CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-071

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-071**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**September 9, 2006**
PRODUCT:	**Lamisil (terbinafine HCl) minitablets**
INTENDED CLINICAL POPULATION:	**Tinea Capitis**
SPONSOR:	**Novartis Pharmaceuticals Corporation**
DOCUMENTS REVIEWED:	**Electronic CTD NDA submission**
REVIEW DIVISION:	**Division of Dermatology and Dental Products (HFD-540)**
PHARM/TOX REVIEWER:	**Barbara Hill, Ph.D.**
PHARM/TOX SUPERVISOR:	**Paul Brown, Ph.D.**
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Date of review submission to Division File System (DFS): 4-11-07

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability – The Lamisil minitablets NDA is approvable from a pharmacological/toxicological perspective.

B. Recommendation for nonclinical studies – None

C. Recommendations on labeling – Recommended wording for the nonclinical portions of the label are provided in the "Suggested Labeling" section located at the end of this review.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings – The primary target organs of toxicity identified for terbinafine in chronic nonclinical oral toxicology studies include the liver and kidney in rats, liver in dogs and retina (refractile bodies noted in the retina) in monkeys. A 52 week oral juvenile dog toxicology study was conducted with terbinafine to support the primarily pediatric tinea capitis indication. Three single episodes of clonic convulsive activity were noted in high dose female dogs in this study during weeks 2, 6 and 17. No additional episodes of clonic convulsive activity were noted in high dose female dogs from weeks 18 – 52 of this study. No treatment related histopathological effects were noted in the brain to correlate with the convulsive like activities. However, it is recommended that this toxicity be included in the Lamisil minitablet label.

Terbinafine is designated as pregnancy category B. Terbinafine was non-genotoxic when evaluated in a battery of in vitro and in vivo genetic toxicology studies. An increase in the incidence of liver tumors was noted in high dose males in an oral rat carcinogenicity study conducted with terbinafine. No increase in tumor incidence was noted in an oral mouse carcinogenicity study conducted with terbinafine.

B. Pharmacologic activity – Antifungal

C. Nonclinical safety issues relevant to clinical use – None at this time

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2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

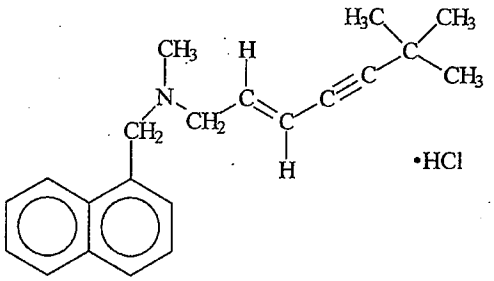
NDA number: 22-071
Review number: 1
Sequence number/date/type of submission: 000 / 9-8-06 / Original NDA submission
000 BL / 3-13-07 / Revised draft label
Information to sponsor: No
Sponsor and/or agent: Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Manufacturer for drug substance: Novartis Pharmaceuticals Corporation

Reviewer name: Barbara Hill
Division name: Dermatologic and Dental Drug Products
HFD #: HFD-540
Review completion date: 3-27-07

Drug:

Trade name: Lamisil minitablets
Generic name: Terbinafine HCl
Code name: SF 86-327
Chemical name: 1-Naphthalenemethanamine, N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-, (E)-, monohydrochloride
CAS registry number: 78628-80-5
Molecular formula/molecular weight: $C_{21}H_{25}N{\bullet}HCl$ / 327.9
Structure:



Relevant INDs/NDAs/DMFs:

1) IND 28,093 (Lamisil tablets {Terbinafine hydrochloride; 250 mg tablet}; Onychomycosis; HFD-540)
2) [redacted] b(4)
3) IND 57,093 (Lamisil minitablets {Terbinafine hydrochloride; 4.6875 mg minitablet}; Tinea Capitis; HFD-540)
4) NDA 20-539 (Lamisil tablets {Terbinafine hydrochloride; 250 mg tablet}; Onychomycosis; HFD-540; approved 5/10/96)

Drug class: Antifungal

Intended clinical population: Tinea Capitis

Clinical formulation:

The composition of the film-coated Lamisil minitablet is provided in the following table. Each individual minitablet contains 4.6875 mg of terbinafine hydrochloride, corresponding to 4.167 mg of terbinafine base.

Ingredient	mg/minitablet
Core	
Terbinafine hydrochloride	[redacted]
Sodium starch glycolate, NF	[redacted]
Microcrystalline cellulose, NF	[redacted]
Hydroxypropyl methylcellulose, USP	[redacted]
Colloidal silicon dioxide, NF	[redacted]
Magnesium stearate, NF	[redacted]
[redacted]	[redacted]
[redacted], USP	[redacted]
Colloidal silicon dioxide, NF	[redacted]
Polyethylene glycol, NF	[redacted]
[redacted]	[redacted]
Basic butylated methacrylate copolymer [redacted] Ph. Eur.[b]	[redacted]
Magnesium stearate, NF	[redacted]
Dibutyl sebacate, NF	[redacted]
Sodium lauryl sulfate, NF	[redacted]
Colloidal silicon dioxide, NF	[redacted]
Total minitablet weight	[redacted]

b(4)

a – Corresponds to 4.167 mg terbinafine base for each minitablet
b – [redacted], has confirmed that these products b(4)

only differ in particle size and their chemical composition is identical. ——— and ——— b(4)

——— This excipient is not listed in the USP/NF, but a monograph for it is included in the *European Pharmacopeia* as "basic butylated methacrylate copolymer." The sponsor states that this excipient will meet the requirements of the *European Pharmacopeia.* The FDA Inactive Ingredient Database indicates that ——— has been used in seven approved oral tablets or capsules. No additional nonclinical toxicology studies were recommended to support the use of this excipient in the Lamisil minitablet formulation. b(4)

For clinical studies, Lamisil minitablets were packaged in glass bottles. For marketing, Lamisil minitablets will be supplied in cartons containing 14 laminated aluminum ——— Each ——— contains approximately 30 or 45 off-white to yellowish, round, biconvex, film-coated tablets, corresponding to single total doses of 125 mg or 187.5 mg (terbinafine base equivalent) per ——— The film-coated mini-tablets are off-white to yellowish, round, biconvex tablets, each having a diameter of approximately 2.1 mm. Each individual mini-tablet contains 4.6875 mg of terbinafine hydrochloride, corresponding to 4.167 mg of terbinafine base. b(4)

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Background:

The sponsor has developed a pediatric formulation of terbinafine HCl (Lamisil minitablets) for the oral treatment of tinea capitis. The sponsor developed an oral terbinafine formulation (Lamisil tablets) for the treatment of onychomycosis and has developed various topical terbinafine formulations (Lamisil cream, Lamisil solution and Lamisil emulsion gel) for treatment of various antifungal indications.

A final Pediatric Written Request (PWR) was faxed to the sponsor on May 15, 2006. The final PWR requested that a clinical pediatric pharmacokinetic study be performed with the pediatric formulation and two Phase 3 pediatric clinical studies be conducted to evaluate the clinical safety and efficacy of the pediatric formulation for the treatment of tinea capitis. In addition, the final PWR contained a recommendation for conduct of the following nonclinical toxicology study under the "Additional information required" subheading.

"It is recommended that a juvenile animal study, covering the period of maturation in a nonrodent species, be conducted at doses up to a maximum tolerated dose (MTD). The species selected should be the species that best expresses the toxicities already seen in humans and which has metabolism most similar to humans.

A study in monkeys would be desirable because the monkeys exhibited the ocular effects, but the sponsor could propose a rationale for a study in dogs.

These studies will reveal possible rare events that may occur in maturing animals and are required because tinea capitis is non-life threatening condition. This study is recommended to

support the use of terbinafine in the pediatric tinea capitis population and is recommended for inclusion with the NDA submission."

The sponsor submitted the first version of the nonclinical oral juvenile animal toxicology study protocol titled "A 52-week oral (gavage) toxicity study in juvenile dogs with a 4 week recovery period" to the IND on July 14, 2003 (Serial #031). It was determined that it was acceptable to perform this study in dogs instead of monkeys due to the long period of time (~42 months; from 6 months old to 48 months old) that would be needed for treatment in monkeys to cover the corresponding child to adolescent age range in humans. It was recommended that the sponsor conduct a dose range finding study in juvenile dogs to support the proposed dose range for the 52 week study in juvenile dogs. The rest of the protocol for this study appeared adequate.

The sponsor submitted the second version of the nonclinical oral juvenile dog toxicology study protocol to the IND on August 27, 2004 (Serial #051) with a final study report for the recommended dose range finding study in juvenile dogs. It was determined that the proposed dose range (0, 10, 30 and 100 mg/kg/day terbinafine), the treatment duration and the proposed toxicity parameters for the 52 week oral toxicity study in juvenile dogs were adequate. This information was relayed to the sponsor via fax on October 8, 2004.

A pre-NDA meeting was conducted with the sponsor on October 24, 2005. The sponsor was informed during the pre-NDA meeting that submission of the final study report for the 52 week oral juvenile dog toxicology study with the NDA submission is acceptable and the adequacy of this study will be determined after review of the final study report. A final study report for a nonclinical toxicology study titled "A 52-week oral (capsule) toxicity study in maturing dogs with a 4-week recovery period" was included in the NDA submission. The FDA Pediatric Exclusivity Board determined that this submission met the requirements stated in the PWR and granted exclusivity on December 4, 2006. The Pediatric Exclusivity Board made the following recommendation for Lamisil minitablets based on evaluation of the submitted information.

"Since this submission triggers the Pediatric Research Equity Act, it was recommended that the review division require additional safety studies at the time they approve the submission to further refine the ophthalmologic safety database which will be tracked as a required postmarketing commitment. Requiring the studies after approval for pediatric use is also consistent with agency practice in instances where the risk is theoretical, and the available safety database, while not perfect, is deemed adequate and does not support a signal of a safety concern."

The sponsor submitted this NDA as an electronic CTD NDA submission for Lamisil minitablets that included labeling in the new PLR format.

Studies reviewed within this submission:

1) A 52-week oral (capsule) toxicity study in maturing dogs with a 4-week recovery period (Study No. 0470001)

Studies not reviewed within this submission: N/A

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Terbinafine hydrochloride is a synthetic allylamine antifungal compound. Terbinafine hydrochloride is hypothesized to act by inhibiting squalene epoxidase, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. In addition, the transformation of squalene to squalene epoxide is inhibited causing an accumulation of squalene in the fungal cell. The accumulation of squalene that occurs in the cell may cause the cell to rupture.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Refer to brief summary

Drug activity related to proposed indication: Refer to brief summary

2.6.2.3 Secondary pharmacodynamics – N/A

2.6.2.4 Safety pharmacology

Safety pharmacology studies conducted with terbinafine indicate that terbinafine has the potential to elicit cardiac effects. In vivo studies conducted in dogs by Novartis indicate that an iv bolus of 10 mg/kg but not 2 mg/kg terbinafine can cause a transient decrease in arterial blood pressure, arterial blood flow and cardiac output. This effect was not seen in cats, but the pharmacokinetics of terbinafine in cats has not been supplied. An in vitro study conducted in isolated guinea pig atria by Jansen demonstrated that terbinafine reduces the contractile force, but not the heart rate, to an extent similar to itraconazole at concentrations of 10^{-6} M and greater. Overall, the data suggest a potential for cardiac effects under exaggerated exposure conditions. However, these exaggerated exposure conditions may not be directly applicable to the clinical conditions of use for terbinafine (oral administration with a lower maximum concentration in the blood than after iv administration).

It was anticipated that the doses proposed for the two phase 3 clinical studies in pediatric subjects with tinea capitis would not approach levels to be of concern. Therefore, no additional safety pharmacology studies for terbinafine were recommended for this indication.

2.6.2.5 Pharmacodynamic drug interactions – N/A

2.6.3 PHARMACOLOGY TABULATED SUMMARY – N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The following clinical pharmacokinetics information is provided in the Lamisil minitablets label in Section 12 CLINICAL PHARMACOLOGY, subsection 12.3 Pharmacokinetics.

b(4)

Reviewer's comments: The Clinical Pharmacology and Biopharmaceutics reviewer will determine the adequacy of this information.

2.6.4.2 Methods of Analysis – N/A

2.6.4.3 Absorption

The extent of systemic absorption after oral administration of terbinafine ranged between 50% – 80% in mice, rats and rabbits and ranged from 20% – 90% in dogs. The extent of systemic absorption after oral administration of terbinafine was not assessed in monkeys. Peak terbinafine concentrations in plasma were observed at 2 hours in male mice and monkeys and at 4 hours in female mice, male rats and dogs after low dose oral terbinafine administration. Peak concentrations in plasma were observed at 4-8 hours in mice, rats and dogs after high dose oral terbinafine administration. The onset of absorption was rapid after oral administration of terbinafine. Terbinafine was detected in the plasma within 0.25 – 0.5 hours after administration in mice, rats and dogs and at 1 hour (initial sampling time) in monkeys.

2.6.4.4 Distribution

The disposition of total radioactivity associated with terbinafine after oral administration appeared to be biphasic in rat, mouse, dog and monkeys. The terminal half-life was ~70 hours in the rat. The terminal half-life could not be calculated in the other species.

Oral autoradiography studies in the mouse showed that at 1 hour, the highest levels of radioactivity were found in the sclera and/or chorida and liver, followed by blood, renal medulla and cortex, salivary and lachrymal glands, seminal vesicles, bone marrow, pancreas and skin. Lower levels of radioactivity were found in muscles and stomach wall with the lowest levels present in the brain. At 24 hours, the highest concentration of radioactivity was present in the gall bladder while most other tissues levels were substantially lower than at 1 hour. By 96 hours, low levels or radioactivity were only present in the eye membranes and intestinal tract. All other tissues and organs were below the limit of detection.

Distribution of radioactivity was similar in both sexes in rats. Radioactive material was rapidly distributed to the tissues after an oral terbinafine dose (100 mg/kg). At 2 hours, the highest concentration was observed in the liver followed by plasma and adrenals. At 24 hours, the highest concentration was noted in the fat of both sexes. Rats treated ip with terbinafine demonstrated uptake of parent drug into claws. Concentrations of terbinafine in claws were similar after 5 and 10 days of daily administration. Terbinafine declined in rat claws with a $t_{½}$ of 10 – 11 days.

The binding of terbinafine to plasma proteins was >99% in humans, mice, rats and dogs.

2.6.4.5 Metabolism

The primary metabolic pathways in humans with the corresponding end products are summarized in the following table. Each pathway was found in at least one animal species. All

metabolites of terbinafine were either only weakly active (86-621, 280-022) or showed no antifungal activity (280-027, 280-047 and 280-154) in tests for in vitro activity against various species or fungi in comparison to terbinafine.

Human Metabolite	Metabolic Pathway	Mouse	Rat	Rabbit	Dog	Monkey
NA	Dealkylation	+	+	+	+	–
HMN	Dealkylation	–	–	+	+	–
86-621	Dealkylation	+	+	–	–	–
280-022	Aliphatic oxidation	+	–	+	–	–
280-027	Aliphatic oxidation	+	+	+	+	+
280-154	Dealkylation aliphatic oxidation	+	+	+	+	+
280-047	Dealkylation aliphatic oxidation	+	+	+	+	+
A/B	Arene oxide / epoxide hydrolase	+	+	+	+	–

+ indicates that metabolite is present
– indicates that metabolite is not present

The following figure provides the metabolic pathways of terbinafine in man.

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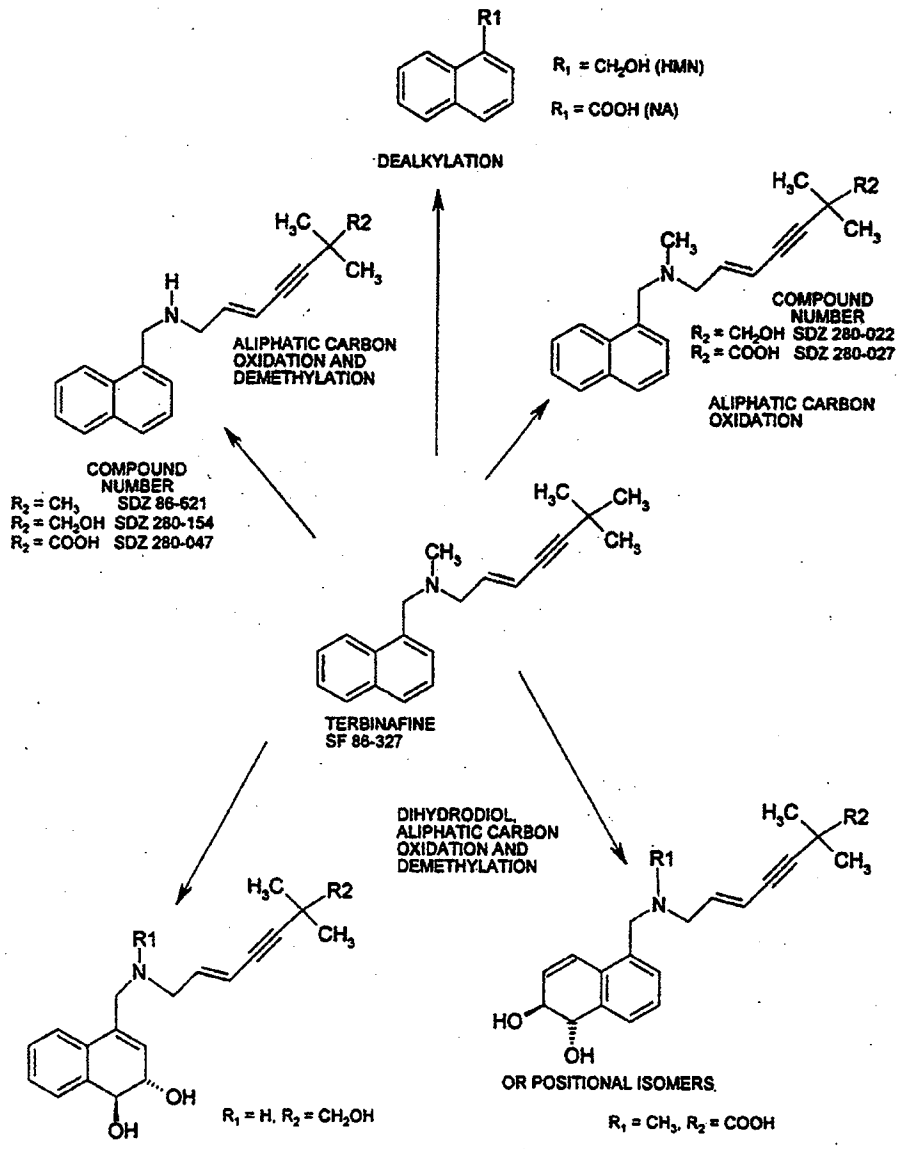
Figure 2 Metabolic pathways of terbinafine in man



2.6.4.6 Excretion

The urinary and fecal route of elimination appeared to be equivalent in the mouse after oral administration of terbinafine. The fecal route of elimination appeared to more important in the rat after oral administration of terbinafine. Approximately 40% of an oral dose was eliminated via the bile of cannulated rats. The fecal route of elimination (70% – 80%) was higher in dogs compared to rodents and humans. The urinary route of elimination appeared to be the

primary route of elimination in rabbits. The overall recovery of radioactivity was >85% in all species.

2.6.4.7 Pharmacokinetic drug interactions – N/A

2.6.4.8 Other Pharmacokinetic Studies – N/A

2.6.4.9 Discussion and Conclusions

Adequate nonclinical pharmacokinetic studies have been conducted with terbinafine. No additional nonclinical pharmacokinetic studies are recommended for terbinafine at this time.

2.6.4.10 Tables and figures to include comparative TK summary – N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY – N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Acute oral and intravenous studies with terbinafine have been conducted in mice and rats. The LD_{50} values in mice and rats were > 4000 mg/kg by the oral route and 393 mg/kg and 213 mg/kg, respectively, when administered intravenously.

Repeat dose oral toxicity studies have been conducted in mice (4 and 13 week studies), rats (4, 13, 26 and 52 week studies), dogs (26 and 52 week studies) and monkeys (26 and 32 week studies). Two 8 week repeat dose oral toxicity studies have been conducted in juvenile rats.

Rats were treated with oral (diet) terbinafine doses of 27, 91 or 268 mg/kg/day (males) and 34, 116 and 349 mg/kg/day (females) for 26 weeks. Increased liver weights associated with enlargement and eosinophilia of centrilobular hepatocytes were noted in mid and high dose animals. A dose dependent increase in the incidence and severity of nephropathy was noted in mid and high dose male rats. Rats were treated with oral (diet) terbinafine doses of 6.9, 20 or 68 mg/kg/day (males) and 9.3, 28 or 95 mg/kg/day (females) for 52 weeks. Increased liver and kidney weights were noted in high dose females and mid and high dose males. No corresponding histopathological changes were noted in either organ. The NOAEL for the 52 week repeat dose oral rat study was 9.3 mg/kg/day for males and 20 mg/kg/day for females.

Juvenile rats were treated from 15 – 70 days with oral (gavage) terbinafine doses of 25, 75 or 250 mg/kg/day in the first study and 10, 25, 45 or 100 mg/kg/day in the second study. Mortality (1, 5 and 6 animals in the low, mid and high dose groups, respectively) was noted in the first study. No corresponding histopathological changes were noted in this study. No treatment related mortality was noted in the second study. It was suggested that the mortality

noted in the first study may have been related to dose administration difficulties rather than associated with terbinafine.

Dogs were treated for 26 weeks with oral terbinafine doses of 20, 60 and 200 mg/kg/day. Treatment related findings included emesis and salivation in high dose animals, reversible increase in liver weight in low and high dose animals, and lamellated intracytoplasmic inclusion bodies in hepatocytes in high dose animals (this finding was still present after a 4 week recovery period). Dogs were treated for 52 weeks with oral terbinafine doses of 10, 25 and 100 mg/kg/day. Clinical signs noted in high dose animals in this study were the same as noted in high dose animals in the 26 week study. Slight hematological and clinical chemistry changes were noted in mid and high dose animals. Minimal to moderate increases in total cytochrome P-450 was found in the livers of mid and high dose animals. No treatment related histopathological effects were noted in either study. Toxicokinetic data obtained in the 52 week study showed a biphasic elimination of terbinafine with a mean terminal half-life of 8.1 hours after a single dose. The terminal half-life increased to 37.6 hours at the end of the treatment period. Plasma AUCs increased 2.5 fold over the 52 week treatment period. The NOAEL for the 52 week repeat dose oral dog study was 10 mg/kg/day.

Monkeys were treated for 32 weeks with oral terbinafine doses of 50, 150 and 300 mg/kg/day. Retinal irregularities were noted in mid and high dose animals during the week 26 ophthalmological examination. Apparently no corresponding histopathological damage to the eye could be identified in this study. The refractile bodies disappeared from the retinas of the monkeys following a 13 week recovery period. The sponsor has hypothesized that the presence of relatively high levels of the t-hydroxyl-N-demethyl metabolite of terbinafine found in the choroid and retinas of high dose animals may suggest that the deposition of this metabolite may have caused the refractile eye changes. Visual disturbances (loss of visual fields as well as color changes) have been associated with terbinafine HCl use in humans. Also, changes in ocular lens and retina in humans have been cause for concern associated with terbinafine HCl use. Therefore, it would appear that the retinal irregularities noted in this monkey study correlate with what has been observed with the clinical use of Lamisil.

It had been determined that adequate nonclinical toxicology studies in a juvenile nonrodent model had not been conducted for terbinafine to support the use of Lamisil for treatment of tinea capitis in pediatric subjects for marketing purposes. Therefore, it was relayed to the sponsor in the pediatric written request for this indication that an appropriate nonclinical toxicology study be conducted in juvenile animals, covering the period of maturation in a nonrodent species. The sponsor conducted a 52 week oral juvenile dog toxicology study and submitted the final study report in the NDA submission.

Juvenile Beagle dogs (9 weeks) were treated through maturation for 52 weeks with oral terbinafine doses of 10, 30 and 100 mg/kg/day. The NOAEL for terbinafine when administered to juvenile Beagle dogs through maturation for 52 weeks was identified as 30 mg/kg/day (60 mg/m^2/day; AUC_{0-24} hr = 7210 ng·hr/ml and 8630 ng·hr/ml for males and females, respectively, at 51 weeks). The NOAEL was identified based on increased liver and heart weights noted in high dose males and convulsive like activities, apparent delay in growth and decreased body weight noted in high dose females. The convulsive like activities, apparent delay in growth and

decreased body weight were noted in high dose females during the earlier part of treatment (up to week 26) with recovery to normal noted in the later part of treatment (weeks 27 – 52).

Conduct of the toxicology study in juvenile Beagle dogs with terbinafine is adequate to fulfill the nonclinical study recommended in the PWR. The convulsive like activities noted in high dose juvenile female dogs is a toxicity that was not noted in adult Beagle dogs. The convulsive like activities were noted on three single occasions during weeks 2, 6 or 17. No convulsive like activities were noted in high dose females from weeks 18 – 52. No treatment related histopathological effects were noted in the brain to correlate with the convulsive like activities. However, it is recommended that this toxicity be included in the Lamisil minitablet label.

No additional general toxicology studies are recommended for Lamisil minitablets at this time.

Genetic toxicology:

Terbinafine has been evaluated in a battery of in vitro and in vivo genetic toxicology studies. Terbinafine (at concentrations ranging from 15 – 3000 μg/plate, in the presence and absence of mammalian metabolic activation system) was not mutagenic in the Ames test using five *Salmonella typhimurium* and two *Escherichia coli* stains. Terbinafine did not demonstrate mutagenic potential in a gene mutation test in V79 CHO cells (concentrations from 9 – 90 μg/ml), in a V79 CHO cell chromosome aberration test (concentrations from 1 – 20 μg/ml), in a sister chromatid exchange test (concentrations from 0.5 – 12 μg/ml), or in a test for DNA repair synthesis (concentrations from 0.0064 – 100 μg/ml). Oral terbinafine did not demonstrate clastogenic effects in a chromosome aberration assay in Chinese hamsters (270, 900 and 2700 mg/kg). Oral terbinafine did not demonstrate genotoxicity in either a micronucleus test in mice (270, 900 and 2700 mg/kg) or a DNA repair test in rats (100 or 500 mg/kg).

The following information is included in the Lamisil tablets label (approved for the treatment of onychomycosis) for the genetic toxicity of terbinafine.

"The results of a variety of *in vitro* (mutations in *E. coli* and *S. typhimurium*, DNA repair in rat hepatocytes, mutagenicity in Chinese hamster fibroblasts, chromosome aberration and sister chromatid exchanges in Chinese hamster lung cells), and *in vivo* (chromosome aberration in Chinese hamsters, micronucleus test in mice) genotoxicity tests gave no evidence of a mutagenic or clastogenic potential."

Appropriate genetic toxicology studies have been conducted for terbinafine. No additional genetic toxicology studies are recommended for Lamisil minitablets at this time.

Carcinogenicity:

An oral mouse carcinogenicity study was conducted with terbinafine for 90 and 100 weeks for females and males, respectively. Oral terbinafine doses of 14, 40 or 130 mg/kg/day were administered to males and 16, 60 or 156 mg/kg/day were administered to females. No

treatment related effect on tumor incidence was noted in this study. An apparent increase in the incidence of leiomyosarcoma tumors of the seminal vesicles was noted in high dose males and ovarian granulosa cell tumors in high dose females. It was determined that these tumors were not related to treatment with terbinafine. The incidence of the seminal vesicle leiomyosarcomas was comparable to that of historical control animals. It was determined that the incidence of granulosa cell tumors in the control groups of this experiment was very low compared to that of historical controls.

A 123 week oral rat carcinogenicity study was conducted at terbinafine doses of 6.9, 20 or 69 mg/kg/day in males and 9.6, 28 or 97 mg/kg/day in females. An increased incidence and severity of hepatic necrosis was noted in high dose females. A slight but statistically significant increase in the incidence of liver tumors was observed in high dose males. The sponsor argued that there was not a dose-related trend, and the tumor incidence was only marginally greater than in historical controls. The sponsor also has stated that no hepatic tumors were noted in mid dose males and the highest incidence of liver tumors was noted in control females. Therefore, the sponsor believed that the hepatic tumors in rats are of equivocal significance for human risk assessment and do not suggest a clear causal relationship to terbinafine administration.

The increase in the incidence of liver tumors observed in high dose males (69 mg/kg/day) was 2X the Maximum Recommended Human Dose (MRHD) based on AUC comparisons of the parent terbinafine. The sponsor was not willing to evaluate higher doses in the oral rat carcinogenicity study, even though dose-limiting toxicity was not achieved at the highest doses tested in this study. It was determined by the Exec CAC that the dose selection for this study was inadequate because a MTD had not been achieved in the study. It was also determined by the Exec CAC that nothing would be gained by an additional evaluation of the liver histopathology in this study. The division determined that since the labeled duration of use for Lamisil tablets was for 3 months, then the division would accept the study. The following information is included in the Lamisil tablets label (approved for the treatment of onychomycosis) for the carcinogenic potential of terbinafine.

"In a 28-month oral carcinogenicity study in rats, an increase in the incidence of liver tumors was observed in males at the highest dose tested, 69 mg/kg/day [2 × the Maximum Recommended Human Dose (MRHD) based on AUC comparisons of the parent terbinafine]; however, even though dose-limiting toxicity was not achieved at the highest tested dose, higher doses were not tested."

The sponsor has argued that peroxisome proliferation induced by terbinafine is a rat specific related cause for the liver tumors observed in the rat carcinogenicity study. It is acknowledged that peroxisome proliferation in the liver is a rat specific finding and that terbinafine is a very weak peroxisome proliferator in rat liver. However, other effects related to liver toxicity, such as increased liver weights and APTT, have been noted in nonclinical toxicology studies conducted in dogs and monkeys. The doses that elicited these liver effects provided a level of systemic exposure that was not much greater than what is seen in humans under conditions of clinical use. Liver toxicity has been noted in humans treated with Lamisil. Therefore, a possible explanation for the liver tumors noted in the rat carcinogenicity study could

be due to a continual low level of liver toxicity that does not get repaired as efficiently over time. This explanation was included in the Lamisil label under the "Animal Toxicology" section. The wording contained in the "Animal Toxicology" section of the Lamisil tablets label (approved for the treatment of onychomycosis) is provided below.

"A wide range of *in vivo* studies in mice, rats, dogs, and monkeys, and *in vitro* studies using rat, monkey, and human hepatocytes suggest that peroxisome proliferation in the liver is a rat-specific finding. However, other effects, including increased liver weights and APTT, occurred in dogs and monkeys at doses giving Css trough levels of the parent terbinafine 2-3 × those seen in humans at the MRHD. Higher doses were not tested."

Additional carcinogenicity studies are not recommended for Lamisil minitablets at this time.

Reproductive toxicology:

A battery of reproductive and developmental toxicity studies were conducted for terbinafine. In a fertility and reproductive development study in male and female rats, terbinafine was administered orally at doses of 10, 50 or 250 mg/kg/day before mating and during pregnancy and lactation. No adverse effects were noted in the low and mid dose groups. Decreased pregnancy rate, mean number of implants, litter size and pup survival were noted in the high dose group (a maternally toxic dose). A slight increase in pre- and perinatal offspring mortality was noted in the high dose group. Physical and functional development was slightly retarded in the high dose group offspring. The sponsor states that these effects may have been secondary to maternal toxicity rather than direct effects of terbinafine. Fertility and general reproductive performance of the offspring were normal in all dose groups.

Embryo-fetal developmental toxicity studies were conducted in rats and rabbits at oral terbinafine doses of 30, 100 and 300 mg/kg/day. No embryolethal or teratogenic effects were noted in either species. A subcutaneous embryo-fetal developmental toxicity study was conducted in rats at terbinafine doses of 10, 30 and 100 mg/kg/day and a dermal (intravaginal application; 3% gel) embryo-fetal developmental toxicity study was conducted in rabbits at doses of 15, 45 and 150 mg/kg/day). No embryolethal or teratogenic effects were noted in either of these studies.

An oral perinatal and postnatal developmental study was conducted in rats with terbinafine doses of 10, 30 and 100 mg/kg/day. No adverse effects on parturition and lactation or on the peri- and postnatal development or survival of the offspring were noted in this study.

The following information is included in the Lamisil tablets label (approved for the treatment of onychomycosis) for the reproductive and developmental toxicity potential of terbinafine. Lamisil is designated as Pregnancy Category B.

b(4)

b(4)

Special toxicology:

No special toxicology studies have been conducted with terbinafine. No special toxicology studies are recommended for Lamisil minitablets at this time.

2.6.6.2 Single-dose toxicity

No nonclinical single-dose toxicity studies were included in this submission.

2.6.6.3 Repeat-dose toxicity

Study title: A 52-week oral (capsule) toxicity study in maturing dogs with a 4-week recovery period

Key study findings:

The NOAEL for terbinafine when administered to juvenile Beagle dogs through maturation for 52 weeks was identified as 30 mg/kg/day (60 mg/m^2/day; AUC_{0-24} hr = 7210 ng·hr/ml and 8630 ng·hr/ml for males and females, respectively, at 51 weeks). The NOAEL was identified based on increased liver and heart weights noted in high dose males and convulsive like activities, apparent delay in growth and decreased body weight noted in high dose females. The convulsive like activities, apparent delay in growth and decreased body weight were noted in high dose females during the earlier part of treatment (up to week 26) with recovery to normal noted in the later part of treatment (weeks 27 – 52).

Study no.: 0470001

Volume #, and page #: Electronic NDA submission, file: pharmtox\tox\0470001.pdf
Conducting laboratory: Novartis Pharmaceuticals Corporation, East Hanover, NJ
Date of study initiation: 10-26-04
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: Terbinafine HCl gelatin capsules, Batch# C0057
Vehicle: Gelatin capsules

Methods

Doses: 0, 10, 30 and 100 mg/kg/day terbinafine

Note: Doses were selected based on a 4 week dose range finding study conducted in juvenile Beagle dogs submitted to IND 57,093 in Serial #051 (8-27-04). Based on the results noted in this study, doses ≥ 150 mg/kg/day exceeded a maximum tolerated dose (based on mortality) in juvenile dogs. It was determined that a high dose of 100 mg/kg/day should be tolerated in a 9 month juvenile dog toxicology study based on the nature of the findings (emesis and fecal changes) noted in high dose animals (100 mg/kg/day) in this study. The reader is referred to the review of the 4 week dose range finding study entered into DFS, if additional information is required.

The previous adult dog 52 week oral (capsule) toxicity study was conducted at doses of 0, 10, 25 and 100 mg/kg/day terbinafine. The doses proposed for the juvenile dog 52 week toxicology study will allow a direct comparison to the doses used in the adult dog study to determine if juvenile dogs express a unique toxicity not noted in adult dogs or exhibit an enhanced sensitivity to a toxicity characterized in adult dogs.

Species/strain: Beagle dogs
Number/sex/group or time point (main study): 4/sex/dose
Route, formulation, volume, and infusion rate: Oral, gelatin capsules
Satellite groups used for toxicokinetics or recovery: 2/sex/dose for control and high dose 4 week recovery animals
Age: 9-10 weeks
Weight: Males: 2.4-4.2 kg; Females: 1.9-3.8 kg
Sampling times: N/A
Unique study design or methodology:

Test article was administered orally via gelatin capsules, once daily, 7 days/week for 9 months. The amount of terbinafine HCl incorporated weekly into gelatin capsules for the daily doses was projected based on the previous week's body weights.

Note: Based on comparative organ system development in the human and the dog, 9 weeks of age in the dog was considered to be equivalent to approximately 2-5 years of age in the human (specifically skeletal age) (Zoetis T, Tassinari M, Bagi C, et al (2003) Species comparison of postnatal bone growth and development. Birth Defects Res; (Part B) 68:86-110) and therefore was deemed an appropriate age to initiate the administration of terbinafine to support the safety

for the targeted clinical population (tinea capitis patients; primary age range 4 – 12 years extending through 16 years). The sponsor proposed a 52 week treatment period with a 4 week recovery period for this study to evaluate the effects of terbinafine administration in juvenile dogs through full maturity. It was determined that this proposal was acceptable.

Observation and Times:

Mortality:	twice daily
Clinical signs:	daily
Physical examination:	during weeks 4, 13, 26 and 52 and recovery week 4 (if needed) (includes external examination and/or body temperature)
Body weights:	twice weekly during weeks 1-13, then once weekly thereafter
Food consumption:	daily
Ophthalmoscopy:	prior to dosing and during weeks 4, 13, 26 and 52 and recovery week 4 (if needed)
ECG:	prior to dosing and during weeks 4, 13, 26 and 52 and recovery week 4 (if needed); measured at 1.5 to 2 hours post dose
Hematology:	prior to dosing and during weeks 4, 13, 26 and 52 and recovery week 4 (if needed)
Clinical chemistry:	prior to dosing and during weeks 4, 13, 26 and 52 and recovery week 4 (if needed)
Urinalysis:	prior to dosing and during weeks 4, 13, 26 and 52 and recovery week 4 (if needed)
Gross pathology:	necropsy
Organ weights:	Adrenals, brain, heart, kidneys, liver, ovaries, pituitary gland, prostate, spleen, testes, thyroid and uterus
Histopathology:	The following organs were preserved from all animals in all treatment groups: adrenals, aorta, bone with bone marrow (femur, sternum), brain, cecum, colon, duodenum, epididymis, esophagus, eye, gall bladder, heart, ileum, jejunum, kidneys, lacrimal gland, lesions, liver, lungs, lymph nodes (bronchial, mesenteric, mandibular), mammary gland, ovaries, pancreas, pituitary gland, prostate, rectum, salivary gland, sciatic nerve, skeletal muscle, skin, spinal cord, spleen, stomach, testes, thymus, thyroid with parathyroid, tongue, trachea, urinary bladder, uterus/cervix and vagina Histological examination was performed for all animals in all dose groups.
Toxicokinetics:	Blood samples were obtained during weeks 1, 4, 14, 25 and 51 from main study animals. Blood samples were obtained from recovery animals during study week 53 and week 56 (end of recovery). Blood samples were obtained prior to dosing and at 1, 2, 5 and 24 hours postdose.

Results:

Mortality: No treatment related effects on mortality were noted in this study.

Clinical signs: No treatment related effects on clinical signs were noted in low and mid dose animals. Treatment related effects noted in high dose animals included: single episodes of clonic convulsions during weeks 2, 6 or 17 (females only); activities associated with convulsions included moderate to severe ataxia, impaired righting reflex, head tilt, hunched posture, decreased locomotor activity and abnormal gait (females only); and increased incidence and/or frequency of fecal changes (both sexes).

Physical examination: No treatment related effects on physical examination parameters were noted in low and mid dose animals and high dose males. Treatment related effects on physical examination parameters noted in two high dose females at weeks 4, 13 and 26 included thin and/or poor body condition, slight dehydration (week 4), developmentally smaller than expected for age (week 13) and small with a low body weight for an animal of its age (week 26). The physical examinations of high dose females at week 52 and the 4 week recovery were normal.

Body weights: No treatment related effects on body weights were noted in low and mid dose animals and high dose males. Treatment related decrease in body weight was noted in high dose females between weeks 2 – 16 (decrease from 10 – 21% compared to control females). The mean body weights for high dose females were comparable to control females from weeks 26 – 52.

Ophthalmoscopy: No treatment related effects on ophthalmologic parameters were noted in this study.

EKG: No treatment related effects on electrocardiographic parameters were noted in this study.

Hematology: No treatment related effects on hematologic parameters were noted in this study.

Clinical chemistry: No treatment related effects on clinical chemistry parameters were noted in low dose animals and mid and high dose males. A slight decrease in serum albumin was noted in mid and high dose females and a slight decrease in calcium concentrations were noted in high dose females on days 14 and 91 only.

Urinalysis: No treatment related effects on urinary parameters were noted in this study.

Gross pathology: No treatment related effects on macroscopic parameters were noted in this study.

Organ weights: No treatment related effects on organ weights were noted in low and mid dose animals and high dose females. A treatment related increase in liver and heart weights (absolute weight increase of 49% and 28%, respectively) were noted in high dose male animals at the terminal necropsy only (not noted in high dose recovery males).

Histopathology: No treatment related effects on microscopic parameters were noted in this study.

Toxicokinetics: A summary of the mean pharmacokinetic parameters for terbinafine HCl measured in this study is provided in the following table.

Dose (mg/kg/day)	C_{max} (ng/ml)		$AUC_{0-24\ hr}$ (ng·hr/ml)		T_{max} (hr)	
	Males	Females	Males	Females	Males	Females
Week 1						
10	629	963	1890	2400	0.5	0.75
30	2690	4710	8890	9600	2	1
100	8200	11700	36000	58100	1.25	1.5
Week 4						
10	1320	1300	2750	2640	1.25	1.25
30	3970	4020	10400	9360	1.25	1.5
100	7460	6050	45300	48900	1.5	1
Week 14						
10	1340	1310	3900	3940	1.5	1.25
30	6270	5590	21700	16900	1.75	1.25
100	6010	9310	71400	78800	2.75	1.75
Week 25						
10	744	736	3400	2510	2.25	1.5
30	3780	2910	16400	12900	1.75	1.25
100	11000	10400	121000	63100	3.5	1.5
Week 51						
10	376	579	1280	2080	0.75	1.75
30	1400	1840	7210	8630	1.75	1.25
100	9410	3380	86200	40100	3.25	2.5
Week 53[a]						
100	4800	3950	57800	58800	2	1.5

a – only high dose animals available for week 53 measurement (2/sex/dose)

A greater than dose proportional increase in systemic exposure (AUC) for terbinafine was noted in male and female animals. No apparent gender differences in systemic exposure to terbinafine were noted in this study. Accumulation of terbinafine was noted from week 1 – 14 in females with a decrease of terbinafine exposure noted from weeks 14 – 51 and then another increase in terbinafine exposure noted between weeks 51 – 53. Accumulation of terbinafine was

noted from week 1 – 14 in males (week 25 in the high dose group) with a decrease of terbinafine exposure noted for the later sampling periods.

Terbinafine concentrations above the lower limit of quantitation (LLOQ: 3 ng/ml) were measured on week 56 in high dose recovery animals. The plasma concentrations ranged from 86.5 – 116 ng/ml in males and from 69.6 and 178 ng/ml in females on week 56. These concentrations were very low compared to C_{max} values observed in the high dose group on week 53 (males: 4800 ng/ml; females: 3950 ng/ml). No concentration of terbinafine above the LLOQ was measured in control animals.

2.6.6.4 Genetic toxicology

No nonclinical genetic toxicology studies were included in this submission.

2.6.6.5 Carcinogenicity

No nonclinical carcinogenicity studies were included in this submission.

2.6.6.6 Reproductive and developmental toxicology

No nonclinical reproductive and developmental toxicology studies were included in this submission.

2.6.6.7 Local tolerance

No nonclinical local tolerance studies were included in this submission.

2.6.6.8 Special toxicology studies

No nonclinical special toxicology studies were included in this submission.

2.6.6.9 Discussion and Conclusions

An oral toxicology study was conducted in juvenile Beagle dogs with terbinafine to fulfill the nonclinical study recommended in the Pediatric Written Request (PWR). Juvenile Beagle dogs (9 weeks) were treated through maturation for 52 weeks with oral terbinafine doses of 10, 30 and 100 mg/kg/day. The NOAEL for terbinafine when administered to juvenile Beagle dogs through maturation for 52 weeks was identified as 30 mg/kg/day (60 mg/m^2/day; AUC_{0-24} hr = 7210 ng·hr/ml and 8630 ng·hr/ml for males and females, respectively, at 51 weeks). The NOAEL was identified based on increased liver and heart weights noted in high dose males and convulsive like activities, apparent delay in growth and decreased body weight noted in high dose females. The convulsive like activities, apparent delay in growth and decreased body weight were noted in high dose females during the earlier part of treatment (up to week 26) with recovery to normal noted in the later part of treatment (weeks 27 – 52).

Conduct of the toxicology study in juvenile Beagle dogs with terbinafine is adequate to fulfill the nonclinical study recommended in the PWR. The convulsive like activities noted in high dose juvenile female dogs is a toxicity that was not noted in adult Beagle dogs. The convulsive like activities were noted on three single occasions during weeks 2, 6 or 17. No convulsive like activities were noted in high dose females from weeks 18 – 52. No treatment related histopathological effects were noted in the brain to correlate with the convulsive like activities. However, it is recommended that this toxicity be included in the Lamisil minitablet label.

The multiples of human exposure for the juvenile dog study are calculated based on the AUC value for a 250 mg terbinafine dose administered in adults (4.56 μg·hr/ml) compared to the AUC values noted after 51 weeks of treatment in mid and high dose animals. The clinical pharmacokinetic information contained in the Lamisil minitablets label indicates that the systemic exposure to terbinafine did not exceed the exposure in adults receiving repeated once daily doses of 250 mg Lamisil.

Treatment related effects noted at 100 mg/kg/day in the juvenile dog study included increased liver and heart rates in males and 3 single episodes of convulsive like activities in females. The 100 mg/kg/day dose is 19 fold (males) and 10 fold (females) greater than the AUC noted after administration of 250 mg Lamisil (males: 86.2 μg·hr/ml ÷ 4.56 = 19; females: 46.1 μg·hr/ml ÷ 4.56 = 10). The NOAEL was identified as 30 mg/kg/day in the juvenile dog study. The NOAEL is 1.6 fold (males) and 1.9 fold (females) greater than the AUC noted after administration of 250 mg Lamisil (males: 7.21 μg·hr/ml ÷ 4.56 = 1.6; females: 8.63 μg·hr/ml ÷ 4.56 = 1.6).

2.6.6.10 Tables and Figures – N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

Refer to summaries provided above.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Based on the nonclinical data available for terbinafine HCl, NDA 22-071 for Lamisil minitablets is approvable from a pharmacology/toxicology perspective provided that the recommended changes in the label discussed in the next section are incorporated into the Lamisil minitablets label.

Unresolved toxicology issues (if any):

There are no unresolved toxicology issues for NDA 22-071, at this time.

Recommendations:

No additional nonclinical toxicology studies are recommended for Lamisil minitablets at this time.

It is recommended that the suggested labeling changes provided in the next section be incorporated into the Lamisil minitablets label.

Suggested labeling:

The sponsor included a label for Lamisil tablets/minitablets in the new PLR format in the NDA submission. The nonclinical portions of the Lamisil tablets/minitablets label are provided below. It is recommended that the underlined highlighted wording be inserted into and the ~~strikeout~~ wording be deleted from the "Pregnancy" (Section 8.1), "Carcinogenicity, Mutagenesis, Impairment of Fertility" (Section 13.1) and "Animal toxicology and/or pharmacology" (Section 13.2) sections of the Lamisil tablets/minitablets label.

It is recommended that the information describing [redacted] from the "Animal toxicology and/or pharmacology" section (section 13.2) of the label since it does not provide any additional useful information.

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1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

cc:
DDDP/DIV DIR/WALKER
DDDP/PHARM SUP/BROWN
DDDP/PHARM/HILL
DDDP/MO/BROWN
DDDP/PM/BHATT

APPENDIX/ATTACHMENTS

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/s/

Barbara Hill
4/12/2007 11:32:17 AM
PHARMACOLOGIST/TOXICOLOGIST

Paul Brown
4/13/2007 11:16:30 AM
PHARMACOLOGIST/TOXICOLOGIST

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Division of Dermatologic and Dental Drug Products (HFD-540)
Pharmacology/Toxicology Checklist for NDA Filing Meeting

Date:	10-18-06
Reviewer:	Barbara Hill
NDA Number:	22-071
Drug Name:	Lamisil (terbinafine hydrochloride) minitablets
CAS Number:	78628-80-5
Drug Type:	3S
Drug Class:	Antifungal
Indication:	Tinea Capitis
Route of Administration:	Oral
Date CDER Received:	9-8-06
User Fee Date:	7-8-07
Date of Draft Review:	4-1-07
Sponsor:	Novartis Pharmaceuticals Corporation, East Hanover, NJ

Fileability:
On initial overview of the NDA application:

(1) Does the pharmacology/toxicology section of the NDA appear to be organized in a manner to allow a substantive review to be completed? YES

This is an electronic NDA submission.

(2) Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner to enable a timely and substantive review? YES

(3) Is the pharmacology/toxicology section of the NDA sufficiently legible to permit a substantive review to be completed? YES

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute studies*, chronic studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? YES

The sponsor has included a final study report for a nonclinical toxicology study titled "A 52-week oral (capsule) toxicity study in maturing dogs with a 4-week recovery period". This nonclinical toxicology study conducted in juvenile dogs was recommended to support use of terbinafine hydrochloride in the proposed pediatric population with tinea capitis. This nonclinical toxicology study was included in the pediatric written request for Lamisil minitablets.

(5)	If the formulation to be marketed is different from the formulation used in the toxicology studies, has the Sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required?	N/A
(6)	Are the proposed labeling sections relative to pharm/tox appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	YES
(7)	Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor?	YES
(8)	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the Sponsor submitted a rationale to justify the alternative route?	YES
(9)	Has the Sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	YES
(10)	Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics?	N/A
(11)	Has the Sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	YES
(12)	From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not.	YES
(13)	If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify:	NO

(14) Issues that should not be conveyed to the Sponsor: N/A

_____
Pharmacology Reviewer

_____
Pharmacology Supervisor

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/s/

Barbara Hill
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Paul Brown
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