PRODUCT MONOGRAPH

[Pr] AURO-TERBINAFINE

(Terbinafine hydrochloride Tablets)

125 mg and 250 mg tablets (as terbinafine base)

Antifungal Agent

Auro Pharma Inc.
1170 Sheppard Ave. West, Unit #16
Toronto, Ontario
M3K 2A3
CANADA
e-mail : dvnmurty@yahoo.com
www.auropharma.ca

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Pr AURO-TERBINAFINE
(terbinafine hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	Tablets 125 mg, 250 mg, terbinafine (as terbinafine hydrochloride)	Not applicable *(For a complete listing see Dosage Forms, Composition and Packaging)*

INDICATIONS AND CLINICAL USE

AURO-TERBINAFINE (terbinafine hydrochloride tablets) 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, Epidermophyton floccosum* and yeasts of the genus *Candida* (eg. *C.albicans*), as well as *Malassezia furfur.*

Terbinafine is indicated in the treatment of onychomycosis (fungal infection of the nail) caused by dermatophyte fungi.

Prior to initiating treatment with terbinafine tablets, appropriate nail or skin specimens should be obtained for laboratory testing (KOH preparation, fungal culture, or nail biopsy) in order to confirm the diagnosis of onychomyocosis or dermatomycosis.

Terbinafine may be considered for the treatment of severe tineal skin infections (tinea corporis, tinea cruris and tinea pedis), which have been unresponsive to topical treatment.

Note: Terbinafine is not effective in pityriasis versicolor.

CONTRAINDICATIONS

Terbinafine is contraindicated in patients with a known hypersensitivity to terbinafine or to any of the excipients of terbinafine. (see **DOSAGE FORMS, COMPOSITION and PACKAGING)**

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Rare cases of liver failure, some leading to death or liver transplant, have occurred with the use of terbinafine tablets for the treatment of onychomycosis and dermatomycosis in individuals with and without pre-existing liver disease.

In the majority of liver cases reported in association with terbinafine use, the patients had serious underlying systemic conditions and an uncertain causal association with terbinafine. The severity of hepatic events and/or their outcome may be worse in patients with active or chronic liver disease. Treatment with terbinafine tablets should be discontinued if biochemical or clinical evidence of liver injury develops.

Hepatic

Terbinafine tablets are not recommended for patients with chronic or active liver disease. Before prescribing terbinafine tablets, pre-existing liver disease should be assessed. Hepatotoxicity may occur in patients with and without pre-existing liver disease. Pre-treatment serum transaminase (ALT and AST) tests are advised for all patients before taking terbinafine tablets. Patients prescribed terbinafine tablets should be warned to report immediately to their physician any symptoms of persistent nausea, anorexia, fatigue, vomiting, right upper abdominal pain or jaundice, dark urine or pale stools. Patients with these symptoms should discontinue taking oral terbinafine, and the patient's liver function should be immediately evaluated.

Renal

The pharmacokinetics of terbinafine have been investigated in patients with renal impairment (creatinine clearance ≤ 50 mL/ min); based on this study the use of terbinafine in renally impaired patients is not recommended (see ***CLINICAL PHARMACOLOGY,*** **Pharmacokinetics).**

Metabolism

In vitro and *in vivo* studies have shown that terbinafine inhibits the CYP2D6 metabolism. Therefore, patients receiving concomitant treatment with drugs predominantly metabolised by this enzyme, e.g. certain members of the following drug classes, tricyclic antidepressants (TCAs), β blockers, selective serotonine reuptake inhibitors (SSRIs), antiarrhythmics class 1A, 1B and 1C and monoamine oxidase inhibitors (MAO-Is) Type B, should be followed up, if the co-administered drug has a narrow therapeutic window (see **DRUG INTERACTIONS).**

Skin

Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis) have been very rarely reported in patients taking terbinafine tablets. If progressive skin rash occurs, treatment with terbinafine tablets should be discontinued.

Ophthalmologic

Changes in the ocular lens and retina have been reported following the use of terbinafine tablets in controlled trials. The changes noted were non-specific and the significance of these changes is unknown.

Immune

Transient decreases in absolute lymphocyte counts (ALC) have been observed in controlled clinical trials. The clinical significance of this observation is unknown. However, in patients with known or suspected immunodeficiency, physicians should consider monitoring complete blood counts in individuals using terbinafine therapy for greater than six weeks.

Lupus erythematosus:
During post-marketing experience, precipitation and exacerbation of cutaneous and systemic lupus erythematosus have been reported infrequently in patients taking terbinafine. Terbinafine therapy should be discontinued in patients with clinical signs and symptoms suggestive of lupus erythematosus.

Hematologic

Very rare cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with terbinafine tablets. Aetiology of any blood dyscrasias that occur in patients treated with terbinafine tablets should be evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with terbinafine tablets.

Carcinogenesis and Mutagenesis

An increase in liver tumours was observed in male rats at the highest dose level (69 mg/kg) during a 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.

General:

Special Populations

Pregnant Women: Animal fetal toxicity and fertility studies did not reveal any teratogenic or embryofetotoxic potential of terbinafine. However, there is only very limited clinical experience with terbinafine in pregnant women; therefore, unless the potential benefits outweigh any potential risks, terbinafine should not be used during pregnancy.

Nursing Women: Terbinafine is excreted in breast milk; therefore mothers receiving treatment with terbinafine should not breast feed.

Geriatrics: 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 in the elderly 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).**

Pediatrics: The safety and efficacy of terbinafine have not been established in pediatric patients. Terbinafine should be kept out of the reach of children.

Occupational Hazards

Effects on ability to drive and use machines

No studies on the effects of terbinafine tablets treatment on the ability to drive and use machines have been performed. Patients who experience dizziness as an undesirable effect should avoid driving vehicles or using machines.

ADVERSE REACTIONS

Adverse Drug reaction Overview

> *Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Frequency estimate: very common ≥ 10%, common ≥ 1% to < 10%, uncommon ≥ 0.1% to < 1%, rare ≥ 0.01 % to < 0.1%, very rare < 0.01 % (includes isolated reports).

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

Clinical Trials Adverse Drug Reactions

In clinical trials submitted for purposes of marketing approval in Canada 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, diarrhoea), 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 of adverse events illustrates some of these results:

Organ System Adverse Event	TERBINAFINE 250 mg(n = 998)	
	Number	(%)
SKIN (overall)	27	2.7%
Erythema or rash	9	0.9
Urticaria	5	0.5
Eczema	1	0.1
Pruritis	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
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

Less Common Clinical Trial Adverse Drug Reactions (<1%)

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. Isolated cases of prolonged taste disturbances have been reported. A decrease of food intake leading to significant weight loss was observed in very few severe cases.

Rare: Idiosyncratic and symptomatic hepatobiliary reactions (2/3 primarily cholestatic in nature and the remainder involving hepatocytic damage or both) have been reported in

association with terbinafine treatment, including very rare cases of serious liver failure (some leading to liver transplant or death). 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) (see **WARNINGS AND PRECAUTIONS).**

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 1:37000 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.

Hepatobiliary dysfunction (primarily cholestatic in nature), very rare cases of serious liver failure (some with a fatal outcome, or requiring liver transplant). In the majority of liver failure cases the patients had serious underlying systemic conditions and a causal association with the intake of terbinafine was uncertain.

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), acute generalized exanthematous pustulosis psoriasiform eruptions or exacerbation of psoriasis (if progressive skin rash occurs, terbinafine treatment should be discontinued). Anaphylactic reactions (including angioedema) have been reported. Precipitation or exacerbation of cutaneous and systemic *lupus erythematosus* have been reported.

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

Hematologic disorders such as neutropenia, agranulocytosis, pancytopenia and thrombocytopenia have been reported (very rare). 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.

Post-Market Adverse Drug Reactions

During post-marketing experience with terbinafine tablets, precipitation and exacerbation of cutaneous and systemic lupus erythematosus have been reported infrequently in patients taking terbinafine. Terbinafine therapy should be discontinued in patients with clinical signs and symptoms suggestive of lupus erythematosus.

The following adverse events were also reported: dizziness, anemia, CPK elevations, rhabdomyolysis, pancytopenia, paresthesia and hypoaesthesia.

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions:

The following medicinal products may increase the effect or plasma concentration of terbinafine:

Cimetidine decreased the clearance of terbinafine by 33%.

The following medicinal products may decrease the effect or plasma concentration of terbinafine:

Rifampicin increased the clearance of terbinafine by 100%.

Effect of terbinafine on other medicinal products;

According to the results from studies undertaken *in vitro* and in healthy volunteers, terbinafine shows negligible potential for inhibiting or enhancing the clearance of most drugs that are metabolised via the cytochrome P450 system (e.g. terfenadine, triazolam, tolbutamide or oral contraceptives) with exception of those metabolised through CYP2D6 (see below).
Terbinafine does not interfere with the clearance of antipyrine or digoxin.

Some cases of menstrual irregularities have been reported in patients taking terbinafine tablets concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

Terbinafine may increase the effect or plasma concentration of the following medicinal products:

Caffeine: Terbinafine decreased the clearance of caffeine administered intravenously by 19%.

Compounds predominantly metabolised by CYP2D6
In vitro and *in vivo* studies have shown that terbinafine inhibits the CYP2D6-mediated metabolism. This finding may be of clinical relevance for compounds predominantly metabolized by this enzyme, e.g. certain members of the following drug classes tricyclic antidepressants (TCAs), β-blockers, selective serotonine reuptake inhibitors (SSRIs), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B, particularly if they also have a narrow therapeutic window (see **WARNINGS AND PRECAUTIONS).**

Terbinafine decreased the clearance of desipramine by 82%.

Terbinafine may decrease the effect or plasma concentration of the following medicinal products:

Terbinafine increased the clearance of ciclosporin by 15%.

DOSAGE AND ADMINISTRATION

Adults: 125 mg b.i.d. or 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 mycolological cure.

Administration:

Oral

DOSING CONSIDERATIONS

Special populations:

Liver impairment
Terbinafine tablets are not recommended for patients with chronic or active liver disease (see Warnings and Precautions).

Renal impairment
The use of terbinafine tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population (see Warnings and Precautions).

OVERDOSAGE

A few cases of overdosage with terbinafine tablets (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.
For the management of suspected overdose, contact your local Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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. Its activity against yeasts is fungicidal or fungistatic, depending on the species.

Pharmacodynamics

Terbinafine interferes specifically with fungal sterol biosynthesis at an early step. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. Terbinafine acts by inhibition of squalene epoxidase in the fungal cell membrane. The enzyme squalene epoxidase is not linked to the cytochrome P450 system.

When given orally, the drug concentrates rapidly in skin, hair and nails at levels associated with fungicidal activity.

Pharmacokinetics

Absorption:

Following oral administration, terbinafine is well absorbed (>70%) and the absolute bioavailability of terbinafine from terbinafine tablets as a result of first-pass metabolism is approximately 50 %. A single 250 mg dose of terbinafine tablets resulted in mean a peak plasma concentration of 1.3 µg/ml within 1.5 hours after administration. At steady-state, in comparison to a single dose, peak

concentration of terbinafine was on average 25% higher and plasma AUC increased by a factor of 2.3. From the increase in plasma AUC an effective half-life of ~30 hours can be calculated. The bioavailability of terbinafine is moderately affected by food (increase in the AUC of less than 20%), but not sufficiently to require dosing adjustments.

Distribution:

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 lipophilic stratum corneum. It is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and sebum-rich skin. There is evidence that terbinafine is distributed in the nail plate within the first few weeks of commencing therapy.

Metabolism & Excretion:

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 isoenzymes are involved in its metabolism with major contributions from CYP 2C9, CYP 1A2, CYP 3A4, CYP 2C8 and CYP 2C19. Biotransformation results in metabolites with no antifungal activity which are excreted predominantly through the urine. No clinically relevant age-dependent changes in steady-state plasma concentrations of terbinafine have been observed.

Following a single 250 mg dose in 12 hepatically impaired cirrhotic (alcoholic) patients, total clearance of terbinafine was reduced by about 40%. In a sample of 12 renally impaired patients (median creatinine clearance of 17.6 mL/min), 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.

STORAGE AND STABILITY

Store at room temperature between 15 and 30 ^{0}C.
Protect from light.

SPECIAL HANDLING INSTRUCTIONS

HDPE bottle: Protect from light.
Blister Pack: Store in the original pack in order to protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form	**Tablets**	
	125 mg	250 mg
Description	White to off white, round uncoated, biconvex, beveled edge tablets having 'D' debossed on one side and '56' on the other side.	White to off white, round uncoated, biconvex, beveled edge tablets with break line and 'D' debossed on one side and '74' on the other side.
Composition	Terbinafine 125 mg (as terbinafine hydrochloride), cellulose microcrystalline, Sodium starch glycolate, Silica colloidal anhydrous, Hypromellose and Magnesium stearate.	Terbinafine 250 mg (as terbinafine hydrochloride), cellulose microcrystalline, Sodium starch glycolate, Silica colloidal anhydrous, Hypromellose and Magnesium stearate.
Packaging	Blister pack of 28 tablets (14 tablets per blister).	HDPE Bottle of 100 tablets. Blister pack of 28 tablets (14 tablets per blister).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

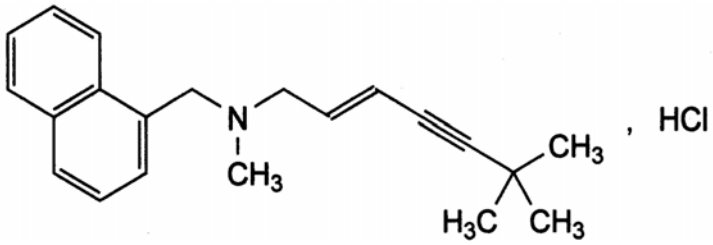
Common Name: Terbinafine Hydrochloride

Chemical Name: (2E)-N,6,6-Trimemyl-*N*- (naphthalen-1-ylmethyl) hept-2-en-4-yn-1-amine hydrochloride.

Molecular Formula: $C_{21}H_{26}NCl$

Molecular Mass: 327.9

Structural formula:



Physicochemical properties:

- White or almost white powder.
- Solubility: very slightly or slightly soluble in water. Freely soluble in anhydrous ethanol and in methanol, slightly soluble in acetone. 0.63% (W/V) in water and > 2% (W/V) in chloroform
- Melting point: 195 ^{o}C to 198 ^{o}C
- PKa (I) value: 7.10
- pH of a solution (0.5%) in methanol/water 4:6 (v/v): ~ 4.7. at 25 ^{0}C.

CLINICAL TRIALS

Comparative Bio-availability data

An open label, randomised, two treatment, two sequence, two period, cross-over, single-dose, comparative oral bioavailability study of Terbinafine hydrochloride 250 mg tablets (Test) of Aurobindo Pharma Ltd., India and LAMISIL 250 mg tablets (Reference) of Novartis Pharmaceuticals Canada Inc., CANADA in 37 healthy, adult, male, human subjects under fasting conditions.

Summary Table of the Comparative Bio-availability Data

Terbinafine hydrochloride tablets (1 X 250 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference**[†]	**% Ratio of Geometric Means**[#]	**90% Confidence Interval**[#]
AUC_{0-72} (hr.ng/mL)	4928.272 5766.032 (61.8)	4849.220 5602.017 (54.0)	101.49	91.76- 112.25
$AUC_{0-\infty}$ (hr.ng/mL)	5619.952 6847.485 (65.8)	5580.267 6554.990 (55.5)	100.71	90.78-111.73
C_{max} (ng/mL)	767.606 869.963 (51.0)	778.906 888.630 (49.9)	98.55	87.61 - 110.86
T_{max}[§] **(h)**	2.25 (0.75-5.00)	2.00 (0.75-5.00)		
$T_{½}$[$] **(h)**	42.700 (51.2)	38.813 (34.9)		

***** Auro-Terbinafine 250 mg manufactured by Aurobindo Pharma Ltd. India for Auro Pharma Inc.
[†] Lamisil 250 mg manufactured by Novartis Pharmaceuticals Canada Inc. were purchased in Canada
[§]Expressed as the Median (Range) instead of Arithmetic Mean (%CV)
[$] Expressed as Arithmetic Mean (%CV) only
[#]Based on the least squares mean estimates

Onychomycosis

Two studies evaluated the efficacy of oral terbinafine in the treatment of toe or fingernail onychomycosis

Study Demographics and Trial Design

Summary of patient demographics for oral terbinafine clinical trials in onychomycosis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender	Race
SF1501	Randomized, double-blind (double-dummy), multicenter, parallel group,stratified enrolment (toe/fingernail) b.i.d. vs o.d. dosage	Terbinafine tablets, oral 125 mg b.i.d up to 48 wk (toenail) or 24 wk (fingernail)	51 enrolled 43 evaluable	45 (18-74)	Male = 34 Female = 9	Not reported
		Terbinafine tablets, 2x125 mg o.d. up to 48 wk (toenail) or 24 wk (fingernail)	52 enrolled 48 evaluable	45 (18-74)	Male = 34 Female = 14	Not reported
SF00423	Randomized, double-blind, multicenter, parallel group, griseofulvin-comparative	Terbinafine capsules: Oral, 250 mg bid for 3-6 months	47 enrolled 29 evaluable	44.6 (21-76yr)	Male = 24	Caucasian 100%
		Griseofulvin capsules: Oral 250 mg bid for up to 6 months (standard treatment period is up to 12 months)	34 enrolled 22 evaluable	43.5 (20-61 yr)	Male =15	Caucasian 100%

Study Results

Results of study SF1501 in onychomycosis

Primary Endpoints	b.i.d. Number (%) patients	o.d. Number (%) patients
Mycological cure (negative KOH and culture) -all infections	Toenails	
	25/31(81%)	28/35 (80%)
	Fingernails	
	10/10 (100%)	10/11(91%)
Effective treatment (negative mycology plus continuous or limited nail growth) at end of treatment at week 24 - all infections	Toenails	
	24/32 (75%)	26/37 (70%)
	Fingernails	
	10/11(91%)	10/11(91%)

There were no significant differences between b.i.d and o.d. treatment regimens with respect to mycological cure rates or rates of effective treatment. Mycological cure at end of treatment was 95 % for fingernails and 80% for toenails. At follow-up visit 3-12 months later, over 81% of toenail onychomycosis were cured without relapse.

Results of study SFO0423 in onychomycosis

Primary Endpoints	Terbinafine Number (%) patients	Comparator Number (%) patients
Effective treatment (negative mycology plus continuous or limited nail growth) at end of, treatment at week 24*	Toenail	
	11/20(55%)	5/12 (42%)
	Fingernail	
	7/9 (78%)	8/10 (80%)
Mycological cure (negative culture and KOH) at week 24	Toenail	
	12/20 (60%)	5/12 (42%)
	Fingernail	
	7/9 (78%)	7/10(70%)

*The combined clinical/mycological endpoint was not specified in the protocol

Effective treatment in the terbinafine treated group was 78% fingernail and 55% toenail with treatment durations of 3-6 months. Griseofulvin was 80% and 42% effective for fingernails and toenails respectively. Thus, short duration therapy (3-6 months) using 500 mg per day of terbinafine appears effective in many patients with onychomycosis due to dermatophyte infections.

Tinea corporis/cruris

Study demographics and trial design

Summary of patient demographics for oral terbinafine clinical trials in tinea corporis/cruris

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age across studies (Range)	Gender	Race: Percent Caucasian
Placebo-controlled: SFO041B 5-OR SFO041C	Randomized, single or multicenter, parallel group, double-blind, placebo controlled	Terbinafine oral, capsules, 125 mg bid for 4 wk; 2 wk follow-up	Entered 79 Evaluable 62	34 - 40 years (18-74)	Male = 50 Female 1 1	71-100%
		Matching placebo	Entered 77 Evaluable 62	37-42 (18-70)	Male = 49 Female = 13	
Griseofulvin-controlled: 11-OR	Randomized, single or multicenter, parallel group, double-blind, double-dummy, griseofulvin-controlled	Terbinafine oral capsules, 125 mg and placebo bid for up to 6 wk; 2-6 wk follow-up	Entered 189 Evaluable 174	37-38 (17-69)	Male = 105 Female = 69	85-99%
SFO044		Griseofulvin oral capsules 2x250 mg bid for up to 6 wk; 2-6 wk follow-up	Entered 192 Evaluable 170	31-34 (17-85)	Male =107 Female = 63	
Ketoconazole controlled: SF 3006 SF 0047	Randomized, single or multicenter, parallel group, double-blind, double-dummy, griseofulvin-controlled	Terbinafine oral capsules, 125 mg and placebo bid for up to 6 wk; 4-8 wk follow-up	Entered 73 Evaluable 65	34-48 (18-80)	Male = 40 Female = 25	60-92%
		Ketoconazole oral capsules 200 mg od (placebo od) for up to 6 wk; 2-6 wk follow-up	Entered = 71 Evaluable = 62	31-43 (16-70)	Male = 40 Female = 22	

Study results

Combined results of placebo-controlled studies SF 0041 B, 5-OR, SF 0041C in tinea corporis/cruris[1]

Primary Endpoints	Terbinafine Number (%)	Placebo Number (%)
Mycological cure (negative culture and KOH) at follow-up	7-30 (100-64%)	0-4 (0-36%)
Effective treatment (mycological cure and no to minimal signs or symptoms) at follow-up	8-30 (62-91%)	0-4 (0-23%)
5-OR: mycological cure results (combined culture and KOH results) were not provided and too few patients returned at follow-up for meaningful assessments. However, at end of treatment, terbinafine was significantly better than placebo in terms of mycological cures and negative KOH results (Negative KOH of 73% vs 17% for active and placebo, p = 0.043; Negative cultures of 73% vs 0% for active and placebo, p = -.007) .		
SF 0041 B: too few placebo patients returned at follow-up for meaningful assessments; however, at end of therapy the proportion of patients with mycological cures was greater in the terbinafine group compared with placebo; effective treatment was noted in 75% and 23% of active and placebo groups		

[1] Range of values represents the highest and lowest values noted across the studies represented

The efficacy of a up to 6 weeks of treatment with terbinafine was consistently positive across 3 placebo-controlled trials both in rates of mycological cures and in the combination of mycological and clinical endpoints. In the placebo-controlled trials, placebo patients often did not return at the post-treatment follow-up to provide meaningful results at that visit. However, results at the end of treatment speak to the high degree of efficacy of terbinafine using clinical and/or mycological endpoints. Results of 4 studies with active comparators show terbinafine to be at least as good as, if not better than, systemically administered griseofulvin and ketoconazole.

Results of griseofulvin-controlled studies 11-OR and SF 0044 in tinea corporis/cruris[1]

Primary Endpoints	Terbinafine Number (%)	Comparator Number (%)
Mycological cure (negative culture and KOH) at follow-up	111-40 (93-100%)	101-36 (94-95%)
Effective treatment (mycological cure and no to minimal signs or symptoms) at follow-up	119-37 (94-77%)	108-36 (86-82%)

[1] Range of values represents the highest and lowest values noted across the studies represented

Results of ketoconazole-controlled studies SF 3006 and SF 0047 in tinea corporis/cruris[1]

Primary Endpoints	Terbinafine Number (%)	Comparator Number (%)
Mycological cure (negative culture and KOH) at follow-up	28-36 (100-97%)	23-31 (92-86)
Effective treatment (mycological cure and no to minimal signs or symptoms) at follow-up	28-35 (100-95%)	23-29 (92-78%)

[1]Range of values represents the highest and lowest values noted across the studies represented

Tinea Pedis

Study demographics and trial design

Summary of patient demographics for clinical trials in tinea pedis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender	Race
39-40OR	Randomized, double-blind, multicenter, placebo-controlled	Terbinafine tablets (or matching placebo) 125 mg bid for 6 weeks; 2 week follow-up	Terbinafine Enrolled 26 Evaluable 23	37 years (20-64)	Male = 15 Female =8	92% Caucasian
			Placebo Enrolled 24 Evaluable 18	40 years (20-68)	Male =13 Female=5	
SF 0508	Randomized, double-blind, multicenter, placebo-controlled	Terbinafine tablets (or matching placebo) 125x2 mg od for 2 weeks; 6 week follow-up	Terbinafine Enrolled 18 Evaluable 14	39 years (19-72)	Male = 20 Female =6	79% Caucasian
			Placebo Enrolled 19 Evaluable 14	45 years (20-82)	Male =23 Female = 4	
SF 0025	Randomized, double-blind, multicenter, griseofulvin	Terbinafine capsules, 125 mg bid for 6 wk; 2 wk follow-up	Enrolled 39 Evaluable 33	38 years (18-79)	Male =17 Female =16	95% Caucasian

	controlled	Griseofulvin capsules 250 mg bid for 6 wk; 2 wk follow-up	Enrolled 37 Evaluable 33	35 years (14-59)	Male =18 Female =15	
20-OR	Randomized, double-blind, multicenter, griseofulvin controlled	Terbinafine capsules, 125 mg bid for 6 wk; 2 wk follow-up	Enrolled 18 Evaluable 16	38 years (22-63)	Male =11 Female = 5	82% Caucasian
		Griseofulvin capsules 250 mg bid for 6 wk; 2 wk follow-up	Enrolled 18 Evaluable 12	36 years (20-49)	Male = 9 Female = 3	

Study results

Results of placebo controlled studies 39-40OR, SFO508 in tinea pedis

Primary Endpoints	Terbinafine Number (%)	Placebo Number (%)
Mycological cure (negative culture and microscopy) at follow-up		
Study 39-40OR*	17/22 (77%)	0/6 (0%)
Study SF0508†	12/14 (86)%	1/14 (7%)
Effective treatment (negative mycology and minimal signs and symptoms) at follow-up		
Study 39-40OR*	15/23 (65%)	0/18 (0%)
Study SF 0508	10/14 (71%)	0/14 (0%)

* Too few placebo patients at follow-up to determine
† P<0.001, Fisher Exact test, one-sided

Placebo-controlled trials demonstrated a consistent treatment effect 2-6 weeks after cessation of treatment, whether assessed solely by mycological results, or when assessed by combined mycological and clinical parameters. Both 6-week and 2-week, o.d., and b.i.d. regimens were effective. In study 39-40OR, too few placebo patients returned at the follow-up visit to allow meaningful statistical analysis of results. Mycological cures and effective treatment rates at end of the 6 week treatment period, however, were significantly greater in the terbinafine treatment group than in the placebo group.

Results of study griseofulvin-controlled studies SF 0025 and 20-OR in tinea pedis

Primary Endpoints	Terbinafine Number (%)	Comparator Number (%)
Mycological cure (negative culture and microscopy) at follow-up		
SF 0025*	32/33 (97%)	28/31(90%)
20-OR*	16/16 (100%)	6/11(55%)
Effective treatment (negative mycology and minimal signs and symptoms) at follow-up		
SF 0025†	32/33 (97%)	26/33 (79%)

20-OR†	14/16(88%)	5/11(45%)

* Statistical significance not reported
† p = 0.054 Fishers Exact test

Two weeks after the end of 6 week courses of treatment, two small studies showed terbinafine to be better than griseofulvin in terms of mycological or combined mycological and clinical parameters.

DETAILED 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.

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.

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
rubrum	0.001 - 0.01
rubrum 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 toruloidea	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
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.mantagrophytes, M. canis, A. fumigatus, Sc. brevicaulis, S. schenkii, and C. parapsilosis, and fungistatic against C. albicans.

TOXICOLOGY

Acute Toxicity

Species	Sex	Route	LD50
Mouse	M,F	Oral	>4 g/kg
Rat	M,F	Oral	>4 g/kg

Long-term toxicity

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.
	52 weeks	oral	M: 6.9, 20, 68 F: 9.3, 28, 95	Reversible ↑ in kidney weight in mid and high-dose males and liver weight in high dose females. No histopathological organ or tissue changes or evidence of drug-related tumorigenesis. No proliferation of smooth endoplasmic reticulum or peroxisomes. No-toxic-effect level in males 68 mg/kg; in females 95 mg/kg.
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 doses 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. Haematological 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 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.
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%& 2%cream)	10,20, 40	Slight erythema and edema in all groups including placebo controls

Reproduction Studies

REPRODUCTION STUDIES

SPECIES	DURATION	ROUTE OF ADMIN.	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 terbinafme tolerated doses up to 100 mg/kg well. Lower body weight gain was seen at 300 mg/kg. No embryolethal or teratogenic effects were seen.
	Peri & post-natal study Day 15 postcoitum to day 21 postpartum	oral	30, 100, 300	Inseminated female rats treated with terbinafine tolerated all doses well. No clinical signs or relevant reproductive changes in any group.
	Embryotoxicity study Day 6 to 15 postcoitum	subcutaneous	10, 30, 100	In the 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 postcoitum	oral	30, 100, 300	Inseminated female rabbits treated with terbinafine tolerated doses up to 100 mg/kg well. In 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.

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

CARCINOGENICITY

SPECIES	DURATION	ROUTE	DOSES (mg/kg)	RESULTS
MICE	100 weeks	oral	M: 14, 40, 130 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 F: 9.6, 28, 97	Ophthalmoscopy revealed an ↑ in incidence of cataracts in males at high doses. 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

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

EFFECTS OF 13-WEEK TREATMENT ON SELECTED TOXICOLOGICAL VARIABLES IN RATS

SPECIES	DURATION	ROUTE	DOSES (mg/kg)	RESULTS
RATS	13 weeks	oral	M:72 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

4-WEEK ORAL TOXICITY STUDY IN MICE

SPECIES	DURATION	ROUTE	DOSES (mg/kg)	RESULTS
MICE	4 weeks	oral	M: 103, 510 F: 107, 512	Slightly impaired liver function in males only. Slight induction of the cytochrome P-450 and b_5 systems was seen (biologically relevant only at the high-dose level 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 perosixomes 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

PRELIMINARY TOXICITY STUDY IN MONKEYS

SPECIES	DURATION	ROUTE	DOSES (mg/kg)	RESULTS
MONKEY	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 perioxisome population or general cellular ultrastructure were seen. Increased activity of hepatic palmitoyl CoA-epoxidase indicated increased perioxisomal fatty oxidation. Cytosolic epoxide hydrolase activity was below detectable limit.

32-week oral toxicity study in monkeys

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 tumour-initiating potential even in combination with a tumour 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.

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PART III: CONSUMER INFORMATION

Pr AURO-TERBINAFINE
(terbinafine hydrochloride)

125 mg and 250 mg tablets (as terbinafine base)

This leaflet is part III of a three-part "Product Monograph" published when AURO-TERBINAFINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AURO-TERBINAFINE. Contact your doctor or pharmacist if you have any questions about the drug.

Keep this leaflet. You may need to read it again. This medicine has been prescribed only for you. Do not give it to anybody else or use it for other illnesses. Read all of this leaflet carefully before you start treatment. Follow all your doctor's instructions carefully, even if they differ from the general information contained in this leaflet.

ABOUT THIS MEDICATION

What the medication is used for:

AURO-TERBINAFINE is used to treat fungal infections of skin, fingernails and toenails:

AURO-TERBINAFINE is used to treat fungal infections of the nail (toes, fingers) and may be used for certain fungal skin infections that do not respond to topical treatment.

Consult your doctor to confirm which type of fungal skin infection you have. Your doctor can determine if AURO-TERBINAFINE is right treatment for you.

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.

What it does

Terbinafine belongs to the group of medicines called antifungal agents and is used to treat fungal infections of the skin, hair and nails. When taken by mouth, it reaches the site of infection in concentrations strong enough to kill the fungus or stop it growing.

When it should not be used:

Do not use AURO-TERBINAFINE if you are allergic to terbinafine (the active antifungal ingredient) or any of the ingredients in the formulation (See *What the nonmedicinal ingredients are).*

If you think you may be allergic, ask your doctor for advice.

Do not take AURO-TERBINAFINE:

- If you have or had any liver problems.
- If you have any kidney problems.

What the medicinal ingredient is:

Terbinafine hydrochloride

What the non-medicinal ingredients are:

Non-medicinal Ingredients (in alphabetical order): Cellulose microcrystalline, hypromellose, magnesium stearate, silica colloidal anhydrous and sodium starch glycolate.

What dosage forms it comes in:

AURO-TERBINAFINE comes as a tablet containing 125 mg & 250 mg of Terbinafine.

WARNINGS AND PRECAUTIONS

General:

Discuss with your doctor the possible side effects that may be caused by this medicine. Before you use AURO-TERBINAFINE tablets, talk to your doctor if you:

- have liver or kidney problems
- are allergic to any medicines, either prescription or non prescription (OTC), or foods;
- are allergic to terbinafine or to any of the ingredients listed in this leaflet.

- are pregnant or intend to become pregnant while using this medicine;
- are breast-feeding; AURO-TERBINAFINE is excreted in breast milk.
- are taking any other medicines, prescription or nonprescription (OTC), especially cimetidine or rifampicin (see *Interactions with this medicine*).

Serious Warnings and Precautions

Rarely AURO-TERBINAFINE tablets can cause liver problems, in very rare cases the liver problems can be serious such as liver failure, some leading to death or liver transplant.

Stop taking AURO-TERBINAFINE tablets and consult your doctor immediately should you develop jaundice (yellowness of skin and/or eyes). See *Table of Serious Side Effects.*

Before you use AURO-TERBINAFINE, talk to your doctor if you:

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

- experience symptoms such as unexplained persistent nausea, vomiting, stomach pain, loss of appetite, unusual tiredness, if your skin or the whites of your eyes look yellow, that your urine is unusually dark or your bowel motions are unusually light in colour (signs of liver problems). Do not take AURO-TERBINAFINE tablets until you have discussed this problem with your doctor, who will check your liver function. Some individuals may be either very sensitive to AURO-TERBINAFINE or may have had some liver disease in the past. These individuals are at risk of developing abnormal liver function. Stop taking AURO-TERBINAFINE and consult your doctor immediately should you develop jaundice (yellowness of skin and/or eyes).

- experience any skin problem such as rash, red skin, blistering of the lips, eyes or mouth, skin peeling (signs of serious skin reactions).

- experience weakness, unusual bleeding, bruising or frequent infections (signs of blood disorders).

Talk to your doctor if the following occurs while taking AURO-TERBINAFINE tablets:

- Very occasionally some patients have developed blood abnormalities while being treated with AURO-TERBINAFINE. These reactions usually resolve on their own after stopping AURO-TERBINAFINE treatment. However, contact your doctor if you develop symptoms such as fever, sore throat, mouth sores, unusual bleeding or bruising.

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.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including herbal medicines, oral contraceptives (birth control pills) and non-prescription medicines. Some other medicines may interact with AURO-TERBINAFINE. These include:

- some antibiotics (e.g. rifampicin),
- caffeine
- some antidepressants (e.g. desipramine),
- some medicines used to treat heart problems (e.g. propafenone),
- some medicines used to treat high blood pressure (e.g. metoprolol),
- some medicines used to treat stomach ulcers (e.g. cimetidine),
- monoamine oxidase inhibitors (medicines used to treat depression).
- cyclosporine, a medicine used to control your body's immune system in order to prevent rejection of transplanted organs.

Be sure to tell your doctor about these, or any other medicines you take.

Some cases of menstrual irregularities and pregnancies have been reported in patients taking AURO-TERBINAFINE concomitantly with oral contraceptives; however the rate of occurrence appears to be within the background incidence for patients taking oral contraceptives alone.

PROPER USE OF THIS MEDICATION

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

Missed Dose:

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 (up to 4 hours), 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.

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.

Usual Adult dose

Follow your doctor's instructions carefully. Do not exceed the recommended dosage. If you have the impression that the effect of AURO-TERBINAFINE is too strong or too weak, talk to your doctor or pharmacist.

Adults: 125 mg twice daily or 250 mg once daily.

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

TABLE I

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

Overdose:

If you think you have taken an overdose of this medicine, check with your doctor. If you have accidentally taken too many tablets, talk to your doctor straight away. You may require medical attention. Symptoms caused by an overdose of AURO-TERBINAFINE tablets include headache, nausea, stomach pain and dizziness.

For the management of suspected overdose, contact your local Poison Control Centre.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In general, AURO-TERBINAFINE is well tolerated. Like all medicines, AURO-TERBINAFINE may cause some unwanted effects (side effects) in some people.

Side effects:

Very common (*likely to affect more that 1 in every 10 patients*): Nausea, mild stomach pain, heartburn, diarrhea, a feeling of fullness in the stomach, loss of appetite, skin rashes, aching joints and muscles.

Common (*likely to affect 1 to 10 in every 100 patients*): Headache.

Uncommon (*likely to affect 1 to 10 in every 1,000 patients*): Loss of or altered sense of taste. This is uncommon and usually recovers within several weeks after stopping treatment with AURO-TERBINAFINE tablets. It may lead to a reduction of appetite and significant weight loss in very few patients. You should tell your doctor if the altered sense of taste lasts for several days.

Very rare (*likely to affect less than 1 in every 10,000 patients*): Hair loss, fatigue, psoriasis-like skin eruptions, worsening of psoriasis, dizziness, decreased physical sensitivity, numbness and tingling. If you suffer dizziness, do not drive or operate machinery.

If any of these affects you severely, discuss this with your doctor.

Other side effects not listed above may also occur in some patients. If you notice any other side effects not mentioned in this leaflet, inform your doctor or pharmacist.

Some rare or very rare effects could be serious:

Rarely AURO-TERBINAFINE tablets can cause liver problems; in very rare cases the liver problems can be serious. Very rare side effects include a decrease in certain types of blood cells, lupus (an autoimmune disease) or serious skin problems, including allergic reactions. Tell your doctor immediately:

- If you experience symptoms such as unexplained persistent nausea, stomach problems, loss of appetite or unusual tiredness or weakness.
- If you notice that your skin or the whites of your eyes look yellow, that your urine is unusually

dark or your bowel motions are unusually light in colour.

- If you develop a sore throat with fever and shivering.
- If you experience unusual bleeding or bruising.
- If you experience difficulty breathing, dizziness, swelling mainly of the face and throat.
- If you develop any skin problems.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Rare	Liver problems, sometimes fatal with symptoms such as persistent nausea and vomiting, abdominal pain, fatigue, loss of appetite, dark urine, pale stools or jaundice (yellowing of the skin and eyes).			√
Very rare	Blood abnormalities with symptoms of sore throat, fever, mouth sore, unusual bleeding or bruising			√
	Serious skin reactions (blistering, peeling skin)			√

HOW TO STORE IT

Store at room temperature between 15 and 30°C.

Protect from light.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:
By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: Canada Vigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your healthcare provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor:
Auro Pharma Inc,
1170 Sheppard Ave. west, Unit #16
Toronto, Ontario
M3K 2A3, Canada

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