PRODUCT MONOGRAPH

[Pr]Jamp-Terbinafine

Terbinafine Tablets

(250 mg Terbinafine as Terbinafine Hydrochloride)

Antifungal Agent

JAMP Pharma Corporation
1380 – 203 Newton Street
Boucherville, Quebec
J4B 5H2

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Table of Contents

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(Terbinafine Hydrochloride)

250 mg Tablets

Antifungal Agent

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 250 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Jamp-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, Epidermophyton floccosum and yeasts of the genus Candida (eg. C. albicans), as well as Malassezia furfur.

Prior to initiating treatment with Jamp-Terbinafine, 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 onychomycosis or dermatomycosis.

Jamp-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, Jamp-Terbinafine may also be indicated in the treatment of lineal skin infections (tinea corporis, tinea cruris and tinea pedis).

Note: Jamp-Terbinafine is not effective in pityriasis versicolor.

Geriatrics (> 65 years of age): No data is available.

Pediatrics: No data is available.

CONTRAINDICATIONS

- Patients with hypersensitivity to terbinafine or any of the excipients. For a complete listing, see the **Dosage Forms, Composition and Packaging** section of the product monograph.

WARNINGS AND PRECAUTIONS

General

Jamp-Terbinafine should be kept out of the reach of children.

Carcinogenesis

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.

Hematologic

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 hydrochloride therapy for greater than six weeks.

Isolated cases of severe neutropenia have been reported. These were reversible upon discontinuation of terbinafine hydrochloride, with or without supportive therapy. If clinical signs and symptoms suggestive of secondary infection occur, a complete blood count should be obtained. If the neutrophil count is 1,000 cells/mm^3, terbinafine hydrochloride should be discontinued and supportive management started. Isolated cases of blood dyscrasias have been reported in patients treated with terbinafine hydrochloride

Hepatic/ Biliary/ Pancreatic

Jamp-Terbinafine (terbinafine hydrochloride) Tablets are not recommended for patients with chronic or active liver disease. Before prescribing Jamp-Terbinafine Tablets, pre-existing liver disease should be assessed. Hepatotoxicity may occur in patients with and without pre-existing liver disease. Pretreatment serum transaminase (ALT and AST) tests are advised for all patients before taking Jamp-Terbinafine Tablets. Patients prescribed Jamp-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 hydrochloride, and the patient's liver function should be immediately evaluated.

Rare cases of liver failure, some leading to death or liver transplant, have occurred with the use of terbinafine hydrochloride 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 hydrochloride use, the patients had serious underlying systemic conditions and an uncertain causal association with terbinafine hydrochloride. The severity of heptic events and/or their outcome may be worse in patients with active or chronic liver disease. Treatment with terbinafine hydrochloride tablets should be discontinued if biochemical or clinical evidence of liver injury develops.

Ophthalmologic
Changes in the ocular lens and retina have been reported following the use of terbinafine hydrochloride in controlled trials. The clinical significance of these changes is unknown.

Renal
In patients with renal impairment (creatinine clearance < 50 mLl min), the use of terbinafine hydrochloride has not been adequately studied, and therefore, is not recommended (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**).

Skin
There have been isolated reports of serious skin reactions (e.g. Stevens-Johnson Syndrome and toxic epidermal necrolysis). If progressive skin rash occurs, treatment with terbinafine hydrochloride should be discontinued.

Special Population

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

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

Pediatrics:
The safety and efficacy of Terbinafine have not been established in pediatric patients.

Geriatrics (>65 years of age):
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 **ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

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 z 10%, common 2 1% to < 10%, uncommon 2 0.1% to < 1%, rare z 0.01% to < 0.1%, very rare <0.01%

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

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 tabulation illustrates some of these results:

TABLE I

Organ System **Adverse Event**	**Terbinafine HCl 250 mg** **(n = 998)**	
		(%)
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
Diarrhoea 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

TABLE I

Organ System Adverse Event	Terbinafine HCl 250 mg (n = 998)	
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%)

Uncommon:
Digestive: 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:
Hepatic: 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 hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride 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 1:15000. Very rare cases of liver failure, some fatal, have been associated with terbinafine hydrochloride treatment and the incidence rate is about 1:1 000 000 exposed patients.

Terbinafine hydrochloride has been rarely associated with systemic allergic reactions including urticaria, angioedema, arthralgia, arthritis and serum-sickness like reactions.

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

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

Isolated cases of photosensitivity have been reported in association with Jamp-Terbinafine.

Hematologic: 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 hydrochloride have not been elucidated.

DRUG INTERACTIONS

Drug-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 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 B_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. chloprornazine, 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 Jamp-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%.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions
There are no known interactions of terbinafine with commonly used laboratory tests.

Drug-Lifestyle Interactions
Interactions with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
The recommended dose for adults is 250 mg once daily.

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

TABLE II

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, orin younger patients, treatment periods of less than 3 months maybe 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: see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics, WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS.

Missed Dose

Patients should attempt to not miss any doses. Should they miss a dose, advise them to take one as soon as possible. However, if it is almost time for their next dose, advise them to skip the missed dose and go back to their regular schedule. Ensure that they are aware not to double the doses and to never make any dose changes on their own.

OVERDOSAGE

A few cases of overdosage with terbinafine hydrochloride 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.

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.

Terbinafine interferes specifically with fungal sterol biosynthesis by inhibition of squalene epoxidase in the fungal cell membrane. 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

Absorption
A single 250 mg dose of Terbinafine hydrochloride tablets results in a peak plasma concentration of 0.97 ug/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 hydrochloride is moderately increased (20%) by food, but not sufficiently to require dosing adjustments.

Distribution
Terbinafine hydrochloride binds strongly to plasma proteins (99%) and is lipophilic. Terbinafine hydrochloride is widely distributed in the body including adipose tissue. Terbinafine hydrochloride 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 Hydrochloride is distributed in the nail plate within the first few weeks of commencing therapy.

Metabolism
Following absorption terbinafine hydrochloride 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 hydrochloride 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.

Excretion
There is evidence that terbinafine hydrochloride is excreted mainly in urine (80%) and in feces (20%).

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.

Special Population and Conditions
Hepatic Insufficiency
Following a single 250 mg dose in 12 hepatically impaired cirrhotic (alcoholic) patients, total clearance of terbinafine hydrochloride was reduced by about 40%.

Renal Insufficiency
In a sample of 12 renally impaired patients (median creatinine clearance of 17.6 mL/min), terbinafine hydrochloride 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 hydrochloride 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

Jamp-Terbinafine tablets should be stored between 15^{o} to 30^{o}C, protected from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

Jamp-Terbinafine (Terbinafine Hydrochloride) is available as round tablets in the following strength as described below:

250 mg: A whitish yellow, round tablet, scored on one side and debossed with "JP" logo on the other side.

Jamp-Terbinafine is supplied in HDPE bottles of 100 tablets and blisters of 3 x 10 tablets format.

Composition

Jamp-Terbinafine (terbinafine hydrochloride) 250 mg tablets contain 250 mg terbinafine, as terbinafine hydrochloride. The tablets also contain the following non-medical ingredients (alphabetically): Colloidal silicon dioxide, hydroxy propyl methyl cellulose, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

Product Monograph available upon request.

JAMP Pharma Corporation
Boucherville, Quebec J4B 5H2

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Terbinafine Hydrochloride

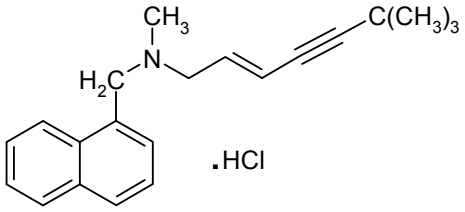
Chemical Name: (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl- 1 -naphthalene-methanamine (-hydrochloride)

Molecular formula: $C_{21}H_{25}N$**.** HCl,

Molecular mass:

Terbinafine base:	291.43 g/mol
Terbinafine Hydrochloride:	327.90 g/mol

Structural formula:



Physicochemical properties: Terbinafine hydrochloride is a White to off-white finely crystalline powder. It is soluble in methanol, methylene dichloride and chloroform, and slightly soluble in acetone. Solubility in water is 0.63% (w/v).

pH and pKa values: The pKa (I) value is 7.10 and the pH of a solution (0.5%) in methanol/water 4:6 9v/v) is ~4.7 at 25

Melting range: 200ºC to 208ºC

CLINICAL TRIALS

Comparative Bioavailability Studies

A two-way, crossover, blinded, single-dose, comparative bioequivalence study was performed in 24 healthy, non-smoking males under fasting conditions on terbinafine hydrochloride tablets using TERBINAFINE 250 mg tablets (Lot # G47567) versus the reference product, LAMISIL® 250 mg Tablets (Lot # C4H03281), by Novartis Pharmaceuticals Canada Inc. The pharmacokinetic data calculated for the TERBINAFINE 250 mg tablets and LAMISIL® 250 mg tablets formulation are tabulated below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Terbinafine Hydrochloride (1 x 250 mg) From measured data **uncorrected for potency** Least-Square Mean Arithmetic Mean (CV %)				
Parameter	Terbinafine	Lamisil, Novartis Pharmaceuticals †	% Ratio of Geometric Means	90% Confidence Interval#
AUC_{0-72} (ng·h/mL)	4277.83 4524.73 (34.18)	4465.34 4783.97 (37.01)	96.04	88.60-104.10
AUC_I (ng·h/mL)	4715.45 4996.28 (34.62)	4809.27 5152.59 (36.69)	96.00	87.70-105.09
C_{max} (ng/mL)	1038.47 1092.10 (31.75)	954.80 1022.61 (35.90)	109.38	98.32-121.68
T_{max} § (h)	1.33 (1.00-2.33)	2.00 (1.00-3.00)		
$T_{½}$ ▯ (h)	21.12 (50.88)	23.36 (45.35)		

† Lamisil was manufactured by Novartis Pharmaceuticals Canada Inc., and was purchased in Canada.
§ Expressed as the median (range) only
▯ Expressed as the arithmetic mean (CV%) only

DETAILED PHARMACOLOGY

The mechanism of action of terbinafine hydrochloride 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 hydrochloride treated fungi. This mechanism distinguishes terbinafine hydrochloride from the azole antimycotics, which affect a later step in ergosterol biosynthesis by inhibiting 14 "-demethylase, a cytochrome P-450 enzyme upon which terbinafine hydrochloride has no effect. In contrast to many azoles, terbinafine hydrochloride does not bind to cytochromes P-450 in mammalian steroidogenic tissues.

Human

In-vivo studies

The pharmacokinetics of orally administered terbinafine hydrochloride 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 hydrochloride has an elimination half-life of 17 hours.

Mean concentrations of terbinafine hydrochloride (in µg/g) measured in the stratum corneum, dermis/epidermis, hair, sweat, and sebum during and after 12 days of 250 mg terbinafine hydrochloride 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.I4
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 $t_{i}n$ was 3-4 days (this implies that the concentrations of terbinafine hydrochloride would remain above the MIC for most dermatophytes for 3 weeks). Another route of terbinafine hydrochloride 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 hydrochloride in the treatment of onychomycosis, plasma levels were measured monthly in 9 patients, half of whom received 250 mg terbinafine hydrochloride q.d. in the evening and the other half 125 mg b.i.d. A pharrnacokinetic 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 tg/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 hydrochloride 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 hydrochloride 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 hydrochloride is much lower with MIC's ranging from 0.1 to > 128 p.g/ml. The efficacy of terbinafine hydrochloride 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 atho enic and opportunistic fungi

Fungus	MIC range (tglmL)
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 hydrochloride was primarily fungicidal against T. mantagrophytes, M. canis, A. fumigatus, Sc. brevicaulis, S. schenkii, and C. parapsilosis, and fimgistatic against C. albicans.

TOXICOLOGY

Acute Toxicity

Species	Sex	Route	LD50
Mouse	M,F M,F M,F	oral i.v. 1% solution orally	>4 g/kg 393 mg/kg > 250 mg/kg
Rat	M,F M,F M,F M,F	oral i.v. 1% cream orally 1% solution orally	213 mg/kg 25 mg/kg (no mortalities) >200 mg/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 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. 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 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.

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 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 terbinafme tolerated up to the high-dose level. No clinical signs or relevant reproductive changes in any group.
RABBITS	Embryotoxicity study day 6 to 18 postcoitum	oral	30, 100, 300	Inseminated female rabbits treated with terbinafine tolerated 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 hydrochloride . In vitro tests of cell transformation to malignancy were negative.

Carcinogenicity

CARCINOGENICITY

SPECIES	DURATION	ROUTE	DOSES (nag/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 T 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. T incidence of enlarged swollen livers and liver nodules in the high dose animals, particularly males. Slight T 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 A 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 pahitoyl-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 (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-epoxidasewas 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

Preliminary toxicity study in monkeys

PRELIMINARY TOXICITY STUDY IN MONKEYS

SPECIES	DURATION	ROUTE	DOSES (mg/kg)	RESULTS
MONKEYS	28 clays	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 increased peroxisomal fatty oxidation. Cytosolic epoxide hydrolase activity was below detectable limit.

32-week oral toxicity in monkeys

32-WEEK ORAL TOXICITY STUDY IN MONKEYS

SPECIES	DURATION	ROUTE	DOSE (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 hydrochloride (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 hydrochloride plus phenobarbital. It was concluded that terbinafine hydrochloride 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 hydrochloride 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 hydrochloride and non-treated control rats were used to evaluate terbinafine hydrochloride for genetic activity. There was no evidence that repeated treatment of rats with terbinafine hydrochloride induces enzymes capable of producing mutagenic intermediates of terbinafine hydrochloride.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION
[Pr]Jamp-Terbinafine
Terbinafine Hydrochloride

This leaflet is part III of a three-part "Product Monograph" published when Jamp-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 Jamp-Terbinafine. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Jamp-Terbinafine is used to treat fungal infections of the skin, fingernails and toenails.

What it does:
Jamp-Terbinafine works by blocking squalene epoxidase, an enzyme responsible for the creation of a component of the fugnal cell membrane called ergosterol. The lack of ergosterol result in fungal cell death. .

When it should not be used:
Do not use Jamp-Terbinafine if you are allergic to terbinafine hydrochloride or any of the ingredients in the medication (see What the non-medicinal ingredients are).

What the medicinal ingredient is:
Terbinafine Hydrochloride

What the nonmedicinal ingredients are:
Colloidal silicon dioxide, hydroxypropyl methyl cellulose, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

What dosage forms it comes in:
Tablets: 250 mg

WARNINGS AND PRECAUTIONS

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.

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; Jamp-Terbinafine is excreted in breast milk;
- are taking any other medicine, prescription or nonprescription (OTC), especially cirnetidine 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. If you have or ever had a problem with your liver, do not take Jamp-Terbinafine tablets until you have discussed this problem with your doctor. He/she will check your liver function.

INTERACTIONS WITH THIS MEDICATION

Taking other medication together with Jamp-Terbinafine:

Before you start taking Jamp-Terbinafine, be sure to tell your doctor about all medicines you are taking or have taken recently including any that you bought without a prescription or any natural products. This is because the effects of Jamp-Terbinafine or the other medicines may be changed or you might get side effects. Furthermore, do not start any new medicine, whether prescription, non-prescription or natural products without first checking with your doctor.

Examples of drugs that may interact with Jamp-Terbinafine are:

- Drugs used to treat depression (i.e. Desipramine, Fluvoxamine, Selegiline)
- Drugs used to treat high blood pressure (i.e. Metoprolol, Propanolol)
- Birth Control
- Drugs used to treat arrhythmic abnormalities (i.e. Flecainide, Propafenone)
- Drugs used to treat mental disorders (i.e Chloprornazine, Haloperidol)
- Rifampin
- Cimetidine
- Fluconazole

PROPER USE OF THIS MEDICATION

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.

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.

Keep your regular appointments with your doctor.

Adult Dose
250 mg once daily

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, 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.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The common side effects associated with taking Jamp-Terbinafine is 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 side effects associated with taking Jamp-Terbinafine include dry mouth, loss of or altered sense of taste (this is uncommon and usually recovers within several weeks after stopping treatment with Jamp-Terbinafine tablets; this 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); 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 side effects associated with taking Jamp-Terbinafine include severe skin problems including allergic reactions, hives. *Sore throat and fever, jaundice (yellowness to skin and/or eyes), unusual fatigue, lack of appetite, dark urine, pale stools. *These signs may indicate blood or liver disorders. Stop taking Jamp-Terbinafine and notify your doctor **immediately.**

If you have any questions, 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.

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	
Common	- diarrhea - cramps - nausea - vomiting - bloating	√		
Rare and serious	- severe skin problems including allergic reactions, hives - Sore throat and fever - yellowness to skin and/or eyes - unusual fatigue - lack of appetite - dark urine - pale stools.			√

This is not a complete list of side effects. If you have any unexpected effects while taking this drug, contact your doctor or pharmacist.

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

HOW TO STORE IT

Store at temperatures between 15 °C and 30° C. Protect tablets from light. Remember, keep this and all other medicines out of reach of children and never share this medicine with others.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll free telephone: 866-234-2345
Toll free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and
Effectivness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting JAMP Pharma Corporation, at 1-866-399-9091

This leaflet was prepared by
JAMP Pharma Corporation
Boucherville, Quebec J4B 5H2

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