# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-958**

# PHARMACOLOGY REVIEW(S)

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: | **21-958** (Rx to OTC Switch) |
| SERIAL NUMBER: | **N000** |
| DATE RECEIVED BY CENTER: | 10-30-2005 |
| PRODUCT: | Lamisil$^{R}$ (terbinafine) DermGel, 1% |
| INTENDED CLINICAL POPULATION: | Adults |
| SPONSOR: | Novartis Consumer Health, Inc. |
| DOCUMENTS REVIEWED: | Vol. 1.1-1.3 |

REVIEW DIVISION: Division of Dermal and Dental Drug Products (HFD-540)

PHARM/TOX REVIEWER: Kumar D. Mainigi

PHARM/TOX SUPERVISOR: Paul Brown

DIVISION DIRECTOR: Stanka Kukich (Acting)

PROJECT MANAGER: Neel Patel

Date of review submission to Division File System (DFS):

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# *EXECUTIVE SUMMARY*

## 1. Recommendations

1.1 Recommendation on approvability: Approvable

1.2 Recommendation for non-clinical studies: None

1.3 Recommendations on labeling: N/A (Rx to nonprescription switch)

## 2. Summary of non-clinical findings

2.1 Brief overview of non-clinical findings: A majority of animal studies for terbinafine were conducted with its oral formulation. In humans, approximately 70% of the oral drug is absorbed, however, because of a substantial first pass metabolism the bioavailability is reduced to 40 percent. In chronic treatment, the drug leads to a number of mild to severe adverse effects such as nausea, cramping, diarrhea and burning, abdominal pain, rash and urticaria. A few incidences of symptomatic hepatobiliary dysfunction including cholestatic hepatitis, and severe neutropenia have also been reported.

At higher oral dose levels, adverse effects in animals included hepatotoxicity, and increased myeloid cells in the bone marrow. However, in animals, some of the drug related lesions are species specific. For instance, the peroxisome proliferation linked to liver tumors in high-dose (69 mg/kg/day) males was restricted to rats.

In monkeys, 150-300 mg of oral terbinafine/kg/day for 26 weeks produced refractile bodies in retinas. Similarly, in humans some vision disturbances such as loss of visual field and changes in lens and color were associated with the long-term use of oral terbinafine.

In a dog study, an intravenous bolus dose of 10mg terbinafine/kg caused a transient decrease in arterial blood pressure, arterial blood flow, and cardiac output.

In the 4-week rabbit study (with two-week recovery period), the topical applications of 1, 2, and 3% terbinafine gel produced no systemic toxicity, and the local toxicity was restricted to a few reversible lesions attributed to ethanol in the formulation. The highest dose in this study with only 5% systemic absorption (7.2mg terbinafine/$m^2$) is 24 times greater than the corresponding topical dose (0.3mg/$m^2$) in humans.

In a spectrum of genotoxicity assays, terrbinafine tested non-genotoxic and non-clastogenic. The rodent ofal carcinogenicity studies conducted at dose levels 1,400-1,600 times ($mg/m^2$) greater than the topical human dose did not reveal any significant tumor formation. No effects on fertility, reproductive performance, perinatal and postnatal development were observed in the oral rat and rabbit studies conducted at dose levels 4,000-5,000 times greater than the human topical dose. Terbinafine did not exhibit any teratogenic potential in rats and rabbits at oral dose levels ranging from 6,000 to 12,000 times the clinical topical dose.

In a nutshell, severe adverse effects in humans developed at comparatively high oral dose levels. No systemic toxicity is expected to develop with comparatively very low levels of topical terbinafine.

2.2 Pharmacologic activity: In a therapeutic efficacy study in guinea pigs, terbinafine emulsion gel was effective in treating experimental trichophytosis. The drug acts as a non-competitive inhibitor of squalene epoxidase, leading to greater accumulation of squalene (the most insoluble substance in the cell) and reduced level of ergosterol. Ergosterol is a critical architectural component of the fungal cell membrane. The structurally dysfunctional membrane permits inward flow of protons eventually leading to membrane burst. The mammalian enzyme requires a 1,000-fold higher concentration of terbinafine to inhibit squalene epoxidase.

The secondary pharmacodynamic activity of terbinafine is related to its blocking of the dimorphic switch i.e. conversion of yeast form to pathogenic mycelial form. However, this action is restricted to dimorphic *Candida* species.

2.3 Non-clinical safety issues relevant to clinical use: None

# *PHARMACOLOGY/TOXICOLOGY REVIEW*

## 3.1 INTRODUCTION AND DRUG HISTORY

The oral formulation (tablet) of terbinafine was introduced in United Kingdom in 1991. It was followed by approval of cream, tablet, solution, and DermGel 1% formulations by USFDA in 1992 (NDA 20-192), 1996 (NDA 20-539), 1997 (NDA 20-749), and 1998 (NDA 20-846).

Both oral and topical formulations of terbinafine are active in humans against a wide variety of fungal skin infections. Topical terbinafine has been used to treat athlete's foot (interdigital tineapedis), jock itch (tinea cruris), and ringworm (tinea corporis). It is systemically used to treat infected nails, extensive cutaneous infections, or infections not treatable topically. Terbinafine formulations are sold globally under the trade names LAMISIL and SEBIFIN.

The adverse effects commonly attributed to chronic oral use of terbinafine include nausea, cramping, mild diarrhea, burning, abdominal pain, rash and urticaria. Rare incidences of symptomatic hepatobiliary dysfunction including cholestatic hepatitis, and severe neutropenia have also been reported. Rare skin hypersensitivity reactions have included Stevens - Johnson syndrome, and epidermal necrolysis.

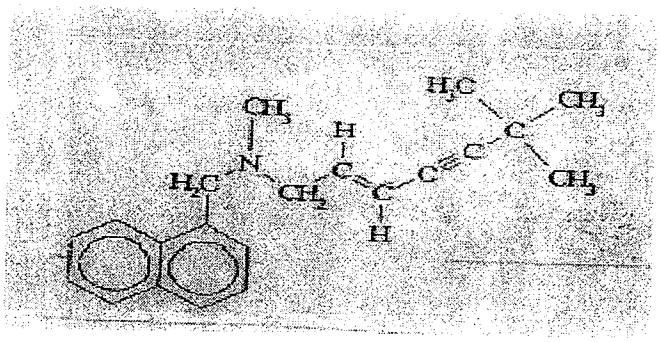
Over the years, the safety of terbinafine had been extensively evaluated in a wide spectrum of *in vivo* and *in vitro* animal studies, and in microbiological assays. In 1997, Lamisil Cream 1% formulation was switched from prescription to nonprescription category. In the current submission, the sponsor has requested a similar switch for Lamisil DermGel 1% formulation. It has been marketed as prescription drug since 1998.

**NDA number**: 21-958
**Review number**: 01
**Sequence number/date/type of submission**: 000/09-30-2005/original
**Information to sponsor**: No
**Sponsor and/or agent**: Novartis Consumer Health, Inc.
200 Kimball Drive
Parisppany, NJ 07054-0622
**Manufacturer for drug substance**: Novartis Pharma Producktions GmbH
Oflinger Strasse 44, D-79664
Wehr, Germany

**Reviewer name**: Kumar D. Mainigi
**Division name**: Division of Dermatologic and Dental Drug Products (HFD# 540)

**Drug**:

Trade name: Lamisil$^{R}$ (terbinafine) DermGel$^{TM}$ 1%
Generic name: Terbinafine
Code name: SF 86-327
Chemical name: (E)-N-(6, 6-Dimethyl-2-hepaten-4-ynyl)-N-methyl-1-naphthalene methanamine
CAS registry number: 91161-71-6
Molecular formula/molecular weight: $C_{21}H_{25}N$/291.43
Structure:



**Relevant INDs/NDAs/DMFs**:
INDs: 22, 218; Lamisil Cream 1%
28, 093; Lamisil tablets
[redacted]; Lamisil tablets (compassionate use)
[redacted], Lamisil capsules (withdrawn 01-13-1989)
33, 068; Lamisil 1% solution
NDAs: 20-192 Lamisil cream 1% (approved 12-30-1992)
20-539 Lamisil tablets (05-10-1996)
20-749 Lamisil solution (10-17-1997)
20-846 Lamisil DermGel 1% (04-29-1998)

**Drug class**: Antifungal

**Indication**: Treatment of interdigital tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm) due to *Epidermophyton floccosum, Trichophyton mentagrophytes* and *Trichophyton rubrum.*

**Clinical formulation**:

| Ingredients | Gms/100g Drug Product |
|---|---|
| Terbinafine base | 1.00 |
| Butylated hydroxytoluene, NF | [redacted] |
| Sodium hydroxide | [redacted] |
| Benzyl alcohol, NF | [redacted] |
| Sorbitan monolaurate, NF | [redacted] |
| Carbomer [redacted] P ([redacted]), NF | [redacted] |
| Polysorbate 20, NF | [redacted] |
| Isopropyl myristate, NF | [redacted] |
| Ethanol [redacted] | [redacted] |
| Water purified, USP | [redacted] |
| [redacted] | |
| [redacted] | |

**Route of administration**: Topical

**Proposed use**: As an over-the-counter topical antifungal agent

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

**Studies reviewed within this submission:** None

**Studies not reviewed within this submission**: N/A

## 3.2 PHARMACOLOGY

**3.2.1 Brief summary**: Terbinafine was crafted after some major structural modifications to the first synthetic allyalmine naftifine. It created an orally effective and more potent antifungal agent. This drug is one of the mainstays of therapy for dermatophytosis. It acts by blocking the biosynthesis of ergosterol through inhibition of enzyme squalene epoxidase. Ergosterol is a critical structural component of the fungal cell membrane.

The antifungal activity of terbinafine depends upon the species of yeast. It is fungicidal against *Candida parapsilosis,* but only fungistatic against *Candida albicans.* Nonsusceptible fungi are *Fusarium species, Pseudallescheria boydii* and *zygomycetes.*

The highly lipophilic terbinafine accumulates in the skin, nails, and fatty tissues, thus permitting shorter courses of therapy, because drug levels exceeding the fungicidal concentrations are still present in the skin one week after discontinuation of treatment.

### 3.2.2 Primary pharmacodynamics

The primary activity of terbinafine is its fungicidal action. The molecule acts as a noncompetitive inhibitor of squalene epoxidase, an early step enzyme in ergosterol synthesis in fungi. Inhibition leads to rising levels of squalene (the most insoluble compound in the cell) and falling levels of ergosterol. The deficiency of ergosterol, an essential component of fungal cell membrane, eventually leads to a structurally deformed and dysfunctional membrane, permitting inward flow of protons leading to membrane burst. The mammalian enzyme requires a 1000-fold higher concentration of terbinafine to inhibit squalene epoxidase. Against *Trichophyton* species (athlete's foot), the inhibition of fungal growth parallels rising levels of squalene.

### 3.2.3 Secondary pharmacodynamics

Fungicidal action against *Candida* species correlates well with the falling levels of ergosterol. *Candida albicans* is a dimorphic fungus, i.e. it can exist either as yeast or as in mycelial form. Latter is the pathogenic form, as it can force its way through tissues. The change from one form to other is called a dimorphic switch. Terbinafine is almost inactive against the yeast form, but very active against the mycelia, blocking the switch. This is a fungistatic action as fungus could revert to the yeast form in the presence of terbinafine but resumes growth in its absence. Terbinafine exhibits noncompetitive inhibition of squalene epoxidase from *C albicans* with a *Ki* of $3x10^{-8}$M. For the same degree of inhibition, rat liver enzyme requires 2000-folds higher concentration of terbinafine.

**3.2.4 Safety pharmacology:** The importance of safety pharmacology in the drug approval process was first recognized in the late 1990s. However, most of the non-clinical studies with terbinafine HCl were conducted earlier. Therefore, except for a few short-term cardiovascular studies in dogs, no other safety studies were conducted.

Neurological effects: No animal studies were conducted; however, to date no neurological effects due to terbinafine have been reported in humans.

Cardiovascular effects: In a dog study, an intravenous bolus dose of 10mg terbinafine/kg caused a transient decrease in the arterial blood pressure, arterial blood flow, and cardiac output; no such changes were observed at 2mg/kg dose level in cats or dogs. However, no studies were conducted at the recommended oral human dose of 4mg/kg/day.

In isolated guinea pig atria, at $10^{-6}$ M concentration, terbinafine reduced the contractile force, but had no affect on the heart rate.

Pulmonary effects: Not investigated

Renal effects: Not investigated

Gastrointestinal effects: Not investigated

Abuse liability: Not known

3.2.5 **Pharmacodynamic drug interactions**: The concurrent use of terbinafine with caffeine, theophylline and naphtylline may increase the toxicity of these drugs. Use of alcohol or hepatoxic medications may increase the risk of liver damage, because terbinafine plasma levels are increased by unpredictable amounts. Cimetidine increases and rifampin decreases the plasma level of terbinafine.

## 3.3 PHARMACOKINETICS/TOXICOKINETICS

**3.3.1 Brief summary**: Oral terbinafine is rapidly absorbed in all test species and humans; systemic absorption ranged between 50 to 80 percent. Cmax was achieved within 2-8 hours. Only 5% or less of topical terbinafine is absorbed. After the oral dose, drug distribution in mice, rats, and monkey is biphasic, it is triphasic in dogs. In all species including humans, more than 90% of the parent drug binds to plasma proteins. Because of its strong lipohilic nature, terbinafine is concentrated in sebum, stratum corneum and nail plates. The metabolic pathways for terbinafine are similar in all species including humans. The major metabolites are terbinafine carboxylic acid and terbinafine N-desmethyl carboxylic acid. The first-pass metabolism occurs in all the species. In mice, rats,

and dogs, a major portion of the parent drug and its metabolites is excreted in the feces; in rabbits and human urine is the major route of elimination.

**3.3.3 Absorption**: After oral administration, terbinafine in the plasma of mouse, rat, and dog was detected within 0.25-0.5 hours, indicating a rapid systemic absorption. The extent of absorption ranged between 50-80 percent. Cmax was achieved at Tm ranging from 2-8 hours.

In humans, drug absorption following oral administration is 70% or greater, however, the bioavailability as a result of a substantial first-pass metabolism is reduced to approximately 40 percent. Cmax is achieved within 2 hours. Food has moderate effect on absorption; there is less than 20% increase in AUC when drug is administered with food.

Topical absorption of terbinafine in all the species is less than 5%.

**3.3.4 Distribution:** The distribution of radioactive terbinafine in mouse, rat, dog and monkey after the oral dose was at least biphasic. In rat, $T_{1/2}$ of elimination was 7-10 and 70 hours, indicating a biphasic distribution and a wider first pass effect. The corresponding values in dog were 1.0-2.5, 15-25 hours and 6 days.

In a mouse radioautographic study, at 2 hours post-dose, the level of radioactivity was in the following decreasing order: sclera and chorida, liver, blood, renal medulla and cortex, salivary and lachrymal glands, seminal vesicles, bone marrow, pancreas, skin, and muscles; stomach and brain contained the minimal amounts of radioactivity. At 24 hours, the highest amount of radioactivity was found in the gall bladder, the levels in the other tissues were much lower than that observed at 1 hour. At 96 hours, except for eye membrane and gastrointestinal tract, the levels in all other tissues were below the detection limit.

In a rat oral (100mg/kg) study at 2 hours post dose, the amount of radioactivity was found in the following decreasing order: liver, plasma, and adrenals. The distribution pattern was similar in both sexes. At 24 hours, the highest concentration of radioactivity was present in the fat.

In all species (humans, mice, rats, dogs), more than 99% of terbinafine was bound to plasma proteins.

Because of its lipophilic nature, terbinafine is widely distributed in the human body; bound strongly to plasma proteins, and concentrated in sebum, stratum corneum and nail plates. Its initial half-life is 12 hours, extending to 200-400 hours at steady state. After chronic oral therapy, terbinafine can be detected in the plasma for 4-8 weeks after discontinuation of treatment.

**3.3.5 Metabolism:** The metabolic pathways are similar in all the species. It includes N-dealkylation, aliphatic side chain oxidation and demethylation, arene oxide formation and conjugation. The major plasma metabolites are terbinafine carboxylic acid and terbinafine N-desmethyl carboxylic acid. It is suggsted that a major portion of conjugated terbinafine carboxylic acid is unconjugated in the gut and recycled (first-pass metabolism).

Both carboxylic acids are considered to be the active forms of the parent drug; their plasma levels differ markedly between the species. In rats at steady state, the AUC for two acids was 25-33 times higher than in man. Under similar exposure conditions, the levels in mice (25-27-folds), dogs (16-folds), and monkeys were 2-4-folds greater than man.

In rat hepatocytes, the terbinafine carboxylic acid was a strong inducer of palmitolyl-CoA oxidation and carnitine acetyl transferase. In fact, it was more potent than clofibrate used as a standard reference for peroxisome proliferation. In primary hepatocyte cultures prepared from human biopsies (3 females, 1 male), this acid exhibited no effect on peroxisome proliferation. It was inferred that terbinafine-induced peroxisome proliferation was specific to rats. It was also established that the terbinafine peroxisome proliferation is not solely due to parent drug but more likely due to its carboxylic acid metabolites.

**3.3.6 Excretion:** In rat, mouse, and dog, the major route of elimination is bile. In rats, 71% of the absorbed dose is excreted in the feces, and 0.5-2% of the parent drug is eliminated in the urine. In rabbits and humans, renal route is the primary route of elimination. In humans, 80% of terbinafine/metabolites are excreted in the urine, and rest in the feces. Only trace amount of the parent drug is found in the urine. The $T_{1/2}$ of elimination is 11-16 hours.

**3.3.7 Pharmacokinetic drug interactions**: Whereas ketoconazole metabolism occupies more than 60% of the total cytochrome P-450 capacity of the liver, the corresponding value for terbinafine is less than 5 percent. Consequently, terbinafine does not significantly alter the metabolism of drugs involving cytochrome P-450 isoenzymes. It includes cyclosporine, terfenadine, tolbutamide, ethinyl estradiol, ethoxycoumarin, and midazolam. Terbinafine does decrease the clearance of intravenous caffeine by approximately 20%, indicating that it may inhibit drugs with type I binding to hepatic microsomes, but not drugs requiring type II binding.

**3.3.10 Tables and figures to include comparative TK summary**

## 3.4 TOXICOLOGY

### 3.4.1 Overall toxicology summary

General toxicology: In acute oral (mice 250mg/kg; rats 200mg/kg) toxicity studies, during 14 post-dose days, no drug related deaths, or gross and microscopic lesions were observed. In other studies, the oral $LD_{50}$ values in both species were greater than 4g/kg; the corresponding values for two species via the intravenous route were 393 and 213mg/kg, respectively. The maximum recommended oral dose in human is 4mg/kg/day (250mg tablet/day).

In primary rabbit skin irritation assay, a well-defined erythema and slight edema observed on days1-2 disappeared on day 3, indicating that the topical formulation was non-irritant.

Most of the non-clinical studies with terbinafine were conducted with the oral formulation at dose levels ranging from 15 to 530mg/kg/day for duration ranging from 2 to 52 weeks.

Mice: Two-week dietary study (16, 49, and 155mg/kg/day) indicated no drug-related clinical signs of toxicity, or changes in body weights and food consumption. The parent drug and or metabolites were not detected in the plasma at the low- and mid-dose levels. The high-dose pharmacokinetic profile suggested lack of any significant drug accumulation.

In a 4-week dietary study (105 and 465 mg/kg/day), liver weights were increased significantly, however, the electron microscopic examination revealed no changes in the organ morphology, suggesting adaptive/compensatory hyperplasia.

Rats: In two-week dietary study (25 and 86 in males and 25 and 79 mg/kg/day in females), no drug-related toxicity or change in any in-life parameters were observed.

At high-dose level (100, 465 in males and 108 and 530mg/kg/day in females) in a four-week dietary study, a significant increase in the absolute and relative liver weights, and mild centrilobular hypertrophy were observed in 1/12 males and 9/12 females. The electron microscopic examination revealed a marked increase in the number and size of peroxisomes. However, no hepatotoxicity was observed in a 13-week study conducted at lower terbinafine concentrations (69 in males and 97 mg/kg/day in females).

In the 26-week dietary study (27, 91, and 268 in males and 34, 116 and 349 mg/kg/day in females), liver hypertrophy was associated with eosinophilia of centrilobular hepatocytes in the mid- and high-dose males. In the same groups, a dose-related nephropathy was also observed.

Animals receiving dietary terbinafine (males 6.9, 20.0 or 68.0, females 9.3, 28.0, or 95 mg/kg/day) for 52 weeks had increased liver and kidney weights at the mid- and high-dose levels, however, the changes were not associated with any relevant microscopic lesions. In both sexes, under the study conditions, the lowest dose was established as NOAEL for the gender.

Rat Juvenile Studies:

In the first study, rats received gavage doses (25, 75, or 250 mg/kg/day) of terbinafine for 15-70 days; in the second study, rats received much reduced levels (10, 25, or 45 mg/kg/day) of drug for the same duration.

In the first study, dose-related deaths occurred in all the groups (1, 5, and 6 deaths in the low-, mid- and high-dose level, respectively). Reportedly these casualties occurred due to a faulty gavage technique. However, the sponsor's assumption does not carry much weight. First, there was a dose-related trend. Second, the dose levels in the first study were much higher. Third, no deaths occurred in the low-dose (second) study. Apparently, the deaths in the first study were drug and dose-related.

Rabbits: In a 4-week study with two weeks of recovery period, rabbits treated with 1, 2, and 3% DermGel (10, 20, and 30 mg terbinafine/rabbit) exhibited dermal irritation (well-defined erythema, slight edema and scabs) in all the groups. Since all the control animals had similar lesions, dermal reactions were attributed to ethanol component of the formulation.

Monkeys: In the 32-week study (50, 150, and 300 mg/kg/day), at week 26, retinal lesions (refractile bodies) were observed in the mid- and high-dose animals. However, these changes were not associated with any histopathological lesions. In addition, the refractive bodies disappeared during 13 weeks of recovery period. It was suggested that deposit of hydroxyl-N-demethyl metabolite in choroids caused the refractive changes.

Some visual disturbances such as loss of visual field and changes in the lens and color have been associated with the chronic use of oral Lamisil in humans.

Dogs: In 26-week oral (20, 60, and 200mg/kg/day) study, the drug-related changes in the high-dose animals included emesis/salivation and an increase in liver weights associated with lamellated intracytoplasmic inclusion bodies in the hepatocytes. These bodies were still present at the end of four weeks of recovery period.

The drug-related changes in the high-dose (10, 25, 100 mg/kg/day) animals in the 52-week oral study were similar to that observed in the 26-week study. In

females, and 2) an increased incidence of liver tumors was recorded in the high-dose males.

The tumor formation in males was associated with drug-induced peroxisome proliferation. In a spectrum of studies with hepatocytes from mice, rats, dogs, monkeys and humans, it became apparent that peroxisome proliferation was restricted to rats. Liver tumors in male rats were developed at 17 times (in mg/kg) the maximum recommended human dose. However, in terms of AUC, the difference was only two-fold.

In 22-25-month mouse (males 14, 40, 130, and females 16, 60, 156 mg/kg/day) study, no significant increase in tumors was observed in either of the sexes. The increased incidence of leiomyosarcomas of the seminal vesicles in the high-dose males was within the range of historical control data. The incidence of ovarian granulosa cell tumors in high-dose females was actually lower that in the historical control.

The findings of rodent studies were presented to Carcinogenicity Assessment Committee (CAC) on March 21, 1992 (Mainigi). It was pointed out that both studies were deficient as no dose-range finding studies were conducted to establish the maximum tolerated dose. After eight years, the sponsor submitted the same data, reanalyzed using some new statistical and histopathological methods. Second presentation was made to Executive CAC on August 29, 2000 (Jacobs). However, committee upheld its previous decision declaring that the data from inadequate studies was still not acceptable. Instead "The Committee recommended adding an animal toxicology section to the labeling to describe effects on liver in multiple species.

Reproductive toxicology: In segment I (general fertility and reproductive performance) oral study (10, 50, 250 mg/kg/day), only the high-dose caused maternal toxicity. At this dose level, a decrease in pregnancy rate, mean number of implants, and pup survival was recorded. In addition, the functional development was slightly retarded, and the mortality in pre- and perinatal offspring was increased.

The oral segment II (embryo-fetal development) studies conducted at dose levels of 30, 100, and 300mg/kg/day in rats and rabbits, indicated no teratogenic or embryo lethal effects. Similar findings were made in the subcutaneous (30, 100, and 300 mg/kg/day) and topical (intravaginal) (15, 45, and 150mg/kg/day) studies in rabbits.

In the segment III (perinatal and postnatal development) oral (10, 30, and 100 mg/kg/day) rabbit study, no drug-related effects were observed on parturition, lactation, and perinatal and postnatal survival of offspring.

Based on the above mentioned studies, terbinafine was placed in Pregnancy category B.

**3.4.7 Local tolerance:** In primary rabbit dermal irritation assay, the drug was well tolerated. In primary rabbit eye irritation test, terbinafine did not produce any ocular lesions.

**3.4.8 Special toxicology studies:** The topical applications of 1, 2, and 3% terbinafine solutions were nonsensitizing in guinea pig maximization test. Furthermore, the same solutions did not produce any phototoxicity or photosensitivity in guinea pigs.

## 3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Terbinafine is one of the most extensively tested antifungal agents. It is marketed in oral (tablets) and topical (cream, solution, gel) formulations. Most of the clinical and non-clinical studies with terbinafine were conducted with its oral formulation. The high systemic absorption (70% or greater) in animals and humans caused a wide spectrum of adverse effects such as nausea, cramping, mild diarrhea, burning, abdominal pain, rash and urticaria. Rare incidences of symptomatic hepatobiliary dysfunction including cholestatic hepatitis, severe neutropenia, apalstic anemia, agranulocytosis, and thrombocytopenia have also been reported.

In comparison, less than 5% topical absorption caused no systemic toxicity, and the local toxicity was restricted to reversible irritation in animals. In a 4-week topical rabbit study with 1, 2 and 3% DermGel, no systemic toxicity was observed throughout the study period. The dermal reactions (well-defined erythema, slight edema, and scabs) were attributed to ethanol component of the formulation.

For approximately 2.5 kg rabbit, a topical dose of 30mg/day with 5% absorption will provide 7.2 mg terbinafine/$m^2$/day. The corresponding value in humans will be 0.3 mg/$m^2$/day, i.e. 24 times lower than the highest test dose in rabbits. The corresponding value of 109 mg/$m^2$/day for the oral dose with 70% absorption will be 363 times greater than the topical dose.

$LD_{50}$ values for DermGel in mice and rats exceeded 250 and 100 mg/kg, respectively.

In primary eye irritation and skin irritation assays in rabbits, DermGel, 1% tested non-irritant. In a guinea pig assay, gel did not induce any sensitization, or produced any photosensitivity or phototoxicity.

In a spectrum of *in vitro* and *in vivo* genotoxicity assays, terbinafine did not exhibit any mutagenic or clastogenic potentials. In another *in vitro* assay, the drug did not express any tumor-initiating or cell proliferation activities.

In oral carcinogenicity studies, no significant tumor formation was observed in mice up to 1560 times ($mg/m^2$) the topical dose level in humans.

A wide range of oral studies in mice, rats, dogs, and monkeys and *in vitro* assays with primary hepatocyte cultures from rat, monkey, and human indicated that the development of liver tumors in high-dose (69mg/kg/day=1380 times the topical dose in humans) male rats was associated with peroxisome proliferation specific to the species.

The oral reproductive and developmental studies in rats and rabbits conducted at 4,000-12,000 times the human topical dose ($mg/m^2$) did not affect the fertility, reproductive performance, perinatal and postnatal development. The drug also did not exhibit any teratogenic potential.

[Note: In the original NDA review for DermGel 1%, the calculations for safety margin were based on (hypothetical) 100% absorption in all species including humans. Now, it is known that topical absorption in animals as well as in humans is approximately 5%, therefore, in this report all the values are recalculated to make the comparison more realistic]

The toxicity profile emerged from the non-clinical studies overwhelmingly support the safe topical use of DermGel 1% in humans.

Unresolved toxicology issues (if any): None

Recommendations: I have no objection to the proposed switch of Lamisil DermGel, 1% from prescription to the nonprescription category.

Suggested labeling: N/A

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

## *3.7.* APPENDIX/ATTACHMENTS

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/s/

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Kumar Mainigi
5/22/2006 09:46:38 AM
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