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Application Number 21-159

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

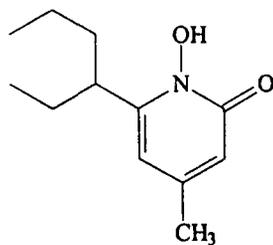
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Information to sponsor: Yes () No (X)
Sponsor and/or agent: Medicis Pharmaceutical Corp.
8125 North Hayden Road
Scottsdale, AZ 85258

Manufacturer for drug substance: Aventis (Hoechst Marion Roussel), Frankfurt, Germany

Reviewer name: Barbara Hill
Division name: Dermatologic and Dental Drug Products
HFD #: HFD-540
Review completion date: 1-6-03

Drug:

Trade name: Loprox shampoo, 1%
Generic name (list alphabetically): Ciclopirox shampoo, 1%
Code name: HOE296b
Chemical name: 6-cyclohexyl-1-hydroxy-4-methyl-2(1 H)-pyridone
CAS registry number: 29342-05-0
Mole file number: N/A
Molecular formula/molecular weight: $C_{12}H_{17}NO_2$ / _____
Structure:



Relevant INDs/NDAs/DMFs:

- 1) _____
- 2) _____
- 3) _____

- 4) NDA 18-748 (Loprox {Ciclopirox} cream, 0.77%; topical treatment of dermal fungal infections; HFD-540; approved 12/30/82; Medicis)
- 5) NDA 19-824 (Loprox {Ciclopirox} lotion, 0.77%; topical treatment of dermal fungal infections; HFD-540; approved 12/30/88; Medicis)
- 6) NDA 20-519 (Loprox {Ciclopirox} gel, 0.77%; topical treatment of interdigital tinea pedis/Tinea corporis and tinea cruris and for the treatment of seborrheic dermatitis; HFD-540; approved 7/21/97; Medicis)
- 7) NDA 21-022 (Penlac {Ciclopirox} solution, 8.0%; Onychomycosis; HFD-540; approved 12/17/99; Aventis Pharm)

Drug class: Antifungal

Indication: Topical treatment and prevention of recurrence of seborrheic dermatitis of the scalp

Clinical formulation:

Loprox[®] shampoo is formulated for clinical use as a 1% ciclopirox shampoo formulation. The composition of the Loprox[®] shampoo is provided in the following table.

Ingredient	% w/w
Ciclopirox	1.0
Sodium chloride	
Water	

Route of administration: Topical

Proposed use: Approximately 5-10 ml of Loprox shampoo is to be applied to the scalp. Individuals with longer hair may use 10 ml of shampoo. Loprox shampoo is to remain on the hair and scalp for 3 minutes then rinsed off. Loprox shampoo is to be applied twice per week for four weeks.

The maximum recommended human dose is 10 ml Loprox shampoo/application applied 2X/week. This would equal 3.34 mg/kg/week for a 60 kg individual (10 mg/ml x 10 ml/application x 2 applications/week ÷ 60 kg = 3.34 mg/kg/week). A daily application equivalent for calculation of multiples of human exposure would be 0.48 mg/kg/day (17.8 mg/m²/day).

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Introduction and drug history:

Ciclopirox is a synthetic hydroxypyridone antifungal agent. Several ciclopirox formulations have been approved for marketing purposes. Loprox (ciclopirox) cream, 0.77%, was approved for marketing in the US for the treatment of tinea pedis, tinea cruris, and tinea corporis and cutaneous candidiasis (moniliasis) and tinea (pityriasis) versicolor on December 30, 1982. Loprox (ciclopirox) lotion, 0.77%, was approved for marketing in the US for the treatment of tinea pedis, tinea cruris, tinea corporis and cutaneous candidiasis (moniliasis) and tinea (pityriasis) versicolor on December 30, 1988. Loprox (ciclopirox) gel, 0.77%, was approved for marketing in the US for the treatment of interdigital tinea pedis, tinea corporis and tinea cruris and for the treatment of seborrheic dermatitis on July 21, 1997. Penlac (ciclopirox) solution, 8.0%, was approved for marketing in the US for the treatment of onychomycosis on December 17, 1999.

The original NDA for Loprox shampoo was submitted on September 7, 1999. A non-approval letter for this NDA was relayed to the sponsor on September 6, 2000. The non-approval letter contained several chemistry and clinical deficiencies that needed to be addressed for the Loprox shampoo NDA. The sponsor has submitted this major amendment to the NDA on September 3, 2002 to address each of the chemistry and clinical deficiencies listed in the non-approval letter.

The non-approval letter also included a nonclinical recommendation for a phase 4 commitment to conduct either a traditional 2 year dermal carcinogenicity study or a 6 month Tg.AC mouse dermal carcinogenicity study. The sponsor submitted a new correspondence submission to the NDA on 10/24/02. The new correspondence submission contained a proposal by the sponsor to fulfill the recommended phase 4 commitment. A summary of this proposal and the division's response that has been relayed to the sponsor is provided in the "Carcinogenicity" section of this review.

Studies reviewed within this submission:

No nonclinical studies were included in this submission. The sponsor is relying on previous nonclinical studies conducted with various ciclopirox containing formulations. The sponsor has ownership of all the nonclinical toxicology studies that have been conducted with Loprox cream, Loprox gel, Loprox lotion, Loprox shampoo and Penlac. A brief integrated summary of the nonclinical toxicology data available from these studies will be provided under the appropriate nonclinical section of this review.

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The NDA is approvable from a pharmacology/toxicology perspective provided that the recommended labeling changes are incorporated into the label.

B. Recommendation for Nonclinical Studies

The sponsor has agreed to conduct the recommended dermal carcinogenicity study for ciclopirox shampoo, 1% as phase 4 commitment.

C. Recommendations on Labeling

Recommended wording for the nonclinical portions of the label are provided in the labeling recommendations section located at the end of this review.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

No major nonclinical toxicological findings were noted in the nonclinical toxicology studies conducted to support ciclopirox.

B. Pharmacologic Activity

Ciclopirox is an anti-fungal agent.

C. Nonclinical Safety Issues Relevant to Clinical Use

No nonclinical safety issues were identified that would be relevant to the clinical use of ciclopirox shampoo, 1% for the seborrheic dermatitis indication.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

HFD-540/DIV DIR/WILKIN

HFD-540/ PHARM SUP/JACOBS

HFD-540/PHARM/HILL

HFD-540/MO/HUENE

HFD-540/CHEM/GAUTAMBASAK

HFD-540/PM/SMITH

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**APPEARS THIS WAY
ON ORIGINAL**

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Pharmacology summary:

The antifungal mechanism of ciclopirox differs chemically and mechanistically from other marketed antifungal agents. Ciclopirox acts by chelation of polyvalent cations (e.g., Fe^{3+} and Al^{3+}) resulting in the inhibition of metal dependent enzymes including those responsible for the degradation of peroxides within the fungal cell. In contrast, other marketed antifungal agents alter various steps on sterol biosyntheses of fungal membranes.

Ciclopirox exhibits in vitro fungicidal activity against isolates of *Trichophyton rubrum*, *T. metagrophytes*, *Epidermophyton floccosum*, *Microsporum canis*, and *Candida albicans*. Apparently ciclopirox has also demonstrated anti-inflammatory activity in various in vitro and in vivo models.

II. SAFETY PHARMACOLOGY:

Safety pharmacology summary:

An intravenous dose (5-10 mg/kg) of ciclopirox olamine (the ethanolamine salt of ciclopirox) resulted into a decrease in spontaneous behavior, irregular respiration, and a decrease in body temperature in mice and rats. No effects on blood pressure and respiration were observed in rabbits and cats receiving intravenous doses of 5 and 10 mg/kg ciclopirox olamine, respectively. In mice, subcutaneous and oral doses ranging from 40 to 80 mg/kg ciclopirox olamine did not produce any analgesic or anticonvulsive effects, or changes in the functioning of the central nervous system and hexobarbitone sleep time.

In rats, oral doses of ciclopirox olamine (40 and 100 mg/kg in 0.9% NaCl solution) caused no anti-inflammatory effect on the Aerosil edema of the paw, urine output, or biliary secretion. In dogs, an intravenous dose of 10 mg/kg of ciclopirox olamine in distilled water caused a transient hypotensive effect, decrease in heart rate, and an increase in the respiratory rate and minute volume. No effects on coagulation and hematologic parameters were noted after 12-15 daily subcutaneous or oral doses of 12.5 mg/kg ciclopirox olamine.

Safety pharmacology conclusions:

There is a concern about the potential cardiotoxicity of repeated doses of ciclopirox (refer to "General Toxicology" section below for additional details). The sponsor was informed of this concern in comments relayed to them during development of Loprox shampoo. The sponsor submitted information to address this concern to _____ on April 20, 1999. The pharmacology/toxicology reviewer, Amy Nostrandt, determined that the submitted information was adequate to address the concern about potential cardiotoxicity of repeated doses of ciclopirox for the Loprox shampoo. A brief summary of the relevant details that this decision was based on is provided below.

In a 90 day repeat oral dose toxicology study conducted in dogs, cardiotoxic effects (changes in the myocardium which included necrosis of muscle fibers) were noted at doses of 30 and 100 mg/kg/day ciclopirox. The NOAEL dose in this study was 10 mg/kg/day. ECG examinations were performed before the start of dosing, after 6 weeks of dosing and at the end of the study. No ECG changes were noted at the NOAEL dose of 10 mg/kg/day. Only negative T-waves were observed in leads I-III at doses of 30 or 100 mg/kg/day after 6 weeks and at the end of the study. This alteration may reflect a change in cardiac electrical vector secondary to pathologic changes to the heart, rather than a primary disturbance in conduction.

In clinical studies where ciclopirox cream or gel was applied repeatedly to patients with atopic dermatitis or tinea cruris, C_{max} values were as high as 237 ng/ml. In clinical studies of ciclopirox shampoo in seborrheic dermatitis patients, C_{max} values were reported to be as high as 18.0 ng/ml. The C_{max} in dogs after a dose of 10 mg/kg (NOAEL dose in 90 day study) was reported to average 3.9 µg/ml. The C_{max} obtained at the NOAEL in dogs is ~16 fold greater than the C_{max} obtained after repeated doses of ciclopirox cream or gel and ~216 fold greater than the C_{max} obtained after repeated doses of ciclopirox shampoo. It was determined that the fold exposure levels were adequate to provide an appropriate safety margin for potential cardiotoxic effects for clinical use of ciclopirox shampoo.

The submission included a statement by the sponsor that the human studies conducted to date with ciclopirox containing drug products have included pulse and blood pressure monitoring, measurement of serum enzymes indicative of myocardial damage, and 12-lead ECG and Holter monitoring. Apparently, no treatment related cardiac effects have been noted in clinical studies to date.

No additional safety pharmacology studies are recommended for Loprox shampoo at this time.

III. PHARMACOKINETICS/TOXICOKINETICS:

PK/TK summary:

In 2-week dietary toxicokinetic studies in rats and dogs, conducted at the NOAEL (10 mg/kg/day ciclopirox olamine or 7.7mg/kg/day ciclopirox; refer to "General Toxicology" section below for additional detail) identified in 3 month rat and dog repeat oral toxicology studies, the maximum serum ciclopirox levels ranged between _____ ng/ml. The serum ciclopirox levels associated with the dose at which systemic toxicity (30 mg/kg/day ciclopirox olamine) was noted in rats and dogs ranged between _____ ng/ml. The serum level of ciclopirox was below the detection limit in a 4-week rabbit dermal repeat dose study with a maximum dose of 1,000 mg/kg/day Loprox cream, 1%.

In a 5-day dog study following the oral administration of ^{14}C -ciclopirox olamine in PEG 400 at 15 mg/kg/day level, C_{max} (2-7.5 µg/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 µg/g in liver and kidneys), 0.5 µg/g in muscle, and 0.13 µg/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 the topical application of ¹⁴C ciclopirox olamine cream, 1% (2 mg/kg) to dogs, within 3 hours, 85-100% of the dose could still be wiped off the treatment site. In another dog study (2 mg/kg ¹⁴C-ciclopirox olamine in Macrogol), 5 to 15% of the topical dose was absorbed during 4 weeks of monitoring; the blood levels of drug during this period were near or below 1 ng/ml. In a similar rat study (10 mg/kg ¹⁴C-ciclopirox olamine in PEG-400), radioactivity began to appear at one hour post-application and peaked at 6 hours. Approximately 10% of the administered dose was absorbed in the rat study.

After the topical application of ¹⁴C ciclopirox olamine (in PEG-400) 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 the drug did not penetrate through the human skin in significant amounts. After 1.5 and 6 hours, 0.8 to 1.6% of the applied 0.5 ml of ¹⁴C-ciclopirox olamine cream 1% was absorbed through the excised skin from human cadaver. The epidermal concentration of drug ranged from 78 to 353 µg/cm³ after 1.5 hours. The amount decreased by half for every 250-340 µm depth of the skin.

Ciclopirox olamine is rapidly eliminated primarily in the urine in humans. Following the topical application of ¹⁴C-ciclopirox olamine cream 1%, 82% of the total radioactivity eliminated via kidney was excreted by 8 hours. The biological half-life was 1.7 hours. Approximately 96% of ciclopirox olamine was bound to human serum proteins.

Following the oral administration of 10mg of ¹⁴C-ciclopirox olamine in water to 6 healthy volunteers, about 70% of the radioactivity excreted in the urine was in the form of glucuronide conjugated ciclopirox, 15% was a different glucuronide form of ciclopirox, and 1-2% was in two forms which could have been N-deoxyciclopirox and monodehydrociclopirox.

A maximum of 3% of the administered dose of ciclopirox was absorbed in an exaggerated dose study where patients with seborrheic dermatitis of the scalp received daily application of 5 ml Loprox shampoo 1% for 28 days. The highest serum drug level in the subjects was 72-90 times lower than the serum level achieved at NOAEL of 7.7 mg/kg ciclopirox in 13-week oral studies in rats and dogs. Ciclopirox was detected in the serum of only 4/263 patients, at the projected clinical dose level. Mild erythema without infiltrate was the most commonly observed adverse effect in the clinical studies conducted with Loprox shampoo.

(This information was obtained from the submitted label for Loprox shampoo)

Two clinical pharmacokinetic studies were conducted with ciclopirox. One study used the normal regimen, in which subjects with seborrheic dermatitis of the scalp applied 5 mL LOPROX Shampoo twice per week for 4 weeks, resulting in an exposure time of 3 minutes per application. Serum levels of total ciclopirox (free and conjugated) were detectable in 6 out of 18 subjects. The maximum serum concentration was 13.2 ng/mL. The second pharmacokinetic

study was an exaggerated-use study. Subjects with seborrheic dermatitis of the scalp applied 5 mL LOPROX Shampoo daily for 4 weeks. Serum levels of total ciclopirox (free and conjugated) were detectable in 9 out of 12 subjects on Day 1, 6 out of 12 subjects on Day 15, and 11 out of 12 subjects on Day 29. Exposure to the study medication was doubled to 6 minutes from Day 16 onwards. The maximum serum concentration was \sim ng/mL, measured on Day 29.

In the pharmacokinetic study using the normal regimen, the total median amount of ciclopirox excreted in urine during the 24-hour post-administration period was 207.8 μ g (0.42% of administered dose) on Day 1, and 172.84 μ g (0.35% of administered dose) on Day 29. In the exaggerated-use study, the total median amount of ciclopirox excreted in urine during the 24-hour post-administration period was 511.9 μ g (1.02% of administered dose) on Day 1, 477.5 μ g (0.96% of administered dose) on Day 15, and 679.7 μ g (1.36% of administered dose) on Day 29. There were no statistically significant differences among the amounts of ciclopirox excreted on Days 1, 15, and 29.

In clinical studies in subjects with seborrheic dermatitis of the scalp, treated with vehicle or LOPROX Shampoo, once or twice weekly for 4 weeks, ciclopirox serum levels were detectable in 4 out of 263 subjects. Three of these subjects received LOPROX Shampoo twice per week and one received LOPROX Shampoo once per week. The serum levels ranged from below the limit of quantification --- The highest value was found in a subject in the twice-per-week group.

In subjects treated prophylactically for 3 months, ciclopirox levels were detectable in serum in 2 of 94 subjects. One value --- , in a subject who received LOPROX Shampoo twice per week for 4 weeks and then received vehicle for 3 months, was considered an artifact. The second value --- occurred in a subject who received LOPROX Shampoo once per week for 4 months.

Urinary excretion was measured at the end of 4 weeks of ciclopirox treatment and again after 3 months of prophylactic ciclopirox treatment. The median amounts of ciclopirox excreted in the urine after 4 weeks of treatment were 240 μ g (0.48% of administered dose) in subjects who received LOPROX Shampoo twice per week and 259 μ g (0.52% of administered dose) in subjects who received LOPROX Shampoo once per week. The median amounts of ciclopirox excreted in urine after 3 months of treatment were 242 μ g (0.48% of administered dose) in subjects treated once per week and 137 μ g (0.27% of administered dose) in subjects treated once every 2 weeks.

PK/TK conclusions:

No additional nonclinical pharmacokinetic studies are recommended for Loprox shampoo at this time.

IV. GENERAL TOXICOLOGY:

Acute toxicology summary:

The acute toxicity of ciclopirox olamine was determined in the mouse, rat and rabbit by various routes of administration. The oral and subcutaneous LD₅₀ ranged from 1700 – >2500 mg/kg. The intravenous LD₅₀ ranged from 71 – 79 mg/kg and the intraperitoneal LD₅₀ ranged from 83 – 172 mg/kg. Principal signs of systemic toxicity included irregular respiration and clonic convulsions. Necrosis was noted at the injection site after subcutaneous injection. The oral LD₅₀ was 445 mg/kg in neonatal rat (7 days of age). An intraperitoneal dose of 20 mg/kg to neonatal rats did not elicit any signs of systemic toxicity.

The acute toxicity of ciclopirox olamine and ciclopirox free acid were comparatively determined after oral and intraperitoneal administration to mice and rats. The oral LD₅₀ ranged from 1240 – 3200 mg/kg. The parenteral LD₅₀ ranged from 79 – 663 mg/kg. The signs of systemic toxicity were similar for both forms of the drug (irregular respiration and clonic convulsions). In general, the free acid demonstrated less acute toxicity compared to the olamine salt.

Repeat dose oral toxicology summary:

No repeat dose systemic toxicology studies have been conducted with ciclopirox. Repeat dose oral toxicology studies have been conducted with ciclopirox olamine.

Repeat dose oral toxicology studies (3 months duration) with ciclopirox olamine have been conducted in rats and dogs. Oral doses (via food) of 10, 30, 100 and 300 mg/kg/day ciclopirox olamine were administered to rats for 3 months. The NOAEL dose was identified as 10 mg/kg/day ciclopirox olamine (7.7 mg/kg/day ciclopirox). Dose related increase in myocardial degeneration was noted at doses \geq 30 mg/kg/day. Thirty percent of the animals died in the high dose group. Histological evaluation of high dose animals noted severe degenerative changes in heart, liver and lungs. In addition, necrosis of myocardial fibers resulting in parietal thrombosis, which in some cases extended to the vena cava, was noted in high dose animals.

Oral doses (via capsules) of 10, 30 and 100 mg/kg/day ciclopirox olamine were administered to dogs for 13 weeks. The NOAEL dose was identified as 10 mg/kg/day ciclopirox olamine (7.7 mg/kg/day ciclopirox). Two dogs died and two moribund dogs were sacrificed between the 7th and 10th weeks of treatment in the mid dose group. Gross necropsy results noted serous fluid in the pleural cavity, slight pulmonary edema and lobular demarcation in the liver and serous fluid in the pericardium and peritoneal cavity. None of the high dose animals survived in this study. All of the previous noted toxic effects in the lungs, liver and heart were observed in high dose animals to an increased degree of severity. In particular, necrosis of the myocardium and parenchyma of the liver was observed in high dose animals.

Repeat dose dermal toxicology summary:

No repeat dose dermal toxicology studies have been conducted with the Loprox shampoo formulation. Repeat dose dermal toxicology studies have been conducted in which the active ingredient, ciclopirox olamine, was in either the Loprox cream or Loprox gel formulation or dissolved in PEG 400.

Several repeat dose dermal toxicology studies with a duration of 3 – 4 weeks were conducted in rabbits. Various ciclopirox olamine formulations were tested in these studies including in PEG 400, the cream or gel formulations. The different formulations were applied to intact and abraded skin sites. No systemic toxicity was noted in these studies. A general dose dependent increase in dermal irritation was noted in these studies independent of the ciclopirox olamine formulation applied to the treatment site. The greatest level of dermal irritation was noted in the 3 week repeat dose study conducted with the ciclopirox olamine gel 1% (equivalent to 0.77% ciclopirox). Topical doses of 0 (untreated control), 500 mg/kg/day vehicle gel (vehicle control), 200 mg/kg/day ciclopirox olamine gel 1% and 500 mg/kg/day ciclopirox olamine gel 1% were applied to the shaved intact skin sites. A dose dependent increase in erythema, eschar formation and fissuring was noted in this study. The dermal irritation effects were noted in the vehicle treated animals but to a lesser extent than ciclopirox olamine gel 1% treated animals. In the studies conducted with 1%, 2% or 4% ciclopirox olamine dissolved in PEG 400 administered topically daily to rabbits for 3 weeks, the highest concentration induced a moderate to pronounced thickening in the region of the stratum germinativum, hyperkeratosis and inflammation of the upper layers of the coreum. The extent of dermal irritation at intact and abraded skin sites was approximately equivalent.

A preliminary pharmacokinetic study was conducted at a dose level of 500 mg/kg/day of the ciclopirox gel 0.77% applied to intact and abraded skin sites on rabbits for 4 weeks. Ciclopirox was below the level of detection (5 ng/ml) in blood samples drawn from animals with intact skin sites and 3/11 blood samples from animals with abraded skin sites contained levels of ciclopirox above the level of detection.

A 3 month repeat dose dermal toxicology study was conducted in rabbits. Daily doses of 0%, 1%, 3% and 10% ciclopirox olamine in PEG 400 (1.5 ml/animal) were applied to intact and abraded skin sites. A 4 week recovery period for mid dose animals was included in this study. No systemic toxicity was noted in this study. The extent of dermal irritation (reddening and scab formation) noted was equivalent on intact and abraded skin sites. Histological evaluation of the treatment sites demonstrated a dose dependent thickening of the epidermis with hyperkeratosis and chronic inflammation of the superficial coreum. The lesions in the mid dose group showed recovery after 4 weeks.

A 6 month repeat dose dermal toxicology study was conducted in dogs. Daily doses of 0%, 1%, 3% and 10% ciclopirox olamine in PEG 400 (exact amount not specified) were applied to intact and abraded skin sites. A 4 week recovery period for high dose animals was included in this study. No systemic toxicity was noted in this study. A dose dependent increase in dermal irritation was noted at the treatment sites. The extent of dermal irritation (ranged from slight transient erythema to marked exfoliation) was equivalent at intact and abraded treatment sites. histopathological evaluation of the treatment sites noted thickening of the stratum germinativum and parakeratosis in the mid and high dose groups. The lesions in the high dose group showed recovery after 4 weeks.

Toxicology conclusions:

The toxicology of systemically administered ciclopirox olamine was assessed in 3 month repeat dose oral toxicology studies conducted in rats and dogs. Repeat dose dermal toxicology

studies conducted with ciclopirox olamine in PEG 400 were performed in rabbits (3 months) and dogs (6 months). No repeat dose dermal toxicology studies have been conducted with the Loprox shampoo formulation. The sponsor has agreed to conduct a dermal carcinogenicity study in Tg.AC mice with the Loprox shampoo formulation. In addition to addressing the carcinogenic potential possibly associated with Loprox shampoo, this study will serve as a long term repeat dose dermal toxicology study with Loprox shampoo. Therefore, no additional nonclinical general toxicology studies are recommended for Loprox shampoo at this time.

V. GENETIC TOXICOLOGY:

Genetic toxicology summary:

A series of in vitro and in vivo genetic toxicology studies have been conducted with ciclopirox olamine and ciclopirox. Ciclopirox olamine was negative in the following in vitro genetic toxicology tests: a) Ames test (\pm S9; 0.04 – 30 μ g/plate) and b) mutagenicity in *Saccharomyces cerevisiae* assay (0.25 and 1.0 mg/ml). Ciclopirox olamine was negative in the following in vivo genetic toxicology tests: a) Mouse dominant lethal assay (500 mg/kg, single gavage dose) and b) mouse micronucleus assay (500 mg/kg, single oral dose).

Ciclopirox was negative in the following in vitro genetic toxicology tests: a) Ames test (\pm S9; 0.16 – 100 μ g/plate), b) gene mutation in HGPRT test with V79 Chinese hamster lung fibroblast cells (+S9, 1.5, 2.0, 3.0 and 4.0 μ g/ml; -S9, 0.2, 0.5, 1.0 and 1.5 μ g/ml), c) unscheduled DNA synthesis in human A549 cells (\pm S9; 0.3 – 1000 μ g/ml) and d) cell transformation assay in mouse embryo fibroblast BALB/3T3 cells (+S9, 0.04, 0.10, 0.20 and 0.40 μ g/ml; -S9, 0.01, 0.05, 0.08 and 1.0 μ g/ml). Ciclopirox was positive in an in vitro chromosomal aberration assay in V79 Chinese hamster cells (\pm S9; 0.01, 0.05, 0.1, 0.2, 0.5, 1.0 and 2.0 μ g/ml). A second in vitro chromosomal aberration assay in V79 Chinese hamster cells conducted under the same conditions but in the presence of supplemental Fe^{3+} was negative. It was proposed that the positive response noted in the in vitro chromosomal aberration assay in V79 cells without supplemental Fe^{3+} was due to the chelating properties of ciclopirox. However, only the positive result was incorporated into the label. It is recommended that the results of the second study, in the presence of supplemental Fe^{3+} , be added to the Loprox shampoo label and future updates of the Loprox line of antifungal product labels. Ciclopirox was negative for chromosomal aberrations in an in vivo Chinese hamster bone marrow cytogenetic assay (5000 mg/kg; single oral dose).

The sponsor conducted a whole-body autoradiographic study in Chinese hamsters using single oral doses of 500 and 2000 mg/kg ^{14}C -ciclopirox olamine. Radioactivity was detected in the bone marrow at both dose levels at 1, 4, and 24 hours post dose. The results of this study provided supporting data that the negative results noted in the in vivo Chinese hamster bone marrow cytogenetic assay was not due to the test article not reaching the target site (bone marrow).

The following genetic toxicology information is contained in the Loprox cream/lotion label.

The following *in vitro* and *in vivo* genotoxicity tests have been conducted with ciclopirox olamine: studies to evaluate gene mutation in the Ames *Salmonella* /Mammalian Microsome Assay (negative) and Yeast *Saccharomyces Cerevisiae* Assay (negative) and studies to evaluate chromosome aberrations *in vivo* in the Mouse Dominant Lethal Assay and in the Mouse Micronucleus Assay at 500 mg/kg (negative).

The following battery of *in vitro* genotoxicity tests were conducted with ciclopirox: a chromosome aberration assay in V79 Chinese Hamster Cells, with and without metabolic activation (positive); a gene mutation assay in the HGPRT - test with V79 Chinese Hamster Cells (negative); and a primary DNA damage assay (i.e., unscheduled DNA Synthesis Assay in A549 Human Cells (negative)). An *in vitro* Cell Transformation Assay in BALB/C3T3 Cells was negative for cell transformation. In an *in vivo* Chinese Hamster Bone Marrow Cytogenetic Assay, ciclopirox was negative for chromosome aberrations at 5000 mg/kg.

The following genetic toxicology information is contained in the Loprox gel label:

The following battery of *in vitro* genotoxicity tests was conducted with ciclopirox: evaluation of gene mutation in the Ames *Salmonella* and *E. coli* assays (negative); chromosome aberration assays in V79 Chinese hamster cells, with and without metabolic activation (positive); gene mutation assays in the HGPRT-test with V79 Chinese hamster cells (negative); and a primary DNA damage assay (i.e., unscheduled DNA synthesis assay in A549 human cells) (negative). An *in vitro* cell transformation assay in BALB/c 3T3 cells was negative for cell transformation. In an *in vivo* Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at 5000 mg/kg.

Genetic toxicology conclusions:

Adequate genetic toxicology studies have been conducted for ciclopirox. No additional genetic toxicology studies are recommended for the Loprox shampoo at this time.

Labeling recommendations:

It is recommended that the negative results noted in a second *in vitro* chromosomal aberration assay in V79 Chinese hamster cells conducted in the presence of supplemental Fe^{3+} be incorporated into the Loprox shampoo label. It is possible that the positive response noted in the *in vitro* chromosomal aberration assay conducted in V79 cells without supplemental Fe^{3+} was due to the chelating properties of ciclopirox.

VI. CARCINOGENICITY:

Carcinogenicity summary:

The non-approval letter for the initial NDA submission included a nonclinical recommendation for a phase 4 commitment to conduct either a traditional 2 year dermal carcinogenicity study or a 6 month Tg.AC mouse dermal carcinogenicity study. The sponsor submitted a new correspondence submission to the NDA on 10/24/02. The new correspondence

submission contained a proposal by the sponsor to fulfill the recommended nonclinical phase 4 commitment.

The sponsor proposed to conduct a 6 month Tg.AC mouse dermal carcinogenicity study. In addition, the sponsor requested clarification on the potential ramifications of this decision. The sponsor wanted the division to confirm that if the transgenic mouse test is positive, then they would be allowed to repeat the carcinogenicity study using the traditional 2 year study as the definitive assay prior to affecting a labeling change. If the transgenic mouse study were negative, the sponsor would like the division to consider the product negative. The sponsor's proposal basically proposes to only place potential negative dermal carcinogenicity results in the Loprox shampoo label. This is not an acceptable proposal. The following recommendations were relayed via Fax to the sponsor on 10-30-02 concerning their proposal.

- 1) It is acceptable to conduct a 6 month Tg.AC dermal mouse carcinogenicity study with the Loprox shampoo formulation. If the results of the Tg.AC dermal mouse carcinogenicity study are positive, then these positive results would be incorporated into the Loprox Shampoo label without waiting for the results of any other studies. It would be acceptable for the sponsor to conduct a second traditional 2 year dermal mouse carcinogenicity study if the results of the 6 month Tg.AC dermal mouse carcinogenicity study were positive. It would not be necessary for the sponsor to conduct another dermal carcinogenicity if the results of the 6 month Tg.AC dermal mouse carcinogenicity study were positive. Incorporation of the positive results of the 6 month Tg.AC dermal mouse carcinogenicity study into the Loprox shampoo label will fulfill the recommended Phase 4 commitment. If the sponsor should decide to conduct a traditional 2 year dermal mouse carcinogenicity study after conduct of a 6 month Tg.AC dermal mouse carcinogenicity study, then the traditional 2 year mouse dermal carcinogenicity study would not be viewed as the definitive dermal carcinogenicity study. If the results of the traditional 2 year mouse dermal carcinogenicity study were negative, this would not replace the potential positive results obtained in the 6 month Tg.AC mouse dermal carcinogenicity study. The results from both dermal carcinogenicity studies would be incorporated (potential positive results in 6 month Tg.AC mouse dermal carcinogenicity study and potential negative results in traditional 2 year mouse dermal carcinogenicity study) into the Loprox shampoo label.
- 2) If the results of the 6 month Tg.AC mouse dermal carcinogenicity study with the Loprox shampoo formulation were negative, then the label would incorporate the potential negative results of this study into the label. However, the label would not state that the carcinogenic potential of the Loprox shampoo formulation is negative. It would be more appropriate to incorporate the negative results of the 6 month Tg.AC dermal mouse carcinogenicity study into the Loprox shampoo label. This would fulfill the recommended Phase 4 commitment.
- 3) It is recommended that the protocol for the dermal carcinogenicity study (6 month Tg.AC mouse dermal carcinogenicity study or traditional 2 year mouse dermal carcinogenicity study) be submitted to the division, with appropriate results from a dose range finding study, prior to initiation of the study. The protocol for the study, along with the supporting dose range finding study, will be presented to the Exec CAC for concurrence.

The results from the Exec CAC meeting will be shared with the sponsor within a 45 day period if the dermal carcinogenicity study is submitted as a special protocol. Refer to the following guidances for additional information.

- a) Guidance for Industry – Carcinogenicity Study Protocol Submissions (May 2002)
- b) Guidance for Industry – Special Protocol Assessment (May 2002)

A 50 week inadequate dermal carcinogenicity study was conducted in female mice (n = 40/group) with ciclopirox olamine. Female mice were treated with 1% or 5% ciclopirox olamine in polyethylene glycol 400 twice weekly for 50 weeks followed by a 6-month recovery period. No tumors were observed at the treatment site, and the overall incidence of neoplasms was similar in treated and control groups.

This study was conducted about 20 years ago and does not meet the current agency standards for carcinogenicity studies¹. This study was not conducted to meet any regulatory needs. However, the results from this study have been part of the label for several Loprox (ciclopirox) formulations (refer to wording for label below). It is not clear how extensively the animals were evaluated for neoplasia in this study. This chronic study was not an adequate carcinogenicity study. The duration was too short, animals of both sexes should have been evaluated, daily treatment should have been performed, and a clinically relevant formulation should have been used. To adequately evaluate the potential dermal carcinogenic potential of ciclopirox, this study should have been performed in male and female mice with a relevant marketed Loprox formulation, with daily application of an appropriate dose range over a period approximating the animals' lifetime (2 years). Therefore, it has been determined that the results from this study are deficient and not acceptable for labeling purposes for future ciclopirox formulations.

The following carcinogenicity information is contained in the Loprox cream/lotion label.

A carcinogenicity study 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 site.

The following carcinogenicity information is contained in the Loprox gel label.

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 site.

Reviewer's comment: The wording for the inadequate dermal carcinogenicity study conducted with ciclopirox is different between the Loprox cream/lotion and Loprox gel labels. The rationale for this may be that an attempt to update the wording appears to have occurred in the Loprox gel, which is the more recent of the two labels. It will be recommended for future labels

¹ Alpermann, H.G and Schutz E. Studies on the Pharmacology and Toxicology of Ciclopirox olamine. *Arzeim-Forsch/Drug Res.* 31: 1328-1332, 1981.

of ciclopirox containing products that the results of this study be removed from the label and to insert a statement that adequate carcinogenicity evaluation has not been performed for ciclopirox. The results of a properly conducted dermal carcinogenicity study will be incorporated into future revisions of the Loprox drug product labels after completion of the study.

Carcinogenicity conclusions:

The sponsor's proposal to conduct a dermal carcinogenicity study in Tg.AC mice as a phase 4 commitment is acceptable to fulfill the division's recommendations for determining the carcinogenic potential of Loprox shampoo.

The proposed method of application of Loprox shampoo does not allow for application to skin that would be exposed to sunlight. Therefore, a study to determine the photocarcinogenic potential of Loprox shampoo is not recommended at this time.

Labeling Recommendations:

It is recommended that the reference to the _____ be removed for the Loprox shampoo label. It is recommended that a statement be inserted into the Loprox shampoo label that adequate carcinogenicity evaluation has not been performed for ciclopirox. The results of the dermal carcinogenicity study conducted in Tg.AC mice should be incorporated into a future revision of the Loprox shampoo label after completion of the study.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Reproductive and developmental toxicology summary:

A combined oral fertility and embryofetal developmental study was conducted in male and female rats with ciclopirox olamine. Oral embryofetal developmental studies were conducted in mice, rats, rabbits and monkeys with ciclopirox olamine or ciclopirox. Subcutaneous embryofetal developmental studies were conducted in mice and rats with ciclopirox olamine. Dermal embryofetal developmental studies were conducted in rats and rabbits with ciclopirox olamine dissolved in PEG 400. An oral peri- and post-natal developmental study was conducted in rats with ciclopirox olamine.

An oral fertility and embryofetal developmental study was conducted in rats. Oral (via gavage) doses of 0.2, 1 and 5 mg/kg/day ciclopirox olamine were administered in this study. Males were dosed 60 days prior to mating and females were dosed 14 days prior to mating. Dosing continued until caesarean section or parturition. Ciclopirox olamine was administered to pups at the same dose levels from day 4 to 21 days of age. No toxic effects were noted for fertility, reproductive performance, pup body weight or survival in this study. The oral NOAEL for fertility and reproductive performance was 5 mg/kg/day ciclopirox olamine (30 mg/m²/day) or 3.85 mg/kg/day ciclopirox (23 mg/m²/day) in rats.

Oral embryofetal developmental studies were conducted in mice, rats, rabbits and monkeys. Oral doses of 10, 30 and 100 mg/kg/day ciclopirox olamine were administered to pregnant female mice on gestational days 7 – 12. No maternal toxicity was noted in this study (no effect on maternal body weight gain). No effects on placental weight, number of dead and viable fetuses, fetal body weight or crown-rump length were noted in this study. No external, skeletal or visceral abnormalities were noted in this study. The oral NOAEL for embryofetal development was 100 mg/kg/day ciclopirox olamine (300 mg/m²/day) or 77 mg/kg/day ciclopirox (231 mg/m²/day) in mice in this study.

Oral doses of 3, 10 and 30 mg/kg/day ciclopirox olamine were administered to pregnant female rats on gestational days 9 – 14. No maternal toxicity was noted in this study (no effect on maternal body weight gain). No effects on placental weight, resorptions, number of dead and viable fetuses, fetal body weight or crown-rump length were noted in this study. No external, skeletal or visceral abnormalities were noted in this study. The oral NOAEL for embryofetal development was 30 mg/kg/day ciclopirox olamine (180 mg/m²/day) or 23.1 mg/kg/day ciclopirox (139 mg/m²/day) in rats in this study.

In a second oral rat embryofetal developmental study that was included in the original NDA 21-159 submission, oral doses of 20, 50 and 125 mg/kg ciclopirox were administered to pregnant female rats on gestational days 7 – 18. No maternal toxicity was noted in this study (no effect on maternal body weight gain). No effects on placental weight, resorptions, number of dead and viable fetuses, fetal body weight or crown-rump length were noted in this study. No external, skeletal or visceral abnormalities were noted in this study. The oral NOAEL for embryofetal development was 125 mg/kg/day ciclopirox (750 mg/m²/day) in rats in this study.

Oral doses of 3, 10 and 30 mg/kg/day ciclopirox olamine were administered to pregnant female rabbits on gestational days 7 – 19. No maternal toxicity or teratogenic effects were noted in this study. The oral NOAEL for embryofetal development was 30 mg/kg/day ciclopirox olamine (360 mg/m²/day) or 23.1 mg/kg/day ciclopirox (277 mg/m²/day) in rabbits in this study.

In a second oral rabbit embryofetal developmental study that was included in the original NDA 21-159 submission, oral doses of 12.5, 32 and 80 mg/kg/day ciclopirox were administered to pregnant female rabbits on gestational days 6 - 18. No maternal toxicity was noted in this study (no effect on maternal body weight gain). No effects on placental weight, resorptions, number of dead and viable fetuses, fetal body weight or crown-rump length were noted in this study. No external, skeletal or visceral abnormalities were noted in this study. The oral NOAEL for embryofetal development was 80 mg/kg/day ciclopirox (960 mg/m²/day) in rabbits in this study.

An oral dose of 50 mg/kg/day ciclopirox was administered to pregnant female monkeys on gestational days 20 – 42. No maternal toxicity or teratogenic effects were noted in this study. The oral NOAEL for embryofetal development was 50 mg/kg/day ciclopirox olamine (600 mg/m²/day) or 38.5 mg/kg/day ciclopirox (462 mg/m²/day) in monkeys in this study.

Subcutaneous doses of 1, 3 and 10 mg/kg/day ciclopirox olamine were administered to pregnant female mice on gestational days 7 – 12. No maternal toxicity was noted in this study (no

effect on maternal body weight gain). No effects on placental weight, resorptions, number of dead and viable fetuses, fetal body weight or crown-rump length were noted in this study. No external, skeletal or visceral abnormalities were noted in this study. The subcutaneous NOAEL for embryofetal development was 10 mg/kg/day ciclopirox olamine (30 mg/m²/day) or 7.7 mg/kg/day ciclopirox (23 mg/m²/day) in mice in this study.

Subcutaneous doses of 1, 3 and 10 mg/kg/day ciclopirox olamine were administered to pregnant female rats on gestational days 9 – 14. No maternal toxicity was noted in this study (no effect on maternal body weight gain). No effects on placental weight, resorptions, number of dead and viable fetuses, fetal body weight or crown-rump length were noted in this study. No external, skeletal or visceral abnormalities were noted in this study. The subcutaneous NOAEL for embryofetal development was 10 mg/kg/day ciclopirox olamine (60 mg/m²/day) or 7.7 mg/kg/day ciclopirox (46 mg/m²/day) in rats in this study.

Dermal doses of 1, 3 and 10% ciclopirox olamine in PEG 400 were administered to pregnant female rabbits on gestational days 7 – 19. No external, skeletal or visceral abnormalities were noted in this study. The high dose group (10% ciclopirox olamine) was equivalent to 100mg/kg/day ciclopirox olamine. The dermal NOAEL for embryofetal development was 100 mg/kg/day ciclopirox olamine (1200 mg/m²/day) or 77 mg/kg/day ciclopirox (924 mg/m²/day) in rabbits in this study.

Dermal doses of 1, 3 and 10% ciclopirox olamine in PEG 400 were administered to pregnant rats on gestational days 7 – 16. No differences in fetal death rate were noted in this study. No external, skeletal or visceral abnormalities were noted in this study. The high dose group (10% ciclopirox) was equivalent to 120 mg/kg/day ciclopirox olamine. The dermal NOAEL for embryofetal development was 120 mg/kg/day ciclopirox olamine (720 mg/m²/day) or 92.4 mg/kg/day ciclopirox (554 mg/m²/day) in rats in this study.

An oral peri- and post-natal developmental study was conducted in rats. Oral (via gavage) doses of 0.2, 1 and 5 mg/kg/day ciclopirox olamine were administered in this study. Doses were administered from day 15 of gestation through lactation to weaning. No toxic effects on fetal or maternal parameters were noted in this study. It is unclear what level of developmental measures were obtained in this oral peri- and post-natal developmental study. Therefore, an oral NOAEL for peri- and post-natal developmental effects can not be established for ciclopirox olamine in rats based on the results of this study.

The following reproductive and developmental toxicology information is contained in the Loprox cream/lotion label. Loprox cream/lotion is designated as a Pregnancy category B drug.

Reproduction studies have been performed in the mouse, rat, rabbit, and monkey, (via various routes of administration) at doses 10 times or more the topical human dose and have revealed no significant evidence of impaired fertility or harm to the fetus due to ciclopirox. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

The following reproductive and developmental toxicology information is contained in the Loprox gel label. Loprox gel is designated as a Pregnancy category B drug.

Reproduction studies of ciclopirox revealed no significant evidence of impaired fertility in rats exposed orally up to 5 mg/kg body weight (approximately 5 times the maximum recommended topical human dose based on surface area). No fetotoxicity was shown due to ciclopirox in the mouse, rat, rabbit, and monkey at oral doses up to 100, 30, 30, and 50 mg/kg body weight, respectively (approximately 37.5, 30, 44, and 77 times the maximum recommended topical human dose based on surface area). By the dermal route of administration, no fetotoxicity was shown due to ciclopirox in the rat and rabbit at doses up to 120 and 100 mg/kg body weight, respectively (approximately 121 and 147 times, respectively, the maximum recommended topical human dose based on surface area).

Reviewer's comment: The wording for the reproductive and developmental toxicology section of the label is different between the Loprox cream/lotion and Loprox gel labels. The rationale for this may be that an attempt to update the wording appears to have occurred in the Loprox gel label, which is the more recent of the two labels.

Reproductive and developmental toxicology conclusions:

Nonclinical reproductive and developmental toxicology studies have been conducted with ciclopirox olamine or ciclopirox. It would have been preferable if the nonclinical reproductive and developmental toxicology studies had been conducted with a high dose that generated some degree of maternal toxicity. None of the nonclinical reproductive and developmental toxicology studies conducted with ciclopirox olamine or ciclopirox demonstrated any maternal toxicity. Under current standards, these studies may have been interpreted as inadequate. However, since the drug product is applied topically with very limited systemic absorption, it is adequate to use the results of these studies for labeling purposes. However, if an oral formulation of ciclopirox were to be developed, then it would probably be recommended to conduct nonclinical reproductive and developmental toxicology studies according to ICH guidelines incorporating a high dose group that elicits maternal toxicity.

It would have been preferable if the dermal embryofetal development studies could have been conducted with one of the marketed Loprox formulations instead of with ciclopirox olamine dissolved in PEG 400. However, it is not necessary to recommend that a dermal embryofetal developmental study be repeated using one of the marketed Loprox formulations since the oral embryofetal developmental studies did not demonstrate any potential signal for teratogenicity.

It is unclear what developmental parameters were evaluated in the oral peri- and post-natal developmental study conducted in rats with ciclopirox olamine. Therefore, it is not possible to determine if this was an adequate study or not. It is not necessary to recommend that this study be repeated at this time since limited systemic exposure is anticipated after labeled use of the Loprox shampoo formulation. However, if an oral formatuion of ciclopirox were to be developed, then it would probably be recommended to repeat this study according to ICH guidelines.

No additional nonclinical reproductive and developmental toxicology studies are recommended for Loprox shampoo at this time.

Labeling recommendations:

Pregnancy Category B would be appropriate for Loprox shampoo based on the results of the oral reproductive and developmental toxicology studies conducted with ciclopirox olamine or ciclopirox.

VIII. SPECIAL TOXICOLOGY STUDIES:

Special Toxicology Summary:

Nonclinical dermal irritation studies were conducted in rabbits (applied to intact and abraded skin sites) with Loprox nail lacquer, Loprox cream and Loprox shampoo. None of the tested Loprox formulations were considered primary dermal irritants in rabbits.

Nonclinical ocular irritation studies were conducted in rabbits with several Loprox formulations. Ciclopirox 1% dissolved in PEG 400 caused slight ocular irritation at 2 and 24 hours. Ciclopirox 1% dissolved in sterile water caused slight lacrimation and irritation at the 1 hour timepoint only. Ciclopirox powder (100 mg) caused severe ocular irritation. Loprox cream 1% (100 mg) did not cause any ocular irritation. Loprox nail lacquer 8% caused ocular irritation that was observed up to 72 hours after administration. Loprox shampoo 1% was a severe ocular irritant but did not cause any ocular irritation when administered as a 10:1 dilution.

Ciclopirox olamine (1% in PEG 400) applied to intact skin of mice followed by UVA irradiation was not phototoxic. It would have been preferable to conduct the nonclinical phototoxicity test with a marketed Loprox formulation. In addition, it would have been preferable to conduct the nonclinical phototoxicity test under solar simulated light conditions (UVB/UVA/Vis spectrum). However, it has not recommended that another nonclinical phototoxicity study be performed with a marketed Loprox formulation due to the extensive human exposure data obtained for currently marketed Loprox formulations.

The following information was included in the Loprox shampoo label included in this submission

Special Toxicology Conclusions:

Special toxicology studies have been conducted with several Loprox formulations. Additional special toxicology studies are not recommended for Loprox shampoo at this time.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

Based on the nonclinical data available for ciclopirox olamine and ciclopirox, my recommendation for NDA 21-159 is that it is approvable from a pharmacology/toxicology perspective provided that the recommended changes in the label discussed in the Labeling section below are incorporated into the label.

General Toxicology Issues:

Outstanding general toxicology issues for Loprox shampoo include the following:

- 1) The sponsor has agreed to conduct a dermal carcinogenicity study in Tg.AC mice as a Phase 4 commitment.

Recommendations:

The following wording is recommended for the potential approval letter for Loprox shampoo concerning the nonclinical phase 4 commitment.

1. The applicant commits to conducting an alternative, dermal carcinogenicity study in transgenic mice _____ with the ciclopirox shampoo, 1%.

Protocol submission: Within 4 months of the date of this letter

Study Start: Within 6 months of the date of the approval of the protocol

Final Report Submission: Within 12 months after the study completion

Labeling with basis for findings:

The entire electronic version of the Loprox[®] shampoo label submitted to the NDA is inserted below. Comments about the portions that relate to nonclinical pharmacology/toxicology will be inserted directly in the appropriate sections. Recommended sections to be deleted are marked by ~~strikeout~~. Recommended sections to be added are marked by [REDACTED] Reviewer's comments in support of recommended labeling changes are provided in *italics*.

↑
DRAFT LABELING
↓

Number of Pages
Redacted 6



Draft Labeling
(not releasable)

**APPEARS THIS WAY
ON ORIGINAL**

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this page is the manifestation of the electronic signature.**

/s/

Barbara Hill
1/7/03 09:19:19 AM
PHARMACOLOGIST

Abby Jacobs
1/7/03 09:49:27 AM
PHARMACOLOGIST

**APPEARS THIS WAY
ON ORIGINAL**

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: 04-26-000

APR 27 2000

Electronic File Number:

NDA 21-159

000/09-01-1999/original application

Information to sponsor: Yes (X)

Sponsor: Medicis Pharmaceutical Corporation

4343 East Camelback Road

Phoenix, AZ 85018-2700

Manufacturer: Patheon Inc.

Syntex Court Operations

2100 Syntex Court, Mississauga, Ontario L5N 7K9

Drug: Code Name HOE 296b

Generic Name: Ciclopirox

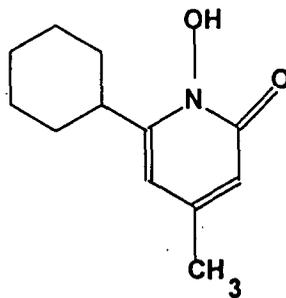
Trade Name: LOPROX^R (ciclopirox) Shampoo 1%

Chemical Name: 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridinone

CAS Registry Number: 29342-05-0

Molecular Formula/Molecular Weight: C₁₂H₁₇NO₂/ —

Structure:



Relevant INDs/NDAs:

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)

NDA 21-022 Loprox (ciclopirox) Nail Lacquer 8% (approved 12-17-1999)

Drug Class: Antifungal

Indication: For the topical treatment of seborrheic dermatitis of the scalp

Clinical formulation (and components):

Components	Function	mg/g shampoo
Ciclopirox	active ingredient	10.0
Sodium chloride	thickening agent	
Purified water	solvent	

*Sodium laureth sulfate

Route of administration: Topical

Disclaimer: The information submitted by the sponsor is utilized to prepare this review.

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. Primarily, the lack of energy deprives the cell of nutrients because of poor uptake. The secondary mechanism involves the intracellular depletion of nucleotides and essential amino acids leading to reduced synthesis of nucleic acids and protein. An *in vitro* study had also indicated that ciclopirox olamine modified the plasma membrane of dermatophytes and *Candida albicans*. An *in vivo* electron microscopy study, it was revealed that ciclopirox caused disorganization of internal substructures and gross damage to the cell membranes. The compound also appeared to inhibit adherence of *Candida albicans* to human buccal cavity and vaginal cells. Ciclopirox also inhibits the activities of catalase and peroxidase, which are responsible for the degradation of toxic peroxides in the fungal cell. According to the sponsor, because of ciclopirox's complex mechanism of action, it is less likely that fungal cell will develop any significant resistance against this compound.

Proposed Clinical Use: It is proposed that during the initial period of treatment, about 5 mL of shampoo should be applied to the entire surface of the skull, once or twice/week for four weeks. After four minutes of exposure, the shampoo should be washed off with

the warm water.

Subjects with shoulder length hair may use 10 mL shampoo.

Previous clinical experience: Ciclopirox shampoo has been evaluated for its safety and efficacy in four phase I, four phase II, and two phase III studies. In these European studies over 2400 subjects were treated. Among these, 3% of drug and 2% of vehicle treated individuals exhibited some treatment related adverse effects including pruritis, rash, and hair disorders.

Introduction and drug history: Two ciclopirox formulations Loprox Cream 1% and Loprox Lotion 1% are currently marketed in the United States. Ciclopirox Nail Lacquer 8% is marketed in several European, Latin American, Asian, and African countries, and New Zealand, and has been recently approved for the U.S. market.

The following new (reproductive and developmental toxicology) studies were included in this submission. All other studies listed by the sponsor have been reviewed under the previous submissions.

1. **HOE 296b: Study for effects on embryo-fetal development after oral administration in Wistar rats** (study # 96.0077; Vol. 1.4, pp 151-428; February-March 1996).
2. **HOE 296b: Study for effects on embryo-fetal development after oral administration in Himalayan Rabbits** (Study # 96.0034; Vol. 1.5, pp 1-203; February-March 1996).

Facility: Hoechst AG

Hoechst Marion Russel
Preclinical Development Drug Safety
65926 Frankfurt am Main
Germany

GLP/ICH guidelines: The reports included signed GLP compliance statement. The studies were conducted according to ICH 4.1.3.

Drug batch number: 000 L054

The sponsor did not submit protocols for these studies for pre-approval.

MATERIALS AND METHODS

Animals: Twenty 8-10 weeks old mated female rats (avg. bw.220g)/group
Twenty 6-10 months old mated female rabbits (2.732-2.762Kg)/group

Dosages: Each daily gavage dose of ciclopirox (mg/Kg) was prepared as

water). **Rats:** 5mL vehicle/Kgbw, or 20, 50, 125 mg of ciclopirox/Kgbw

Rabbits: 5mL vehicle/Kg, or 12.5, 32.0, 80 mg of ciclopirox/Kgbw

Interval of dosing: Pregnancy days 7-18 and 6-18 in rats and rabbits, respectively.

Parameters and endpoints evaluated

Clinical observations: Daily

Food consumption: Rats: on pregnancy days 1, 7, 14, 19 and 21 Rabbits: on pregnancy days 6, 13, 19, and 29.

Body weights: Twice weekly

Blood collection for toxicokinetic studies: Rats: Samples from 2 females/drug group at 0.5, 1, 4, 7 and 24 hr. were collected after the 1st and 8th dose, and from 5 control animals on pregnancy days 7 and 14. Rabbits: Samples from 2 females/dose group were collected at 0.5, 1, 2, 4, 6, and 24 hr. after the 11th dose, and from 5 controls after the 1st and 11th dose of vehicle. At all collection points, samples were collected from the same animals. The drug level in each serum sample was determined in two ways, before and after deconjugation (i.e., total amount of ciclopirox) with *E. coli* glucuronidase.

Cesarean sections: The surviving rats and rabbits killed on pregnancy days 21 and 29, respectively, were delivered by cesarean section and examined for their uterine content. The placentas and corpora lutea in the ovaries were counted and examined macroscopically.

Examination of fetuses: Fetuses removed from the uterus were examined for survival, skeletal abnormalities, and visceral anomalies.

Autopsy of dams: Following the cesarean section, the dams were dissected and their organs were macroscopically examined.

Statistical treatment of data: Univariate analysis was made for relative food consumption, maternal body weight, crown-rump length. One-sided Wilcoxon test was employed for number of implants, corpora lutea, number of dead fetuses, conceptuses undergoing resorption, and 24 hours survival rate of fetuses. Fisher test was used to determine the relative frequencies of other findings (e.g., number of fetuses/liter) in drug groups compared to the control group.

RESULTS

Clinical observations and Mortality

Rats: One female in the mid-dose group died after the third dose on pregnancy day 9 without exhibiting any sign of toxicity. Rabbits: One high-dose female died on day 6 after the first dose; another female of this group exhibited sign of abortion (red-discoloration of urine) on day 19, and was subsequently killed. One mid-dose female after delivering prematurely died on day 22.

Food composition and Body weights

Rats: A slight decrease (7-9%) in food consumption in the mid- and high-dose females on days 7 to 19 was not associated with any change in body weights. No inter-group differences in either of the parameters were observed at the end of the treatment period.

Rabbits: No inter-group differences were observed.

Toxicokinetics: Because the data in the table below were obtained from a small number of animals, no statistical treatment of this data was possible. With the exception of mid-dose rats, the peak concentrations of total ciclopirox (conjugated+unconjugated) in both species were achieved at 0.5 hour post-dose. The drug levels at two determination points were not significantly different in either of the species. Compared to the total, the amount of free (unconjugated) drug in both species was considerably lower, indicating that ciclopirox-glucuronide was the major drug related compound present in the maternal serum. In rat, the elimination was not distinctly monoexponential. However, because of insufficient data, $T_{1/2}$ in this species was not calculated. The $T_{1/2}$ in rabbit ranged from 2.6 to 5.7 hours. Once again, because of lack of data, $T_{1/2}$ and AUC for the free drug in rabbit were not calculated. In most cases, the serum level of free drug was below the detection limit of 0.1 $\mu\text{g}/\text{mL}$. In both the species, C_{max} and AUC increased with the dose. Whereas, the increase in C_{max} was less than proportional, the increase in AUC was virtually linear.

Pharmacokinetic parameters in pregnant rats after the 1st dose

Parameter	Total			Free		
	LD	MD	HD	LD	MD	HD
$C_{\text{max}}(\mu\text{g}/\text{mL})$	11.2	23.6	46.5	0.7	2.7	8.4
$T_{\text{max}}(\text{h})$	0.5	1.0	0.5	0.5	1.0	0.5
$\text{AUC}(0-24\text{h})(\mu\text{g}\cdot\text{h}/\text{mL})$	32.5	92.5	219.6	nc	7.4	20.6

After the 8th dose

C_{max}	8.9	23.2	34.2	0.6	2.2	8.8
T_{max}	0.5	0.5	0.5	0.5	0.5	0.5
AUC	32.1	75.1	225.9	2.9	5.4	21.2

Pharmacokinetic parameters in pregnant rabbits after the 1st dose

$C_{\text{max}}(\mu\text{g}/\text{mL})$	5.7	11.4	23.7	<0.1	nc	0.3
$T_{\text{max}}(\text{h})$	0.5	0.5	0.5	nd	nd	0.5
$T_{1/2}(\text{hr.})$	5.7	3.6	2.6	nc	nc	nc
$\text{AUC}(0-24\text{h})(\mu\text{g}\cdot\text{h}/\text{mL})$	12.6	24.2	70.0	nc	nc	0.5

After the 11th dose

C_{max}	5.5	13.0	26.0	<0.1	0.2	0.4
T_{max}	0.5	0.5	0.5	nd	0.5	0.5
$T_{1/2}(\text{hr.})$	5.4	5.2	2.7	nc	nc	nc
AUC	10.9	18.8	59.9	nc	nc	0.6

nc= not calculated because of lack of data; nd= not determined

Terminal and Necroscopic evaluations:

Rats: No maternal deaths occurred during the study period. Rate of pregnancy was not affected by the drug treatment. The slightly reduced (7-9%) food intake in the mid- and high-dose dams not associated with any corresponding changes in the body weights simply reflected borderline toxicity at 50 mg/Kg (300 mg/m²) and the higher dose levels. No macroscopic lesions were observed in the mid- and high-dose dams. In the high dose group, the renal pelvis was dilated in two dams. There were no drug or dose-related changes in the values for corpora lutea, implantations, pre- and post implantation losses, total intrauterine deaths, live fetuses, sex ratio, fetal body weights, crown to rump length, and placental weights.

Rabbits: Because of autolysis, the internal organs of one high-dose animal died after the first dose could not be examined. Nineteen high-dose females became pregnant, the rate of pregnancy in other groups was 100%. One mid-dose female aborted between days 21 and 22 after mating. In this rabbit, 5 stunted dead fetuses and one empty implantation site in the uterus were found. One high-dose female aborted on Day 19. This animal had 7 conceptuses undergoing resorption. In both dams, two blood vessels and the surrounding fatty tissue between the spleen and stomach were markedly red colored; the mucosa in the stomach was also damaged and furrowed.

When compared to the control, no effects of drug or dose were observed in the values for uterus weights, corpora lutea, implantations, pre- and post-implantation losses, late and total intrauterine deaths, live fetuses, body weights of fetuses, number of male fetuses, crown to rump length, 24 hour survival rate of fetuses, and the placental weights.

Offsprings:

Rats: None of the live fetuses were retarded. No particular drug-induced malformations were observed. A few visceral defects such as hematoma or blood in the brain, thoracic or abdominal cavity, in the liver, or on the kidney, throat or hind limb, were considered as minor sporadically distributed abnormalities found in all the groups. Minor skeletal defects such as splitting at the interperital bone, fused vertebral arches, shortened 13th rib, bent or shortened scapula etc. were found in the individual fetuses of all the treatment groups.

Rabbits: A normal development was observed in all the live fetuses. In the mid-dose group, two fetuses from the same litter exhibited a cleft palate, scoliosis, dysplasia of the 1st or 2nd to the 7th rib bilaterally, and deflected forepaws. The live fetuses in the drug groups were almost at the same stage of skeletal development as the control fetuses. In a large number of fetuses from the drug groups, the sternbrae were not completely ossified, and in numerous fetuses in the low- and mid-dose groups, less than 13 caudal

vertebral centra were ossified. Since the degree of ossification in the high-dose fetuses was comparatively high, a dose-response was not established. In addition, according to the study author, all the observed abnormalities were within the range of historical control data archived in the sponsor's testing facility.

Conclusion: Under the assay conditions, ciclopirox did not exhibit any teratogenic activity.

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

The oral and parenteral LD₅₀s 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 LD₅₀ 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).

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/m²) for 4 weeks, only 3/11 blood samples drawn from the abraded rabbits contained levels of ciclopirox above the detection limit (5 ng/mL). 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 (7.7 mg ciclopirox/Kg/day) in both the 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 extended 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, conducted at NOEL, the maximum serum drug levels ranged between _____ 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 _____ In a 5-day dog study following the oral administration of ^{14}C ciclopirox olamine at 15mg/kg/day level, C_{max} (2-7.5 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 the topical application of ^{14}C ciclopirox (2 mg/Kg) to dogs, within 3 hours, 85-100% of the dose could still be wiped off.

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. According to the current standards, this carcinogenicity study conducted about two decades ago would be considered deficient and unacceptable. However, the same study has been the part of the label for several approved formulations of ciclopirox/ciclopirox olamine since 1982. The previous reviewer for the current NDA (Dr. Nostrandt) while withdrawing the request for an additional dog study to re-evaluate cardiotoxicity, had requested a phase IV dermal carcinogenicity study.

_____ instead, the sponsor has used DEREK_s computer program to evaluate structure-activity relationship of ciclopirox to determine its carcinogenic potential. It is reported that the test did not reveal any carcinogenic hazards. Currently, there is no provision in the label to include findings of such tests. Therefore, once again, the sponsor should be encouraged to conduct a phase IV dermal carcinogenicity study, or at least a short-term study using transgenic (TG.AC) mouse model. However, for the current submission, at this stage, the findings of the same carcinogenicity study in the label should be permitted.

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, ciclopirox was nonmutagenic. In a whole-body autoradiographic 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 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 one *in vitro* (*Saccharomyces cerevisiae*) assay.

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/m²/day). Teratology studies in mice, rats, rabbits and monkeys conducted at oral doses of up to 100, 125, 80, or 50 mg/Kg/day (300,750, 960, or 1000 mg/m²/day), respectively, or in rats and rabbits receiving topical doses of 120 and 100mg/Kg/day (720 and 1,200mg/m²/day) produced no significant fetal malformations.

After the topical application of ¹⁴C ciclopirox olamine (in PEG) 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. A maximum of 3% of the administered dose of ciclopirox was absorbed in an exaggerated dose study where patients with seborrheic dermatitis of the scalp received daily application of 5 mL Loprox Shampoo 1% for 28 days. The highest serum drug level in the subjects was 72-90 times lower than achieved at NOEL of 7.7 mg ciclopirox/Kg in 13-week oral studies in rats and dogs. At the proposed dose level, ciclopirox was detected in the serum of only 4/263 patients. Mild erythema without infiltrate was the most commonly observed adverse effect in the clinical studies. This effect was not directly related to the drug action. During the proposed 4 weeks of treatment, each subject will receive a maximum cumulative dose of 13 mg ciclopirox/Kg (481mg/m²). The cumulative dose in the exaggerated dose study was 23 mg/Kg (851 mg/m²). The proposed maximum daily dose of 1.7 mg/Kg (63 mg/m²) is 0.7 to 2.4 times lower than the oral NOEL in rats and dogs. In humans, about 98% of the administered drug is excreted through the kidneys, most of it rapidly (~4 hours). The safety factors such as low absorption, rapid elimination, and washout only after a short exposure of four minutes, put together, project a comfortable margin of safety for Loprox Shampoo 1%.

In the local tolerance studies, ciclopirox shampoo tested as an ocular irritant in rabbit, but did not produce any dermal lesions in the same species. In an *in vitro* assay using excised pig skin, 1% shampoo exhibited a dose-dependent effect (24-63% as compared to vehicle control) on the viability of *Pityrosporum ovale*. In a similar test, ciclopirox rapidly penetrated into the stratum corneum in a dose-dependent fashion.

A number of animal studies were conducted with sodium laureth sulfate, a major anionic surfactant in the shampoo formulation. This compound with LD₅₀ greater than 2,000 mg/Kg, was found to be an ocular and dermal irritant (rats), nonmutagenic in Ames test, and a nonsensitizer in a maximization test in guinea pig. Exactly similar observations were made in case of thickening agent

LABELING: The draft submitted by the sponsor has been extensively modified.

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 one *in vivo* Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at 5,000 mg/Kg.

Pregnancy:

Teratogenic effects: Pregnancy Category B

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There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women.

Regulatory conclusion: I have no objection to the approval of this new drug application, provided the sponsor agrees to make the essential changes in the label.

Regulatory Recommendation: The sponsor should be encouraged to conduct either a regular phase IV dermal carcinogenicity study, or a short-term study using the transgenic (TG.AC) mouse model.

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

04/26/00

Original NDA 21159
HFD-82
HFD-502
MO/Huene
Pharm/Mainigi
Chem/Gautam-Basak
PM/Lutvak

Concurrence:

A. Jacobs, TL/HFD-540 *a.j. 4/20/00 INDFS*
J. Wilkin, Dir./HFD-540

qw 4/22/00 DFS