CENTER FOR DRUG EVALUATION AND RESEARCH

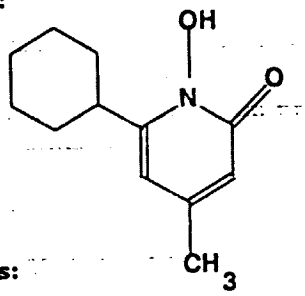
APPLICATION NUMBER: 21-022

PHARMACOLOGY REVIEW(S)

SEP 2 4 1999

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

KEY WORDS:
Reviewer Name: Kumar D. Mainigi
Division Name: Dermatologic and Dental Drug Products
HFD-540
Review Completion Date: ~~06-30-1999~~ 51
Electronic File Number: 09/24/99
NDA 21-022
000/12-18-1998/original application
Information to sponsor: Yes ( ) No (X)
Sponsor: Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
Kansas City, MO 64134-0527
Manufacturer: Sponsor
Drug: **Code Name** HOE 296b
Generic Name: Ciclopirox
Trade Name: LOPROX® (ciclopirox) Nail Lacquer 8%
Chemical Name: 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridinone
CAS Registry Number: 29342-05-0
Molecular Formula/Molecular Weight: $C_{12}H_{17}NO_2$/207.3
Structure:



Relevant INDs/NDAs:

IND ——— Loprox (ciclopirox) Nail Lacquer 8%
IND ——— Loprox (ciclopirox) Gel 0.77%
NDA 18-748 Loprox (ciclopirox) Cream 1% (approved 12-30-1982)

NDA 19-824 Loprox (ciclopirox olamine) Lotion 1% (approved 12-30-1988)
NDA 20-519 Loprox (ciclopirox) Gel 0.77% (approved 07-21-1997)

Drug Class: Antifungal
Indication: For the topical treatment (fingernails and toenails) of mild to moderate onychomycosis without lunula involvement due to *Trichophyton rubrum*

Clinical formulation (and components):

Component	Grams/3 g Bottle
Ciclopirox (HOE 296b)	
Gantrez ES-435 resin (butyl monoester of polymethylvinyl ether/maleic acid in isopropyl alcohol solution	
Ethylacetate NF	
Isopropyl alcohol USP	
Total weight	

Route of Administration: Topical

Mechanism of Action: The proposed antifungal action of ciclopirox primarily involves chelation of trivalent cations such as Fe^{3+}. The trapping of metal co-factors inhibits the activities of cytochrome enzymes; consequently, the mitochondrial electron transport system located in the fungal cell membrane is switched off. Lack of energy deprives the cell of nutrients because of poor uptake. According to the sponsor, ciclopirox also inhibits the activities of catalase and peroxidase, which are responsible for the degradation of toxic peroxides in the fungal cell.

Proposed Clinical Use: Loprox® Nail Lacquer 8% shall be applied once daily before bedtime to all affected toenails and or fingernails. The residue shall be removed only after seven applications. The proposed duration of treatment is 48 weeks.

Previous Clinical Experience: Ciclopirox Nail Lacquer 8% was evaluated for its safety and efficacy in five Phase II/III studies conducted in U. S. Six additional studies were performed in Europe. In these studies, a total of 5,689 male and female patients with tinea unguium of the fingernails or toenails were treated for a maximum period of 48 weeks. The commonly reported adverse effects of Ciclopirox Nail Lacquer 8% have included transient mild to moderate periungual erythema in some cases during the first three to four weeks of treatment.

Introduction and Drug History: Two ciclopirox formulations Loprox Cream 1% and Loprox Lotion 1% are currently marketed in United States. Ciclopirox Nail Lacquer 8% is currently marketed under various trade names (Loprox, Batrafen, Mycofen, Mycoster, Nagel Batrafen, Ciclochem, and Nibulen) in 12 European, 20 Latin American, 8 Asian countries, and New Zealand. It has been approved for sale in Egypt (1997), Phillipines (1994), and Taiwan (1996).

Studies reviewed within this submission: No new non-clinical studies were submitted.

Background: All the animal safety data discussed under the ' Overall Toxicology Summary' were reviewed by Dr. Joshi under a number of submissions for ciclopirox and ciclopirox olamine formulations (1982-1989). In 1995, the Review Medical Officer (Dr. Franz) raised the issues of cardiotoxicity of ciclopirox and genotoxicity of Gantrez ES-435. Based on extensive re-evaluation and discussions with the original reviewer it was concluded that no additional animal studies were required to further support the safety of Ciclopirox Nail Lacquer 8%. The sponsor was informed about this decision through a memorandum on March 8, 1995. This decision was again confirmed in another memo dated August 8,1995. The current reviewer and the team leader initialed this memorandum.

Dr. Joshi after evaluation of cardiotoxicity data of two 13-week oral toxicity studies in rat and dog had reached to the conclusion that a 10mg/kg/day dose of Ciclopirox olamine was well tolerated (NDA 18-748; Loprox Cream 1%; review dated 07-14-1982; NDA approved 12-30-1982). This value (NOEL) is used to calculate the margin of safety in the current review. In a later review, he had once again confirmed the safety of the active ingredient, but was not satisfied with the limited safety data provided for Gantrez ES-435 (IND —— Loprox Nail Lacquer 8%, review dated 07-22-1988). Under the column "recommendations" it is stated that "The sponsor should be requested to provide us safety data for ES-435; in the meantime the clinical study should be put on hold." The sponsor provided all the relevant information. In a divisional memo dated September 7, 1988,

the sponsor was informed that "We have completed the review of additional information submitted concerning the exipient (sic) Gantrez ES435 and conclude that it is satisfactory. Therefore, your proposed clinical study be initiated." In this submission, the sponsor has essentially included the same information. The genotoxicity studies with Gantrez ES-435 were conducted in 1980-1981.

Overall Toxicology Summary: Since review of its first drug application (IND ——— Loprox Cream 1%) in January 1974, ciclopirox (free acid) and its salt ciclopirox olamine have been extensively evaluated in cream, lotion, gel and lacquer formulations in a wide spectrum of multispecies *in vivo* and *in vitro* studies.

The oral and parenteral LD_{50s} for ciclopirox and ciclopirox olamine in rodents ranged from 1,240 to 3,200 mg/kg and 79 to 663 mg/kg, respectively. The primary systemic adverse effects of acute doses included irregular respiration and clonic convulsions. In 7-day old rats, the oral LD_{50} was 445 mg/kg, and an intraperitoneal dose of 20 mg/kg was tolerated without any adverse effects. The free acid (ciclopirox, HOE 296b) was found to be less toxic than its olamine salt (HOE 296).

The oral LD_{50} in rats for ethyl and butyl ester of PVM/MA copolymers (Gantrez ES 435) was greater than 26.6 g/kg.

In 3-4 week long multiple dose topical studies in rabbits, no systemic toxicity was observed. At a dose level of 500 mg/kg/day (6.0 g/m^2) for 4 weeks, only 3/11 blood samples drawn from the abraded rabbits contained levels of ciclopirox above the detection limit ———). In rabbits with intact skin, the drug level in the blood was below the detection limit. In a 3-month study in rabbits and 6-month study in dogs, daily topical applications of free acid at 10% concentration did not cause any systemic toxicity. The local lesions developed in a dose-dependent fashion involved moderate to pronounced thickening of the stratum germinativum of the epidermis, with hyperkeratosis in rabbits and parakeratosis in dogs, and a chronic inflammatory reaction in the subepidermal corium. These lesions disappeared in 4-6 weeks.

The oral doses of 10mg ciclopirox olamine/kg/day in 3-month studies in rat and dog did not produce any toxic effects or changes in ECG.Therefore, this dose was established as NOEL in both species. However, doses of 30 mg and higher caused deaths and degenerative changes in the heart. In rats, it included necrosis of myocardial fibers resulting in parietal thrombosis, which in some cases extedned to the vena cava. In dogs, damages were observed in the lungs, heart and liver; in particular, necrosis of the myocardium and parenchyma of the liver was observed.

In 2-week oral toxicokinetic studies in rats and dogs, at NOEL, the maximum serum drug levels ranged between 2,790 and 3,570 ng/mL, while in a 4-week rabbit dermal study at dosing up to 1,000mg/kg/day, the serum level of ciclopirox was below the detection limit. In the same oral studies, the serum drug levels associated with the systemic toxicity at 30 mg/kg/day ranged between 4,920 and 18,490 ng/mL. In a 5-day dog study following the oral administration of ^{14}C ciclopirox olamine at15mg/kg/day level, Cmax —— ug/mL) was achieved within 1.5-2 hours. At the peak drug level in the blood, the highest amount of radioactivity was found in the excretory organs (4-150 ug/g in liver and kidneys), 0.5 ug/g in muscle, and 0.13 ug/g in the brain. Excretion occurred in three phases with half-lives of 1-2 hours, 8-14 hours and 2-5 days. Within 2-3 days, 95-97% of the administered dose was excreted in the urine and feces.

Following application of ^{14}C ciclopirox (2 mg/kg) to dogs, within 3 hours, 85-100% of the dose could still be wiped off.

Three basic toxicity studies were conducted with Loprox 8% Nail Lacquer. In a rat acute oral toxicity study (10mL/kg to 10 rats/sex), one male died on day 1. Necropsy examination of the dead rat and 19 rats sacrificed on day 7 revealed hardened pea size drug pellets in the stomach. LD_{50} was considered greater than 800 mg/kg. In rabbit assays, nail lacquer formulation exhibited ocular toxicity but caused no dermal irritation.

After the topical application of ^{14}C ciclopirox olamine in humans, only 1.1% of the dose was excreted in the urine and less than 0.1% in the feces. It was concluded that drug did not penetrate through the human skin in significant amounts. The penetration of 8% ciclopirox in Gantrez lacquer across the excised human toenails was tested using an ——— The preparation containing ^{14}C-ciclopirox was applied to nails every 3 days for one month. The amount of radioactivity found in the receptor fluid ranged from 0.01 to 0.07% of the administered dose. In human systemic tolerability studies following multiple applications in subjects with distal subungual onychomycosis, the average maximal serum level of ciclopirox was 31±28 ng/mL after two months of treatment.

In a 50-week dermal carcinogenicity study in female mice followed by a 6-month recovery period prior to necropsy revealed no evidence for tumors at the application sites.

In two microbial (Ames Salmonella/mammalian microsome and E.Coli assays) and three *in vitro* mammalian cell assays (gene mutation in HGPRT-test with V79 Chinese hamster lung fibroblasts cells, unscheduled DNA synthesis in human A549 cells, and cell transformation assay in mouse embryo fibroblast BALB/3T3 cells), ciclopirox was indicated nonmutagenic. In an *in vitro* assay in V79 Chinese hamster cells, ciclopirox (only in the absence of Fe^{3+}) induced chromosomal aberrations in the presence and absence of rat metabolic activation system. However, ciclopirox-Fe tested nonmutagenic in the same assay with or without metabolic activation. The positive response in the first assay was attributed to the chelating properties of ciclopirox. In the *in vivo* Chinese hamster (source of V79 cells) bone marrow cytogenetic assay, ciclpirox was nonmutagenic. In a ——— study conducted in Chinese hamsters using a single oral dose (500 and 2,000 mg/kg) of ^{14}C ciclopirox olamine, radioactivity was detected in the bone marrow at both dose levels at all the postdose time points (1, 4, 24 hours), supporting the fact that in the *in vivo* assay the compound was nonmutagenic irrespective of its availability at the action site. Ciclopirox olamine tested nonmutagenic in two *in vivo* (mouse dominant lethal and mouse micronucleus tests) and an *in vitro* (*Saccharomyces cervisiae*) assay.

Loprox Nail Lacquer 8% was nonmutagenic in Ames test. Since ciclopirox tested nonmutagenic in the *in vitro* cell transformation assay with BALB/c3T3 cells, a weak transforming activity exhibited by Loprox Nail Lacquer 8% in this system was attributed to Gantrez ES-435 (alkyl monoester resin) component which also tested positive in this assay. It must be mentioned that this cell assay is considered predictive of carcinogenesis. However, it is quite possible that c3T3 assay was confounded because of the film-forming nature of the resin. Gantrez ES-435 tested nonmutagenic in the mouse lymphoma forward mutation assay with or without metabolic activation; it was also inactive in the unscheduled DNA synthesis in rat hepatocytes. According to a

survey report, the EthylEster of PVM/MA copolymers widely used in cosmetics and hair preparations are safe to use topically. The concentration of copolymer exceeds 25% in hair sprays and other noncoloring hair preparations [Final Report on the Safety Assessment of Ethyl Ester of PVM/MA Copolymer and Butyl Ester of PVM/MA Copolymer, JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY: 12 (3), 243-256, 1993]. The Loprox Nail Lacquer 8% contains 15% of Gantrez ES-435. The cosmetics and hair preparations are for lifetime use.

No effects on the fetal or maternal parameters were observed in segments III and I rat studies where animals received oral doses of up to 5mg ciclopirox/kg/day (30 mg/m^2/day). Teratology studies in mice, rats, rabbits and monkeys conducted at oral doses of up to 100, 30, 30, or 50 mg/kg/day (300, 180, 360, or 600 mg/m^2/day), respectively, or in rats and rabbits receiving topical doses of 120 and 100mg/kg/day (720 and 1,200mg/m^2/day) produced no significant fetal malformations.

Evaluation and Interpretation of Safety Data: Cardiotoxicity in rats and dogs was observed at 30 and 100 mg/kg/day dose level. At a given dose level, adverse effects were more severe in dogs than rats. Both the subchronic animal studies were conducted with ciclopirox olamine which is more toxic than the free acid (ciclopirox) used in the nail lacquer formulation. The NOEL in both studies was established at 10 mg/kg/day (equivalent to 60 mg/m^2 in rats and 200 mg/m^2 in dogs). No dose level between 10 and 30 mg was used in these studies.

Even under occlusion, less than 1.5% of the topically applied ciclopirox olamine is absorbed into the systemic circulation, and no systemic accumulation occurs because of its short half-life of 1.7 hours (Goodman and Gilman, 9th edition, p 1187, 1996). According to the sponsor, the topical application of 0.339g (27.12mg ciclopirox) of the lacquer formulation will cover all the fingernails and toenails including 5 mm proximal and lateral fold area plus onycholysis to a maximal extent of 50 percent. In an *in vitro* study, a maximum of 0.07% (0.111 mg/m^2 of nail) of the applied dose of radiolabeled ciclopirox in 8% Nail Lacquer formulation penetrated through the excised human toenails. Taking this figure into account, the margin of safety based on NOEL in rat and dog will be 540 and1, 802 times, respectively. On the other hand, assuming 100% absorption (an extremely hypothetical possibility) of ciclopirox, the margin of safety will be between 4 and 12 times. In systemic tolerability studies in subjects with distal subungual onychomycosis, the average maximal serum level of 31±28ng ciclopirox/mL was achieved after two months of treatment. It was 159 times lower than the lowest toxic dose (4, 920 ng/mL), and 115 times lower than the highest nontoxic dose (3,570 ng/mL) in animals. It must be mentioned that no adverse effects or changes in any clinically significant laboratory parameters were observed in subjects with detectable serum levels of ciclopirox. Furthermore, only a few subjects had detectable level of drug in the serum. Therefore, it is fairly safe to assume that the systemic absorption of ciclopirox following topical applications shall be much lower than the nontoxic drug levels in the animals.

In six *in vitro* (three microbial and three mammalian cell assays) and three *in vivo* tests ciclopirox and ciclopirox olamine were found nonmutagenic and clastogenic. The positive clastogenic response of ciclopirox was limited to an *in vitro* chromosomal aberration assay in V79 Chinese hamster cells. Since it tested negative in the *in vivo* Chinese hamster (source of V79 cells) cytogenetic test and in another *in vitro* assay in V79 Chinese hamster cells where ciclopirox-Fe instead of ciclopirox was used, the positive response was attributed to the chelating properties of ciclopirox.

Loprox Nail Lacquer 8% was nonmutagenic in Ames test, and its weak transforming activity in BALB/c3T3 cells was due to its butyl ester copolymer (Gantrez ES-435) component, which also tested positive in the same test. However, ES-435 was tested nonmutagenic in two other *in vitro* assays. Because of its insolubility in the aqueous medium and the film-forming property, it will be difficult to conduct an *in vivo* mutagenicity assay with this copolymer. In the *in vivo* studies, lacquer formulation formed pellets in the GI-tract because of ES-435. However, looking into the high molecular weight (52,700) of copolymer, it is impossible to assume that any significant systemic absorption of this compound can occur. Based on the negative results obtained from three *in vivo* and six *in vitro* genotoxicity tests and a dermal carcinogenicity study, the genotoxic risk from the nail lacquer should be negligible.

Looking collectively into the animal, genotoxicity, and human pharmacokinetic data, it is safe to assume that the topical applications of ciclopirox nail lacquer should not produce any significant toxicity in humans.

Labeling: The draft submitted by the sponsor has been modified.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No carcinogenicity study was conducted with Loprox® Nail Lacquer 8% formulation. A carcinogenicity study of ciclopirox (1% and 5% solutions in polyethylene glycol 400) in female mice dosed cutaneously twice per week for 50 weeks followed by a 6-month drug free observation period prior to necropsy revealed no evidence of tumors at the application sites.

In human systemic tolerability studies following daily application (~340 mg of Loprox Nail Lacquer 8%) in subjects with distal subungual onychomycosis, the average maximal serum level of ciclopirox was 31±28ng/mL after two months of once daily applications. This level was 159 times lower than the lowest toxic dose and 115 times lower than the highest nontoxic dose in rats and dogs fed ——— ciclopirox olamine/kg/day. ———

The following *in vitro* genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in Ames *Salmonella* and *E. coli* assays (negative); chromosome aberration assays in V79 Chinese hamster cells, with and without metabolic activation (positive); gene mutation assay in the HGPRT-test with V79 Chinese hamster lung fibroblasts (negative); unscheduled DNA synthesis in human A549 cells (negative); and BALB/c 3T3 cell transformation assay (negative). In an *in vivo* Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at 5,000 mg/kg.

The following *in vitro* genotoxicity tests were conducted with Loprox Nail Lacquer 8%: Ames *Salmonella* test (negative); unscheduled DNA synthesis in the rat hepatocytes (negative); cell transformation assay in BALB/3T3 cell assay (positive). The positive response of lacquer formulation in the BALB/3T3 test was attributed to its ——— (Gantrez ES-435), which also tested positive in this test. The cell transformation assay may have been confounded because of film-forming nature of the resin. Gantrez ES-435 tested nonmutagenic in the *in vitro* mouse lymphoma forward mutation assay with or without activation, and unscheduled DNA synthesis in rat hepatocytes.

Oral reproduction studies in rats at doses up to — ciclopirox olamine/kg/day [equivalent to approximately — times the maximum potential exposure at the recommended human topical dose (MRHTD)*] did not reveal any specific effects on fertility or other reproductive parameters.

Pregnancy:

Teratogenic effects: Pregnancy Category B

Teratology studies in mice, rats, rabbits, and monkeys at oral doses of up to ——— ——— ciclopirox olamine/kg/day ——— times of MRHTD), or in rats and rabbits receiving topical doses of up to ——— mg/kg/day, respectively — and — times of MRHTD), did not indicate any significant fetal malformations.

There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. Loprox® Nail Lacquer 8% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

[redacted]

Regulatory conclusion: The non-clinical safety of Loprox Nail Lacquer 8% has been adequately established. I have no objection to the approval of this new drug application, provided sponsor agrees to make the suggested changes in the label.

Regulatory recommendations: None.

/S/ 9/24/99

Kumar D. Mainigi, Ph.D., M.P.H., D.A.B.T.
Toxicologist

Original NDA 21-022
HFD-82
HFD-540
MO/Vaughan
Chem/Hathaway
Micro/Gosey
Pharm/Mainigi
Pharm/Jacobs
Biopharm/Lee

Concurrence:
A.Jacobs, TL, HFD-540 /S/ 9/24/99
J.Wilkin, Dir, HFD-540 /S/ 10/4/99

DEC 3 1999

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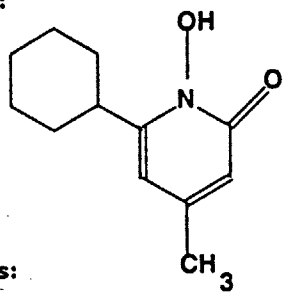
Structure:



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Following application of ^{14}C ciclopirox (2 mg/kg) to dogs, within 3 hours, 85-100% of the dose could still be wiped off.

Three basic toxicity studies were conducted with Loprox 8% Nail Lacquer. In a rat acute oral toxicity study (10mL/kg to 10 rats/sex), one male died on day 1. Necropsy examination of the dead rat and 19 rats sacrificed on day 7 revealed hardened pea size drug pellets in the stomach. LD_{50} was considered greater than 800 mg/kg. In rabbit assays, nail lacquer formulation exhibited ocular toxicity but caused no dermal irritation.

After the topical application of ^{14}C ciclopirox olamine in humans, only 1.1% of the dose was excreted in the urine and less than 0.1% in the feces. It was concluded that drug did not penetrate through the human skin in significant amounts. The penetration of 8% ciclopirox in Gantrez lacquer across the excised human toenails was tested using an _____ . The preparation containing ^{14}C-ciclopirox was applied to nails every 3 days for one month. The amount of radioactivity found in the receptor fluid ranged from 0.01 to 0.07% of the administered dose. In human systemic tolerability studies following multiple applications in subjects with distal subungual onychomycosis, the average maximal serum level of ciclopirox was 31±28 ng/mL after two months of treatment.

In a 50-week dermal carcinogenicity study in female mice followed by a 6-month recovery period prior to necropsy revealed no evidence for tumors at the application sites.

In two microbial (Ames Salmonella/mammalian microsome and E.Coli assays) and three *in vitro* mammalian cell assays (gene mutation in HGPRT-test with V79 Chinese hamster lung fibroblasts cells, unscheduled DNA synthesis in human A549 cells, and cell transformation assay in mouse embryo fibroblast BALB/3T3 cells), ciclopirox was indicated nonmutagenic. In an *in vitro* assay in V79 Chinese hamster cells, ciclopirox (only in the absence of Fe^{3+}) induced chromosomal aberrations in the presence and absence of rat metabolic activation system. However, ciclopirox-Fe tested nonmutagenic in the same assay with or without metabolic activation. The positive response in the first assay was attributed to the chelating properties of ciclopirox. In the *in vivo* Chinese hamster (source of V79 cells) bone marrow cytogenetic assay, ciclpirox was nonmutagenic. In a _____ study conducted in Chinese hamsters using a single oral dose (500 and 2,000 mg/kg) of ^{14}C ciclopirox olamine, radioactivity was detected in the bone marrow at both dose levels at all the postdose time points (1, 4, 24 hours), supporting the fact that in the *in vivo* assay the compound was nonmutagenic irrespective of its availability at the action site. Ciclopirox olamine tested nonmutagenic in two *in vivo* (mouse dominant lethal and mouse micronucleus tests) and an *in vitro* (*Saccharomyces cervisiae*) assay.

Loprox Nail Lacquer 8% was nonmutagenic in Ames test. Since ciclopirox tested nonmutagenic in the *in vitro* cell transformation assay with BALB/c3T3 cells, a weak transforming activity exhibited by Loprox Nail Lacquer 8% in this system was attributed to Gantrez ES-435 (alkyl monoester resin) component which also tested positive in this assay. It must be mentioned that this cell assay is considered predictive of carcinogenesis. However, it is quite possible that c3T3 assay was confounded because of the film-forming nature of the resin. Gantrez ES-435 tested nonmutagenic in the mouse lymphoma forward mutation assay with or without metabolic activation; it was also inactive in the unscheduled DNA synthesis in rat hepatocytes. According to a

survey report, the EthylEster of PVM/MA copolymers widely used in cosmetics and hair preparations are safe to use topically. The concentration of copolymer exceeds 25% in hair sprays and other noncoloring hair preparations [Final Report on the Safety Assessment of Ethyl Ester of PVM/MA Copolymer and Butyl Ester of PVM/MA Copolymer, JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY: 12 (3), 243-256, 1993]. The Loprox Nail Lacquer 8% contains 15% of Gantrez ES-435. The cosmetics and hair preparations are for lifetime use.

No effects on the fetal or maternal parameters were observed in segments III and I rat studies where animals received oral doses of up to 5mg ciclopirox/kg/day (30 mg/m^2/day). Teratology studies in mice, rats, rabbits and monkeys conducted at oral doses of up to 100, 30, 30, or 50 mg/kg/day (300, 180, 360, or 600 mg/m^2/day), respectively, or in rats and rabbits receiving topical doses of 120 and 100mg/kg/day (720 and 1,200mg/m^2/day) produced no significant fetal malformations.

Evaluation and Interpretation of Safety Data: Cardiotoxicity in rats and dogs was observed at 30 and 100 mg/kg/day dose level. At a given dose level, adverse effects were more severe in dogs than rats. Both the subchronic animal studies were conducted with ciclopirox olamine which is more toxic than the free acid (ciclopirox) used in the nail lacquer formulation. The NOEL in both studies was established at 10 mg/kg/day (equivalent to 60 mg/m^2 in rats and 200 mg/m^2 in dogs). No dose level between 10 and 30 mg was used in these studies.

Even under occlusion, less than 1.5% of the topically applied ciclopirox olamine is absorbed into the systemic circulation, and no systemic accumulation occurs because of its short half-life of 1.7 hours (Goodman and Gilman, 9th edition, p 1187, 1996). According to the sponsor, the topical application of 0.339g (27.12mg ciclopirox) of the lacquer formulation will cover all the fingernails and toenails including 5 mm proximal and lateral fold area plus onycholysis to a maximal extent of 50 percent. In an *in vitro* study, a maximum of 0.07% (0.111 mg/m^2 of nail) of the applied dose of radiolabeled ciclopirox in 8% Nail Lacquer formulation penetrated through the excised human toenails. Taking this figure into account, the margin of safety based on NOEL in rat and dog will be 540 and1, 802 times, respectively. On the other hand, assuming 100% absorption (an extremely hypothetical possibility) of ciclopirox, the margin of safety will be between 4 and 12 times. In systemic tolerability studies in subjects with distal subungual onychomycosis, the average maximal serum level of 31±28ng ciclopirox/mL was achieved after two months of treatment. It was 159 times lower than the lowest toxic dose (4, 920 ng/mL), and 115 times lower than the highest nontoxic dose (3,570 ng/mL) in animals. It must be mentioned that no adverse effects or changes in any clinically significant laboratory parameters were observed in subjects with detectable serum levels of ciclopirox. Furthermore, only a few subjects had detectable level of drug in the serum. Therefore, it is fairly safe to assume that the systemic absorption of ciclopirox following topical applications shall be much lower than the nontoxic drug levels in the animals.

In six *in vitro* (three microbial and three mammalian cell assays) and three *in vivo* tests ciclopirox and ciclopirox olamine were found nonmutagenic and clastogenic. The positive clastogenic response of ciclopirox was limited to an *in vitro* chromosomal aberration assay in V79 Chinese hamster cells. Since it tested negative in the *in vivo* Chinese hamster (source of V79 cells) cytogenetic test and in another *in vitro* assay in V79 Chinese hamster cells where ciclopirox-Fe instead of ciclopirox was used, the positive response was attributed to the chelating properties of ciclopirox.

Loprox Nail Lacquer 8% was nonmutagenic in Ames test, and its weak transforming activity in BALB/c3T3 cells was due to its butyl ester copolymer (Gantrez ES-435) component, which also tested positive in the same test. However, ES-435 was tested nonmutagenic in two other *in vitro* assays. Because of its insolubility in the aqueous medium and the film-forming property, it will be difficult to conduct an *in vivo* mutagenicity assay with this copolymer. In the *in vivo* studies, lacquer formulation formed pellets in the GI-tract because of ES-435. However, looking into the high molecular weight (52,700) of copolymer, it is impossible to assume that any significant systemic absorption of this compound can occur. Based on the negative results obtained from three *in vivo* and six *in vitro* genotoxicity tests and a dermal carcinogenicity study, the genotoxic risk from the nail lacquer should be negligible.

Looking collectively into the animal, genotoxicity, and human pharmacokinetic data, it is safe to assume that the topical applications of ciclopirox nail lacquer should not produce any significant toxicity in humans.

Labeling: The draft submitted by the sponsor has been modified. All the values are calculated in terms of ciclopirox. In the second paragraph, the value of 300 mg/kg/day is corrected to 30 mg/kg/day.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No carcinogenicity study was conducted with Loprox® Nail Lacquer 8% formulation. A carcinogenicity study of ciclopirox (1% and 5% solutions in polyethylene glycol 400) in female mice dosed topically twice per week for 50 weeks followed by a 6-month drug free observation period prior to necropsy revealed no evidence of tumors at the application sites.

In human systemic tolerability studies following daily application (~340 mg of Loprox Nail Lacquer 8%) in subjects with distal subungual onychomycosis, the average maximal serum level of ciclopirox was 31±28ng/mL after two months of once daily applications. This level was 159 times lower than the lowest toxic dose and 115 times lower than the highest nontoxic dose in rats and dogs fed 7.7 and 23.1 mg ciclopirox as ciclopirox olamine/kg/day.

The following *in vitro* genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in Ames *Salmonella* and *E. coli* assays (negative); chromosome aberration assays in V79 Chinese hamster cells, with and without metabolic activation (positive); gene mutation assay in the HGPRT-test with V79 Chinese hamster lung fibroblasts (negative); unscheduled DNA synthesis in human A549 cells (negative); and BALB/c 3T3 cell transformation assay (negative). In an *in vivo* Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at 5,000 mg/kg.

The following *in vitro* genotoxicity tests were conducted with Loprox Nail Lacquer 8%: Ames *Salmonella* test (negative); unscheduled DNA synthesis in the rat hepatocytes (negative); cell transformation assay in BALB/3T3 cell assay (positive). The positive response of lacquer formulation in the BALB/3T3 test was attributed to its alkyl monoester resin component (Gantrez ES-435), which also tested positive in this test. The cell transformation assay may have been confounded because of the film-forming nature of the resin. Gantrez ES-435 tested nonmutagenic in the *in vitro* mouse

lymphoma forward mutation assay with or without activation, and unscheduled DNA synthesis in rat hepatocytes.

Oral reproduction studies in rats at doses up to 3.85 g ciclopirox as ciclopirox olamine/kg/day [equivalent to approximately 1.4 times the potential exposure at the maximum recommended human topical dose (MRHTD)*] did not reveal any specific effects on fertility or other reproductive parameters.

Pregnancy:

Teratogenic effects: Pregnancy Category B

Teratology studies in mice, rats, rabbits, and monkeys at oral doses of up to 77, 23, 23, or 38.5 mg ciclopirox as ciclopirox olamine/kg/day (14, 8, 17, and 28 times of MRHTD), or in rats and rabbits receiving topical doses of up to 92.4 and 77 mg/kg/day, respectively (33 and 55 times of MRHTD), did not indicate any significant fetal malformations.

There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. Loprox® Nail Lacquer 8% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

[redacted]

Regulatory conclusion: The non-clinical safety of Loprox Nail Lacquer 8% has been adequately established. I have no objection to the approval of this new drug application, provided sponsor agrees to make the suggested changes in the label.

Regulatory recommendations: None.

/S/ 12/3/99

Kumar D. Mainigi, Ph.D., M.P.H., D.A.B.T.
Toxicologist

Original NDA 21-022
HFD-82
HFD-540
MO/Vaughan
Chem/Hathaway
Micro/Gosey
Pharm/Mainigi
Pharm/Jacobs

Concurrence:
A.Jacobs, TL, HFD-540 /S/ 12/3/99
J.Wilkin, Dir, HFD-540 /S/ 12/8/99 DHS

Biopharm/Lee

Revised label: Ciclopirox Nail Liquor 8%

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