patients from Center 7 enrolled was described by the sponsor as continued treatment for 6 months with active medication. This continued treatment was for patients who showed improvement. According to the sponsor, this continuation of therapy was implemented under an amendment (Vol. 1.64, pg.026 for Study 211). According to the submission received 09-03-99, these patients were included in the Integrated Safety Summary.

Mycology
The infecting dermatophyte organisms were not provided.

Sponsor's Efficacy Conclusion:
The proportion of subjects with a clinical response of cured or greatly improved at the last visit did not differ significantly between the treatment groups. There were no statistically significant differences between treatment groups in terms of post-treatment evaluations.

Reviewer's comment: *The statistical review by the Division supported the sponsor's findings regarding lack of efficacy for Complete Cure and Mycological Cure.*

8.2.3.1.4.3 Safety
Local Safety
Application site reactions and nail bed irritation results will be reviewed jointly under Study 212.

According to the sponsor's summary, in Protocol 211, treatment-emergent adverse events (TEAEs) occurred in 60% (25/42) of ciclopirox nail lacquer 8% and 35% (15/43) of vehicle subjects. The most frequent TEAEs in both groups were related to the Respiratory System, Skin and Appendages Systems, and Body as a Whole. The most frequent TEAEs considered causally related to the study drugs in the ciclopirox nail lacquer 8% group were dry skin (ciclopirox: 2% [1/42]; vehicle: none) and nail disorder (ciclopirox: 2% [1/42]; vehicle: none).

No deaths occurred in either group; there was one discontinuation due to TEAE in each treatment group. One ciclopirox nail lacquer 8% subject and five vehicle subjects reported a total of eight treatment-emergent serious adverse events (SAEs). None of the SAEs were considered to be causally related to study drugs.

Reviewer's comment:
Efficacy (See Statistical Review)

Safety (Tabulations of TEAEs by body system regardless of causality and local safety are presented at the end of Study 212.)
Other adverse events appeared to be similar between the active and vehicle groups. No systemic safety signals were noted.

8.2.4 Indication #1 Dermatophytic Onychomycosis of the Fingernails
8.2.4.1 Trial #4 Sponsor's Study HOE 296 Protocol 212
Title: A Double-Blind Study of the Safety and Efficacy of Ciclopirox (Loprox®) Nail Lacquer 8% vs. Its Lacquer Vehicle in Patients with Dermatophytic Onychomycosis of the Fingernails

Study dates: October 1988 to May 1989

8.2.4.1 Objective
This study was designed to compare the safety and efficacy of 8% ciclopirox nail lacquer with that of the vehicle in the treatment of patients with distal subungual onychomycosis of the fingernail.

8.2.4.2 Study Design
This was a multicenter, randomized, double-blind, vehicle-controlled, parallel group, comparative study in a total of 110 patients from 7 centers. It was designed to compare the safety and efficacy of the 8% ciclopirox nail lacquer with that of the vehicle in the treatment of fingernail onychomycosis. The design and conduct of Study 212 was identical to Study 211 as described above.

Reviewer's comments:
The sponsor submitted Study 212 to the NDA as a Phase 2 Study in support of safety. Protocol 212 was conducted under IND [redacted] According to the sponsor, IND [redacted]

8.2.4.4. Study Results
A total of 110 patients from seven centers received study drug (54 in the Loprox nail 8% lacquer group and 56 in the lacquer vehicle group).

Investigator Number Previously Used	Investigator/ Number	Patient Numbers
001	Harry Roth, MD/030 & Raza Aly, PhD/026	101 - 120
002	Dennise Babel, PhD/033& Edward Krull, MD/045	201 - 220
003	Charles Ellis, MD/035	301 - 320
004	Phillip Fleckman, MD/036	401 - 420
005	James Kalivas, MD/038	501 - 520
006*	Richard P. Kaplan, MD/030	601 - 620
007	Manuel Morman, MD/041	701 - 720
008	Jerome Shupack, MD/047	801 - 820

* No patients were listed as being recruited at this center.

No record of patient recruitment was recorded for Center 6. The sponsor did not provide any information regarding this discrepancy.

8.2.4.4.1 Demographics, Evaluability

Table 43 Demographics (Partial Extraction from Sponsor's Table 3)

Characteristic	Ciclopirox lacquer 8% (N = 45)	Lacquer vehicle (N =56)
Sex		
Male	51 (94%)	49 (88%)
Female	3 (6%)	7 (13%)
Age (Yrs.)		
Mean	56.4	56.6
Std	15.8	12.4
Minimum	18.0	27.0
Maximum	91.0	78.0
Race		
White	45 (83%)	49 (88%)
Black	2 (4%)	4 (7%)
Oriental	1 (2%)	0 (0)
Hispanic	5 (9%)	3 (5%)
Other	1 (2%)	0 (0)

Both the active and vehicle groups appear to be similar.

Study Completion Status

Table 44 Completion Status (Study 212)

	Intent to Treat Subjects	
	HOE 29NL	Vehicle
No. of subjects treated	54	56
Completed Study	42	51
Did not complete Study	8	5
Entered Post-treatment Observation	45	52
Entered Open-label Extension Study*	1	0
Reason for not completing study		
Abnormal Safety	3	1
Lost to follow-up	3	1
Lack of efficacy	0	1
Subject request	2	0
Other	0	1
Subject unreliable	0	1

The AEs listed as abnormal safety were as follows:

Active Group

1) Severe chest pain was reported in Pt. 4 of Center 5, a 62-y.o. male, one day after stopping the medication.
2) Chronic bronchitis the same day the study drug was stopped in Pt.18 of Center 5, a 55-y.o. male.
3) Pt. 15 of Center 7, a 66 y.o. male diagnosed with pancreatitis and prostate cancer.

Vehicle Group

Severe tenderness, burning, and bleeding of the nail beds was reported in Pt. 11 of Center 3, a 62 y.o. male.

Reviewer's comment:

The open-label extension study to which one patient from Center 5 was enrolled was described by the sponsor as continued treatment for 6 months with active medication. Continued treatment was for patients who showed improvement. According to the sponsor, this continuation of therapy was implemented under an amendment (Vol. 1.64, pg.026 for Study 211). According to the submission received 09-03-99, this patient was included in the Integrated Safety Summary.

Sponsor's Efficacy Conclusion

There were no statistically significant differences in post-treatment evaluations between treatment groups.

Reviewer's comment: *The statistical review by the Division supported the sponsor's findings regarding lack of efficacy for Complete Cure and Mycological Cure.*

8.2.4.4.3 **Safety**

Local Safety for both Studies 211 and 212 are presented.

Table 45 Subjects* †with Slight to moderate Skin Irritation

(Sponsor's Table R13, Vol. 1.59)

	Ciclopirox		Vehicle	
	N (no. evaluated)	%	N (no. evaluated)	%
Baseline	3 (96)	3	8 (99)	8
Week 4	10 (95)	11	6 (98)	6
Week 8	11 (94)	12	6 (98)	6
Week 12	11 (94)	11 (94)	5 (94)	5
Week 16	6 (92)	7	2 (91)	2
Week 20	4 (90)	4	6 (91)	7
Week 24	3 (85)	4	1 (86)	1
Week 28	2 (82)	2	0 (0)	0

* Some subjects experienced skin irritation at more than one visit

† Subjects had slight to moderate erythema with no induration

The sponsor has not presented phototoxicity/photoallergy topical safety testing for the product. Patients can be expected to have clothing/shoes covering the product on the feet, but will usually

have the hands exposed to sunlight. As this product absorbs light in the range of 302 to 317 nm (depending upon the conditions of testing) there is a potential concern for photoreactions. The data above do not reassure the reviewer that there is no evidence of a local adverse affect due to the drug product.

There were three reports of intense erythema with induration in the vehicle group and no reports of intense erythema with induration in the active group.

Nail bed irritation was graded as present or absent. Severity was not assessed.

Table 46 Subjects* with Nail Bed Irritation (Sponsor's Table R15, Vol. 1.59)

	Ciclopirox		Vehicle	
	N (no. evaluated)	%	N (no. evaluated)	%
Baseline	2 (96)	2	3 (99)	3
Week 4	2 (95)	2	2 (98)	2
Week 8	2 (94)	2	2 (98)	2
Week 12	1 (94)	1	4 (94)	4
Week 16	2 (92)	2	2 (91)	2
Week 20	0 (90)	0	3 (91)	3
Week 24	2 (85)	2	1 (86)	1
Week 28	1 (82)	1	1 (0)	1

* Some subjects experienced nail bed irritation at more than one visit

Safety (Study 212)

A total of 98 adverse events were reported within the ciclopirox nail lacquer 8% treatment group and 52 within the lacquer vehicle group. A wide range of AEs were reported in both groups and the majority of these were considered to be unrelated to study drug.

Adverse events thought to be remotely related to the study drug numbered 4% (2/46) in the Loprox Nail Lacquer group. Palpitations and headaches were reported for Patient 14 of Center 5 (active group) and classified by the investigator as remotely related.

In the vehicle group, 6% (3/52) of reported AEs were classified by the investigator as remotely related to therapy. These AEs considered remotely related to therapy were paronychia, lymphadenitis, and increasing paresthesia in the little finger.

Pregnancy

Patient 030/0103 [redacted] was discontinued from the study because of a positive pregnancy test reported at Visit 5 [redacted] The patient was assigned to the active group.

Reviewer's comment:

According to the sponsor's response to information request received 09-03-99, pregnancy outcome is not available at this time

Treatment-Emergent Adverse Events Table for US Studies, Phase 2 Vehicle-Controlled Studies (Protocols 211 and 212) follows:

Table 47 Treatment-Emergent Adverse Events in US Studies (Protocols 211 and 212)

Sponsor's Table III.1A (Modified)

Treatment-Emergent Adverse Events in US Studies:
Phase 2 Vehicle-Controlled Studies (Protocols 211 and 212)

	Protocol 211				Protocol 212				Phase II Total			
	Ciclopirox		Vehicle		Ciclopirox		Vehicle		Ciclopirox		Vehicle	
	N	%	N	%	N	%	N	%	N	%	N	%
No of Subjects Treated	42	100.0	43	100.0	54	100.0	56	100.0	96	100.0	99	100.0
Subjects With Adverse Events	25	59.5	15	34.9	29	53.7	26	46.4	54	56.3	41	41.4
Body as a whole												
Abdominal pain	7	16.7	6	14.0	6	11.1	11	19.6	13	13.5	17	17.2
Accidental injury	1	2.4	0	0.0	1	1.9	0	0.0	2	2.1	0	0.0
Alcohol intolerance	2	4.8	2	4.7	0	0.0	3	5.4	2	2.1	5	5.1
Back pain	0	0.0	0	0.0	1	1.9	0	0.0	1	1.0	0	0.0
Cyst	1	2.4	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0
Fever	0	0.0	1	2.3	0	0.0	0	0.0	0	0.0	1	1.0
Flu syndrome	1	2.4	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0
Infection	1	2.4	0	0.0	1	1.9	2	3.6	2	2.1	2	2.0
Laboratory test abnormal	1	2.4	1	2.3	3	5.6	4	7.1	4	4.2	5	5.1
Pain	0	0.0	1	2.3	0	0.0	0	0.0	0	0.0	1	1.0
Pain in extremity	0	0.0	1	2.3	0	0.0	2	3.6	0	0.0	3	3.0
Sepsis	1	2.4	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0
	1	2.4	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0
Cardiovascular system												
Arrhythmia	2	4.8	1	2.3	2	3.7	2	3.6	4	4.2	3	3.0
Chest pain	0	0.0	1	2.3	0	0.0	0	0.0	0	0.0	1	1.0
Hemorrhage	0	0.0	0	0.0	1	1.9	0	0.0	1	1.0	0	0.0
Migraine	1	2.4	0	0.0	0	0.0	1	1.8	1	1.0	1	1.0
Palpitation	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0	1	1.0
	1	2.4	0	0.0	1	1.9	0	0.0	2	2.1	0	0.0
Digestive system												
Diarrhea	4	9.5	3	7.0	4	7.4	4	7.1	8	8.3	7	7.1
Dyspepsia	1	2.4	1	2.3	0	0.0	0	0.0	1	1.0	1	1.0
Gastrointestinal disorder	0	0.0	0	0.0	1	1.9	0	0.0	1	1.0	0	0.0
Gum disorder	1	2.4	1	2.3	0	0.0	1	1.8	1	1.0	2	2.0
Hemorrhoids	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0	1	1.0
Nausea	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0	1	1.0
Pancreatitis	1	2.4	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0
Rectal bleeding	0	0.0	0	0.0	1	1.9	0	0.0	1	1.0	0	0.0
Sore throat	0	0.0	1	2.3	0	0.0	0	0.0	0	0.0	1	1.0
Tooth disorder	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0	1	1.0
Endocrine system	1	2.4	0	0.0	2	3.7	0	0.0	3	3.1	0	0.0
Thyroid disorder	0	0.0	0	0.0	1	1.9	0	0.0	1	1.0	0	0.0
	0	0.0	0	0.0	1	1.9	0	0.0	1	1.0	0	0.0
Hemic and lymphatic system												
Anemia	0	0.0	1	2.3	1	1.9	1	1.8	1	1.0	2	2.0
Lymphadenopathy	0	0.0	1	2.3	1	1.9	0	0.0	1	1.0	1	1.0
	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0	1	1.0
Metabolic and nutritional disorders												
Hypercholesterolemia	0	0.0	0	0.0	1	1.9	2	3.6	1	1.0	2	2.0
SGOT increased	0	0.0	0	0.0	1	1.9	1	1.8	1	1.0	1	1.0
Musculo-skeletal system	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0	1	1.0
Arthralgia	3	7.1	1	2.3	1	1.9	0	0.0	4	4.2	1	1.0
Arthritis	1	2.4	1	2.3	0	0.0	0	0.0	1	1.0	1	1.0
Myalgia	1	2.4	0	0.0	1	1.9	0	0.0	2	2.1	0	0.0
	1	2.4	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0
Nervous system												
Anxiety	5	11.9	1	2.3	3	5.6	3	5.4	8	8.3	4	4.0
Dizziness	1	2.4	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0
Facial paralysis	2	4.8	0	0.0	0	0.0	0	0.0	2	2.1	0	0.0
Headache	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0	1	1.0
Multiple sclerosis	2	4.8	1	2.3	3	5.6	0	0.0	5	5.2	1	1.0
Paresthesia	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0	1	1.0
Respiratory system	1	2.4	0	0.0	0	0.0	1	1.8	1	1.0	1	1.0
Asthma	7	16.7	4	9.3	11	20.4	11	19.6	18	18.8	15	15.2
Bronchitis	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0	1	1.0
Cough increased	0	0.0	2	4.7	2	3.7	2	3.6	2	2.1	4	4.0
Dyspnea	1	2.4	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0
Rhinitis	1	2.4	0	0.0	0	0.0	1	1.8	1	1.0	1	1.0
Sinusitis	0	0.0	0	0.0	1	1.9	1	1.8	1	1.0	1	1.0
Upper respiratory infection	2	4.8	2	4.7	0	0.0	0	0.0	2	2.1	2	2.0
Voice alteration	3	7.1	2	4.7	9	16.7	7	12.5	12	12.5	9	9.1
	1	2.4	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0

	Protocol 211				Protocol 212				Phase II Total			
	Ciclopirox		Vehicle		Ciclopirox		Vehicle		Ciclopirox		Vehicle	
	N	%	N	%	N	%	N	%	N	%	N	%
No. of Subjects Treated	42	100.0	43	100.0	54	100.0	56	100.0	96	100.0	99	100.0
Skin and appendages	7	16.7	6	14.0	9	16.7	8	14.3	16	16.7	14	14.1
Breast neoplasm	0	0.0	1	2.3	0	0.0	0	0.0	0	0.0	1	1.0
Burning sensation skin	0	0.0	0	0.0	0	0.0	1	1.8	0	0.0	1	1.0
Contact dermatitis	0	0.0	1	2.3	0	0.0	0	0.0	0	0.0	1	1.0
Dry skin	2	4.8	0	0.0	0	0.0	0	0.0	2	2.1	0	0.0
Eczema	0	0.0	1	2.3	0	0.0	0	0.0	0	0.0	1	1.0
Fungal dermatitis	0	0.0	0	0.0	4	7.4	2	3.6	4	4.2	2	2.0
Nail disorder	1	2.4	0	0.0	0	0.0	2	3.6	1	1.0	2	2.0
Pruritus	0	0.0	0	0.0	2	3.7	1	1.8	2	2.1	1	1.0
Rash	1	2.4	1	2.3	1	1.9	2	3.6	2	2.1	3	3.0
Seborrhea	0	0.0	0	0.0	1	1.9	0	0.0	1	1.0	0	0.0
Skin benign neoplasm	1	2.4	2	4.7	0	0.0	0	0.0	1	1.0	2	2.0
Skin carcinoma	0	0.0	1	2.3	1	1.9	0	0.0	1	1.0	1	1.0

According to the sponsor's study synopsis, in Protocol 212, TEAEs occurred in 54% (29/54) of subjects treated with ciclopirox nail lacquer 8% and 45% (25/56) subjects treated with vehicle. In both groups, the most frequently occurring TEAEs were related to the Respiratory System, Skin and Appendages Systems, and Body as a Whole. The most frequently occurring TEAEs considered causally related to ciclopirox nail lacquer 8% group were pruritus (ciclopirox: 2% [1/54]; vehicle: none) and skin discoloration (ciclopirox: 2% [1/54]; vehicle: none).

No deaths occurred in either group; there was one study drug related discontinuation due to a TEAE in the ciclopirox nail lacquer 8% group, and there was one related to study drug in the vehicle group. A total of five treatment-emergent SAEs were reported by three ciclopirox nail lacquer 8% subjects and one vehicle subject. None of the SAEs were considered to be causally related to study drugs.

8.2.4.5 Reviewer's Conclusion of Study Results

Efficacy

According to the Statistical Review dated 9/22/99, no statistical significance was demonstrated between active over vehicle in Complete Cure or Mycological Cure at 8 weeks and LOCF in Study 212.

Safety

Skin (adjacent to the Target nail) irritation was graded slight to moderate in intensity and decreased over time for Studies 211 and 212. Other adverse events (TEAE) appeared to be similar between the active and vehicle groups. No systemic safety signals were noted. Pregnancy outcome information for one patient was not available.

As the drug product absorbs in the UV range, the sponsor should present evidence to demonstrate that ciclopirox nail lacquer does not exhibit phototoxicity/photoallergy

Indication #1 **Distal Subungual Tinea Ungium of the Toenails**
8.2.5 Trial #5 **Sponsor's Study 320 (HOE 296NL/8/USA/3012/NM)**
AN OPEN-LABEL STUDY OF CICLOPIROX (HOE 296 NL) NAIL LACQUER 8% IN SUBJECTS WITH DISTAL SUBUNGUAL TINEA UNGUIUM OF THE TOENAILS

Study dates: **June 9, 1995 - April 16, 1997**
Study period is defined as beginning at the time the subject signed the informed consent form at the last visit in the double-blind study (or up to four weeks after that visit) and ended 14 days after the last application of test material.

8.2.5.1 Objective/Rationale
The objective was to monitor the safety of ciclopirox nail lacquer during a 48 week course of treatment of subjects with distal subungual tinea unguium after 48 weeks of double-blind treatment in ciclopirox nail lacquer Protocol 312 or 313. According to the sponsor, the study was to establish the long-term safety of ciclopoirox nail lacquer as applied for the treatment of distal subungual tinea unguium.

8.2.5.1 Design
This was a one-arm, multi-center, open-labeled, 48-week study extension study conducted in the United States at 18 centers. This study enrolled subjects that had been treated during the previous 48-week period with either ciclopirox nail lacquer or its vehicle as a part of either ciclopirox nail lacquer Protocol 312 or 313.

The sponsor called this a compassionate use study allowing the patients to continue treatment with ciclopirox nail lacquer. Efficacy variables were evaluated to determine the clinical status of the disease to determine continuation of open-label treatment. According to the sponsor, efficacy evaluation data did not permit discriminating analysis of efficacy because the categories used to collect data were very broad; consequently, a definitive assessment of the clinical response to the ciclopirox nail lacquer was not made.

8.4.5.2 **Protocol Overview**

The Baseline (Day 1) visit for this study was to be either the last treatment visit of the double-blind study (Protocol 312/313) or up to 4 weeks after their final treatment phase visit in Protocols 312/313. Subjects enrolled in Protocol 312/313 whose target toenail cleared clinically and had negative mycology (KOH and culture) were **not** eligible for enrollment.

Ciclopirox nail lacquer 8% was applied once daily, and removed once weekly. Subjects were treated for 48 weeks. Subjects were seen every 8 weeks for return visits.

Ciclopirox nail lacquer application procedures were the same as in the Studies 312 and 313. Subjects could treat any involved toenail or fingernail with the test material. All affected/treated nails will be evaluated clinically. Subjects were scheduled for return visits every 8 weeks during treatment. If a clinical cure of all treated nails could be documented, the subject could discontinue from the study.

A clinical cure was defined as no visible signs of infection.

Safety
Safety variables were assessed as follows:
The occurrence of adverse events (local and systemic), changes in physical examinations, changes in clinical laboratory values (hematology, serum chemistry, urinalysis), and pregnancy testing. The chemistry panel differed slightly from Protocol 312/313. CK or requirement for sub-typing of LDH or CK isoenzymes was omitted in Protocol 320.. Specimens for routine clinical laboratory assessments (serum chemistry, hematology and urinalysis) were obtained at Day 1 and at select return visits (weeks 16, 32, and 48).

Systemic levels of ciclopirox were not measured. If any of the final laboratory results from P312/313 were abnormal and considered to be clinically important, the subject was not to be enrolled in Protocol 320. Local safety assessments (e.g., application site reactions) were not specifically performed.

For females of childbearing potential, urine pregnancy tests were performed at each visit. Results must be negative if the subject is to be enrolled or continued in the study. Adverse events were assessed/monitored at Day 1 and at each return visit.

Statistical Methods
No inferential statistical tests were performed.

Reviewer's comments: *This study will be reviewed in support of safety.*

8.2.5.4 Study 320 - Results

Eighteen investigator sites study sites in the USA participated. These study sites were identical to the study sites listed for Study 312 and 313. A total of 281 patients were treated with active drug. There were 143 patients designated CC (previously treated with active drug from Studies 312 and 313) and 138 patients designated VC who previously were treated with vehicle.

8.2.5.4.1 Demographics

Table 48 Demographic and Background Characteristics (Sponsor's Table 2, Vol. 1.53)

Characteristic	CC N (%)	VC N (%)	Total N (%)
Gender			
Male	116 (81.1%)	107 (77.5%)	223 (79.4%)
Female	27 (18.9%)	31 (22.5%)	58 (20.6%)
Age (yr.)*			
Number	143	138	281
Median	52.0	51.0	51.0
Mean	52.5	50.8	51.7
SD	10.2	12.1	11.2
Range	28 – 70	21 70	21 – 70
Race			
White	131 (91.6)	128 (92.8%)	259 (92.2%)
Black	3 (2.1%)	3 (2.2%)	6 (2.1%)
Oriental	3 (2.1%)	0 (0.0)%)	3 (1.1%)
Hispanic	5 (3.5%)	5 (3.6%)	10 (3.6%)
Other	1 (0.7%)	2 (1.4%)	3 (1.1%)

* Age information was extracted from 312/313 database.

Table 49 Study Completion Status (Sponsor's Table R6, Vol. 1.53)

	Total		CC		VC	
	N	%	N	%	N	%
All subjects Treated*	281	100	143	100	138	100
Completed Study	235	84	123	86	112	81
Did not complete study	46	16	20	14	26	19
Reason for not completing:						
Did not meet protocol criteria	3	1	1	1	2	1
Unreliable	7	3	4	3	3	2
Moved or lost to follow-up	13	5	4	3	9	7
Safety-laboratory	1	<1	0	0	1	1
Died	2	1	0	0	2	1
Lack of efficacy	6	2	2	1	4	3
Subject request	13	5	8	6	5	4
Other	1	<1	1	1	0	0

* Two CC subjects were considered "not treated" because they had no clinical data recrded after the Baseline visit.

Table 50 Duration of Ciclopirox Treatment in Protocol 320 (Partial extraction of Sponsor's Table 3.1, Vol. 1.53)

Treatment Duration (Days)*	CC N	VC N	Total N
Number	143	137	280
Median	336.0	336.0	336.0
Mean	312.2	306.8	309.5
SD	78.2	80.1	79.1
Range			

* Treatment duration is calculated as: date of first dose minus date of last dose plus one regardless of dose skipped/adjusted.

Table 51 Total Duration of Ciclopirox Treatment – Study 312 or 313 and Study 320 – For Patients Treated in protocol 320 (Partial extraction of Sponsor's Table 3.2, Vol. 1.53)

Treatment Duration (Days)*	CC N	VC N	Total N
Number	143	137	280
Median	673.0	336.0	406.0
Mean	652.7	306.8	483.5
SD	77.6	80.1	190.3
Range			

There were 262 (93.2%) of the patients used at least one concomitant medication. In the CC group N= 135 or 94.4%. In the VC group 127 or 92.0% of the patients used at least one concomitant medication. The most frequently used Concomitant medication was ciclopirox (72.7%) in the CC group and 99 (71.7%) in the VC group.

8.2.5.4.3 Safety

Table 52 Adverse Events That Led to Permanent Discontinuation of Treatment

Group	Subject ID	Adverse Event	Severity	Investigator's Assessment of Casual Relationship to Therapy	Outcome
CC	063/1515	Fungal dermatitis/Did not meet protocol criteria	Mod	Not Related	Ongoing
CC	085/0807	Nail disorder	Mild	Related	Resolved
VC	052/0412	Creatine phosphokinase increased	Mild	Related	Ongoing
VC	072/0525	GI disorder	Mod	Not Related	Resolved
VC	086/1902	Suicide attempt other than overdose	Severe	Not Related	Died
VC	086/1926	Myocardial infarction	Severe	Not Related	Died

Seventy-two percent of subjects experienced at least one TEAE. Respiratory System, Skin and Appendages, and Body as a Whole were the highest ranking body systems in terms of incidence of AEs.

Table 53 that follows lists either a new event that emerged during Protocol 320 or an event that first emerged in Protocol 312/313 that then either increased in severity or changed causality from not related to related.

Table 53 Treatment Emergent Adverse Events (TEAE) By Decreasing Rates Related to Study Drug (Partial extraction of Sponsor's Table 5.2.2, Vol. 1.53)

Total No. of Subjects Treated	Total	
	N	%
No. of Subjects Treated	281	100
No. Without TEAE Related to Study Drug	272	96.8
No. With TEAE Related to Study Drug	9	3
Nail disorder	4	1
Rash	2	1
Accidental injury*	1	<1
Creatine phosphokinase increased	1	<1
Electrolyte Abnormality	1	<1
Enzymatic Abnormality	1	<1
Hyperglycemia	1	<1
Pain in Extremity	1	<1

*inflamed right great toe

Reviewer's comment:

Patient 052/0412, a 43-year old Caucasian male, was discontinued from Study 320 because of increased creatine phosphokinase (CPK) level of 736 U/L (normal range, 22 – 198 U/L). The patient had been randomized to the vehicle arm in Study 312. According to data listings (Table 14.3.6, Vol. 1.39), the patients CPK had been elevated at Baseline and throughout study particpation in Study 312. Additionally, CK-MB levels were elevated at Week-38 and at Week 48, 9.800 ng/mL and 12.700 ng/mL (normal range 0.000-4.999 ng/mL) respectively, prior to entering open-label treatment with ciclopirox nail lacquer 8%. The patient received active treatment in Study 320 from 08-02-95 to 09-19-95 and CPK values were reported as 551, 750, and 571. CK-MB were reported as 10.200 and 10.100. No concomitant medications were reported and the patient reported no relevant medical history according to the sponsor. According to the comments provided by the sponsor for Study 312, the abnormal CK-MB levels were attributed to exercise. It is unknown why the same investigator made a causal relationship assessment to therapy at this juncture.

8.2.5.4 Reviewer's Conclusion of Study Results

Efficacy

According to the sponsor (Vol. 1.53, pg. 004), there were no apparent differences in the scoring categories before or after treatment. The range of the categories was too large to allow measurement of clinical response in this safety study.

Safety

There were two deaths reported. One subject died of a myocardial infarction and there was one suicide. Neither death was thought causally related to drug therapy.

One patient was discontinued from the study because of increased creatine phosphokinase (CPK) and CK-MB levels. The chemistry panel for this study did not include monitoring of CK or requirement for sub-typing of LDH or CK isoenzymes; however, these values were obtained for this patient. It is unknown why the investigator assessed a causal relationship to therapy.

Overall, 86% of patients entering the completed the study; therefore, it appears that the therapy with the active drug was tolerable.

8.2.6 Non-US Studies

Efficacy and safety summaries were provided by the sponsor for 22 non-US studies. No efficacy data were submitted to the Division for analysis. Study synopses were submitted for completed studies that follow in Table 54 . The sponsor did not provided any interim reports for ongoing studies (start dates in parenthesis): [redacted] Although data were not submitted Discussion of the safety data from these studies are located in Section 10 of this review.

Table Clinical Studies Conducted Outside of the USA

Table 54 below shows key aspects of European studies.

Sponsor's Table R2, Vol. 1.59 Clinical Studies Conducted Outside of the USA

Study No. Indication	Design	Completion Status (Start Date)	Number Subjects Treated	Age Range	M/F	Treatment: Dose	Treatment: Frequency	Treatment: Duration	Sponsor's outcome assessment
Phase I Open-Label Non-US Study									
A3	open-label cross-over	Complete (7/95)	20 20	22-57	5/15	CIC 8% Amorolfine 5%	1/day	one day	Efficacy not assessed
Phase II Non-US Studies[1]									
B3 Mainly fingernails	open-label uncontrolled	Complete (6/88)	302	20-70	117/185	CIC 8%	1/day	16 weeks	Descriptive stats, nail growth paired t-test
B4	open-label uncontrolled	Complete (11/86)	75	18-79	44/31	CIC 8%	1/day	24 weeks	Descriptive stats only
B5	Double-blind parallel group	Complete (4/85)	15 15	12-74	17/13	CIC 4% CIC 8%	1/day (q.o.d.)	24 weeks	Partially analyzed
B6 Fingernails	Double-blind parallel group	Complete (Spring 1986)	15 15	12-74	17/13	CIC 4% CIC 8%	1/day (q.o.d.)	16 weeks	No significant difference between the concentrations.
Phase III Double-Blind Non-US Studies[2]									
C4 Fingernails & toenails	Double-blind parallel group	Complete (3/88)	28 28	UNK	UNK	CIC 8% KET 200mg	1/day 1/day	24 weeks	Comparable efficacy (Chi-square test)
C5 Fingernails & toenails	Double-blind parallel group	Complete (7/90)	41 40	19-70	54/27	CIC 8% VEH	1/day 1/day	24 weeks	Not analyzed due to great no. of drop-outs
Phase III Open-Label Non-US Studies[3]									
C6 - C12	open-label uncontrolled	Complete (2/85)	2202	2-87	UNK	CIC 8%	1/day to 3/week	16 weeks to 24 weeks	
Phase IV Non-US Studies[4]									
D3	Open-label uncontrolled	Complete (10/94)	37	UNK	UNK	CIC 8%	1/day	24 weeks	Not available
D4	Open-label parallel group	Complete (5/94)	30 30	UNK	29/31	CIC 8% CIC 8%	1/day 2/week	24 weeks	Inconclusive results
D5	Open-label uncontrolled	Complete (4/94)	105	20-79	UNK	CIC 8%	1/day x 4wks., then 2/week	24 weeks	Effective
Post-Marketing Surveillance Non-US Studies[5]									
E2	Open-label uncontrolled	Complete (10/92)	3666	2-100	UNK	CIC 8%	1/day	24 weeks	

q.o.d.=every other day
UNK=unknown
M=male subjects
F=female subjects
CIC 4%=ciclopirox nail lacquer 4%
CIC 8%=ciclopirox nail lacquer 8%
KET=ketoconazole
VEH=vehicle

[1] Total subjects treated in Phase 2 studies: CIC 8%=407; CIC 4%=30.
[2] Total subjects treated in Phase 3 double-blind studies: CIC 8%=69; VEH=40; KET=28.
[3] Total subjects treated in Phase 3 open-label studies: CIC 8%=2202.
[4] Total subjects treated in completed Phase 4 studies: CIC 8%=202.
[5] Total subjects treated in completed post-marketing surveillance studies: CIC 8%=3666.

According to the sponsor, Studies B5 and B6 are Phase 2 studies. These studies appear to be dose ranging studies and were therefore selected for comment since no dose ranging studies are known to have been conducted. Both were double-blind randomized studies.

Study B5 (B%/HOE296/2/A/201/NM

Title: "A Randomized, Double-Blind, Parallel Study to Assess the Efficacy, Tolerability and Safety of Batrafen® (Ciclopirox) Nail Lacquer 4% and 8% in Treatment of Patients with Onychomycoses."

Conclusion:

According to the sponsor, the study could only be partially analyzed as planned by the study protocol because of irregularities within the randomization procedure.

Study B6 (B6/HOE296NL/2/SF/201/NM) was a Phase II Study.

Title: "A Double-Blind Comparative Study With HOE 296 Nail Lacquer 4% Versus 8% Ciclopirox in Fingernail Onychomycoses."

The stated objective was assessment of efficacy, tolerability and safety of HOE 296 nail lacquer containing either 4% or 8% ciclopirox in the treatment of patients with fingernail onychomycosis.

The results are as follows(Vol. 1.59, pg 023):

	4%	8%
Total number of patients:	15	15
Male	7	10
Female	8	5
Age:	<20 - >60 years	
Median (years)	47	39.5
Culture:		
Trichophyton rubrum	8	8
Trichophyton mentagrophytes	7	7

Treatment duration: 4 months

Statistical Procedures:
A generalization of Fisher's exact probability test was used.

Efficacy (Evaluation of affected target nail plate)
Efficacy was assessed on the increase of the unaffected length of the target nails and by the number of patients who had negative findings in the KOH and culture examination after the study.
Safety:
According to the sponsor, "No side effects were reported during the whole study."

Conclusions:
According to the sponsor, no significant differences between HOE 296 4% and 8% preparations were found in any parameter.

Reviewer's comments:
Studies B5 and B6 appear to be dose ranging studies. According to the sponsor, B5 was only partially analyzed because of irregularities within the randomization procedure. However, according to the sponsor, Study B6 found no significant differences between 4% and 8% ciclopirox nail lacquer

8 Overview of Efficacy

Studies 312 and 313 were submitted by the sponsor in support of the efficacy of ciclopirox nail lacquer 8% in treatment of distal onychomycosis of the toenails in conjunction with monthly professional nail trimming and debridement by the investigator. Complete Cure is defined as no visible signs of infection (global improvement score = 0) plus a negative KOH exam and a negative culture. Complete Cure was assessed at the end of treatment and at 12 or 24-Week post-treatment follow-up period. Almost Clear/Treatment Success (Effectively Treated) is defined as ≤10% nail involvement, KOH negative, and culture negative, and was assessed at end of study, and end of study (LOCF). Mycologic cure is defined as negative KOH plus negative culture and was ~~assessed at end of study and end of study LOCF~~.

For the ITT population in Study 312, statistical significance was not demonstrated for Complete Cure. Fisher p-values were 0.370, 0.369, 1.000, and 1.000 at 48 weeks, for LOCF-48 weeks, 12 Week plus LOCF and 24 Week plus LOCF respectively. Results were somewhat more favorable for Study 313, for Complete Cure, statistical significance of ciclopirox nail lacquer 8% over vehicle was not demonstrated at either post-treatment follow visit. Fisher Exact Test p-values was 0.058 (barely significant), 0.023, and 0.477 at 48 weeks, LOCF-48 weeks, and 12 Week plus LOCF respectively.

The sponsor did demonstrate statistical significance of active over vehicle for the Almost Clear/Effectively Treated (Treatment Success) and Mycological Cure categories at Week 48 and Week 48 (LOCF) for Studies 312 and 313; however, sustained efficacy was not demonstrated during the post-treatment period. Efficacy of ciclopirox topical solution, 8% at a post-treatment follow-up was difficult to assess because only Complete Cure subset was followed and the

number of patients was small. For the ITT population for Study 313, Fisher p-values were 0.007, 0.002, 0.122, and 0.240 at 48 weeks, LOCF-48 weeks, 12 Week plus LOCF and 24 Week plus LOCF respectively. Statistical significance was not demonstrated at post-treatment follow-up.

The sponsor collected post-treatment data only for patients with Complete Cure; therefore, post-treatment data are not available for all subjects categorized as Almost Clear/Effectively Treated (Treatment Success) and a majority of the patients with Mycological Cure. Without post-treatment data, sustained efficacy for Effectively Treated or Mycological Cure categories can not be validated.

This NDA was the presented to the 51st Meeting of the Center for Drug Evaluation and Research Dermatologic and Ophthalmic Drugs Advisory Committee (DDODAC) held on November 4, 1999 for discussion and recommendations. A majority of the committee recommended approval of ciclopirox topical nail solution, 8% in treatment of distal subungual onychomycosis as adjunctive therapy with professional monthly nail trimming. There seemed to be the following consensus with which this Reviewer concurs:

1) Novel topical therapy for which there is currently a void (i.e., only systemic therapies are currently approved for this indication) for an indication that is chronic and difficult to treatment.
2) Ciclopirox topical Solution, 8% has a relatively safe drug profile (discussed in detail below)
3) Almost Clear/Effectively Treated defined as ≤10% nail involvement in combination with professional nail trimming as conducted during the studies did demonstrate statistical significance in both studies and would provide alternative therapy to systemic treatment.

This recommendation is also in agreement with recommendations of the 40th meeting of DDOAC, held September 22 & 23, 1994. In summary, both Committees and this Reviewer concur that a clear nail bed is the standard; however, improvement could be acceptable if the drug product presents no significant risk.

9 Overview of Safety

The sponsor presented safety profiles from both US and foreign clinical trials. Special safety studies submitted include PK Study 111 and one dermatoxicity study, Study 1003, to assess irritation and sensitization potental will be discussed in section 10.2.3 (Special Studies). Phototoxicity and Photocontact Allergenicity topical safety studies were not submitted to the NDA.

- Clinical Trials Conducted in the US – the safety data from trials 211, 212, 312, and 313 were presently in an integrated summary of safety. Special safety assessments included systemic absorption of study drug (ciclopirox serum levels), CPK level determinations (reflex CK-MB determination) in Studies 312 and 313, in addition to adverse events reporting and laboratory monitoring.

In the Phase 2/3 studies, Loprox Cream was used as comcomitant medication in a total of 327 (50%) out of 655 (100%) subjects treated and 574 (88%) with concomitant medication. In the active group, 174 (53%) used Loprox Cream 1% and 153 (47%) used the cream in the vehicle group. As previously mentioned, TEAE adverse events reporting would have been clinically relevant if presented as follows: ciclopirox nail lacquer 8%, ciclopirox nail lacquer 8% + concomitant ciclopirox, vehicle, and Vehicle + concomitant ciclopirox.

Table 55 (Sponsor's Table R22) that follows, lists TEAEs, irrespective of the causal relationship to study drug, reported in ≥5% of subjects in either treatment group are presented by body system.

Table 55 Incidence of TEAE, Irrespective of Causal Relationship to Study Drug, Occurring in ≥5% of Subjects in Either Treatment Group (Phase 2/3 Studies)

Sponsor's Table R22, Vol. 1.59 Incidence of TEAE, Irrespective of Causal Relationship to Study Drug, Occurring in ≥5% of Subjects in Either Treatment Group (Phase II/III Studies)

	Ciclopirox		Vehicle	
	n	%	N	%
Total No. of Subjects Treated	327	100	328	100
No. of Subjects With at Least One TEAE	245	75	237	72
Respiratory Disorders	131	40	120	37
Upper respiratory infection	84	26	84	26
Sinusitis	29	9	20	6
Rhinitis	28	9	12	4
Bronchitis	9	3	15	5
Skin and Appendages	116	36	113	35
Fungal dermatitis	35	11	45	14
Rash	25	8	17	5
Nail disorder	17	5	14	4
Body as a Whole	90	28	103	31
Accidental injury	32	10	43	13
Flu syndrome	26	8	22	7
Nervous System	47	14	38	12
Headache	32	10	23	7
Musculo-Skeletal System	44	14	37	11
Arthralgia	16	5	12	4

Source: Statistical Table III.1A.

Overall, the intensity of TEAEs was similar between the treatment groups. In the ciclopirox group, 31% (101/327) of subjects experienced adverse events classified by the investigator as mild; for 33% (109/327) the greatest intensity was moderate, and for 11% (35/327) the greatest intensity was severe. In the vehicle group, 26% (85/328) of subjects experienced adverse events classified as mild, for 35% (116/328) the greatest intensity was moderate, and for 11% (36/328) the greatest intensity was severe. The intensities of the most frequently reported TEAEs (crude incidence rate ≥5% in any treatment group) in the Phase 2/3 studies are presented in Sponsor's Table R. Additional information about the intensity of TEAEs, irrespective of causal relationship to study drug, is presented in Statistical Table III.1B.

Table 56 Intensity of Most Frequently Occurring Treatment-Emergent Adverse Events (Phase 2/3 Studies)

Sponsor's Table R23, Vol. 1.59 Intensity of Most Frequently Occurring Treatment-Emergent Adverse Events (Phase 2/3 Studies)

	Ciclopirox n (%)			Vehicle n (%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
No. of Subjects With at Least One TEAE	101 (31)	109 (33)	35 (11)	85 (26)	116 (35)	36 (11)
Upper respiratory infection	55 (17)	27 (8)	2 (1)	53 (16)	26 (8)	5 (2)
Fungal dermatitis	25 (8)	10 (3)	0 (0)	30 (9)	15 (5)	0 (0)
Rhinitis	22 (7)	6 (2)	0 (0)	9 (3)	3 (1)	0 (0)
Rash	19 (6)	5 (2)	1 (1)	13 (4)	4 (1)	0 (0)
Headache	19 (6)	13 (4)	0 (0)	16 (5)	4 (1)	3 (1)
Accidental injury	19 (6)	11 (3)	2 (1)	24 (7)	18 (6)	1 (1)
Sinusitis	17 (5)	11 (3)	1 (1)	8 (2)	10 (3)	2 (1)
Nail disorder	12 (4)	5 (2)	0 (0)	8 (2)	3 (1)	2 (1)
Flu syndrome	9 (3)	17 (5)	0 (0)	9 (3)	13 (4)	0 (0)
Arthralgia	8 (2)	7 (2)	1 (1)	5 (2)	6 (2)	1 (1)
Bronchitis	1 (1)	7 (2)	1 (1)	1 (1)	6 (2)	8 (2)

Source: Statistical Table III.1B.

Adverse Events Occurring Within 30 Days of Measurable Ciclopirox Serum Levels

Subjects with adverse events occurring within 30 days of measurable ciclopirox serum levels are presented in Sponsor's Table R2 that follows. Of those subjects with at least one detectable level of ciclopirox, 13 in the ciclopirox nail lacquer 8% group and three in the vehicle group experienced adverse events within 30 days of measurable ciclopirox serum levels. Only one subject in the ciclopirox nail lacquer 8% group experienced a mild nail disorder that was

considered by the investigator to be related to the study drug. The subject had an ingrown toenail of the right great toe that occurred around Week 40 when the measured ciclopirox level was 16.1 ng/mL. This regressed in the same week without special treatment (non study) or stopping the ciclopirox, making a relationship of this common, and generally long-standing, disorder of nail anatomy and growth unlikely.

All other adverse events were considered by the investigator to be unrelated to the study drug; most resolved without residual effects.

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Table 57 Subjects with Adverse Events Within 30 Days of Measurable Ciclopirox Serum Levels

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Sponsor's Table R2 Subjects with Adverse Events Within 30 Days of Measurable Ciclopirox Serum Levels

Subject ID	Adverse Event	Age	Sex	Concomitant Medication	Onset Day	End Day	Intensity	Outcome	Causal Relationship
Study 312 – Ciclopirox Nail Lacquer 8% Group									
026/0126	Upper respiratory infection	56	M	Yes	225	—	Mild	Ongoing	Not related
026/0130	Fungal dermatitis	47	M	No	99	—	Mild	Ongoing	Not related
085/0812	Penis disorder Gout Atrial fibrillation	68	M	Yes	309 316 322	317 320 336	Moderate Mild Moderate	Resolved Resolved Resolved	Not related Not related Not related
Study 312 - Vehicle Group									
026/0115	Fungal dermatitis	32	M	Yes	301	—	Mild	Ongoing	Not related
Study 313 – Ciclopirox Nail Lacquer 8% Group									
036/1202	Headache Nail disorder Gastrointestinal disorder Headache	37	F	No	257 278 313 342	257 280 320 344	Moderate Mild Moderate Moderate	Resolved Resolved Resolved Resolved	Not related Related Not related Not related
036/1209	Accidental injury Upper respiratory infection Diarrhea	55	M	No	316 324 338	339 334 340	Moderate Moderate Mild	Resolved Resolved Resolved	Not related Not related Not related
036/1220	Infection Arthralgia Upper respiratory infection	60	M	Yes	134 181 181	140 182 186	Mild Severe Mild	Resolved Resolved Resolved	Not related Not related Not related
036/1227	Tenosynovitis	48	M	No	153	239	Mild	Resolved	Not related
044/1309	Fungal dermatitis Tooth disorder Rhinitis	37	M	No	57 82 316	— 82 —	Moderate Moderate Moderate	Ongoing Resolved Ongoing	Not related Not related Not related
044/1314	Upper respiratory infection	31	M	Yes	109	114	Mild	Resolved	Not related
044/1321	Diarrhea	29	M	No	84	85	Moderate	Resolved	Not related
044/1330	Bursitis	43	M	No	277	—	Mild	Ongoing	Not related
047/1405	Accidental injury Rhinitis Cholecystitis	48	M	Yes	252 317 354	282 345 355	Moderate Mild Moderate	Resolved* Resolved Resolved	Not related Not related Not related
047/1412	Rhinitis	42	M	No	215	237	Mild	Resolved	Not related
Study 313 - Vehicle Group									
036/1204	Maculopapular rash Rhinitis Accidental injury	31	M	No	36 71 87	60 130 87	Mild Mild Moderate	Resolved Resolved Resolved*	Not related Not related Not related
036/1225	Fungal dermatitis Metrorrhagia	41	F	Yes	194 195	— 253	Moderate Mild	Ongoing Resolved	Not related Not related

Source: ISS (Statistical Tables 20.1.5) and individual study reports.
* Resolved with residual effects.
M=Male, F=Female, W=White

Reviewer's comment: *Of particular interest is the reported cardiac event, atrial fibrillation. No additional data was presented for this patient and the significance of this event in assocaition with a detectable ciclopirox level is unknown.*

10.2.2 Laboratory Findings, Vital Signs, ECGs

Clinical laboratory evaluations were made for all subjects treated in the Phase 2/3 studies: 327 subjects treated with ciclopirox and 328 subjects treated with vehicle.

Table 58 Subjects with Clinically Noteworthy Abnormal LaboratoryValues (Phase 2/3 Studies)

Sponsor's Table R21, Vol. 1.59 Subjects with Clinically Noteworthy Abnormal Laboratory Values (Phase 2/3 Studies)

Protocol	Subject ID	Age	Sex	Parameter	Normal Range	Visit	Lab Value
Ciclopirox Group							
211	046/0704	75	F	Eosinophils	0 - 0.63 G/L	Week 28	0.75 HC
212	036/0401	64	M	Neutrophils	1.92 – 7.96 G/L	Week 24	9.07 HC
	047/0804	32	M	Eosinophils	0 - 0.6 G/L	Week 16	1.44 HC
312	041/0222	69	F	Neutrophils	1.62 – 8.06 G/L	Week 4	10.55 HC
	041/0228	29	M	CPK	22 – 198 U/L	Week 48	620 HC
	052/0423	24	M	CPK	22 – 198 U/L	Baseline	797 HC
	072/0530	61	M	CPK	22 – 198 U/L	Baseline Week 24 Week 28	907 HC 827 HC 1186 HC
313	036/1203	53	M	Eosinophils	0 - 0.73 G/L	Week 48	1.01 HC
	047/1415	52	M	CPK	22 – 198 U/L	Week 36	605 HC
	063/1509	39	M	CPK	22 – 198 U/L	Week 24	1902 HC
	066/1717	56	M	Neutrophils	1.62 – 8.06 G/L	Week 48	8.37 HC
	086/1906	49	M	CPK	22 – 198 U/L	Week 48	918 HC
Vehicle Group							
211	018/0406	47	M	Neutrophils	1.8 - 8.175 G/L	Week 24	13.7 HC
	037/0308	40	M	SGOT (AST) SGPT (ALT)	0 – 40 U/L 0 – 45 U/L	Week 16 Week 16	101 HC 270 HC
312	052/0401	62	M	CPK	22 – 198 U/L	Week 40	1169 HC
	052/0412	43	M	CPK	22 – 198 U/L	Week 36 Week 48 Week 48	668 HC 736 HC 750 HC
	072/0503	30	M	CPK	22 – 198 U/L	Week 12	637 HC
	072/0505	58	M	CPK	22 – 198 U/L	Baseline	1175 HC
	075/0609	21	M	CPK	22 – 198 U/L	Week 12	719 HC
	087/0922	47	M	CPK	22 – 198 U/L	Week 12 Week 12 Week 12 Week 48	1168 HC 735 HC 766 HC 952 HC
	087/928	53	M	Neutrophils	1.62 – 8.06 G/L	Week 48	1.62 LC
313	036/1204	31	M	Neutrophils	1.62 – 8.06 G/L	Week 48	8.22 HC
	044/1313	50	M	CPK	22 – 198 U/L	Week 12	594 HC
	044/1329	40	M	CPK	22 – 198 U/L	Week 36	3148 HC
	064/1605	30	M	Neutrophils	1.62 – 8.06 G/L	Week 48	9.87 HC
	066/1712	62	M	CPK	22 – 198 U/L	Week 24	1064 HC
	066/1726	69	M	CPK	22 – 198 U/L	Week 24	915 HC

Source: Statistical Table III.9. H=High with respect to normal range given; L=Low with respect to normal

range given; C=clinically noteworthy value.

Reviewer's comments: *The sponsor did not include abnormal CK-MB levels in Clinically Noteworthy Abnormal Laboratory Values (Phase 2/3 Studies) listing. In the Phase 3 studies, serum samples having elevated creatine kinase (CK/CPK) levels were automatically analyzed for the isoenzymes CK-MB.*

The number of patients with abnormal creatine kinase-MB levels follows:

Table 59 Abnormal Creatine Kinase-MB Levels

	No. of Patients with ciclopirox exposure	No. of Patients without ciclopirox exposure
Study 312	7	3
Study 313	4	0
Total	11	3

A total of 7 out of 10 patients with exposure to ciclopirox (nail lacquer and topical cream) had elevated CK-MB levels in Study 312. In Study 313, all patients, 4 of 4, with abnormal serum CK-MB levels had ciclopirox listed as a concomitant medication.

Reviewer's comments: *According to the sponsor, the elevated CK-MB values found in the placebo and active groups are distributed in a statistically random manner between the individual time segments (weeks 12, 24,36, 40, and f/u. The elevated CK-MB values found in both groups exhibit no relationship to reported AEs, dose modification or concomitant ciclopirox cream medication. Additionally, neither placebo nor active group patients complained of cardiac symptoms.*

- Non-US Clinical Studies

According to the sponsor (Vol. 1.59, pg. 024), pooled safety data from 22 studies were submitted in support of this NDA; however, [redacted] studies were ongoing at the time of the report. Sixteen of the 22 non-US studies were open-labeled. Two double-blind, parallel group studies, listed as B5 and B6, compared ciclopirox 4 and 8%.

According to the submission a total of 6,546 subjects have been treated with ciclopirox nail lacquer 8% in studies outside of the US; most subjects were treated for at least six months. Of these, 6,502 were included in the safety analysis. Six of the studies were performed in Europe. Four of the six studies followed an open, non-controlled design (Phase 2 and 3 studies), one was a double blind comparative pilot study (Phase 2), and one was a post-marketing surveillance (PMS) study (Phase 4). However, according to the sponsor, contrary to current practices, some studies involving 5% (351/6546) of the patients, reported only adverse events with a suspicion of causal relationship to study drug.

Study No. E2/HOE296NL/5/D/C009/NM (92-0296-049-Pr) was submitted as a post-marketing surveillance (PMS) study (Phase 4). The purpose of such a study is not clear; however, it was an uncontrolled open-label study of 6 months duration. According to the sponsor, there were once daily applications in 81.4% of the cases during the first 3 months and 69.8% of the cases

during the second 3 months of the study. Safety results were submitted for a total of 3,666 subjects from 1,171 centers. According to the submission, only 12 (0.3%) of the patients (age range of 2 – 100 years) reported 13 adverse events (AEs). The sponsor did not categorize the AEs as to causality; however, it would seem reasonable that more AEs would have been reported among 3,666 subjects. Additionally, the AEs were difficult to interpret as reported (e.g., reddening – 3x, contact allergy – 2x, surgery (hallux valgus) – 1x, diarrhea – 1x, discoloration of the nail – 1x, worsening of mycosis 1x, irritation – 1x, exfoliation of nail – 1x, allergic rhinitis – 1x, and edema – 1x.) No data regarding participating investigators or centers were provided. No definitive safety or efficacy conslusions can be drawn from this type of study design.

Reviewer's comment:
One conclusion from this post-marketing surveillance was that patients with diabetes mellitus responded slightly better, definitely not less than the total population; yet, subjects with insulin dependent diabetes mellitus were excluded from the pivotal Studies 312 and 313 conducted in the US.

- World Health Organization Database Query was submitted.
- Post-Marketing Surveillence

According to the sponsor, in January 1996, The German Federal Institute for Medical Products and Devices (BfArM) requested a review of all adverse event reports of local ciculatory disorders, pain, burning, paresthesia, keratinization, delayed wound healing, and necrosis associated with the use of ciclopirox, especially the nail lacquer because of its higher ciclopirox concentration. According to the sponsor, a causal relationship to any of the available ciclopirox preparations was felt to be unlikely. The impetus for this query is unknown.

10.1 Significant/Potentially Significant Events

10.1.1 Deaths

A total of five deaths were reported . Four of these deaths occurred during clinical trials for the nail lacquer. One death was reported for the cream formulation in the post-marketing period. Details of these reports follow.

A death was reported in 1987 to the WHO database (WHO Rec. No. 870781537) with a causal relationship to topical ciclopirox drug therapy assessment. The patient, a 51year old male, developed pruritis on the first day of Loprox Cream use for treatment of tinea inguinalis. The patient developed an anaphylactic reaction on the third day and subsequently expired. The cause of death was listed as anaphylactic shock, cardiac failure, and ventricular fibrillation. The patient was also taking Geriplasm in addition to numerous other unspecified drugs. Assessment by three expert physicians commissioned by the German Drug Commission tended to regard Geriplasm (extract of heart, liver, and spleen) as a more likely cause of the anaphylactic reaction than the Loprox.

Two deaths occurred during the open-label extension study, Protocol 320. One subject committed suicide and died from carbon monoxide poisoning. The other patient died from a

myocardial infarction. Neither death was considered causally related to the study drug. There were no deaths reported for either treatment group from the Phase 2/3 studies.

One death was reported in a 69 year-old male (Subject 0062/0007) suffering from bronchial carcinoma in a completed non-US study.

10.1.2 Other Significant/ Potentially Significant Events

Unexpected Adverse Events

- Allergic Contact Dermatitis

Report of serious unexpected adverse event was received from the sponsor on 04-12-99. The event is a spontaneous report to the sponsor of a patch test positive allergic contact dermatitis to Batrafen® Nail Lacquer (International Case ID 199813164 — requiring hospitalization of a 49 y.o. female. According to the sponsor, the need to amend the product label is being assessed by HMR.

Additional reports of a patch test positive allergic contact dermatitis are noted. A patch test positive allergic reaction (not further specified) after three weeks therapy with ciclopirox in a 54 y.o. male (— 199400028, causality: probable) and patch test positive acute eczema (— 199712179, causality: probable) in a 76 y.o. female.

- Nephrotic Syndrome with Anuria

Development of nephrotic syndrome with anuria lasting 24 hours that developed one day after ingestion of 30cc of Loprox Lotion by an 8 y.o. girl (— 199020489, causality: probable).

Other Singular (unlabeled) Reported Adverse Events

These AEs are skin and nail discoloration, peeling, abnormal vision, paresthesia, tingling, neuritis, pain, edema, vasodilation, arthralgia, nausea, and impotence. No additional data provided.

Adverse Events Leading to Discontinuation

In the Phase 2/3 studies, one subject in the ciclopirox group was withdrawn following the appearance of local rash. Initially, the rash not considered by the investigator not to be causally related to study drug. However, a causal relationship was subsequently assessed by the investigator.

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Table 60 TEAEs Leading to Discontinuation of Subjects (Phase 2/3 Studies)

Table R19, Vol. 1.59 Treatment-Emergent Adverse Events That Led to Discontinuation (Phase II/III Studies)

Subject ID	Adverse Event	Age	Sex	Race	Onset Day*	End Day*	Intensity	Outcome	Study drug Action Taken	Causal Relation
Ciclopirox Group										
Study 211										
034/0107	Rash	72	M	W	139	146	Severe	Resolved	Perm disc	Related
Vehicle Group										
Study 211										
034/0106	Anemia	74	M	W	71	71	Severe	Resolved	Perm disc	Not related
Study 212										
035/0311	Hemorrhage†	62	M	W	14	20	Severe	Resolved	Perm disc	Related
	Pain†				---	---	Severe	Resolved	Perm disc	Related
Study 312										
087/0922	Myopathy	47	M	W	86	---	Mild	Ongoing	Perm disc	Not related
087/0928	Liver function test abnormal	53	M	W	265	---	Moderate	Ongoing	Perm disc	Not related
Study 313										
036/1210	Dyspepsia	55	M	W	112	---	Moderate	Ongoing	Perm disc	Not related

Source: Statistical Table III.7.
* Day calculated relative to the date of first dose.
† Both events were localized to the nail bed.

The incidence of SAEs in the Phase 2/3 studies was similar in subjects treated with ciclopirox and those treated with vehicle (7% in both treatment groups). The same is applicable for the proportion of SAEs that resolved without sequelae (57% of subjects in the ciclopirox group and 55% of subjects in the vehicle group). The most frequently reported SAEs in both treatment groups were carcinoma (ten subjects in the ciclopirox group and five subjects in the vehicle group). None of the SAEs were considered causally related to the study drugs by the investigators

10.2 Other Safety Findings

FDA Division of Pharmacovigilance and Epidemiology provided results of Adverse Events Reporting System database query for cardiotoxic events associated with approved formulations of Loprox. A total of nine unduplicated reports were identified under the system organ class (SOC) term "cardiac disorders" associated with ciclopirox. Of the nine cases identified, there

did not appear to be any cardiac related adverse events that were directly associated with ciclopirox olamine.

10.2.3 Special Studies

Table 54, a summary table of human pharmacokinetic studies follows on the next page. See the Biopharm review for a detailed review of these studies. Study (Protocol 1003), Repeat Insult Patch Study to Assess the Irritation and Sensitization Potential of Topically Applied Loprox Nail Lacquer 8% is also reviewed in this section. As previously stated, Phototoxicity Potential Assay and Photocontact Allergenicity Assay studies were not submitted

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Table 61 Summary Table of Human Pharmacokinetic Studies

Sponsor's Table R3 Summary Table of Human Pharmacokinetic Studies

Protocol No. Country Investigators	Dates of Study	Study Design	No. of Subjects Sex Age Range (yrs)	Group Formulation[a]	Dose Duration
Toulouse, France C.H. Roques G. Michel	Date of report July 13, 1989	open-label, uncontrolled study in healthy volunteers	9 subjects NA NA	Ciclopirox 8% = 9 Formulation B	Topical: once daily to all fingernails
Toulouse, France C.H. Roques G. Michel	Date of report 1990	open-label, uncontrolled study in healthy volunteers	5 subjects NA NA	Ciclopirox 8% = 5 Formulation B	Topical: once daily to all toenails
111 US Jarratt, Austin TX	May, 1989 – July, 1990	open-label, uncontrolled study in subjects w/ distal subungual onychomycosis of the fingernails	Male = 4 Female = 1 Age = 34-74	Ciclopirox 8% = 5 Formulation B	Topical: once daily to all fingernails and toenails 24 weeks
312 US Aly, San Francisco CA Morman, Rutherford NJ Scher, New York NY Lucky, Cincinnati OH Hanifin, Portland OR Lowe, Santa Monica CA Jones, Bryan TX Kang, Ann Arbor MI Stiller, Boston MA	July, 1994 - March, 1996	Randomized, double-blinded, vehicle-controlled, parallel group, stratified by % of involvement; subjects w/ distal subungual tinea unguium of the toenails	Male = 175 Female = 48 Age = 18-70	Ciclopirox 8% = 29/112[b] Formulation B Vehicle = 22/111[b] Formulation A	Topical: once daily to all toenails and all affected fingernails 48 weeks

Protocol No. Country Investigators	Dates of Study	Study Design	No. of Subjects Sex Age Range (yrs)	Group Formulation[a]	Dose Duration
313 US Katz, Fridley MN Fleckman, Seattle WA Jarratt, Austin TX Shupack, New York NY Pariser, Norfolk VA Stewart, Clinton Township MI Levine, Tucson AZ Friedman, Providence RI Rapini, Lubbock TX	July, 1994 - April, 1996	Randomized, double-blinded, vehicle-controlled, parallel group, stratified by % of involvement; subjects w/ distal subungual tinea unguium of the toenails	Male = 183 Female = 54 Age = 19-70	Ciclopirox 8% = 45/119[c] Formulation B Vehicle = 45/118[c] Formulation A	Topical: once daily to all toenails and all affected fingernails 48 weeks

NOTE: Demographic data for Protocols 312 and 313 are based on the intent-to-treat population..
NA = Information not available.
A Formulation B = proposed commercial formulation; Formulation A = vehicle-control formulation.
B Only two of nine sites collected serum samples to assess systemic absorption of ciclopirox.
C Only three of nine sites collected serum samples to assess systemic absorption of ciclopirox.

In the first study, conducted in France, nine healthy volunteers applied ciclopirox nail lacquer 8% daily to the fingernails; the lacquer was removed once each week. After 7, 14, 30, and 45 days of treatment, the distal portions of the nails were sampled. In four subjects, additional samples were obtained seven and 14 days after treatment was stopped. Two samples, taken from two different nails, were obtained. One was used to determine the quantity of ciclopirox present in the whole nail. Transverse sections of the other sample were divided into four layers of equal volume to determine the penetration of ciclopirox through the thickness of the nail. A [redacted] based upon the antifungal activity of ciclopirox against *Candida pseudotropicalis*, was used.

In the second study, also conducted in France, five healthy volunteers applied ciclopirox nail lacquer 8% daily to the toenails; the lacquer was removed once each week. The distal portions of the nail were sampled after 7, 14, 30, and 45 days of treatment and seven and 14 days post-treatment using the techniques described above.

Systemic Absorption Studies

As shown in Sponsor's Table **R3** three studies evaluated the systemic absorption of topical administration of ciclopirox nail lacquer 8%. Hoechst Marion Roussel, Inc. (HMRI) conducted all studies in the US. Serum drug levels were analyzed in Protocol 111, and at selected sites in Protocols 312 and 313. In Protocol 111, five subjects had serum samples collected during treatment. (Weeks 12, 24, 36 and 48 during treatment and post-treatment weeks 2 and 4) for determination of the serum levels of ciclopirox and its glucuronide metabolite.

Protocol 111 (See Biopharm Review for comments)

Title: "An Open-Label Study to Determine the Systemic Absorption of Ciclopirox Nail Lacquer 8% in Subjects With Dermatophytic Onychomycoses of the Fingernails"

Protocol 111 was a single center, open-label study involving subjects with distal subungual onychomycosis of the fingernails. Ciclopirox nail lacquer 8% was applied once a day at bedtime with applications approximately 24 hours apart. Subjects were treated for 24 weeks, with the lacquer applied to all toenails and fingernails. Before applying a fresh coat, the old coat was removed with soap and water, and each nail was swabbed with isopropyl alcohol.

Concentrations of total ciclopirox (ciclopirox plus its glucuronide metabolite) were determined in serum and in urine by [redacted] Serum samples were collected at Baseline (Day 1), at Months 2, 4, and 6, and at four weeks post-treatment. The first two subjects enrolled were to have additional serum samples drawn at Week 2 and Month 1. Twenty-four hour urine collections were started 24 hours before the serum samples were drawn at Baseline (Day 1), at Months 2, 4, and 6, and at four weeks post-treatment. Two subjects had

additional concentration determinations at Week 2 and Month 1. No statistical analyses were performed. Safety was determined by evaluation of treatment-emergent adverse events (TEAEs) and changes from Baseline in clinical laboratory values.

The lower limit of detection of ciclopirox was ——— in serum and ———, in urine. During the study, all subjects had serum and urine concentrations of ciclopirox above the limit of detection. Three of the five subjects had urine concentrations in excess of 800 ng/mL (maximum urine concentration was 4685 ng/mL). The maximum serum concentration for each subject ranged from ——— ng/mL (median: 16 ng/mL). There was considerable variation among subjects. The timing of the blood draw in relation to the time of last application of nail lacquer was not standardized; this may have contributed to the variability. Twenty-three to 35 days after cessation of treatment, ciclopirox was not detectable in the serum or urine of any subject.

The lacquer was applied evenly over the entire nail plate and the proximal and lateral nail fold areas, approximately 5 mm into the folds. According to the sponsor, because the area of application on the skin and nails was comparable, absorption through the skin and passage into the urine is as likely, if not more likely, to originate from percutaneous than periungual absorption.

Four subjects evaluated according to Protocol 111 experienced at least one TEAE. Two of these TEAEs (gastroenteritis and dehydration) were severe and the rest were of moderate intensity. None was considered by the investigator to be causally related to study drug. One subject in Study 111 was hospitalized for severe dehydration. The condition resolved and the subject continued to apply ciclopirox while in the hospital. This serious adverse event (SAE) was considered by the investigator to be unrelated to study drug. No deaths or discontinuations occurred during the study.

Protocols 312 and 313 (See Biopharm Review for comments)

Two Double-Blind Studies to Determine the Systemic Absorption of Nail Lacquer 8% in Subjects With Distal Subungual Tinea Unguium of the Toenails

Two study centers in Protocol 312 and three study centers in Protocol 313 collected blood samples from each subject before, during, and after treatment for measurement of serum levels of total ciclopirox (ciclopirox plus its glucuronide metabolite). A total of five investigators collected blood samples from 74 subjects in the ciclopirox group and 67 subjects in the vehicle group. No statistical analyses were performed.

In the ciclopirox nail lacquer 8% group, one subject had no Baseline evaluation; eight subjects had no assessments after Baseline. Of the 66 subjects with post-Baseline assessments, 42 had serum concentrations that remained below the limit of quantification during treatment. Twenty-four subjects with detectable levels had maximum serum concentrations ranging from 10.0 ng/mL to 24.6 ng/mL. One subject had detectable serum ciclopirox throughout treatment and three subjects had detectable levels three times during the course of the study. Of the 24 subjects with detectable ciclopirox levels, 11 took concomitant medication containing ciclopirox (Loprox® Cream 1%); 13 did not take concomitant medication containing ciclopirox.

Post-treatment serum concentration assessments, available for two subjects, were below the limit of quantification.

In the vehicle group (N=67), two subjects had no Baseline assessments; two subjects had no assessments after Baseline. Of the 65 subjects with post-Baseline assessments, 57 had serum concentrations that remained below the limit of quantification during treatment.

Three subjects treated under Protocol 313 (one in the ciclopirox group and two in the vehicle group) had a single quantifiable ciclopirox serum level at Baseline. All of these levels were low (<13 ng/mL) and subsequently fell below the limit of quantification. None of these subjects reported using a concomitant medication containing ciclopirox.

Eight subjects treated with vehicle had single instances of detectable ciclopirox (ranging from 11.1 ng/mL to 24.3 ng/mL); most were found in the last week of the study. Four of these subjects were using concomitant medication containing ciclopirox. A post-treatment serum concentration, available for one subject, was below the limit of quantification.

Dermatotoxicity Studies
Reviewer's comments:
Phototoxicity and photocontact allergenicity studies were not submitted to the NDA in support of safety. Absorption maximum at 302 plus/minus 2 nm is reported for ciclopirox (Vol. 1.1, pg. 189). If there is absorption in the UV range for the drug substance and/or vehicle phototoxicity and photocontact allergenicity studies are required.

Study (Protocol 1003)
Repeat Insult Patch Study to Assess the Irritation and Sensitization Potential of Topically Applied Loprox Nail Lacquer 8%

Objectives
The primary objective was to assess the potential of repeated applications of Loprox Nail Lacquer8% and its vehicle base to induce irritation and sensitization to the skin of normal healthy volunteers.

Study Dates: November 6, 1996 – December 19, 1996

This study consisted of three (3) phases over a 38-day period. Study materials were applied on Mondays, Wednesdays, and Fridays over a period of three weeks. The phases were: an induction phase in which subjects were exposed to ciclopirox nail lacquer 8%, the vehicle base, and petrolatum for three weeks and skin reactions were graded; an 11-day rest phase; and a challenge phase of four days to determine if the subject became sensitized. During induction, each study drug was applied in a randomized sequence to a study site on the infrascapular area of the back either on the right or left of the midline. For the challenge phase, the study drugs were applied to the opposite side of the back using the same randomization sequence. All applications will be made by a third party. All observations were be made by a dermatologic grader who was blinded as to the identity of the study materials.

Results:
Two hundred thirty healthy subjects, 190 females and 40 males, ages 19 to 74 (mean age of 47.7 years, median age of 45) were enrolled into the study. There were 225 Caucasians (97.8%), four Hispanics (1.7%), and one Oriental (0.4%) enrolled. Two hundred five subjects completed all phases. Twenty-five subjects discontinued prior to the challenge phase. None of the discontinuations were due to the study drugs. Of these, 11 subjects did not return to the study site for post-baseline readings. There were no adverse events reported.

Subjects with skin reactions at any time during the induction phase were as follows:
Sponsor's Table 1

Total subjects evaluated	219 (100%)
No skin reactions	92 (42.0%)
Numbers with any skin reaction	127 (58.0%)
(*L*)oprox site only	55 (25.1%)
(*V*)ehicle site only	23 (10.4%)
(*P*)etolatum site only	3 (1.4%)
L and *V* sites	44 (20.1%)
L and *P* sites	0 (0.0%)
V and *P* sites	1 (0.5%)
L and *V* and *P* sites	1 (0.5%)

No reaction of greater severity than mild erythema (score = 1) was observed. Irritancy was made on a 5-point ordinal scale (0 – 4) .

Thirteen of the 205 subjects assessed 48 hours after challenge showed a reaction grade of 1 for Loprox nail lacquer and 5 continued to show a grade one reaction at 72 hours. Four of these subjects showed no response at 96 hours. The fifth patient was unable to return for the 96-hour assessment.

Five subjects showed a grade 1 reaction to vehicle at the 48-hour challenge, one at 72 hours, and none at 96 hours. For petrolatum, only one subject showed a grade 1 at 48 hours and the response had resolved by 72 hours.

Conclusion
Ciclopirox nail lacquer 8% appears to be mildly irritating. Based on the results of this study, Ciclopirox nail lacquer 8% does not appear to induce sensitization. However, based on the reports of patch test positive contact dermatitis reported under post-marketing surveillance, (e.g., as previously noted, a spontaneous report of a patch test positive allergic contact dermatitis to Batrafen® Nail Lacquer, International Case ID 199813164 —— etc.) it appears that ciclopirox nail lacquer 8%, does have sensitization potential.

10.2.4 Drug-Demographic Interactions
More males than females were treated in the Phase 2/3 studies. Although more females reported more TEAEs, irrespective of causal relationship to study drug, the crude incidence rate

was similar between treatment groups. The crude incidence rate of TEAEs at least possibly causally related to ciclopirox was similar for males and females in Phase 2/3 studies. Only males, the majority of whom were in the vehicle group, experienced TEAEs that led to discontinuation.

More Caucasian subjects than non-Caucasian subjects were treated in the Phase 2/3 studies; however, the non-white enrollment in these studies was small. The crude incidence rate of TEAEs considered by the investigator to be at least possibly causally related to study drug was greater in non-Caucasian than in Caucasian subjects. The most frequently reported TEAE was rash. However, fewer non-whites subjects treated with ciclopirox reported TEAEs, irrespective of causal relation to study drug than whites. The significance of this finding is unclear.

The number of subjects experiencing TEAEs was similar across age categories. This was also the same observation made for TEAEs that led to discontinuation.

10.2.5 Drug Disease Interactions

According to the sponsor, results of stratified analysis of the US studies did not provide any evidence of drug-disease interactions.

10.2.6 Drug-Drug Interactions

According to the sponsor, results of stratified analysis of the US studies did not provide any evidence of drug-drug interactions.

10.2.7 Withdrawal Phenomena/Drug Abuse Potential

According to the sponsor, ciclopirox nail lacquer 8% does not have any psychoactive or CNS effects that could sustain patterns of non-medical self-administration resulting in disruptive or undesirable consequences; however, no known studies have been conducted to substantiate this conclusion. According to the sponsor, the likelihood of over-dosage from topical administration of ciclopirox nail lacquer 8% is extremely low, and over-dosage by oral ingestion would probably be limited by the unpalatable taste of the product.

10.2.8 Human Reproductive Data

No data was provided. It should be noted that under discussions of risk benefits, Vol.1.100, pg. 171, the sponsor lists advantages of topical therapy of onychomycosis as the treatment of choice in physiological states (e.g., pregnancy, the elderly). Pregnant females were excluded per protocol from the US studies and no other data were submitted in support of safe use in pregnant females. Pregnancy outcome data from the sponsor regarding Pt. 030/0103, Study 212 is unavailable.

11 Resistance

Dermatophyte resistance will be addressed in the Microbiology Review.

12 Labeling Recommendations – see label generated at Divisional labeling meeting 11/22/99.

13 Recommendation

NDA 21-022 is approvable for the use of ciclopirox nail lacquer 8% in treatment of mild to moderate distal subungual onychomycosis without lunula involvement due to *Trichophyton rubrum* of the toenails, as adjunctive therapy to regular professional nail trimming.

Phase 4 commitments:
The safety database for application of this product to the fingernails is incomplete. Phototoxicity and photocontact allergenicity studies were not submitted to the NDA in support of safety. Absorption maximum at 302 plus/minus 2 nm is reported for ciclopirox (Vol. 1.1, pg. 189). As there is absorption in the UV range for the drug substance, phototoxicity and photocontact allergenicity studies are required as there is a lack of evidence to demonstrate patient safety.

/S/ 11/23/99

Brenda E. Vaughan, M.D.
Medical Officer

cc:
Orig NDA 21-022
HFD-540
HFD-540/Div Dir/Wilkin
HFD-540/DermTL/Walker /S/ 11/24/99
HFD-540/MO/Vaughan
HFD-540/ChemTL/DeCamp
HFD-540/Hawthaway
HFD-540/PH Tox TL/Jacobs /S/ 11/26/99
HFD-540/PH Tox/Mainigi
HFD-540/MicroTL/
HFD-540/Micro/Gosey
HFD-725/Biostat TL/Srinivasan
HFD-725/Biostat/Thomson
HFD-880/Biopharm TL/Bashaw
HFD-880/Biopharm/Lee

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ON ORIGINAL

Hoechst Marion Roussel

120-DAY SAFETY UPDATE FOR CICLOPIROX (HOE 296NL) NAIL LACQUER 8%

NDA No. 21-022

Date of Report: 19 April, 1999

Report Type: 120-Day Safety Update

Report Origin: PAREXEL International Corporation
Research Triangle Park, North Carolina 27713
United States

Hoechst
Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

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INFORMATIONAL APPENDICES

1. Literature/Published Articles

LIST OF ABBREVIATIONS AND GLOSSARY

CIC 4%	ciclopirox nail lacquer 4%
CIC 8%	ciclopirox nail lacquer 8%
DB	double-blind
F	female subjects
Fitzpatrick skin type	categorization of the skin with regard to color, sensitivity to UV radiation, and tanning properties I white, very sensitive, always burns easily, never tans II white, very sensitive, always burns easily, tans minimally III white, slightly sensitive, burns minimally, tans gradually and uniformly IV light brown, moderately sensitive, burns minimally, always tans well
g	gram
G	giga (10^9)
GGT	gamma glutamyl transferase
HMR	Hoechst Marion Roussel
Intensity	intensity of an adverse event categorized as mild-moderate-severe
ISS	Integrated Summary of Safety
KET	ketoconazole
Kg	kilogram
L	liter
M	male subjects
MCN	Manufacturer's Control Number
mg	milligram
µg	microgram
mL	milliliter
mild/moderate/severe	• a mild event was transient and resolved spontaneously, it did not cause any concern, require treatment, or affect the continuation of treatment. • a moderate event was transient, may have caused some discomfort or concern, and required treatment before resolving. The study drug was continued. • severe events caused considerable discomfort or concern, required treatment and/or temporary or permanent discontinuation of the study drug. The event may have had sequelae and mostly categorized as "serious".
N/A	not applicable
NDA	New Drug Application
NW	non-white
PCA	pre-defined change abnormal— A PCA is an abnormal laboratory value that is • above the upper limit of the normal range, and has increased from the Baseline value by a pre-defined amount; • below the lower limit of the normal range, and has decreased from the Baseline value by a pre-defined amount.
PET	Petrolatum
PO	per os
PSUR	periodic safety update reports

LIST OF ABBREVIATIONS AND GLOSSARY (continued)

q.o.d.	every other day
related/not related	• adverse events classified as "possibly", "probably" and "very probably" related were considered to be related to study drug; when the investigator failed to specify a relationship to study drug, the adverse event was treated as related to study drug. • adverse events classified as "remote" and "not related" were considered to be not related to study drug.
SAE	serious adverse event; defined as an event that • was fatal. • was immediately life-threatening. • required or prolonged hospitalization. • was permanently or significantly disabling. • involved cancer, a congenital anomaly, or occurred as a result of overdose. • suggested a significant hazard, contraindication, or precaution.
T	Tera (10^{12})
TEAE	Treatment-emergent adverse event is an event (see Appendix D) • that was not present before treatment started but emerged during the study and for up to two weeks from the date of the last dose; • that was present before treatment started but increased in intensity during the study and for up to two weeks from the date of the last dose.
U	unit
UNK	unknown
US	United States
VEH	vehicle
VC	vehicle-controlled
W	white
WBC	white blood cell

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1. INTRODUCTION

Ciclopirox olamine is a broad-spectrum antifungal agent that is effective against the major human fungal pathogens responsible for onychomycosis.[1] The free acid of ciclopirox has been shown to have properties similar to its olamine salt in preclinical and clinical studies. Since ciclopirox olamine penetrates through hard keratin such as that found in human nails,[2] the salt as well as the free acid are likely therapies for the treatment of onychomycosis.

A formulation containing ciclopirox in a clear nail lacquer base was developed to facilitate treatment of onychomycosis. *In-vitro* studies suggested that good penetration of drug in this vehicle through toenails is possible. Open-label clinical studies indicated that ciclopirox nail lacquer 8% can successfully be used for treatment of distal subungual onychomycosis.

The New Drug Application (NDA) for ciclopirox nail lacquer 8% was filed with the US Food and Drug Administration (FDA) on 18 December, 1998 (NDA No. 21-022). The primary analytical focus of the data within that application was on safety results obtained from four double-blind, vehicle-controlled trials conducted in the United States (US). Preclinical toxicology data and additional safety information derived from two Phase I US studies, an open-label Phase III extension study, and non-US studies as well as an overview of safety information derived from a post-marketing pharmacovigilance database (including literature) provided additional information. For the non-US studies, data from individual studies were summarized and entered into a separate database. The non-US and US studies differed in study design and the manner in which adverse events were reported. In addition, more than half of the subjects in the non-US studies were in compassionate-use trials. For these reasons, the non-US studies are not comparable to US studies and the databases were not combined.

2. PRECLINICAL TOXICOLOGY DATA

Preclinical toxicology data on ciclopirox olamine and ciclopirox free acid in various formulations do not indicate untoward hazards for the clinical use of ciclopirox nail lacquer 8%.

3. CLINICAL SAFETY DATA

Based on toxicology studies and wide marketing experience outside the US, the safety profile of ciclopirox nail lacquer 8%, was investigated in seven US clinical studies reported in the original NDA. Safety information also was obtained from 22 non-US clinical studies, and periodic safety update reports on marketed ciclopirox formulations were considered because these reports reflect world-wide experience based on extensive post-marketing exposure to ciclopirox nail lacquer 8% and all other ciclopirox olamine preparations. The NDA for ciclopirox nail lacquer 8%, filed on 18 December, 1998, included safety data through 1 April, 1998. This 120-Day Safety update includes information obtained by Hoechst Marion Roussel's (HMR) Global Drug Surveillance for Ciclopirox during the period of 2 April, 1998—1 October, 1998. Since 2 October, 1998, no reports have been received that would change the benefit/risk profile of ciclopirox nail lacquer 8%. In addition, the literature were reviewed and are summarized herein.

4. CLINICAL STUDIES SUMMARIZED IN THE ORIGINAL NDA

4.1 US Studies in the Original NDA

The clinical studies conducted in the US are summarized in Table R1. The number of subjects enrolled is the number of subjects who gave written informed consent. Seven hundred subjects received ciclopirox, 328 received vehicle, and 230 subjects received petrolatum; one subject was enrolled but did not receive treatment.

It should be noted that subjects included in Study 1003 received three different treatments simultaneously for intra-individual comparison. As Study 320 was an open-label extension study, 138 subjects included here received vehicle in the preceding studies (Studies 312 and 313).

Table R1 Table of Clinical Studies Conducted in the US

Protocol # Design	Completion Status (Start Date)	Treatment Dose	Number Subjects Treated	Frequency	Age Range	M/F W/NW	Treatment Duration
Phase I Open-Label US Study							
111 open label uncontrolled	Complete (5/89)	CIC 8%	5	1/day	34-74	4/1 5/0	24 weeks
Phase I Intra-individual Controlled (Dermatotoxicity) US Study							
1003 randomized controlled observer blind	Complete (11/96)	CIC 8% 50 mg VEH 50 mg PET 50 mg	230 230 230	each subject received all treatments (3/week)	19-74	40/190 225/5	4 weeks
Phase II/III Vehicle-Controlled US Studies[1]							
211 randomized DB, VC Parallel group	Complete (11/88)	CIC 8% VEH	42 43	1/day 1/day	18-79	73/12 83/2	24 weeks
212 randomized DB, VC Parallel group	Complete (10/88)	CIC 8% VEH	54 56	1/day 1/day	18-91	100/10 94/16	24 weeks
312 randomized DB, VC Parallel group	Complete (7/94)	CIC 8% VEH	112 111	1/day 1/day	18-70	175/48 208/15	48 weeks
313 randomized DB, VC Parallel group	Complete (7/94)	CIC 8% VEH	119 118	1/day 1/day	19-70	183/54 207/30	48 weeks
Phase III Open-Label Extension US Study[2]							
320 open-label uncontrolled	Complete (6/95)	CIC 8%	281	1/day	21-70	223/58 259/22	48 weeks

M=male subjects, F=female subjects; W=white subjects; NW=non-white subjects; DB=double blind, VC=vehicle-controlled; CIC 8%=ciclopirox nail lacquer 8%, VEH=vehicle, PET=petrolatum.
[1] Total number of subjects in the Phase II/III vehicle-controlled studies: CIC 8%=327; VEH=328.
[2] 281 subjects were treated with CIC in the open-label extension study; 138 received VEH in preceding double-blind studies (312 and 313).

4.2 Non-US Experience Summarized in the NDA

The clinical studies conducted outside the US are summarized in Table R2.

Table R2 Non-US Clinical Studies

Protocol # Design	Completion Status (Start Date)	Treatment Dose	Number Subjects Treated	Frequency	Age Range	M/F	Treatment Duration
Phase I Open-Label Non-US Study							
A3 open-label cross-over	Complete (7/95)	CIC 8% Amorolfine 5%	20 20	1/day	22-57	5/15	one day
Phase II Non-US Studies[1]							
B3 open-label uncontrolled	Complete (6/88)	CIC 8%	302	1/day	20-70	117/185	16 weeks
B4 open-label uncontrolled	Complete (11/86)	CIC 8%	75	1/day	18-79	44/31	24 weeks
B5 double-blind parallel group	Complete (4/85)	CIC 4% CIC 8%	15 15	1/day (q.o.d.)	12-74	17/13	24 weeks
B6 double-blind parallel group	Complete (Spring 1986)	CIC 4% CIC 8%	15 15	1/day (q.o.d.)	12-74	17/13	16 weeks
Phase III Double-Blind Non-US Studies[2]							
C4 double-blind parallel group	Complete (3/88)	CIC 8% KET 200 mg	28 28	1/day 1/day	UNK	UNK	24 weeks
C5 double-blind parallel group	Complete (7/90)	CIC 8% VEH	41 40	1/day 1/day	19-70	54/27 —	24 weeks

q.o.d.=every other day.
M=male subjects, F=female subjects; CIC 4%=ciclopirox nail lacquer 4%; CIC 8%=ciclopirox nail lacquer 8%, KET=ketoconazole, VEH=vehicle; UNK=unknown.
[1] Total subjects treated in Phase II studies: CIC 8%=407; CIC 4%=30.
[2] Total subjects treated in Phase III double-blind studies: CIC 8%=69; VEH=40; KET=28.
[3] Total subjects treated in Phase III open-label studies: CIC 8%=2202.
[4] Total subjects treated in completed Phase IV studies: CIC 8%=202.
[5] Total subjects treated in completed post-marketing surveillance studies: CIC 8%=3666.

Continued

Table R2 Non-US Clinical Studies (Continued)

Protocol # Design	Completion Status (Start Date)	Treatment Dose	Number Subjects Treated	Frequency	Age Range	M/F	Treatment Duration
Phase III Open-Label Non-US Studies[3]							
C6 - C12 open-label uncontrolled	Complete (2/85)	CIC 8%	2202	1/day to 3/week	2-87	UNK	16 weeks to 24 weeks
Phase IV Non-US Studies[4]							
D3 open-label uncontrolled	Complete (10/94)	CIC 8%	37	1/day	UNK	UNK	24 weeks
D4 open-label parallel group	Complete (5/94)	CIC 8% CIC 8%	30 30	1/day 2/week	UNK	29/31	24 weeks
D5 open-label uncontrolled	Complete (4/94)	CIC 8%	105	2/week	20-79	UNK	24 weeks
Post-Marketing Surveillance Non-US Studies[5]							
E2 open-label uncontrolled	Complete (10/92)	CIC 8%	3666	1/day	2-100	UNK	24 weeks

Source: Statistical Table I.1.
q.o.d.=every other day.
M=male subjects, F=female subjects; CIC 4%=ciclopirox nail lacquer 4%; CIC 8%=ciclopirox nail lacquer 8%, KET=ketoconazole, VEH=vehicle; UNK=unknown.
[1] Total subjects treated in Phase II studies: CIC 8%=407; CIC 4%=30.
[2] Total subjects treated in Phase III double-blind studies: CIC 8%=69; VEH=40; KET=28.
[3] Total subjects treated in Phase III open-label studies: CIC 8%=2202.
[4] Total subjects treated in completed Phase IV studies: CIC 8%=202.
[5] Total subjects treated in completed post-marketing surveillance studies: CIC 8%=3666.

5. SUMMARY OF PERIODIC SAFETY UPDATE REPORTS

This section summarizes the results of one periodic safety update report (PSUR) that has been written by HMR during the period of 2 April, 1998—1 October, 1998. Since 2 October, 1998, no reports have been received that would change the benefit/risk profile of ciclopirox nail lacquer 8%.

Ciclopirox was first introduced to the market in Argentina on April 2, 1975 (international birth date) and is now marketed in more than 70 countries world-wide under the following trade names: Batrafen®, Loprox®, Mycoster®, Nibulen®, or Obytin®. There have been no rejections of applications, suspensions, or restrictions of distribution for safety reasons.

The following galenical forms of ciclopirox are available: solution (10 mg/ml), powder and cream/vaginal cream (10 mg/g), and nail lacquer (80 mg/g).

5.1 Serious and Unexpected Adverse Events

One subject experienced a serious and unexpected adverse event during the period 2 April, 1998 to 1 October, 1998.

Allergic Contact Dermatitis (International Case ID: 199813164DDC)

This spontaneous report of a serious and unexpected adverse event involved a 49-year-old female with a three-and-one-half year history of scaling of the hands and feet and swelling of the hands and itching of the fingers. She also had a history of chronic fungal nail infection of the fourth digit on the right hand. The nail had been surgically removed in ~~1~~992 and again in 1994; however, the problem recurred when the nail re-grew. In January 1998, she visited a physician regarding her finger and began treatment with Batrafen® (ciclopirox) Nail Lacquer and Nizoral® tablets and was given an unspecified injection. About one week later, she started to develop an itch on the mid-palm of her hand and crusting, itching, and burning of her lips. Her feet were also involved. She used Lotrimin® and ChapStick® with some improvement. Nizoral® tablets were discontinued and Mycospor® solution and cream and nystatin were started. Batrafen® Nail Lacquer was continued. The itching on her hands and fingers got worse and was associated with scaling and darkening of the skin and worsening of the feet and legs. She was admitted to the hospital on 6 April, 1998. Her physical examination revealed numerous blisters and pustules on the palmar surface of both hands.

The skin around the fingers was hyperpigmented, scaly, and tender to touch. Blisters were also observed on the fingertips and the distal portions of the fingers were swollen. The nail on the fourth digit of the right hand was thickened with subungual hyperkeratosis. All nails of the hands were stained. On the feet, a few blisters were seen along the sides of the toes and on the dorsum of both feet. There were papules on the left mid-thigh and the distal leg and lips were hyperpigmented. Batrafen® was discontinued and the subject began treatment with emulsifying ointment, potassium permanganate, nerisone ointment, betnovate ointment, polysporin, prednisone, and azithromycin. She was treated in the hospital for 26 days. Her condition began to improve and Lamisil® (terbinafine) and Piriton® (chlorfeniramine) were added to her treatment regimen. On 11 April, 1998, she had an episode of diastolic hypertension (110 mmHg) and was treated with Aldomet® 500 mg. Results of a microbiological swab taken on admission showed heavy growth of *Streptococcus Group D* and light growth of *Staphylococcus aureus*. On 22 April, 1998, she complained of having difficulty passing urine. Her vaginal and abdominal examinations were normal and she was seen by a urologist for possible bladder outlet dysfunction and treated with Hytrin® (terazosin) 2 mg. Subsequent abdominal ultrasound was normal. Patch tests were performed and exhibited positive reactions to Batrafen® Nail Lacquer and Batrafen® Solution.

Allergic contact dermatitis, hypertension, and bladder outlet dysfunction are not labeled in the core data sheet for ciclopirox. Based on the information received for this case, as well as current scientific knowledge for ciclopirox, a reasonable possibility of a causal relationship between the allergic contact dermatitis and treatment with ciclopirox cannot be excluded. However, diastolic hypertension and bladder dysfunction are more likely due to underlying medical problems that had not been previously diagnosed rather than due to ciclopirox.

Upon review of the ciclopirox database, three cases of contact dermatitis were identified that have at least a reasonable association with ciclopirox. No significant confounding factors were present in these cases, and allergy skin testing were positive in each case. The need to amend the product labeling is being evaluated by HMR.

5.2 Serious and Expected Adverse Events

No serious and expected adverse events have been reported during the period 2 April, 1998 to 1 October, 1998.

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5.3 Non-serious and Unexpected Adverse Events

Five non-serious and unexpected adverse events have been reported during the period 2 April, 1998 to 1 October, 1998. The patients with these events are described below.

Case 199811117 —— : On 8 April, 1998, a 46-year-old male reported swelling of the knees that began on 25 January, 1998. Both the reporter (consumer) and HMR assessed that the likelihood that the event was related to ciclopirox nail lacquer as highly probable. Swelling did not resolve completely according to the consumer.

Case 199812650 —— On 21 August, 1998, a 73-year-old female reported dryness and flaking of the skin around the lips and mouth. The event began in August (exact day unknown). The reporter (consumer) assessed both events as possibly related to ciclopirox cream. HMR's causality assessment was "conditional." The event was ongoing at last report.

Case 199813652—— In January 1998, a 26-year-old female reported periungual erythematous rash. The exact date of onset was not provided. The reporter (health professional) assessed the events as unlikely related to ciclopirox topical ointment. HMR considers data to be insufficient to make an assessment. The subject recovered.

Case 199813979——On 21 July, 1998, a 6-year-old male developed swollen, lumpy, scaly skin and had a hypersensitive skin reaction. The reporter (consumer) and HMR considered the event to be possibly related to ciclopirox cream.

Case 199814286 —— In May 1998 (exact date unknown), a 35-year-old female developed vulvovaginal edema. HMR considered the event possibly related to ciclopirox vaginal cream. The event resolved.

5.4 Non-serious and Expected Adverse Events

Case 199811963 —— On 10 June, 1998, a 52-year-old female reported increased irritation of her toes (date of onset unknown). The reporter (consumer) considered the event to be possibly related to study medication. HMR considered the causality to be "conditional."

Case 199813040 —— On 1 August, 1998, a 69-year-old male reported fungal infection (lack of drug effect). HMR considered the causality to be "conditional."

6. LITERATURE

For this submission, the world medical literature was searched to identify the following:

1. All review articles published since January 1998 (inclusive) on the treatment methods for onychomycosis in humans. The MEDLINE (U.S. National Library of Medicine), EMBASE®, and EMBASE® ALERT (Elsevier Science B.V.) databases were searched via The Dialog Corporation's Dialog Information Retrieval System. The search was limited to articles where "onychomycosis – drug therapy" or "onychomycosis – therapy" were considered "major" descriptor terms or keywords, where only studies on humans were under discussion, and the articles also had descriptor terms indicating that they were "Review" articles (review; review literature; review of reported cases; review, academic; review, multicase; review, tutorial).

2. All articles published since January 1998 (inclusive) on the safety of the use of Loprox® or ciclopirox in the treatment of onychomycosis in humans. Key words were "onychomycosis" and "Loprox" or "ciclopirox," limited to "human," and combined with any one of the following words: "safe", "safety", "adverse", "impact", "impacts", "side effect", or "side effects."

No new unexpected safety concerns were identified in the two applicable articles found and reviewed (see Appendix 1 for a copy of these).

7. CONCLUSIONS

An estimated ——— subjects have been exposed to ciclopirox nail lacquer 8% during the past 6 years. Furthermore, taking into account the results of post-marketing surveillance since introduction of ciclopirox 22 years ago, no safety problems have been encountered that required specific clinical, toxicological, or epidemiological studies or a change in the adverse event profile.

The events reported and discussed herein demonstrate that the pattern of relevant adverse events experienced by subjects treated with ciclopirox is unchanged. There has been no change in the benefit/risk assessment during the period covered by this report.

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MYCOSES 41, 349–351 (1998) ACCEPTED: JUNE 30, 1998

CASE REPORT

Onychomycosis due to *Microsporum gypseum*

Nagelmykosen mit *Microsporum gypseum* als Erreger

C. Romano

Key words. Onychomycosis, *Microsporum gypseum*, itraconazole, ciclopirox.
Schlüsselwörter. Onychomycosis, *Microsporum gypseum*, Itraconazol, Ciclopirox.

Summary. The first four cases of onychomycosis due to *Microsporum gypseum* observed in Italy between 1990 and 1997 are reported. Clinical manifestation was distal subungual onychomycosis in all cases. The lesions were asymptomatic in two patients. Three patients were treated with oral itraconazole (pulsed therapy) and the other with ciclopirox 8% nail lacquer. Clinical and mycological recovery was achieved in all cases. The cases are reported because of their rarity.

Zusammenfassung. Wir beschreiben die ersten vier der in Italien zwischen 1990 und 1997 beobachteten Fälle von Nagelmykosen mit *Microsporum gypseum* als Erreger. Das klinische Bild war in allen Fällen durch eine distale subunguale Onychomycoses gekennzeichnet. Die Läsionen waren in zwei Patienten asymptomatisch. Drei der Patienten wurden mit Itraconazol gemäss dem Pulstherapieschema behandelt, während ein Patient lokal 6 Monate lang mit Ciclopirox behandelt wurde. Alle Fälle heilten klinisch und mykologisch vollständig ab. Wir beschreiben diese Fälle wegen ihrer Seltenheit.

Introduction

Microsporum gypseum is a geophilic dermatophyte that lives as a saprophyte in the soil. It causes tinea corporis, capitis, pedis, cruris and kerion in subjects who have contact with soil. These infections are all sporadic, often associated with accentuated inflammation; they do not tend to become chronic and are not particularly contagious. The only known epidemic caused by the dermatophyte occurred in Czechoslovakian plant nursery workers [1]. *Microsporum gypseum* is rarely transmitted to humans by animals or other humans. The first case of onychomycosis due to *Microsporum gypseum* was reported in 1953 [2]. Between 1953 and 1978, only 11 cases have been described [3–12]. Since then six cases have been reported [13, 14]: four by Ginter [1] in the 1980s and one in 1995 [15]. The cases reported here are the first observed in Italy.

Patients and methods

1. Gentleman farmer, male, 51 years, with a 3-year history of thickening and yellowing of the nails of the big toes.
2. Clerk, female, 39 years, passionate gardener; complained of pain in both big toes, the nails of which were thickened and yellowish.
3. Housewife, 63 years, with chronic gastritis and thyroid struma, contact with garden soil; complained of pain in the left big toe and thumb, the nails of which were thickened, yellowish and with signs of onycholysis.
4. Driver, male, 62 years, with liver disease, psoriasis and several months history of yellowing of the right big toenail. His family doctor regarded it as an expression of psoriasis.

In all four patients, the clinical picture was that of distal subungual onychomycosis: thickening and

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VOL. 11 Supplement 2 SEPTEMBER 1998 ISSN:0926-9959
JEAVEQ 11 (Suppl. 2) S1-S356 (1998)

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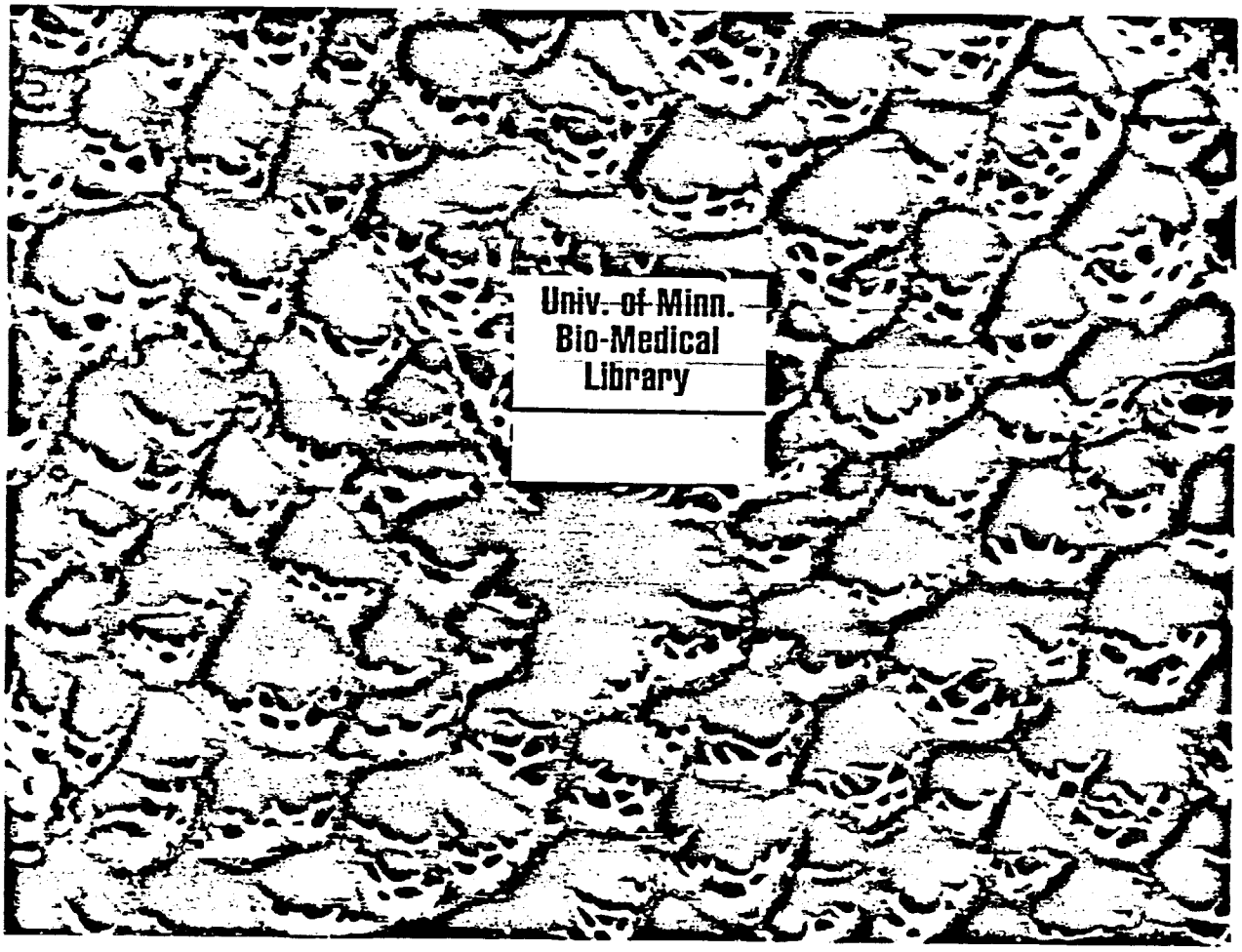
JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY



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Abstracts of the 7th Congress of the European Academy of Dermatology and Venereology, Nice, 7–11 October 1998

time onychomycoses in the toenails and fingernails (43% men. 47% women). In the fingernail infections yeasts were isolated in 72% of the cases. especially in women. dermatophytes in 10%. moulds in 5.6% of the cases and 12.4% were mixed infections. In the toenail infections dermatophytes were isolated in 72.3% of the cases. especially in women. moulds in 9.6%. yeasts in 2% and 16.1% were mixed infections.

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P201 Ciclopirox nail lacquer in the treatment of toenail distal subungual onychomycosis

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The aim of this study was to assess the efficacy and tolerability of topical treatment with ciclopirox nail lacquer in distal subungual onychomycosis. 30 consecutive patients with a mycologically proven dermatophyte onychomycosis limited to the distal 1/3 of 1 or 2 toenail (10 females and 20 males. ageing from 40 to 89 years. mean age 67.5 years) entered an open study. Patients treated with systemic antifungals within 1 year before the beginning of the study were excluded. *T. rubrum* was isolated in 20 patients and *T. interdigitale* in 10 patients. Patients were instructed to apply the lacquer daily for 8 months. Clinical and mycological evaluations were performed every 4 months until one year after the beginning of treatment. 19 patients (63.3%) had a negative mycology at month 12. 16 of these 19 patients were clinically cured. whereas the remaining 3 patients showed a residual traumatic onychodystrophy. 11 patients still had a positive microscopy and/or culture at month 12. The clinical examination of these patients revealed improvement of the onychomycosis in 4 cases. non change in 5. and proximal progression in 2 cases.

This study shows that topical treatment with ciclopirox nail laquer is effective and well tolerated in the therapy of toenail onychomycosis limited to the distal nail.

P202 Prevalence of onychomycosis in Poland: Omnibus study

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Aim of the study was assess the prevalence of onychomycosis in Poland. The method chosen for the research was individual questionnaire interview in the respondents' houses. The field-work was carried out in June 1996. 1141 were under study. aged over 18. selected representatively for adult population of Poland. Among 27 964 600 of Polish people 5 209 407 have a onychomycosis (18.6%). and 3 074 183 have a onychomycosis of finger nails (11%) and 2 135 224 have a onychomycosis of toe nails (7.6%) or every 5 person have a onychomycosis. and every 9 person have a onychomycosis of finger nail. and every 13 person have a onychomycosis of toe nails. In 79.5% sore nails were onychomycosis. and in 72.2% of finger nails and in 92.9% of toe nails. Over 4/5 of adult population of Poland with sore finger nails (85.4%) and sore toe nails (84.8%) belives that problems are something normal which does not require seeing a dermatologist. On the contrary only 0.6% of persons with sore finger nails and 5.4% persons with sore toe nails belives that problems are onychomycosis. In 1996 every 10 adult Poles with onychomycosis of finger nails and every 7 adult Poles with onychomycosis of toe nails were treated.

P203 Mitogen-induced response and flow cytometric analysys of lymphocyte subsets in patients with onychmycosis treatment using pulses of itraconazole

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The increase in the frequency of mycotic infections and the observed resistance of fungal strains to commonly applied drugs explain the necessity to introduce and assess new antifungal drugs. Multinational studies have shown that three cycles of Itraconazole 400 mg daily for one week/month for toenail onychomycosis is effective therapy. This study was designed to compare certain lymphocyte functions and receptor expression in 30 patients with onychomycosis before treatment. and two weeks after the last cycl of Itraconazole. We examined subsets of blood lymphocytes (CD3. CD19. CD4. CD8. CD4/CD45RO. CD8/CD45RO and NK cells) and expression of activation antigens CD3/CD25. CD3/CD69. CD3/HLADR using monoclonal antibodies and flow cytometry. The mitogen-induced lymphocyte response (PHA) was also evaluated. We observed no evidence of lymphocyte phenotypes and activities in patients compared to healthy controls.

P204 Mycospor onychoset and mycospor cream in the treatment of onychomycosis

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The aim of the study was to assess the therapeutic efficacy of Mycospor Onychoset (1% bifonasole with 40% urea) and Mycospor cream manufactured by Bayer in the treatment of onychomycosis. It was carried out on 40 patients including 28 women and 12 men aged from 24–78 years. Diagnosis was established basing on the clinical assessment. direct mycologic examination in KOH solution with the addition of dimethyl sulphoxide (DMSO) and culture on the medium of Mycoline by bioMèrieux. The patients who had no more than 4 nail plates involved have been qualified into treatment. Mycospor Onychoset was used until exfoliation of the nail plate and negative direct examination. Then Mycospor cream was used once a day for 4 weeks. Direct follow-up examinations were performed after 1. 2. and 6 weeks and the culture was performed just after 2 and 6 weeks of therapy. 4 and 12 weeks just after finishing the treatment direct follow-up and culture were done. The most common pathogens were Trichophyton rubrum and