# PRODUCT MONOGRAPH

## NU-TERBINAFINE

**Terbinafine Hydrochloride Tablets**

**250 mg terbinafine/tablet**

**Antifungal Agent**

**NU-PHARM INC.**
**50 Mural Street, Units 1 & 2**
**Richmond Hill, Ontario**
**L4B 1E4**
Control #: 089008

**DATE OF PREPARATION:**
March 25, 1999
**DATE OF REVISION:**
**January 12, 2004**

## PRODUCT MONOGRAPH

NU-TERBINAFINE

Terbinafine Hydrochloride Tablets

250 mg Terbinafine/Tablet

## THERAPEUTIC CLASSIFICATION

Antifungal Agent

## ACTIONS AND CLINICAL PHARMACOLOGY

Terbinafine is an allylamine which has a broad spectrum of antifungal activity. At low concentrations, terbinafine is fungicidal against dermatophytes, molds and certain dimorphic fungi. The activity against yeasts is fungicidal or fungistatic, depending on the species.

Terbinafine interferes specifically with fungal sterol biosynthesis by inhibition of squalene epoxidase in the fungal cell membrane. The enzyme squalene epoxidase is not a cytochrome P450 enzyme. Its inhibition leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. When given orally, the drug concentrates rapidly in skin, hair and nails at levels associated with fungicidal activity.

### Pharmacokinetics

A single oral dose of 250 mg terbinafine results in peak plasma concentrations of 0.97 μg/mL within 2 hours after administration. Seventy percent of the dose is absorbed by the gastrointestinal tract. The absorption half-life is 0.8 hours and the distribution half-life is 4.6 hours. The peak plasma concentration and bioavailability (AUC) roughly double when steady state is reached at 10-14 days. The bioavailability of terbinafine is moderately increased (20%) by food, but not sufficiently to require dosing adjustments.

Terbinafine binds strongly to plasma proteins (99%) and is lipophilic. Terbinafine is widely distributed in the body including adipose tissue. It rapidly diffuses through the dermis and concentrates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and in sebum-rich skin. There is evidence that terbinafine is distributed into the nail plate within the first few weeks of commencing therapy.

Terbinafine is excreted mainly in urine (80%) and in feces (20%). Following absorption terbinafine is metabolised rapidly and extensively by the liver. At least seven cytochrome P450 isoenzymes are involved in its metabolism with major contributions from CYP 2C9, CYP 1A2, CYP 3A4, CYP 2C8 and CYP 2C19. Terbinafine inhibits, but is not metabolized by CYP 2D6. Biotransformation is nearly complete and results in at least 15 identified metabolites all of which are excreted in the urine and lack antifungal activity. The plasma elimination half-life is 17 hours and the terminal half-life in stratum corneum, nail, hair, dermis and epidermis ranges from 22 to 28 days. Higher plasma concentrations were noted in older adults and in hypertensives and lower concentrations were noted in smokers.

Following a single 250 mg dose in 12 hepatically impaired cirrhotic (alcoholic) patients; elimination of terbinafine was reduced by about 40%. Despite this difference in the mean clearance of terbinafine between cirrhotic patients and healthy subjects, the ranges of estimated clearances overlapped. Wide intra and intersubject variation was noted in normal volunteers. The AUC was two-fold compared to the normal volunteers, but Cmax and Tmax were unchanged. In a sample of 12 renally impaired patients (median creatinine clearance of 17.6 mL/sec), terbinafine clearance following a single 250 mg dose was halved resulting in the doubling or more of peak plasma concentrations or AUC. Patients at the highest and lowest ends of the renal impairment spectrum were not represented. There was no direct correlation between creatinine

clearance and terbinafine clearance in renally impaired patients, the metabolism of the drug having been impaired in these patients due to competition between metabolite and parent drug.

Comparative Bioavailability

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of terbinafine was measured and compared following a single oral 250 mg dose of NU-TERBINAFINE (terbinafine hydrochloride) or Lamisil 250 mg tablets. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data
Terbinafine (Dose: 250 mg) From Measured Data

| Parameter | Geometric Mean<br>Arithmetic Mean (CV%) | | Ratio of Geometric Means (%)** |
|---|---|---|---|
| | NU-TERBINAFINE | Lamisil®† | |
| $AUC_{0-72}$ (ng●hr/mL) | 4134<br>4317 (28) | 4290<br>4416 (23) | 95.9 |
| $AUC_I$ (ng●hr/mL) | 4416<br>4611 (29) | 4578<br>4718 (24) | 96.0 |
| $C_{max}$ (ng/mL) | 827<br>861 (27) | 838<br>883 (30) | 99.0 |
| $T_{max}$ (hr)* | 1.81 (33) | 2.07 (38) | -- |
| $t_{1/2}$ (hr)* | 30.8 (12) | 31.4 (16) | -- |

* The $T_{max}$ and $t_{1/2}$ parameters are expressed as the arithmetic means (CV%).
** Based on the least squares estimate.
† Lamisil® (Sandoz Canada Inc.) was purchased at a Canadian retail pharmacy.

## INDICATIONS AND CLINICAL USE

NU-TERBINAFINE (terbinafine hydrochloride) is indicated in the treatment of fungal infections of the skin and nails caused by dermatophytes such as Trichophyton (e.g. T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum), Microsporum canis and Epidermophyton floccosum.

Oral NU-TERBINAFINE is indicated in the treatment of onychomycosis (fungal infection of the nail) caused by dermatophyte fungi.

Where oral therapy is considered appropriate owing to the site, severity or extent of the infection, NU-TERBINAFINE tablets may also be indicated in the treatment of tineal skin infections (tinea corporis, tinea cruris and tinea pedis).

Note: Oral terbinafine is not effective in pityriasis versicolor.

## CONTRAINDICATIONS

NU-TERBINAFINE (terbinafine hydrochloride) tablets are contraindicated in patients with a hypersensitivity to terbinafine or any of the excipients (see Composition).

## WARNINGS

Rare cases of symptomatic hepatobiliary dysfunction including cholestatic hepatitis and very rarely liver failure have been reported.

If a patient presents with signs or symptoms of liver dysfunction such as unexplained persistent nausea, anorexia, tiredness, abdominal pain, jaundice, pale stools or dark urine, treatment should

immediately be discontinued and hepatic origin verified (See PRECAUTIONS, ADVERSE REACTIONS).

There have been isolated reports of anaphylactoid and serious skin reactions (e.g. Stevens Johnson Syndrome and Toxic Epidermal Necrolysis and Erythema Multiforme). If progressive skin rash occurs, treatment with terbinafine should be discontinued.

Isolated cases of blood dyscrasias have been reported in patients treated with terbinafine.

## PRECAUTIONS

General

Indications of liver dysfunction ranging from asymptomatic liver enzyme increases to symptomatic cholestatic and hepatocytic injury have been reported with oral NU-TERBINAFINE (terbinafine hydrochloride). These have been observed at various times after treatment initiation, but on average, peak between 3 and 8 weeks. Though not always predictive, the monitoring of liver enzymes may be useful.

NU-TERBINAFINE should be kept out of the reach of children.

Use in Patients with Hepatic or Renal Impairment

There is very limited experience on the use of NU-TERBINAFINE in patients with liver disease or renal impairment. Plasma clearance appears to be reduced in some of these patients (see Pharmacokinetics).

Caution should be exercised in patients at higher risk of developing hepatic dysfunction (e.g. those receiving potentially hepatotoxic drugs; those with a history of alcoholism or suspicion of liver disorder). If the benefits of treatment are judged to outweigh potential risks in these patients liver function tests conducted at baseline and periodically during NU-TERBINAFINE treatment should be considered.

Use in Pregnancy and Lactation

Though fetal toxicity and fertility studies have shown no adverse effects in animals, there is only very limited clinical experience with NU-TERBINAFINE (terbinafine hydrochloride) in pregnant women; therefore, unless the potential benefits outweigh any potential risks, NU-TERBINAFINE should not be used during pregnancy.

Terbinafine is excreted in breast milk; therefore mothers receiving oral treatment with NU-TERBINAFINE should not breast-feed.

Use in the Elderly

Plasma concentrations and drug half-life appear to be slightly higher in elderly patients than in the general population. In addition, the incidence of all adverse events in a Post Marketing Surveillance study appeared to be slightly higher at normal adult doses; however, the overall rate of adverse events possibly or probably related to terbinafine did not appear to be different compared to the general population. When prescribing tablets for patients in this age group, the possibility of pre-existing impairment of liver or kidney function should be considered (see Pharmacokinetics).

Use in Pediatrics

There is limited experience with terbinafine in children.

Drug Interactions

Many categories of drugs are known to inhibit or induce drug metabolism by cytochrome P450 (CYP) enzymes located in the liver and intestine. Coadministration of such drugs may impact metabolic elimination of drugs, and in some cases, bioavailability may be either increased or decreased and possibly necessitate dosage adjustments.

Results from *in vitro* experiments and *in vivo* studies in healthy volunteers suggest that, in general, there is a low potential for terbinafine inhibition or induction of the elimination of drugs metabolised by various CYP isoenzymes (e.g. coumarin (warfarin), ethinyl estradiol, cyclosporine, terfenadine, triazolam, and tolbutamide). Some cases of menstrual irregularities and pregnancies have been reported in patients taking NU-TERBINAFINE concomitantly with oral contraceptives; however, the rate of occurrence appears to be within the background incidence for patients taking oral contraceptives alone.

*In vitro* and clinical studies, however, have shown that terbinafine is a potent inhibitor of the ethnically polymorphic CYP 2D6 isoenzyme, which is responsible for the metabolism of a wide variety of drugs. Caution should be exercised in patients receiving concomitant therapy with drugs metabolized by CYP 2D6, especially those with a narrow therapeutic window. This includes, but is not limited to, tricyclic and serotonin-reuptake inhibitor antidepressants (e.g. desipramine, fluvoxamine), antihypertensives such as $\beta_1$-adrenergic blocking agents (e.g. metoprolol, propranolol), certain antiarrhythmic agents (e.g. flecainide, propafenone), monoamine

oxidase inhibitors Type B (e.g. selegiline) and antipsychotics (e.g. chlopromazine, haloperidol). For such drugs, which are metabolized by CYP 2D6, and where therapeutic activity is dependent upon the parent compound, an increased effect (or toxicity) may be produced. In contrast, for compounds such as codeine, where a metabolite is primarily responsible for drug action, a decrease in therapeutic effect may be realized.

Because multiple CYP enzyme pathways are involved in the metabolism of terbinafine, alternate pathways are available if one is inhibited by a competing substrate. Therefore, it is expected that few interactions will occur that result in significant increases in terbinafine plasma concentrations. However, the plasma clearance of oral terbinafine has been shown to be increased by inducers of CYP enzyme metabolism (CL increased 100% by rifampin) and decreased by inhibitors (CL decreased 33% by cimetidine; and 42% by fluconazole). Where co-administration of such drugs is necessary NU-TERBINAFINE dosage may need to be adjusted accordingly.

Terbinafine co-administration has been reported to reduce plasma clearance of caffeine by 19% and of theophylline by 14%.

Carcinogenesis

An increase in liver tumours was observed in male rats at the highest dose level (69 mg/kg) during the life-time (123 weeks) carcinogenicity study. The changes included increased enzyme activity, peroxisome proliferation and altered triglyceride metabolism. The changes have been shown to be species specific since they were not seen in mice or monkeys.

## ADVERSE REACTIONS

*Frequency estimate: very common ≥ 10%, common ≥ 1% to < 10%, uncommon ≥ 0.1% to < 1%, rare ≥ 0.01% to < 0.1%, very rare < 0.01%.*

Terbinafine Hydrochloride Tablets

In general, terbinafine is well tolerated. Side effects are mild to moderate in severity, and transient.

In clinical trials adverse events occurred in 10.4% of patients receiving the recommended oral dose. Of these, 5% were mild to moderate gastrointestinal events (feeling of fullness, loss of appetite, dyspepsia, nausea, mild abdominal pain, diarrhea), 3% were non-serious forms of skin reactions (rash, urticaria) and the remainder were for musculoskeletal reactions (arthralgia, myalgia) and miscellaneous non-specific events such as malaise or tiredness.

The following table lists adverse events observed in clinical trials with oral terbinafine, by organ system.

| Organ System Adverse Event | Terbinafine 250 mg (n=998) | |
|---|---|---|
| | | (%) |
| SKIN (overall) | 27 | 2.7 |
| Erythema or rash | 9 | 0.9 |
| Urticaria | 5 | 0.5 |
| Eczema | 1 | 0.1 |
| Pruritus | 4 | 0.4 |
| Other | 8 | 0.8 |
| GI (overall) | 52 | 5.2 |
| Diarrhea and/or cramps | 10 | 1.0 |
| Nausea and/or vomiting | 11 | 1.1 |
| Fullness | 5 | 0.5 |
| Sickness | 1 | 0.1 |
| G.I. irritation, dyspepsia, gastritis | 22 | 2.2 |
| Other | 3 | 0.3 |
| CNS (overall) | 12 | 1.2 |
| Headache | 9 | 0.9 |
| Concentration | 2 | 0.2 |
| Other | 1 | 0.1 |
| OTHER (overall) | 11 | 1.1 |
| Tiredness, fatigue | 3 | 0.3 |

| Organ System Adverse Event | Terbinafine 250 mg (n=998) | |
|---|---|---|
| Pain (back, knee, legs, feet, kidney) | 1 | 0.1 |
| Change of taste or dry mouth | 1 | 0.1 |
| Other | 6 | 0.6 |
| LABORATORY ADVERSE CHANGES (overall) | 2 | 0.2 |
| Hypoglycemia | 1 | 0.1 |
| Elevated liver enzymes | 1 | 0.1 |
| TOTAL | 104 | 10.4 |

Adverse events not frequently observed include the following:

Uncommon: Taste disturbances, including taste loss, which usually recover within several weeks after discontinuation of the drug were reported.

Rare: Hepatobiliary dysfunction (2/3 primarily cholestatic in nature and the remainder involving hepatocytic damage or both) has been reported in association with terbinafine treatment, including very rare cases of liver failure. Unspecific prodromal symptoms (nausea, anorexia, fatigue, general malaise) have been reported. Liver enzyme increases have been noted in asymptomatic patients as well as in patients with more specific symptoms of hepatic dysfunction jaundice, upper abdominal right quadrant pain, pruritus, pale stools, dark urine).

The frequency of reported apparent hepatic dysfunctions has varied. An analysis of 7 key placebo-controlled trials (262 placebo vs 1624 terbinafine patients) suggested increases of 1.4% vs 3.4% in liver function test indicators (APase, SGPT (AST), SGOT (ALT), g-GT, bilirubin >2x

above upper normal). In a European post-marketing study in 25 884 patients, asymptomatic liver enzyme increases were reported in 0.17% of patients treated. The reporting frequency for symptomatic liver disorder possibly related to terbinafine was 1:13 000. The relative risk of acute liver injury in this group was considered to be 4.2 times the background incidence. In the less controlled circumstances of spontaneous worldwide reporting, the development of clinically significant signs and symptoms of hepatobiliary dysfunction for which no other cause was apparent, and in which terbinafine was considered the possible causative agent was calculated to be approximately 1:37 000 treated patients. The reporting frequency overall for hepatobiliary events including elevations in liver enzymes was 1:15 000. Very rare cases of liver failure, some fatal, have been associated with terbinafine treatment and the incidence rate is about 1:1 000 000 exposed patients.

Oral terbinafine has been rarely associated with systemic allergic reactions including urticaria, angioedema, arthralgia, arthritis and serum sickness like reactions.

Very rare: Serious skin reactions (e.g. Stevens Johnson Syndrome, Toxic Epidermal Necrolysis and Erythema Multiforme) and anaphylactoid reactions have been reported.

Hair loss has been reported, however, a causal relationship has not been established.

Haematological disorders such as neutropenia, agranulocytosis, pancytopenia and thrombocytopenia have been reported. Very rare cases of thrombotic thrombocytopenic purpura (TTP) have been reported. The mechanism of TPP induction and the role of terbinafine have not been elucidated.

Isolated cases of photosensitivity have been reported in association with terbinafine.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

A few cases of overdosage with terbinafine of (up to 5 g) have been reported, giving rise to headache, nausea, epigastric pain and dizziness. The recommended treatment of overdosage consists of eliminating the drug primarily by the administration of activated charcoal and giving, symptomatic supportive therapy, if needed.

## DOSAGE AND ADMINISTRATION

NU-TERBINAFINE (terbinafine hydrochloride) Tablets

Adult Dosage: 250 mg once daily.

The duration of treatment varies according to the indication and the severity of infection:

| Indication | Duration of Treatment |
|---|---|
| Onychomycosis (of fingers and toes)* | 6 weeks to 3 months |
| Skin Infections ** | |
| Tinea pedis (interdigital & plantar/moccasin type) | 2-6 weeks |
| Tinea corporis, cruris | 2 - 4 weeks |

* In patients with fingernail infections or toenail infections other than the big toe, or in younger patients, treatment periods of less than 3 months may be adequate. In patients with infections of the big toenail, treatment for 3 months is usually sufficient, although some patients may require treatment for 6 months or

longer. Poor nail outgrowth during the first weeks of treatment may enable identification of those patients in whom longer therapy is required.

In onychomycosis the optimal clinical effect is seen some months after mycological cure and cessation of treatment. This is related to the period required for outgrowth of healthy nail tissue.

** Complete resolution of the signs and symptoms may not occur until several weeks after mycological cure.

Patients with Hepatic or Renal Impairment

There is very limited experience on the use of NU-TERBINAFINE in patients with liver disease or renal impairment. In patients with pre-existing stable chronic liver dysfunction baseline liver function tests should be established and close follow-up is required (see Pharmacokinetics-PRECAUTIONS, ADVERSE REACTIONS).

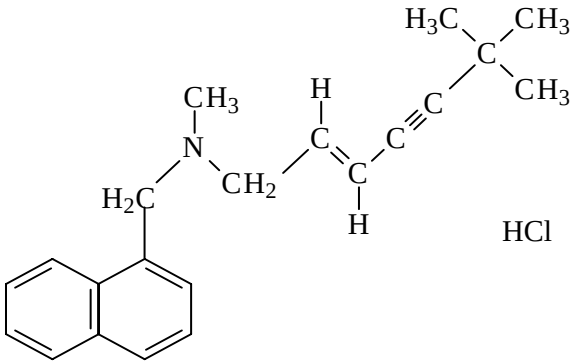
## PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: terbinafine hydrochloride

Chemical Name: (E)–N–(6,6–dimethyl–2–hepten–4–inyl)–N–methyl–1–naphthaline–methanamine hydrochloride

Structural Formula:




Molecular Formula: $C_{21}H_{25}N \bullet HCl$

Molecular Weight: 327.90

Description: Terbinafine hydrochloride is a white to off-white finely crystalline powder with a melting point of ~205°C. The pKa (I) value is 7.10 and the pH of a solution (0.5%) in methanol/water 4:6 (v/v) is ~4.7 at 25°C. The solubility of terbinafine hydrochloride is 0.63% (w/v) in water and >2% (w/v) in chloroform.

Composition

In addition to terbinafine hydrochloride, each tablet contains the non-medicinal ingredients methylcellulose, croscarmellose sodium, magnesium stearate, and colloidal silicon dioxide.

Stability and Storage Recommendations

Store at temperatures between 15° and 30°C. Protect from light.

## AVAILABILITY OF DOSAGE FORMS

NU–TERBINAFINE 250 mg: Each round, white, biconvex, beveled-edged tablet, engraved 'APO' on one side, and scored and engraved 'TER' over '250' on the other contains terbinafine hydrochloride equivalent to 250 mg terbinafine. Available in bottles of 100.

## INFORMATION FOR THE PATIENT

NU-TERBINAFINE (ORAL) Patient Information Leaflet

Take once daily, preferably at the same time each day.

ABOUT YOUR MEDICINE

NU-TERBINAFINE is used to treat fungal infections of the skin, fingernails and toenails. The treatment should only be taken as prescribed by your doctor. Some evidence of infection may still be present at the end of treatment. This will gradually diminish.

If any of the information in this leaflet causes you special concern or if you want additional information about your medicine and its use, contact your doctor or pharmacist. Remember, keep this and all other medicines out of the reach of children and never share your medicines with others.

BEFORE USING THIS MEDICINE

Discuss with your doctor the possible side effects that may be caused by this medicine.

Tell your doctor if you:

– are allergic to any medicines, either prescription or nonprescription (OTC), or foods;

– are pregnant or intend to become pregnant while using this medicine;

– are breast-feeding; terbinafine is excreted in breast milk;

– are taking any other medicine, prescription or nonprescription (OTC), especially cimetidine or rifampicin;

– have a history of other medical problems, especially liver diseases such as jaundice (yellowness to skin and/or eyes), kidney disease, alcohol abuse, serious skin reactions, or blood diseases such as anemia.

PROPER USE OF THIS MEDICINE

To help clear up your infection completely, it is very important that you keep taking this medicine for the prescribed treatment period, even if your symptoms begin to clear up or you begin to feel better after a few days. Since fungal infections may be very slow to clear up, stopping your medication too soon can cause the symptoms and the fungal infection to flare up again. Try not to miss any doses. If you do miss a dose, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular schedule. Do not double the doses and never make dose changes on your own. Take as prescribed by your doctor.

– Keep your regular appointments with your doctor.

– If you think you have taken an overdose of this medicine, check with your doctor.

– Store at temperatures between 15°C and 30°C. Protect tablets from light.

PRECAUTIONS WHILE USING NU-TERBINAFINE

Some individuals may be either very sensitive to terbinafine or may have had some liver disease in the past. These individuals are at risk of developing abnormal liver function. Stop taking NU-TERBINAFINE and consult your doctor immediately should you develop jaundice (yellowness to skin and/or eyes).

Very occasionally some patients have developed blood abnormalities while being treated with NU-TERBINAFINE. These reactions usually resolve on their own after stopping NU-TERBINAFINE treatment.

If you have any questions about this, check with your doctor.

Always remember to follow your doctor's instructions and have any medical tests done that your doctor may request. Keep your appointments for follow-up visits.

POSSIBLE SIDE EFFECTS OF NU-TERBINAFINE

**TELL** your doctor if you notice any of these possible side effects:

| | **Signs/Symptoms** | **Course of Action** |
|---|---|---|
| Common | Gastrointestinal discomfort (diarrhea, cramps, nausea, vomiting, feeling of fullness or bloating). | These possible side effects may go away during treatment; however, if they continue or are bothersome, contact your doctor. |
| Less Common | Dry mouth, taste disturbance, tiredness, lack of concentration, non-serious skin disorders (red, itchy skin), headache, pain (back, knee, legs, feet, kidney) | These side effects should be reported to your doctor **as soon as possible.** |
| Rare and Serious | Severe skin rash, hives.<br>* Sore throat and fever, jaundice (yellowness to skin and/or eyes), unusual fatigue, lack of appetite, dark urine, pale stools.<br>* These signs may indicate blood or liver disorders. | Stop taking NU-TERBINAFINE and notify your doctor **immediately.** Your doctor will decide whether or not you should continue your NU-TERBINAFINE treatment. |

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

**ASK** your doctor if you do not understand these instructions or want more information.

## MICROBIOLOGY

In vitro

The minimum inhibitory concentrations (MICs) of terbinafine were determined by serial dilution tests against yeasts, molds, dermatophytes, the mycelial form of Candida albicans, Pityrosporum spp., and Sporothrix schenkil. The spectrum and MIC values obtained for the various species and strains of fungi at different research laboratories (summarized as a range of activity in the following table) demonstrate that terbinafine possesses a high activity against dermatophytes, aspergilli, and dimorphous or dermatiaceous fungi. The susceptibility of blastospores of various species and strains of yeasts to terbinafine is much lower with MIC's ranging from 0.1 to >128 μg/mL. The efficacy of terbinafine against 2 clinically important yeasts was confirmed by an evaluation of the susceptibility of 78 clinical isolates of Candida albicans and 20 of Candida parapsilosis. Blastophores of the Candida parapsilosis were more sensitive than those of Candida albicans, but the mycelial growth form of the Candida albicans (considered the pathogenic form) was the most sensitive form ($MIC_{50}$ = 0.195 μg/mL).

Summary of results published on in vitro activities

of terbinafine against pathogenic and opportunistic fungi

| | Fungus | MIC Range (µg/mL) | | |
|---|---|---|---|---|
| I. | **Dermatophytic Fungi** | | | |
| | Trichophyton mentagrophytes | 0.001 | - | 0.01 |
| | T. rubrum | 0.001 | - | 0.01 |
| | T. verrucosum | 0.001 | - | 0.006 |
| | Epidermophyton floccosum | 0.001 | - | <0.06 |
| | Microsporum canis | 0.005 | - | 0.01 |
| | Microsporum gypseum | 0.005 | - | 0.01 |
| | Microsporum persicolor | 0.002 | - | 0.003 |
| II. | **Filamentous Fungi** | | | |
| | Aspergillus spp. | 0.005 | - | 5.0 |
| | Aspergillus flavus | 0.01 | - | 0.5 |
| | Aspergillus fumigatus | 0.02 | - | 5.0 |
| | Aspergillus niger | 0.005 | - | 0.5 |
| | Aspergillus terreus | 0.05 | - | 5.0 |
| | Pseudallescheria boydii | 32.00 | - | >64.0 |
| | Mucor, Rhizopus spp. | 64.0 | - | >128.00 |
| | Acremonium spp. | 1.0 | - | 4.0 |
| | Curcularia fallax | 0.25 | - | 0.5 |
| | Fusarium spp. | 32.0 | - | >64.0 |
| | Hendersonula toruloides | 1.0 | - | 4.0 |
| | Lasiodiplodia theobromae | 0.25 | - | 0.5 |
| | Paecilomycea spp. | 8.0 | - | 64.0 |
| | Scopulariopsis brevicaulis | 0.5 | - | 8.8 |
| | Scytalidium hyalinum | 1.0 | - | 4.0 |
| III. | **Dimorphic Fungi** | | | |
| | Blastomyces dermatitidis | ≤0.05 | - | 0.39 |
| | Histoplasma capsulatum | ≤0.05 | - | 0.2 |
| | Sporothrix schenckii | ≤0.05 | - | 2.0 |
| IV. | **Pathogenic Yeasts** | | | |
| | Candida albicans (yeast form) | 6.25 | - | >128.0 |
| | Candida albicans (mycelial form) | 0.098 | - | 0.78 |
| | Candida parapsilosis | 0.1 | - | 3.13 |
| | Candida tropicalis | 10.0 | - | 128.0 |

| Fungus | | MIC Range (µg/mL) | | |
|---|---|---|---|---|
| | Candida pseudotropicalis | 0.5 | - | 50.0 |
| | Candida krusei | 50.0 | - | >100.0 |
| | Candida guilliermondii | 6.25 | - | 100.0 |
| | Candida glabrata (T. glabrata) | >100.0 | - | >128.0 |
| | Cryptococcus neoformans | 0.25 | - | 2.0 |
| | Pityrosporum spp. | 0.2 | - | 0.8 |
| V. | **Dematiacese** | | | |
| | Phaechyphomycosis complex* | <0.06 | - | 0.5 |
| | Chromoblastomycosis complex** | ≤0.06 | - | 2.0 |

* *Exophiala jeanselmei, Wangiella dermatitidies, Cladosporium bantianum*

* * *Fonseceas pedrosoi, Phialophora spp.*

Terbinafine was primarily fungicidal against T. mentagrophytes, M. canis, A. fumigatus, Sc. brevicaulis, S. schenkii, and C. parapsilosis, and fungistatic against C. albicans.

## PHARMACOLOGY

The mechanism of action of terbinafine involves specific inhibition of fungal ergosterol biosynthesis at the point of squalene epoxidation, leading to a deficiency of an essential component of the fungal cell membranes (i.e. ergosterol) and to intracellular accumulation of the precursor squalene. The latter effect appears to be responsible for the primary fungicidal activity, its consequent disruption of cell membranes and cell wall synthesis having been noted in ultrastructural studies of terbinafine treated fungi. This mechanism distinguishes terbinafine from the azole antimycotics, which affect a later step in ergosterol biosynthesis by inhibiting 14 α-demethylase, a cytochrome P-450 enzyme, upon which terbinafine has no effect. In contrast to many azoles, terbinafine does not bind to cytochromes P-450 in mammalian steroidogenic tissues.

The pharmacokinetics of orally administered terbinafine in plasma can best be described by a 2–compartment model. More than 80% of the dose is absorbed, clearance of the drug is high, it is extensively metabolized in the liver, and it is extensively distributed in the tissues. The peak plasma concentration is proportional to the dose, and the time to peak is ~2 hours, independent of the dose. Terbinafine has an elimination half-life of 17 hours.

Mean concentrations of terbinafine (in μg/g) measured in the stratum corneum, dermis/ epidermis, hair, sweat, and sebum during and after 12 days of 250 mg terbinafine per day in 10 healthy volunteers were as follows before (day 0), during (days 2, 6, 12) and after treatment (days 13 and 16).

| Day | 0 | 2 | 6 | 12 | 13 | 16 |
|---|---|---|---|---|---|---|
| stratum corneum | 0.11 | 0.86 | 2.84 | 9.05 | 5.08 | 3.06 |
| derm/epiderm | 0 | 0.05 | 0.23 | 0.35 | 0.11 | 0.14 |
| sebum | 0 | 38.2 | 43.1 | 39.7 | 45.1 | 18.8 |
| hair | 0.02 | 0.24 | 1.30 | 2.60 | 2.11 | 1.35 |
| sweat | 0 | 0 | 0 | 0 | 0 | 0 |

The pattern of tissue distribution suggests a rapid diffusion of drug through the dermis/lower epidermis into the stratum corneum, where maximal concentrations were achieved at day 12, and the $t_{1/2}$ was 3-4 days (this implies that the concentrations of terbinafine would remain above the MIC for most dermatophytes for 3 weeks). Another route of terbinafine distribution likely to be important for the treatment of dermatomycosis would be secretion into sebum, in which drug levels were high and persisted for several days after cessation of treatment.

In a study evaluating the efficacy of terbinafine in the treatment of onychomycosis, plasma levels were measured monthly in 9 patients, half of whom received 250 mg terbinafine q.d. in the evening and the other half 125 mg b.i.d. A pharmacokinetic steady state was attained at or before 4 weeks, the first analysis time point available. The steady-state plasma concentrations were 0.22 - 0.56 and 0.15 - 0.35 μg/mL for the b.i.d. and q.d. doses, respectively, and did not increase over time.

## TOXICOLOGY

Acute Toxicity

| Species | Sex | Route | LD50 |
|---|---|---|---|
| Mouse | M, F<br>M, F<br>M, F | oral<br>i.v.<br>1% solution orally | >4 g/kg<br>393 mg/kg<br>>250 mg/kg |
| Rat | M, F<br>M, F | oral<br>i.v. | >4 g/kg<br>213 mg/kg |

| | | | |
|---|---|---|---|
| | M, F<br>M, F | 1% cream orally<br>1% solution orally | 25 mg/kg (no mortalities)<br>>200 mg/kg |
| Rabbits | M, F | topical (suspension) | >1.5 g/kg |

Long Term Toxicity

| **Species** | **Length of Admin.** | **Route** | **Doses (mg/kg)** | **Results** |
|---|---|---|---|---|
| Rat | 26 weeks | oral | 0, 30, 100, 300 | ↑ in liver weights in the mid & high dose groups; ↑ in kidney and heart weights in high dose group; ↑ adrenal weight all dose groups. In all animals allowed a recovery period organ weights showed signs of reversibility. At all doses males showed ↑ incidence & severity of spontaneous nephropathy. At mid & high doses, livers of female rats showed enlargement of centrilobular hepatocytes. Histological evidence of recovery in liver but not in kidney on cessation of treatment. |
| Pre and Post Pubertal Rats | 55 days | oral | 0, 25, 75, 250 | In 15 day old rats treated until 70 days of age, the mid and high dose groups were toxic as shown by death of some animals at these dose levels. Reduction in mean body weight gain was also seen in these dose groups. |
| Juvenile Rats | 55 days | oral | 0, 10, 25, 45, 100 | Well tolerated in rats treated from 15 to 70 days of age. 1 death in low dose group. Slight increase in liver weights of high dose females. |
| Dogs | 26 weeks | oral | 0, 20, 60, 200 | Initial hypersalivation in mid and high dose groups; sporadic emesis in high dose group. Hematological parameters remained unchanged throughout experiment. At end of treatment livers of 3 of 4 high dose dogs contained lamellated intracytoplasmic inclusions. The no-toxic-effect level in doses was 60 mg/kg. |
| | 52 weeks | oral | 0, 10, 25, 100 | Mid and high dose groups showed sporadic emesis and slightly inhibited body weight gain. High dose groups showed sporadic hypersalivation and reduced food intake. Females of all dose groups showed slightly lower triglyceride values. |

| Species | Length of Admin. | Route | Doses (mg/kg) | Results |
|---|---|---|---|---|
| | | | | |
| Rabbits | 4 weeks | topical (2% cream) | 10, 20, 40 | Moderate reactions (erythema) at the application site. |
| | 4 weeks | topical (1% solution) | 0, 5, 15, 30 | Skin site showed erythema, edema and papules in all groups including placebo controls. |
| | 26 weeks | topical (1% and 2% cream) | 10, 20, 40 | Slight erythema and edema in all groups, including placebo controls. |

Reproduction Studies

| Species | Duration | Route | Doses (mg/kg) | Results |
|---|---|---|---|---|
| Rats | Fertility & Reproduction Study M: 63 days prior to mating F: 14 days prior to mating to weaning | oral | 10, 50, 250 | In the high dose group a lower pregnancy rate, mean number of implants and living pups per dam were observed as well as a high pre- and perinatal offspring mortality. Physical and functional development of the offspring was also retarded. The fertility and general reproductive performance of the offspring were normal at all dose levels tested. |
| | Embryotoxicity study days 6 to 15 postcoitum | oral | 30, 100, 300 | Inseminated female rats treated with terbinafine tolerated up to the 100 mg/kg dose well. Lower body weight gain was seen at 300 mg/kg. No embryolethal or teratogenic effects. |
| | Peri & post-natal study day 15 postcoitum to day 21 postpartum | oral | 30, 100, 300 | Inseminated female rats treated with terbinafine tolerated up to the high-dose level. No clinical signs or relevant reproductive changes in any group. |
| | Embryotoxicity study day 6 to 18 postcoitum | subcutaneous | 10, 30, 100 | In high dose group dams gained less body weight and had skin irritation at the injection site. A tendency to lower body weight gains was also noted in the mid dose group. No adverse effects observed on pregnancy or embryonic or fetal development in any group. |
| Rabbits | Embryotoxicity study day 6 to 18 | oral | 30, 100, 300 | Inseminated female rabbits treated with terbinafine tolerated up to 100 mg/kg well. In |

| Species | Duration | Route | Doses (mg/kg) | Results |
|---|---|---|---|---|
| | postcoitum | | | the high-dose group weight loss was observed in some dams, 2 of which had to be euthanized due to poor health. No relevant reproductive alterations were seen at any dose level. |
| | Embryotoxicity study day 6 to 18 postcoitum | topical | 15, 45, 150 | Slight skin irritation (erythema, edema) were observed in all groups including placebo controls. No relevant reproductive alterations at any dose level tested. Pregnancy, litter and fetal data in the treated groups were comparable to control data. |

Mutagenicity

In vitro and in vivo mutagenicity testing revealed no specific mutagenic or genotoxic properties of terbinafine. In vitro tests of cell transformation to malignancy were negative.

Carcinogenicity

| Species | Duration | Route | Doses (mg/kg) | Results |
|---|---|---|---|---|
| Mice | 100 weeks | oral | M: 14, 40, 130<br>F: 16, 60, 156 | There was a slight inhibition of body weight gain in the mid- and high-dose females. Macroscopic and microscopic examinations revealed no neoplastic or other findings which were attributable to treatment with terbinafine. |
| Rats | 123 weeks | oral | M: 6.9, 20, 69<br>F: 9.6, 28, 97 | Ophthalmoscopy revealed an ↑ in incidence of cataracts in the high-dose males. No treatment related cataract changes occurred after 52 weeks, and such eye changes are known to occur spontaneously in old rats. ↑ incidence of enlarged swollen livers and liver nodules in the high dose animals, particularly males. Slight ↑ incidence of hepatocellular tumours in the high dose males. Females of the high dose group showed a slightly greater incidence and extent of hepatocellular necrosis, suggesting the high dose was at the threshold of a toxic response. |

Additional Studies

The following additional chronic toxicity and genotoxicity studies were performed to investigate the findings of the life-time rat study and their relevance to man.

4-week oral toxicity study in rats with special emphasis on hepatic alterations

| Species | Duration | Route | Doses (mg/kg) |
|---|---|---|---|
| Rat | 4 weeks | oral | M: 100, 465; F: 108, 530 |
| **Results** | | | |
| Feed Intake & Body Weight Gain | Only at the high dose level were significant decreases in food intake and body weight gain recorded. | | |
| Clinical Chemistry | At the high-dose level reduced serum glucose (both sexes) and serum triglyceride levels (both sexes) and increased SGPT, SAP (females), and BUN (males) were seen. Significantly lower corticosterone plasma levels were found in high-dose animals and higher testosterone and estradiol plasma levels in low-dose males and females respectively. | | |
| Liver Measurements | Increased cytochrome P-450 content (high dose males) cytochrome $b_5$ contents (high dose males and females), cytochrome $b_5$ reductase activity (high dose males), 7-ethoxy-coumarin-O-deethylase activity (per mg cytochrome P-450; in low- and high-dose females), and peroxisomal palmitoyl-CoA epoxidase activity (low dose females and high dose males and females). Determination of liver compartments indicated a slight reduction of water content (high dose males), an unchanged protein content, and an increased lipid moiety (low dose males and high dose males and females). | | |
| Postmortem Findings | Increased absolute and relative liver, and relative kidney weights (high dose males and females), mild hepatic centrilobular hypertrophy (high-dose only), increase in peroxisome numbers, and abnormal peroxisome shape (high-dose males). Slight increase in hepatic peroxisome size and number (high dose males and females). In high-dose group, numerous abnormal peroxisomes were found in both sexes, as well as a slight proliferation of the SER. | | |

Effects of 13-week treatment on selected toxicological variables in rats

| Species | Duration | Route | Doses (mg/kg) | Results |
|---|---|---|---|---|
| Rats | 13 weeks | oral | M: 72<br>F: 102 | Slight decrease in serum triglycerides (significant in males only), slight increase in albumin (females); these changes were observed in test weeks 5 and 8 only. Relative liver weights were increased as was palmitoyl-CoA epoxidase activity. There was no evidence of hepatic peroxisomal morphological abnormalities; however peroxisome numbers were increased in both sexes. |

4-week oral toxicity study in mice

| Species | Duration | Route | Doses (mg/kg) | Results |
|---|---|---|---|---|
| Mice | 4 weeks | oral | M: 103, 510<br>F: 107, 512 | Slightly impaired liver function in males only. Slight induction of the cytochrome P-450 and $b_5$ systems was seen (only at the high-dose level in a biologically relevant way and more marked in males than females), as well as ethoxycoumarin-O-deethylase activity. The peroxisomal marker palmitoyl-CoA-epoxidase was slightly increased at all dose levels (in both sexes); no changes in the size or number of peroxisomes were seen. There seemed to be a link between the degree of induction of some major hepatic enzyme systems and the moderate hepatic centrilobular hypertrophy observed histologically (and more generally the liver weight increases). Endocrinological examinations revealed higher basal corticosterone levels in a number of low and high-dose animals. |

Preliminary toxicity study in monkeys

| Species | Duration | Route | Doses (mg/kg) | Results |
|---|---|---|---|---|
| Monkeys | 28 days | by gavage | 500 | Emesis and hypersalivation were observed on several occasions. The female showed consistent weight loss during the first 3 weeks and slight recovery thereafter. Liver weights were increased in both the treated animals, but there were no histopathological changes. No treatment-related changes in the peroxisome population or general cellular ultrastructure were seen. Increased activity of hepatic palmitoyl CoA-epoxidase indicated peroxisomal fatty oxidation. Cytosolic epoxide hydrolase activity was below detectable limit. |

32-week oral toxicity study in monkeys

| Species | Duration | Route | Doses (mg/kg) | Results |
|---|---|---|---|---|
| Monkey | 32 weeks | oral | 50, 150, 300 | Eye lesions were seen after 26 weeks of treatment. Ophthalmoscopy revealed white spots on the retina in mid and high dose animals. No similar changes were seen at earlier examination. No morphological changes were seen in any layer of the retina. After withdrawal of terbinafine, the changes described recover (fully after a 13 week recovery period). |

Test for tumour-initiating activity in the rat liver foci bioassay

After partial hepatectomy, rats were treated with a single oral dose of 1 g/kg terbinafine (controls were treated with N-nitrosomorpholine [NNM]) followed by an 8-week treatment with phenobarbital (for promotion of growth of putative preneoplastic foci). A significant increase in

foci/cm was seen only in NNM–treated animals in comparison with the respective control groups. No differences were observed between control animals (treated only with phenobarbital) and those treated with terbinafine plus phenobarbital. It was concluded that terbinafine did not have tumor-initiating potential even in combination with a tumor promoting agent.

Autoradiographic determination of the induction of DNA repair/synthesis and cell replication in rat hepatocyte primary cultures after in vivo treatment

No evidence was found for any induction of either DNA repair or DNA replication in the hepatocytes from terbinafine treated rats, and the frequency of replicating nuclei were in the control range.

Mutagenicity test using Salmonella typhimurium

Liver fractions from male rats treated for 13 weeks with 69 mg/kg/day of terbinafine and non-treated control rats were used to evaluate terbinafine for genetic activity. There was no evidence that repeated treatment of rats with terbinafine induces enzymes capable of producing mutagenic intermediates of terbinafine.

## BIBLIOGRAPHY

1. Battig FA, Nefzger M, Schulz G. Major biotransformation routes of some allylamine antimycotics. IN: Recent trends in the discovery, development and evaluation of antifungal agents. Edit RA Fromtling; Publ JR Prous Science Publishers S.A., Barcelona 1987; pp 479-495.

2. Battig FA, Nefzger M, Czok R. Pharmacokinetics and biotransformation of the 14C labelled drug in laboratory animals and man. IN: Proceedings, 13th International Congr of Chemother Austria, Aug 28-Sept 2, 1983; Edit KH Spitzy, K Krrer; Publ H Egermann, Neulengbach, Austria. Part 116, pp 37-40.

3. Baudraz–Rosselet F, Rakosi T, Wili PB, Kenzelmann R. Treatment of onychomycosis with terbinafine. Br J Derm 1992; 126 (suppl 39).

4. Bechter R. Effects of antimycotic compounds on sperm function, on fertilization and on preimplantation embryos in vitro. Experientia (Basel) 1989; 45 (suppl): p A67 Abstr. no P PHA 332.

5. Bergstresser PR, et al. Topical terbinafine and clotrimazole in interdigital tinea pedis: A multicenter comparison of cure and relapse rates with 1- and 4- week treatment regimens. J Am Acad Dermatol 1993; 28: 648-651.

6. Berman B, et al. Efficacy of a 1 week, twice daily regimen of terbinafine 1% cream in the treatment of interdigital tinea pedis. Results of placebo–controlled, double–blind multicenter trials. J Am Acad Dermatol 1992; 26 (6): 956-960.

7. Bertz RJ, Granneman, GR. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. Clin Pharmacokinet Vo. 32 (3), pp. 210-58, 1997.

8. Clayton YM. Dermatophyte infections. Bailliere's Clin Trop Med Commun Dis 1989; 4(1): 1-29.

9. Cordero C, de la Rosa I, Espinosa Z, et al. Short–term therapy of tinea cruris/corporis with topical terbinafine. J Dermatol Treat 1992; 3(Suppl. 1): 23-24.

10. Del Palacio–Hernanz A, Lopez–Gomez S, Gonzalez–Lastra F, et al. A comparative double–blind study of terbinafine (Lamisil) and griseofulvin in tinea corporis and tinea cruris. Clin Exp Dermatol 1990; 15: 210-216.

11. Del Palacio–Hernanz A, Lopez–Gomez S, Iglesias–Diez L, et al. Clinical evaluation of terbinafine (Lamisil) in dermatophytosis Vol 89, p 40. J Dermatol Treat 1990; 1(suppl 2): 339-40.

12. De–wit RFE. A randomized double–blind multicentre comparative study of Lamisil (terbinafine) versus ketoconazole in tinea corporis. J Dermatol Treat 1990; 1(supp 2): 41-42.

13. Editorial. Onychomycosis and terbinafine. Lancet 1990; 335: 636.

14. Effendy I, Krause W. In vivo effects of terbinafine and ketoconazole on testosterone plasma levels in healthy males. Dermatologica (Basel) 1989; 178: 103-106.

15. Espinel–Ingroff A, Gebhart RJ, Shadomy S. In vitro studies with SF 86-327, an orally active antifungal agents. IN: 24th Interscience conference on antimicrobial agents and chemotherapy Washington, Oct 1984; Publ Amer Soc Microbiology 1984; p 144, Abstr 305.

16. Evans EGV. A double–blind comparison of 1, 3, 5 and 7 day topical therapy with 1% terbinafine (Lamisil ®) cream in tinea pedis. Br J Dermatol 1992; 127: 21.

17. Evans EGV, Seaman RAJ, James IGV. Short–duration therapy with terbinafine 1% cream in dermatophyte skin infections. Br J Dermatol 1994; 130: 83-87.

18. Evans EGV, Shah JM, Joshipura RC. One–week treatment of tinea corporis and tinea cruris with terbinafine (Lamisil®) cream: a placebo–controlled study. J Dermatol Treat 1994; 3: 181-184.

19. Goodfield MJD. Clinical results with terbinafine in onychomycosis. J Dermatol Treat 1990; 1(suppl 2); 55-57.

20. Goodfield MJD, Rowell NR, Forster RA, et al. Treatment of dermatophyte infection of the finger- and toe–nails with terbinafine (SF 86-327, Lamisil) an orally active fungicidal agent. Br J Derm 1989; 121: 753-757.

21. Grimus R, Schuster I. Uptake distribution and metabolism in the rat. A comparison of in vitro and in vivo data (SF 86-327). IN: Proceedings, 13th Internat Congr of Chemother, Austria, Sept 28, 1983. Edit KH Spitzy, K Karrer. Publ H Egermann, Neulengbach, Austria. Part 116 pp 47-51.

22. Jensen JC. Clinical pharmacokinetics of terbinafine (Lamisil). Clin Exp Dermatol 1989; 14: 110-113.

23. Jensen JC. Pharmacokinetics of Lamisil in humans. J Dermatol Treat 1990; 1(suppi 2): 15-18.

24. Jones TC, Villars VV. Terbinafine. Chemotherapy of fungal diseases. Edit JF Ryley. Publ Springer-Verlag, Berlin, Heidelberg, 1990; pp 483-503 (series Handbook of Experimental Pharmacology, vol 96).

25. Kagawa S. Clinical efficacy of terbinafine in 629 Japanese patients with dermatomycosis. Clin Exp Dermatol 1989; 14: 114-115.

26. Lazardi K, Urbina JA, De-Souza W. Ultrastructural alterations induced by two ergosterol biosynthesis inhibitors, ketoconazole and terbinafine, on epimastigotes and amastigotes of trypanosoma (schizotrypanum) Cruzi. Antimicrob Agents Chemother 1990; 34: 2097-2105.

27. Lever LR, Thomas R, Dykes PJ, et al. Investigation of the pharmacokinetics of oral and topical terbinafine. Clin Res 1989; 37: 726A.

28. Male O, Stephen A, Mieth H. Allylamines: a novel therapeutic option in the treatment of fungal skin infections. IN: Recent advances in chemotherapy: antimicrobial section. 14th Internat Congr Chemother, June 23-28 1985. Publ Univ Tokyo Press, 1985; pp 1950-1951.

29. Male O, Villars V. The topical treatment of dermatomycoses with allylamines. IN: Proceed 10th Congr Int Soc for human and animal myocology, Barcelona 1988. Edit JM Torres–Rodriguez; Publ JR Prous Science, Barcelona 1988; pp 227-230.

30. Mekler PH, Richardson BP, Brueggemann S, et al. Evaluation of toxicity in laboratory animals, tolerance and pharmacokinetics after oral application to man. IN: Proceed. 13th Internat Congr of Chemother Vienna, Aug 28 - Sept 2, 1983. Publ H Egermann, Neulengbach, Austria 1983; Vol 89, p 53. Part 116 pp 52-58.

31. Mieth H, Petranyi G. Preclinical evaluation of terbinafine in vivo. Clin Exp Dermatol 1989; 14: 104-107.

32. Millikan LE. Efficacy and tolerability of topical terbinafine in the treatment of tinea cruris. J Amer Acad Dermatol 1990; 23 (no 4/part 2 suppl): 795-799.

33. Nashan D, Knuth UA, Weidinger G, et al. The antimycotic drug terbinafine in contrast to ketoconazole lacks acute effects on the pituitary–testicular function of healthy men: a placebo–controlled double–blind trial. Acta Endocr (Copenh) 1989; 120: 677-681.

34. Petranyi G, Meingassner JG, Mieth H. Experimental chemotherapeutic results with SF 86–327, a new antimycotic agent. ZBL Bakteriol Mikrobiol Hygiene (A) 1986; 262: 158-159.

35. Ryder NS. The mechanism of action of terbinafine. Clin Exp Dermatol 1989; 14: 98-100.

36. Ryder NS. Mode of action of SF 86-327 in candida and trichophyton. IN: 24th Interscience Conference on antimicrobial agents and chemotherapy, Washington US, Oct 1984. Publ Amer Soc Microbiology; Vol 10, pp 104-144. Abstr 306.

37. Ryder NS. Specific inhibition of fungal sterol biosynthesis by SF 86-327, a new allylamine antimycotic agent. Antimicrob Agents Chemother 1985; 27: 252-256.

38. Savin RC. Successful treatment of chronic tinea pedis (moccasin type) with terbinafine (Lamisil). Clin Exp Dermatol 1989; 14: 116-119.

39. Savin RC. Treatment of chronic tinea pedis (athlete's foot type) with topical terbinafine. J Amer Acad Dermatol 1990; 23 (no 4/part 2, suppl): 786-789.

40. Schuster I. The interaction of representative members from two classes of antimycotics - The azoles and the allylamines - with cytochromes -450 in steroidogenic tissues and liver. Xenobiotica 1985; 15: 529-546.

41. Smith EB, Zaias N, Savin RC. Successful treatment of tinea pedis (athlete's foot type) with topical SF 86-327 cream. IN: Progress in antimicrobial and anticancer chemotherapy, Vol 2; 15th Internat Congr Chemother, Istanbul, July 19-24 1987; Publ Ecomed 1987; pp 1017-1019.

42. Stephen A, Czok R, Male O. Terbinafine: initial clinical results. IN: Recent trends in the discovery, development and evaluation of antifungal agents; Publ JR Prous Science Publ SA, Barcelona 1987; pp 511-520.

43. Stephen A, Ganzinger U. Oral treatment of dermatophytosis with a new antifungal agent. IN: Proceed, 13th Internat Congr of Chemother, Vienna, Aug 28-Sept 2 1983; Publ H Egermann, Neulengbach, Austria 1983. Part 116, pp 59-60.

44. Stephen A, Ganzinger U, Czok R. SF 86-327: Results of Phase II studies with a new antifungal agent for oral and topical application. IN: Recent advances in chemotherapy: antimicrobial section; 14th Internat Congress of chemotherapy, Kyoto, June 23-38, 1985. Publ Univ Tokyo Press, 1985; pp 1946-1947.

45. Zaias N. Management of onychomycosis with oral terbinafine. J Amer Acad Dermatol 1990; Vol 23 (no 4/part 2, suppl) pp 810-812.

46. Zaias N, Berman B, Cordero C, et al. Efficacy of a 1–week, once–daily regimen of terbinafine 1% cream in the treatment of T. cruris and T. corporis. J Amer Acad Dermatol, Vol. 29, p. 646-648, 1993.

47. Zaias N, Serrano L. Effectiveness and safety of SF 86-327 (terbinafine) in the treatment of T. rubrum onychomycosis. IN: Dermatology in five continents, Proceed of the 27th World Congr of Dermatol Berlin May 24-29, 1987. Publ Springer-Verlag 1988; pp 913-914.