**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

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| **NDA** | **22-071** | **Submission Date(s)** | September 8th, 2006, December 4th, 2006, December 5th, 2006 and March 20th, 2007 |
| **Brand Name** | | Lamisil ® Mini-tablets | |
| **Generic Name** | | Terbinafine Hydrochloride | |
| **Reviewer** | | Abimbola Adebowale, Ph.D. | |
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| **OCP Division** | | DCP 3 | |
| **OND division** | | HFD-540 | |
| **Sponsor** | | Novartis Pharmaceuticals Corporation, NJ 07936 | |
| **Relevant IND(s)** | | [redacted] and [redacted] | |
| **Submission Type; Code** | | Pediatric Study Reports | 3S |
| **Formulation; Strength(s)** | | Mini-tablets, 125 mg and 187.5 mg | |
| **Indication** | | Treatment of Tinea Capitis | |

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# 1 Executive Summary

Novartis Pharmaceuticals Corporation has submitted an original NDA for Lamisil ® (terbinafine hydrochloride) Mini-tablets for the treatment of Tinea Capitis in children aged 4-12 years. Lamisil® Tablets (terbinafine HCL) equivalent to 250 mg base is currently marketed (NDA # 20-539, approved on 05/10/1996) for the treatment of onychomycosis of the toenails or fingernails in adults. This submission includes labeling revisions to the pediatric use sections and drug interactions sections of the approved Lamisil ® Tablets (250 mg) package insert.

## 1.1 Recommendations

The clinical pharmacology and biopharmaceutics information included in this submission is acceptable provided that a satisfactory agreement is reached between the applicant and the Agency regarding the language to be included in the package insert. Please refer to Section 3 of this document for detailed labeling recommendations that need to be conveyed to the sponsor.

## 1.2 Phase IV Commitments

Not Applicable.

## 1.3 Summary of Clinical Pharmacology Findings and Biopharmaceutics Findings

Two multiple dose pharmacokinetic (PK) studies (# W352 and # C2101) were conducted in children 4-8 years of age with Tinea Capitis. In study C2101 terbinafine mini-tablets were administered as compared to study W352 where the 125-mg tablet (not marketed in the USA) was administered. In addition the applicant also conducted the following studies in adult healthy subjects: a relative bioavailability study (C2303) of the mini-tablets compared to the marketed 250 mg tablets and 2x125mg tablets, two food-effect studies (L2104 and L2306) of a new oral formulation, [redacted] and four drug-drug interaction studies (0152, 0153, 0154 and 0156) using the marketed 250 mg tablets. The applicant also referenced two studies that were conducted in adults [P101 and SF0056] that were previously reviewed in the original submission of NDA 20-539 for terbinafine 250 mg tablets. The applicant also submitted a population PK analysis report that included results from both PK studies in children, sparse samples from an early dose-ranging study in children 4-12 years old with Tinea Capitis and, the historical data in adults.

Only the studies conducted with the mini-tablets (C2101 and C2303) and, the drug-drug interaction studies (0152, 0153, 0154 and 0156) were reviewed in detail.

<u>Pharmacokinetics of terbinafine mini-tablets in children with Tinea Capitis</u>
In study 2101 that was conducted in children 4-8 years of age with Tinea capitis, pharmacokinetics of terbinafine was investigated after the single and repeated (42 days)

daily oral doses of terbinafine mini-tablets. The daily dose was determined according to body weight, i.e. < 25 kg, 125 mg (N=11); 25-35 kg, 187.5 mg (N=4); > 35 kg, 250 mg (1 child). The results of the mean pharmacokinetic parameters are summarized in the table below:

Table 1: Mean (SD) Pharmacokinetic Parameters in children (4-8 years) with Tinea Capitis following single and repeated dosing for 42 days

| **Pharmacokinetic Parameter** | **Dose (N)** | | | | | |
|---|---|---|---|---|---|---|
| | 125 mg (N=11) | | 187.5 mg (N=4) | | 250 mg (N=1) | |
| | Day 1 | Day 42 | Day 1 | Day 42 | Day 1 | Day 42 |
| **AUC0-24 (hr*ng/mL)** | 3311 (1605) | 6513 (4074) | 5109 (1860) | 8653 (4412) | 5253 | 4154 |
| **Cmax (ng/mL)** | 971 (585) | 1118 (713) | 1602 (1010) | 1575 (942) | 1370 | 544 |
| **Tmax (hr)** | 1.8 (0.5) | 2.5 (3.2) | 2.0 (0.0) | 2.0 (0.0) | 2.0 | 2.0 |
| **T 1/2 effective (hr)** | *ND | 26.7 (13.8) | ND | 30.5 (9.3) | ND | ND |
| **Accumulation Ratio (R)**** | ND | 2.1 (0.9) | ND | 1.9 (1.0) | ND | 0.8 |

*ND = not determined
**R= (AUC0-24 on Day 42)/ (AUC0-24 on Day 1)

The results of this study can be summarized as follows:

- The mean Cmax and AUC 0-24 were generally higher in the 187.5 mg group than in the 125 mg group on Day 1 and 42.
- Mean AUC 0-24 values were generally higher after repeated administration (Day 42) when compared to that obtained after the first dose. Although the only patient who received a 250 mg dose showed a lower AUC 0-24 on Day 42 than on Day 1, this was thought to reflect intra-subject variability.
- Inter-individual variability of Cmax and AUC0-24 values of terbinafine were relatively high, which is reflected by coefficient of variation values between 36% and 64%.
- The individual values of the effective half-life obtained for the 125 mg dose group was highly variable (range = 7.9 to 50.6 hours) when compared to that obtained for the 187.5 mg dose group (range = 20.5 to 39.0 hours). However, the mean effective half-life obtained were 26.7 hours and 30.5 hours for the 125 mg and the 187.5 mg dose group, respectively.
- The individual values of the apparent plasma clearance (CLss/F) obtained for the 125 mg and 187.5 mg dose groups were highly variable (range = 8.4 to 50.5 L/ hr)

for both dose groups. The mean CLss/F values of 25.4 L/hr and 27.1 L/hr for the 125 mg and the 187.5 mg dose group, respectively were also comparable. However, the patient receiving the 250 mg dose exhibited a high CLss/F of 60.2 L/hr.

Comparison of the pharmacokinetics of terbinafine in children and adults:
A comparison of the systemic exposure (AUC and Cmax) between terbinafine in the two studies conducted in children [C2101 and W352] and in the two reference studies in adults, showed that, systemic exposure to terbinafine in the children who were administered 187.5 mg terbinafine mini-tablets was similar to that obtained in adults administered 250 mg terbinafine tablets. However, in the children who were administered 125 mg terbinafine mini-tablets, median $AUC_{0-24}$ was 30 to 50 % lower and median Cmax was 31 to 40 % lower than that obtained in adults administered 250 mg terbinafine tablets.

This data was supported by a population PK analysis that included results of both pharmacokinetic studies in children (4-8 years of age), sparse samples from an early dose-ranging study in children (4-12 years of age) and historic data in adults after single and repeated oral doses of 250 mg of terbinafine tablets (18-45 years of age). The analysis indicated that terbinafine pharmacokinetics in plasma are best described by a 4-compartment model. Clearance (CL/F) of terbinafine was found to be dependent on body weight in a nonlinear manner, with an exponential scaling factor of 0.34 for body weight. A dose of 187.5 mg qd given to children with body weights of 25 to 35 kg was predicted to result on average in a similar systemic exposure as a dose of 250 mg qd in adults. A dose of 125 mg qd given to children with body weights of 15 to < 25 kg was predicted to result on average in a somewhat lower exposure than a dose of 250 mg qd in adults. However, based on discussions with the medical reviewer, this lower exposure that was observed with the 125 mg dose did not result in a lower efficacy in the clinical trials (see medical review for details).

In conclusion, with the weight classes and doses of terbinafine proposed for children with Tinea Capitis (i.e. < 25 kg receive 125 mg qd, 25-35 kg receives 187.5 mg qd, > 35 kg receive 250 kg qd) the systemic exposure to terbinafine observed in children of all dose groups did not exceed the highest values observed in adults treated with 250 mg qd.

Food Effect: The mini-tablets were administered with pudding in the pharmacokinetic studies and, in the clinical trials. In addition, in the clinical trials all subjects were instructed to take the mini-tablets with a meal. Although, no special recommendation on drug administration in relation to meals was provided for in the label, following discussions with the medical reviewer, it was decided that the label will include directions for the mini-tablets to be taken with meals.

The applicant did investigate the influence of food on the bioavailability of terbinafine mini-tablets administered as a new oral form, [redacted] in study [L2104] after a single dose and in study [L2306] after repeated doses of 350 mg [redacted] These studies were performed in adult healthy subjects. It should be noted that the

formulations used were also not the same strength as the to-be-marketed formulation. The intent of the applicant was to extrapolate the food –effect seen in the studies performed with the [redacted] to the administration of the mini-tablets based on a comparison of the dissolution profiles. However the dissolution data provided by the applicant indicated that the dissolution profiles of the Lamisil mini-tablets were not similar to that of the [redacted] Therefore the applicant's extrapolation of the food effect data from this formulation to the mini-tablets [redacted] was not considered to be appropriate.

Drug Interactions:
Four pharmacokinetic drug interaction studies of identical design were conducted in healthy volunteers. In these studies, single oral doses of terbinafine tablets were given alone or in combination with the following co-medications: fluconazole [0152], cotrimoxazole [0153], zidovudine [0154] and theophylline [0156]. The results of these studies are summarized in the table below:

Table 2: Summary of drug interaction studies performed with terbinafine in 18 healthy subjects

| Study | Co-medication/Dose | Terbinafine dose | PK effects observed on: | |
|---|---|---|---|---|
| | | | Co-medication | Terbinafine |
| 0152 | Fluconazole/100 mg | 750 mg | PK not altered | **Cmax +52%; AUC +67%** |
| 0153 | Cotrimoxazole/ 160 mg trimethoprim 800 mg sulfamethoxazole | 750 mg | PK not altered | PK not altered |
| 0154 | Zidovudine/200 mg | 750 mg | **AUC +15%; Tmax +41%; Cmax -25%; CL/F -15%; V/F -17%** | PK not altered |
| 0156 | Theophylline/375 mg | 250 mg | PK not altered | **Cmax +23%; AUC +18%; CL/F -23%** |

The results of these studies demonstrated that trimethoprim, sulfamethoxazole, zidovudine and theophylline do not have a clinically meaningful influence on the pharmacokinetics of terbinafine. The resultant increase in AUC (0-∞) and Cmax of terbinafine of 18% and 23%, respectively when co-administered with theophylline was not considered to be clinically meaningful due to the wide safety margin of terbinafine. In addition, terbinafine did not modify the pharmacokinetics of all these co-medications to an extent that was considered to be clinically relevant. The 15 % increase in AUC of zidovudine when co-administered with terbinafine was not considered to be a safety

concern. In addition the applicant stated that it is the minor metabolite of zidovudine, AMT that has been implicated in the bone marrow suppression associated with zidovudine.

A single oral dose of fluconazole increased terbinafine Cmax (52%), AUC (0-tlast) (69%), and AUC (0-∞) (67%), and decreased desmethylterbinafine Cmax (28%) to a statistically significant degree. Co-administration of fluconazole with terbinafine should be done with careful laboratory monitoring of hepatic enzymes (ALT and AST).

Relative bioavailability of the mini-tablets to the currently marketed terbinafine tablets:

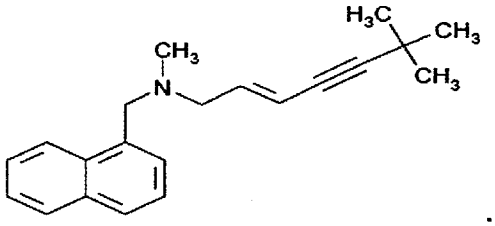
The relative bioavailability of the mini-tablets compared to the marketed tablets was investigated in study C2303. This was a randomized, open-label, single dose, three period crossover study conducted in 24 Caucasian (12 male and 12 female) adult healthy volunteers. The mini-tablets were administered by sprinkling over yoghurt or vanilla pudding while the tablets were administered in the fasted state. The results of study C2303 demonstrated that 250 mg of terbinafine when administered to adult healthy subjects as 60 mini-tablets was bioequivalent to one 250-mg marketed tablet or two 125-mg marketed tablets.

For both comparisons, i.e. mini-tablets vs. 250 mg tablet and mini-tablets vs. 2 x 125 mg tablets, the ratios of the geometric means for Cmax, AUC0-tlast and AUC0-∞ were close to unity (0.95 to 1.04) and the 90% confidence intervals (CI) were all contained within the bioequivalence range of 0.8 to 1.25.

# 2 Question-Based Review

## 2.1 General Attributes of the drug

*2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?*




·HCl

The drug substance for terbinafine mini-tablets is terbinafine hydrochloride (structure shown above). It has the following chemical name: (E)-N-(6, 6-dimethyl-2-hepten-4-inyl)-N-methyl-1-naphthalenemethanamine hydrochloride. The terbinafine free base and the hydrochloride have a molecular weight of [redacted] and 327.9, respectively. In this submission, all doses, concentrations and pharmacokinetic parameters are given in terms of terbinafine free base.

### *2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?*

Terbinafine hydrochloride is an antifungal agent that is believed to have fungicidal activity against several species of dermatophytes. The indication being sought for terbinafine mini-tablets is for the treatment of Tinea capitis. Tinea capitis is a dermatophyte infection of the scalp hair follicles, which occurs primarily in children, less than 10 years of age. This infection is caused by a group of dermatophytes in the genera Trichophyton and Microsporum. Hair loss, hair breakage, scaling, plus various degrees of erythema, pustules and pruritus are the primary clinical signs, which can be associated with Tinea capitis. In addition, cervical or occipital lymphadenopathy may occur in some children. The treatment of Tinea capitis requires oral therapy and currently oral griseofulvin is the only approved drug for this indication. While griseofulvin is effective, the applicant stated that it would be helpful for patients to have other treatment options such as terbinafine.

### *2.1.4 What are the proposed dosage(s) and route(s) of administration?*

Lamisil ® (terbinafine hydrochloride) Mini-tablets are to be taken orally once a day for 6 weeks based upon body weight.

| | |
|---|---|
| <25 kg | 125 mg/day |
| 25-35 kg | 187.5 mg/day |
| >35 kg | 250 mg/day |

## 2.2 General Clinical Pharmacology

### *2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

**Table 3 :Summary of Efficacy Trials**

| Study No. , Study objective, population | Planned patients | Treatment duration | Dosage | Type of control |
|---|---|---|---|---|
| **Dose-finding trials**<br>**W352** Open-label, multiple-dose PK in children 4–8 years with Tinea capitis | 16<br>(22 enrolled) | 28 days for patients with *Trichophyton*<br>42 days for patients with *Microsporum* | terbinafine tablets, by body weight:<br><25 kg - 125 mg/day,<br>25-35 kg - 187.5 mg/day,<br>>35 kg - 250 mg/day | none |
| **C2101** Open-label, multiple-dose PK in children 4–8 years with Tinea capitis | 16<br>(16 enrolled) | 42 days | terbinafine mini-tablets by body weight:<br>15-<25kg = 125 mg/day<br>25-35 kg = 187.5 mg/day<br>>35 kg = 250 mg/day | none |

| | | | | |
|---|---|---|---|---|
| **T201** Randomized, double-blind, parallel-group study to identify a safe and appropriate treatment duration in patients (>4 yrs) with Tinea capitis caused by *Trichophyton* | 150 (177 enrolled) | 1, 2, or 4 weeks | terbinafine tablets <20 kg = 62.5 mg/day 20-40 kg = 125 mg/day >40 kg = 250 mg/day | none |
| **T202** Randomized, double-blind, parallel-group study to identify a safe and appropriate treatment duration in patients (>4 yrs) with Tinea capitis caused by *Microsporum* | 150 (165 enrolled) | 6, 8. 10 or 12 weeks | terbinafine tablets <20 kg = 62.5 mg/day 20-40 kg = 125 mg/day >40 kg = 250 mg/day | active (griseofulvin) |
| **Controlled efficacy trials** | | | | |
| **C2301** Randomized, investigator-blinded, parallel-group safety and efficacy study in patients 4 – 12 years of age with Tinea capitis | 720 (747 enrolled) | 42 days | Terbinafine mini-tablets by body weight: <25 kg - 125 mg/day, 25-35 kg - 187.5 mg/day, >35 kg - 250 mg/day | active (griseofulvin) |
| **C2302** Randomized, investigator-blinded, parallel-group safety and efficacy study in patients 4 – 12 years of age with Tinea capitis | 720 (802 enrolled) | 42 days | Terbinafine mini-tablets by body weight: <25 kg - 125 mg/day, 25-35 kg - 187.5 mg/day, >35 kg - 250 mg/day | active (griseofulvin) |

### *2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?*

The clinical endpoint was based on the antifungal activity of terbinafine hydrochloride and the signs and symptoms associated with Tinea Capitis. The primary efficacy variable in both the pivotal clinical trials was the proportion of patients with complete cure rate at the end of the study i.e. 10 weeks from taking the drug (4 weeks after the last dose). The complete cure was defined as negative dermatophyte culture and negative KOH microscopy (mycological cure) and, complete clearance of baseline Total Signs and Symptoms Score i.e. TSSS=0 (clinical cure).

### *2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

Yes, refer to Section 2.6.4 for the details of the analytical method and validation results.

### *2.2.4 Exposure-Response Evaluation*

***2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.***

The choice of doses for the pivotal studies was based primarily on the data from two phase II clinical trials, [Study T201] and [Study T202]. The clinical pharmacology studies [Study W352], [Study C2101] and [Study L2306] provided support for the doses chosen. Studies T201 and T202 were Phase II randomized, double-blind studies performed, using the terbinafine tablet formulation, to determine the appropriate treatment duration for Tinea capitis infections caused by *Trichophyton* and *Microsporum* species, respectively. Terbinafine was given once daily in both studies. A body weight-based dosage scale was used. Patients weighing <20 kg received 62.5 mg/day, patients weighing 20-40 kg received 125 mg/day, and patients weighing > 40kg received 250 mg/day. Doses in these studies varied between 3 and 6 mg/kg/day (median 4.2 mg/kg/day). In the *Trichophyton* study (T201), 1, 2 and 4 week treatment durations with terbinafine were compared. In the *Microsporum* study (T202), 6, 8, 10 and 12 week treatment durations with terbinafine were compared to 12 weeks of treatment with griseofulvin.

The applicant stated that studies T201 and T202 showed that patients who received >4.5 mg/kg/day terbinafine had a statistically significantly better response to all efficacy parameters. Therefore it was concluded that a higher dosage than previously tested in the Phase 2 studies was required to achieve the desired efficacy response.

An early population pharmacokinetic (POPPK) evaluation had been performed to support dose selection for the pharmacokinetic studies [C2101] and [W352]. This POPPK evaluation included plasma concentration-time data obtained after sparse sampling in children in study T201. The conclusion from this study was that Clearance (CL/F) was influenced by body weight.

This information obtained from the dose-response analysis was then used to derive the dosing for children on a weight basis (i.e., <25 kg to receive 125 mg qd, 25-35 kg to receive 187.5 mg qd and > 35 kg to receive 250 mg qd) for the two double-blind, comparator efficacy and safety studies in children aged 4 to 12 years with a clinical diagnosis of Tinea capitis.

The two pharmacokinetic studies, [C2101] and [W352], in children aged 4-8 years evaluated the doses subsequently used in the pivotal studies. Comparison of plasma concentrations of terbinafine observed in the children of the two studies [W352] and [C2101] were similar to predicted concentrations based on the previously developed **population PK model using each patient's dose** and body weight for calculation. The comparison of the results in children with data in adults treated with 250 mg once daily indicated that children needed higher doses in mg per kg body weight to reach a similar exposure (AUC0-24h) to terbinafine as adults. The individual steady state AUC0-24h values for children receiving the 187.5 mg dose were in a similar range as those in adults given the 250 mg dose. The steady state AUC0-24h values in some children receiving the

125 mg dose tended to be lower (~ 30 – 50%) than the values in adults. Therefore, the recommended 125 mg dose for body weights below 25 kg is a conservative dose as far as safety is concerned however, it suggested an efficacy concern.

*Reviewer's Comments: Following discussions with the medical officer (Dr. Brown) and the statistical reviewer (Dr. Soukop), the lower exposure obtained with the 125 mg was not considered to be clinically relevant based on the efficacy data obtained in the clinical trials.*

***2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?***

There was no dose-response relationship for safety specifically studied following administration of the mini-tablets to children with Tinea Capitis. Basically, the applicant stated that no risks unique to children were identified in the pivotal trials (see clinical review for further details).

## 2.3 Intrinsic Factors

***2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?***

Age and body weight were the two intrinsic factors that were found to influence exposure

See sections 2.2.4.1 and 2.3.2.2 for further details

2.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

See sections 2.2.4.1 and 2.3.2.2

***2.3.2.2 Pediatrics:***

The pharmacokinetics of terbinafine hydrochloride mini-tablets was evaluated in children aged 4-8 years with Tinea Capitis in study C2101. This was an open-label, multiple-dose study conducted in sixteen children with Trichophyton or Microsporum infection. All children were treated for 42 days using the following doses according to weight groups: < 25 kg received 125 mg qd, 25-35 kg received 187.5 mg qd, >35 kg received 250 mg qd. Blood samples for PK evaluation of terbinafine were drawn after the first and last dose (Day 1 and Day 42) at pre-dose and 0.5, 1, 2, 4, 6, 12 and 24 hrs post-dose. One blood sample was collected pre-dose on Day 21. On days with PK blood sampling, terbinafine mini-tablets were given sprinkled over pudding (1 teaspoon or tablespoon) after an

overnight fast. Inserted below are the mean plasma concentrations-time profiles and summary tables of the pharmacokinetic parameters obtained after the first dose and after 42 days of treatment.

Fig 1. Mean (+ or – SD) terbinafine plasma concentrations (ng/mL) in children (N=11) with T.capitis after single and repeated oral doses of 125 mg of terbinafine administered once daily as mini-tablets

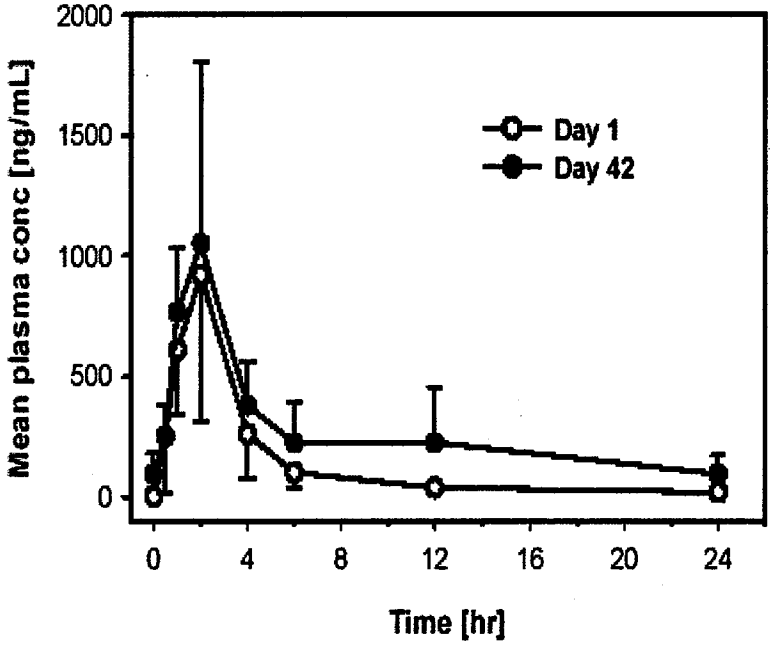



Fig 2. Mean (+ or – SD) terbinafine plasma concentrations (ng/mL) in children (N=4) with T.capitis after single and repeated oral doses of 187.5 mg of terbinafine given once daily as mini-tablets

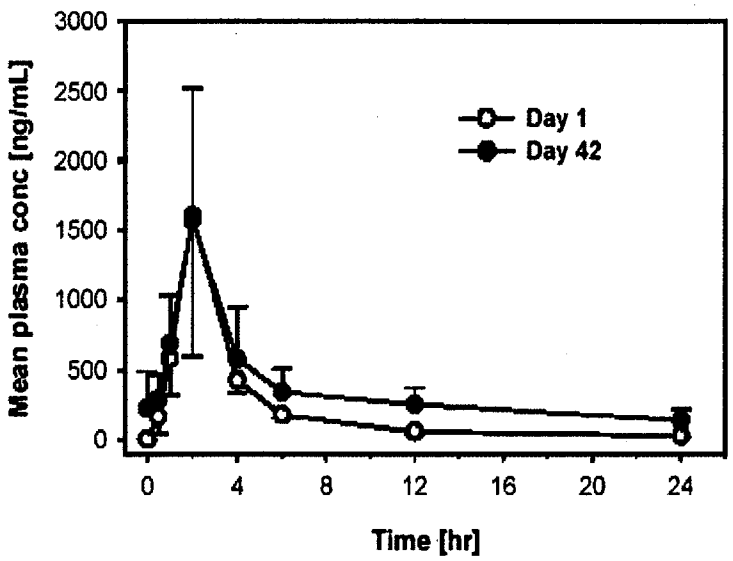



Fig 3. Mean (+ or – SD) terbinafine plasma concentrations (ng/mL) in one child with T.capitis after single and repeated oral doses of 250 mg of terbinafine given once daily as mini-tablets

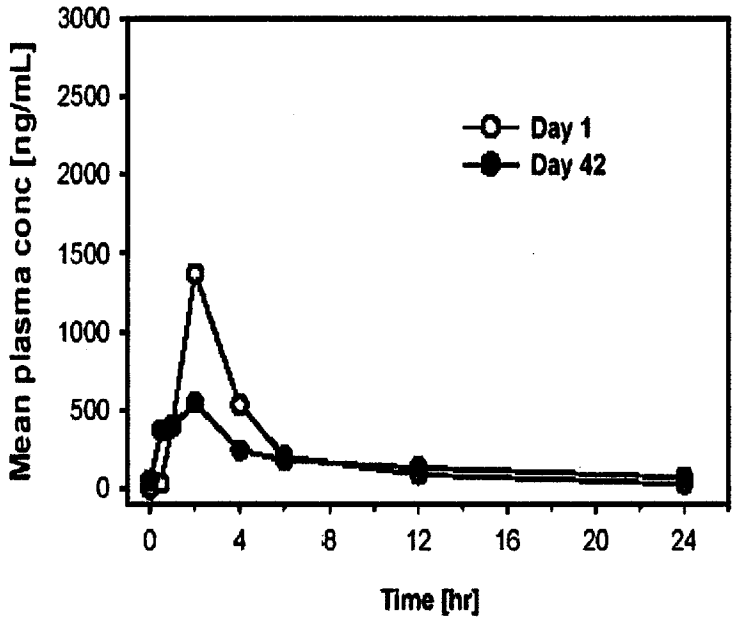


Table 4. Mean (SD) Pharmacokinetic Parameters of Terbinafine in children with T.Capitis on Day 1

| **Pharmacokinetic Parameters** | **Dose (N)** | | |
|---|---|---|---|
| | 125 mg (N=11) | 187.5 mg (N=4) | 250 mg (N=1) |
| **Cmax (ng/mL)** | 971 (585) | 1602 (1010) | 1370 |
| **AUC 0-24 (hr*ng/mL)** | 3311 (1605) | 5109 (1860) | 5253 |
| ***Tmax (hr)** | 2.0 (0.5-2.0) | 2.0 | 2.0 |

*Median (range)

Table 5. Mean (SD) Pharmacokinetic Parameters of Terbinafine in children with T. Capitis on Day 42

| **Pharmacokinetic Parameters** | **Dose (N)** | | |
|---|---|---|---|
| | 125 mg (N=11) | 187.5 mg (N=4) | 250 mg (N=1) |
| **Cmax (ng/mL)** | 1118 (713) | 1575 (942) | 544 |
| **AUC 0-24 (hr*ng/mL)** | 6513 (4074) | 8653 (4412) | 4154 |
| **CLss/F (L/hr)** | 25.4 (12.6) | 27.1 (15.4) | 60.2 |
| **Accumulation Ratio (R)** | 2.1 (0.9) | 1.9 (1.0) | 0.8 |
| **T1/2, eff (hr)** | 26.7 (13.8) | 30.5 (9.3) | ND |
| ***Tmax (hr)** | 2.0 (1.0-12.0) | 2.0 | 2.0 |

*Median (range), ND = not determined

The data in the table and graphs above show that:

- The mean Cmax and AUC 0-24 were generally higher in the 187.5 mg group than in the 125 mg group on Day 1 and 42.
- The Tmax stayed relatively constant over the dosing period with a median value of 2 hours in all dose groups
- Mean AUC 0-24 values were generally higher after repeated administration (Day 42) when compared to that obtained after the first dose. Although the only patient who received a 250 mg dose showed a lower AUC 0-24 on Day 42 than on Day 1. This was thought to reflect intra-subject variability.
- Inter-individual variability of Cmax and AUC0-24 values of terbinafine were relatively high, which is reflected by coefficient of variation values between 36% and 64%.
- The individual values of the effective half-life obtained for the 125 mg dose group was highly variable (range = 7.9 to 50.6 hours) when compared to that obtained

for the 187.5 mg dose groups (range = 20.5 to 39.0 hours). However, the mean effective half-life obtained were 26.7 hours and 30.5 hours for the 125 mg and the 187.5 mg dose group, respectively.

- The individual values of the apparent plasma clearance (CLss/F) obtained for the 125 mg and 187.5 mg dose group was highly variable (range = 8.4 to 50.5 L/ hr) for both dose groups. The mean CLss/F obtained 25.4 L/hr and 27.1 L/hr for the 125 mg and the 187.5 mg dose group, respectively were also comparable. However, the patient receiving the 250 mg dose exhibited a high CLss/F of 60.2 L/hr.

Comparison of the pharmacokinetics of terbinafine in children across studies:

The pharmacokinetics of terbinafine in children with Tinea Capitis from two studies C2101 and W352 were compared. The design of both studies was generally similar with the following exceptions: a) the mini-tablets were administered in C2101 while the oral tablets (as one, one and a half or two 125-mg Lamisil ® tablets) were administered in W352. b) In study C2101 all children were treated for 42 days while in study W352 children were treated for either 28 days or 42 days depending on the causative microorganism of their T.Capitis. c) No patient was recruited into the 250-mg dose group in W352.

Table 6. Comparison of the pharmacokinetic parameters (Mean (SD) obtained on Day 42 for both studies following multiple-dose administration of 125 mg of terbinafine to children with T.capitis

| **Pharmacokinetic Parameters** | **Study # (N) [Dosage Form]** | |
|---|---|---|
| | C2101 (N=11) [Mini-tablets] | W352 (N=16) [Tablets] |
| **Cmax (ng/mL)** | 1118 (713) | 1080 (581) |
| **AUC0-24 (ng*hr/mL)** | 6513 (4074) | 6440 (3827) |
| **CLss/F (L/hr)** | 25.4 (12.6) | 50.1 (80.8) |
| **Accumulation Ratio (R)** | 2.1 (0.9) | 1.33 (0.9) |
| **$T_{1/2}$, eff (hr)** | 26.7 (13.8) | 20.6 (15.7) |
| ***Tmax (hr)** | 2.0 (1.0-12.0) | 2.0 (1.0-2.0) |

*Median (range)

Table 7. Comparison of the pharmacokinetic parameters (Mean (SD) obtained on Day 42 for both studies following multiple-dose administration of 187.5 mg of terbinafine to children with T.capitis

| **Pharmacokinetic Parameters** | **Study # (N) [Dosage form]** |
|---|---|

| | C2101 (N=4) [Mini-tablets] | W352 (N=5) [Tablets] |
|---|---|---|
| **Cmax (ng/mL)** | 1575 (942) | 1738 (837) |
| **AUC 0-24 (ng*hr/mL)** | 8653 (4412) | 9987 (4982) |
| **CLss/F (L/hr)** | 27.1 (15.4) | 22.8 (10.9) |
| **Accumulation Ratio (R)** | 1.9 (1.0) | 1.00 (0.4) |
| **$T_{1/2}$, eff (hr)** | 30.5 (9.3) | 10.8 (3.9) |
| ***Tmax (hr)** | 2.0 | 1.0 (1.0-2.0) |

*Median (range)

Based on the data in Tables 3 and 4 above, the systemic exposure to terbinafine had similarities and differences between the two studies as follows:

- In both studies mean $AUC_{0-24}$ was generally higher in the 187.5-mg dose groups than in the 125-mg dose groups.

- In both studies higher $C_{max}$ values were observed in the 187.5-mg dose groups as compared to the 125-mg dose groups on Days 1 and 42. $C_{max}$ values were somewhat comparable in the two studies for both dose groups.

- The median $t_{max}$ value of terbinafine in plasma was 2 hrs in both studies for all doses and days of observation with the exception of the Day 42 median tmax of 1.0 hr in the 187.5-mg dose group in Study W352.

- The mean accumulation ratios R (i.e. the $AUC_{0-24}$ ratio of Day 28 or 42 to Day 1) were between 1.3 and 2.1 with exception of the 187.5-mg dose group in Study W352 on day 42. In this dose group the mean R suggested that there was no accumulation apparent (R=1.0).

- CLss/F was similar in the two studies for the 187.5 mg dose group but not for the 125 mg dose group. A high mean $CL_{ss}/F$ value (50.1 L/hr) was observed on day 42 in study W352 in the group receiving 125 mg. The applicant stated that this high mean value observed was apparently due to two patients with extremely high $CL_{ss}/F$ values (Patient 5424: 282.9 L/hr and Patient 5423: 91.9 L/hr), reflecting relatively low plasma concentrations and $AUC_{0-24}$values. These two patients also showed very low terbinafine plasma concentrations on Day 1 of treatment.

- The mean effective half-life based on the observed accumulation was comparable between the two studies for the 125 mg dose group but not for the 187.5 mg dose group. A low $T_{1/2, eff}$ was observed in study W352 in the 187.5-mg dose group. In this dose group 2 patients had an R value below 1.0 (no $T_{1/2, eff}$ can be calculated) and the remaining 3 patients had R values between 1.1 and 1.5 resulting in the low $T_{1/2, eff}$.

*Reviewer's Comments: Between the two studies, there were differences in the PK parameters, however, the steady state Cmax and AUC were similar taking into consideration the high inter-subject variability. These differences in the PK parameters indicate that the sponsor's proposal to* [redacted] *in the label is not appropriate*

Comparison of the pharmacokinetics of terbinafine between children and adults

The pharmacokinetic results after repeated oral doses (steady state) in children of studies[W352 and C2101] were compared to pharmacokinetic data from two studies in healthy adults after repeated oral doses of 250 mg of terbinafine given for 15 or 28 days in a Revised Expert Statement by [redacted] 2004. This report was included in this submission and reviewed. A summary of the results of this report is as follows:

Systemic exposure (AUC and Cmax) to terbinafine in the two studies conducted in children and in the two reference studies in adults is shown in Figures 4-5 below as individual and median $AUC_{0-24}$. As shown in Figures4-5, systemic exposure to terbinafine in the children who were administered 187.5 mg terbinafine mini-tablets was similar to that obtained in adults administered 250 mg terbinafine tablets.

However, in the children who were administered 125 mg terbinafine mini-tablets, median $AUC_{0-24}$ was 30 to 50 % lower and median Cmax was 31 to 40 % lower than that obtained in adults administered 250 mg terbinafine tablets. However, there is considerable overlap in the individual values of $AUC_{0-24}$ in adults and children receiving either 125 mg or 187.5 mg.

With the weight classes and doses of terbinafine proposed for children with Tinea Capitis (i.e. < 25 kg receive 125 mg qd, 25-35 kg receives 187.5 mg qd, > 35 kg receive 250 kg qd) the systemic exposure to terbinafine observed in children of all dose groups did not exceed the highest values observed in adults treated with 250 mg qd.

Figure 4: Plasma terbinafine AUC0-24 (ng*hr/mL) at steady state observed in children and adults after repeated oral doses of terbinafine (medians (connected by ····))

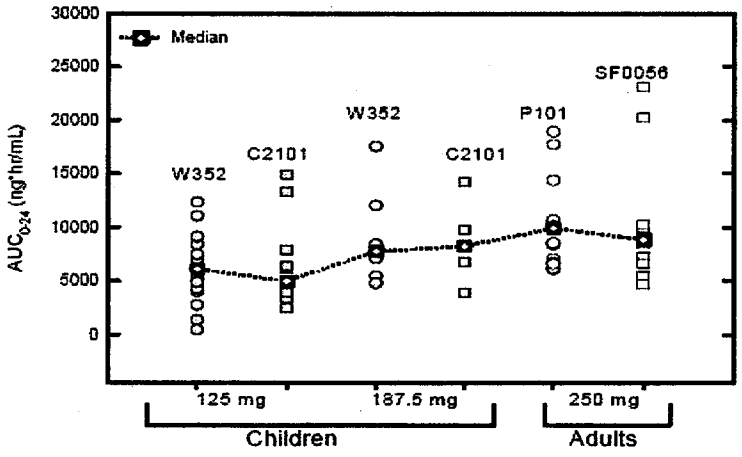
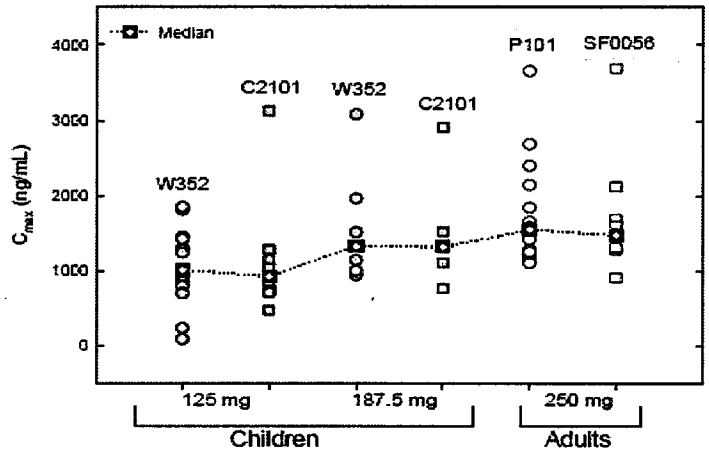
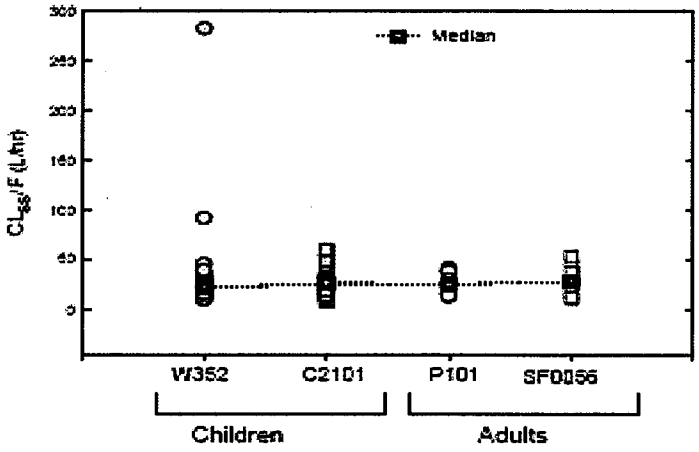


Figure 5: Plasma terbinafine Cmax values (ng/mL) at steady state observed in children and adults after repeated oral doses of terbinafine (medians (connected by ····))




The comparison of the two studies in children with results in adults indicated that there was no apparent difference in clearance $CL_{ss}/F$ of terbinafine between children and adults (with the exception of the two high values observed in study W352). This was confirmed by a statistical comparison of the apparent clearance of terbinafine at steady state ($CL_{ss}/F$) between adults and children that did not show a significant difference ($p = 0.597$) between the two populations. Note that the inter-subject variability was high and that in the statistical test the two high values observed in study W352 were included.

Figure 6: CLss/F values (L/hr) at steady state observed in children and adults after repeated oral doses of terbinafine (medians (connected by ····))




Population Pharmacokinetic Evaluation. A population PK evaluation [RANVR050-051] including results of both pharmacokinetic studies in children [C2101 and W352], sparse

samples from an early dose-range finding study in children [CT201] and historic data in adults after single and repeated oral doses of 250 mg of terbinafine tablets [P101 and SF0056] revealed that terbinafine pharmacokinetics in plasma are best described by a 4-compartment model.

The proposed dose of 187.5 mg qd given to children with body weights of 25 to 35 kg was predicted to result on average in a similar systemic exposure as a dose of 250 mg qd in adults. The proposed dose of 125 mg qd given to children with body weights < 25 kg was predicted to result on average in a lower exposure than a dose of 250 mg qd. in adults.

These observations are in agreement with the findings of the noncompartmental pharmacokinetic analysis of studies W352 and C2101 also showed a lower systemic exposure in the children treated with the 125 mg dose than those treated with the 187.5 mg dose.

Clearance (CL/F) of terbinafine was found to be dependent on body weight in a nonlinear manner, with an exponential scaling factor of 0.34 for body weight. Based on the analysis, for a typical child of 25 kg, CL/F is predicted to be 19 L/h and for a typical adult of 70 kg body weight it is predicted to be 26.9 L/h.

As described earlier in this section, the statistical analysis of the apparent steady state clearance ($CL_{ss}/F$) obtained by non-compartmental analysis did not show a statistically significant difference between children and adults. The population pharmacokinetic analysis, however, showed that body weight is a covariate for terbinafine clearance. Most likely the considerable inter-individual variability of systemic exposure observed in the two studies conducted in children prevented the applicant from detecting significant differences in the clearances between the populations.

Volume (V) of terbinafine was found to be dependent on body weight in a nonlinear manner, with an exponential scaling factor of 0.325 for body weight. Based on the analysis, for a typical child of 25 kg, volume is predicted to be 93.2 L and for a typical adult of 70 kg body weight it is predicted to be 136 L.

Tablet type (i.e. conventional tablet as used in study W352 vs. mini-tablet as used in study C2101) was the only other covariate that had an impact on the PK of terbinafine. Differences between tablet types resulted in a slightly longer duration of absorption for the mini-tablet, with duration being estimated as 2.0 hr for the mini-tablet and 1.6 hr for the conventional tablet. However, it should be noted that only 16 patients provided data for the mini-tablets.

Similarly, in the relative bioavailability study [C2303] in adult volunteers, median $T_{max}$ of terbinafine in plasma was 0.25 hr later for the mini-tablets ($T_{max}$ = 1.75 hr) than for the conventional tablets ($T_{max}$ = 1.5 hr) which is in line with the above results of the population pharmacokinetics modeling. However, this small apparent difference in the absorption kinetics of terbinafine from mini-tablets vs. conventional tablets was not

considered to be clinically relevant. Efficacy of terbinafine is likely related to the concentration maintained at the site of action, mainly skin or hair shaft in case of T.capitis during repeated oral administration of the drug. In such a situation small changes in the absorption kinetics of the drug are not relevant.

## 2.4 Extrinsic Factors

### *2.4.2 Drug-Drug Interactions*

#### *2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

Four drug interaction studies were performed in healthy volunteers. The potential for pharmacokinetic drug interactions in vivo was tested after single oral doses of terbinafine tablets given alone or in combination with the following co-medications: fluconazole [CSFO3270152], cotrimoxazole [CSFO3270153], zidovudine [CSFO3270154] and theophylline [CSFO3270156]. The rationale for each of these clinical studies was based either on a possible interference in excretion mechanisms (fluconazole, cotrimoxazole), effects previously observed with compounds from a similar class (theophylline) or pharmacological effects (zidovudine).

The four studies were of identical design. They were designed as randomized, open-label, single-dose, three-period crossover studies according to a balanced complete two 3 x 3 Latin square design. Eighteen healthy subjects completed each study. The treatments included a single dose of Lamisil alone or together with co-medication and a single dose of co-medication taken without Lamisil. Results of the four drug interaction studies are summarized in Table 6. The results of these studies demonstrated that trimethoprim, sulfamethoxazole, zidovudine and theophylline do not have a clinically relevant influence on the pharmacokinetics of terbinafine. When Lamisil is given together with fluconazole, terbinafine Cmax and AUC were increased by 52 and 67%, respectively.

Table 8: Summary of drug interaction studies performed with terbinafine in 18 healthy subjects

| Study | Co-medication/Dose | Terbinafine dose | PK effects observed on: | |
|---|---|---|---|---|
| | | | Co-medication | Terbinafine |
| 0152 | Fluconazole/100 mg | 750 mg | PK not altered | **Cmax +52%; AUC +67%** |
| 0153 | Cotrimoxazole/ 160 mg trimethoprim 800 mg sulfamethoxazole | 750 mg | PK not altered | PK not altered |
| 0154 | Zidovudine/200 mg | 750 mg | **AUC +15%;** | |

| | | | | |
|---|---|---|---|---|
| | | | **Tmax +41%; Cmax -25%; CL/F -15%; V/F -17%** | PK not altered |
| 0156 | Theophylline/375 mg | 250 mg | PK not altered | **Cmax +23%; AUC +18%; CL/F -23%** |

The results of these drug interaction studies can be summarized as follows:

- A single oral dose of fluconazole increased terbinafine Cmax (52%), AUC (0-tlast) (69%), and AUC (0-∞) (67%), and decreased desmethylterbinafine Cmax (28%) to a statistically significant degree. A concurrent single dose of terbinafine with fluconazole does not alter the pharmacokinetics of fluconazole.
- Concurrent administration of Cotrimoxazole DS with Lamisil® did not alter the disposition of terbinafine or desmethylterbinafine. Concurrent administration of Lamisil® with Cotrimoxazole DS did not alter the pharmacokinetics of trimethoprim or sulfamethoxazole.
- Administration of zidovudine concomitantly with Lamisil did not affect the pharmacokinetic properties of terbinafine or its metabolite desmethylterbinafine. Administration of Lamisil together with zidovudine resulted in a statistically significant increase in AUC (15%) and Tmax of zidovudine, and a decrease in Cmax (25%), CL/F (15%) and V/F (17%). These changes in the pharmacokinetic properties of zidovudine due to Lamisil was not considered to pose a safety concern because it is the minor metabolite of zidovudine, AMT, that has been implicated with the bone marrow suppression associated with zidovudine.
- Concurrent administration of Lamisil with theophylline did not alter the pharmacokinetics of theophylline. Theophylline when given together with Lamisil reduced terbinafine clearance. However, the resultant increase in AUC (0-∞) and Cmax of terbinafine of 18% and 23% respectively was not considered to be clinically meaningful due to the wide safety margin of terbinafine.

*Reviewer's Comments: Note that the doses studied in the drug interaction studies (with the exception of the theophylline study) were 3-fold higher than the recommended single dose in adults and the highest dose in children. The applicant stated that concomitant therapy of terbinafine with fluconazole may need dose adjustment. However, it is not clear how the dose would be adjusted for terbinafine since the terbinafine dose administered in the drug interaction study was much higher than the recommended dose while the fluconazole dose was lower than the maximum therapeutic dose in adults.*

*Further discussions with the medical reviewer indicated that there was no exposure-response relationship for safety observed in the clinical trials. It should also be noted that the current label for terbinafine oral tablets also states that doses up to 5 grams (20 times the therapeutic dose) have been taken without inducing serious adverse reactions. However, because hepatotoxicity is a safety concern screening for hepatic enzymes is considered critical for patients with elevated terbinafine concentrations. Therefore we*

*recommend that co-administration of fluconazole with terbinafine should be done with careful laboratory monitoring of hepatic enzymes (ALT and AST)*

## 2.5 General Biopharmaceutics

Drug Product Composition:

The drug product consists of tablets that are film coated "mini-tablets" in a [redacted] corresponding to strengths of 125 mg (approximately 30 film coated "mini-tablets") and 187.5 mg (approximately 45 film coated "mini-tablets") of terbinafine base respectively. Each [redacted] is intended for use as a single dose. The film coated tablets are off-white to yellowish, round, biconvex "mini-tablets", having a diameter of approx. 2.1 mm and containing 4.6875 mg of terbinafine hydrochloride each (corresponding to 4.167 mg of terbinafine base).

Table 9: Composition of Terbinafine Mini-tablets 125mg, 187.5mg Film coated tablets in [redacted]

| Ingredient | Theoretical amount | |
|---|---|---|
| | 125 mg (approx. 30 minitablets) | 187.5 mg (approx. 45 minitablets) |
| Terbinafine hydrochloride | [redacted] | [redacted] |
| Cellulose, microcrystalline / Microcrystalline cellulose | | |
| Sodium starch glycolate / Sodium starch glycolate | | |
| [redacted] | | |
| Hypromellose / | | |
| [redacted] | | |
| Colloidal silicon dioxide | | |
| Magnesium stearate | | |
| [redacted] | | |
| [redacted] | | |
| Colloidal silicon dioxide | | |
| [redacted] / Polyethylene glycol | | |
| [redacted] | | |
| [redacted] | | |
| Basic butylated methacrylate copolymer | | |
| [redacted] | | |
| Dibutyl sebacate | | |
| [redacted] | | |
| Sodium lauryl sulfate | | |
| [redacted] | | |
| [redacted] | | |
| [redacted] | | |
| **Total weight** | **216.16** | **324.19** |
| Nitrogen | - | - |

1) corresponds to 125 mg of terbinafine base
2) corresponds to 187.5 mg of terbinafine base
3) removed during the manufacturing process

### *2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation compared to the formulation used in the pivotal clinical trials?*

The to-be-marketed pediatric formulation of the mini-tablets was used in the pharmacokinetic study [C2101], the relative bioavailability study [C2303] and, the Phase 3 clinical trials [C2301 and C2302] for Tinea capitis.

Relative bioavailability of the mini-tablets to the currently marketed oral terbinafine tablets

The relative bioavailability of the mini-tablets compared to the marketed tablets was investigated in [Study C2303]. This was a randomized, open-label, single dose, three period crossover study in 24 Caucasian (12 male and 12 female) adult healthy volunteers. The mean (SD) and [range] for the age, weight and height of the subjects were as follows: 34.4 (5.1) [23.44] years, 73.4 (8.2) [57-84] kg and 174.7 (6.6) [164-188] cm, respectively. The mini-tablets were administered by sprinkling over yoghurt or vanilla pudding while the tablets were administered in the fasted state. The results of study C2303 demonstrated that 250 mg of terbinafine when administered to adult healthy subjects as 60 mini-tablets was bioequivalent to one 250-mg marketed tablet or two 125-mg marketed tablets.

For both comparisons, i.e. mini-tablets vs. 250 mg tablet and mini-tablets vs. 2 x 125 mg tablets, the ratios of the geometric means for Cmax, AUC0-tlast and AUC0-∞ were close to unity (0.95 to 1.04) and the 90% confidence intervals (CI) were all contained within the bioequivalence range of 0.8 to 1.25. The pharmacokinetics of terbinafine and the 90 % CI for AUC and Cmax are summarized in the table below.

| **Table 10** | **Terbinafine pharmacokinetic parameters in plasma** | | | | |
|---|---|---|---|---|---|
| **Parameters** | **C** | **A** | **B** | **Ratio C/A*** | **Ratio C/B*** |
| | **60 mini-tablets (n=24)** | **one 250 mg tablet (n=24)** | **two 125 mg tablets (n=24)** | **(90% CI)** | **(90% CI)** |
| **Tmax [hr]** | 1.75 [1.00 – 3.00] | 1.50 [1.00 – 3.00] | 1.50 [1.00 – 4.00] | - | - |
| **Cmax [ng/mL]** | 690 ± 242 (653) | 745 ± 295 (690) | 742 ± 307 (668) | 0.95 (0.82 - 1.09) | 0.98 (0.85 – 1.13) |
| **AUC0-tlast [ng*hr/mL]** | 3508 ± 1173 (3344) | 3577 ± 1379 (3322) | 3582 ± 1326 (3328) | 1.01 (0.94 – 1.08) | 1.00 (0.93 – 1.08) |
| **AUC0-∞ [ng*hr/mL]** | 3850 ± 1510 (3611) *(n=20)* | 3662 ± 1680 (3329) *(n=16)* | 3979 ±1363 (3717) *(n=20)* | 1.04 (0.95 – 1.14) | 1.04 (0.96 – 1.13) |
| **T1/2 [hr]** | 41.0 ± 11.5 (39.5) *(n=20)* | 38.3 ± 5.8 (37.9) *(n=16)* | 40.7 ± 8.3 (39.9) *(n=20)* | - | - |

Values are median [range] for tmax and mean ± SD (geometric mean) for other parameters
*Ratio is test/reference ratio of geometric means and 90% confidence interval from ANOVA
No statistical evaluation was performed for Tmax and T1/2

Median $T_{max}$ was 15 min later for the mini-tablets (1.75 hr) than for the 125 and 250 mg tablets (1.50 hr). However, for all three formulations, the individual $T_{max}$ was observed between 1 and 4 hours after dosing. Thus, the small difference in median $T_{max}$ is not considered to be clinically relevant.

***2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?***

The mini-tablets were administered with food (pudding) in the clinical studies and the pharmacokinetic studies, therefore a food effect study may not be relevant in this caseHowever, the influence of food on the bioavailability of terbinafine mini-tablets administered as a new oral form, [redacted] was investigated in study [L2104] after a single dose and in study [L2306] after repeated doses of 350 mg [redacted] These studies were performed in adult healthy subjects. It should be noted that the formulations used were not the same strength as the to-be-marketed formulation and they were [redacted] The applicant stated that due to the similarity in the dissolution profiles of the [redacted] and the loose mini-tablets, it is assumed that the effects seen in the studies performed with the [redacted] can be extrapolated to the administration of the mini-tablets.

*Reviewer's Comments: The dissolution data provided by the applicant indicated that dissolution profiles of the Lamisil mini-tablets were not similar to that of the [redacted] The f-2 value calculated for the similarity criterion was 33 (FDA guidance criterion for similarity is ≥ 50) demonstrated that the difference is statistically significant. The profiles indicated a delay in the release of the drug from the [redacted] compared to the mini-tablets at the 5 minute time point. There was no IVIVC provided by the applicant based on the dissolution method testing presented. Following discussions with the chemistry reviewer (Dr. Y. Sun), it was decided that the applicant's extrapolation of the food effect data from this formulation to the mini-tablets based on a comparison of the in vitro dissolution profiles alone would not be appropriate. Therefore, it is recommended that this information [redacted]*

Although the mini-tablets, for ease of administration, were given together with pudding in the pharmacokinetic studies and the clinical trials, no special recommendation on drug intake in relation to meals was provided for the label.

*Reviewer's Comments: The mini-tablets were administered with pudding in the pharmacokinetic studies and, in the clinical trials. In addition, all subjects were instructed to take the mini-tablets with a meal in the clinical trials. The sponsor did not propose any recommendation on drug administration in relation to meals. Following discussions with the medical reviewer, it was decided that the label will include directions for the mini-tablets to be taken with meals in the dosage and administration section of the label.*

2.6 Analytical Section

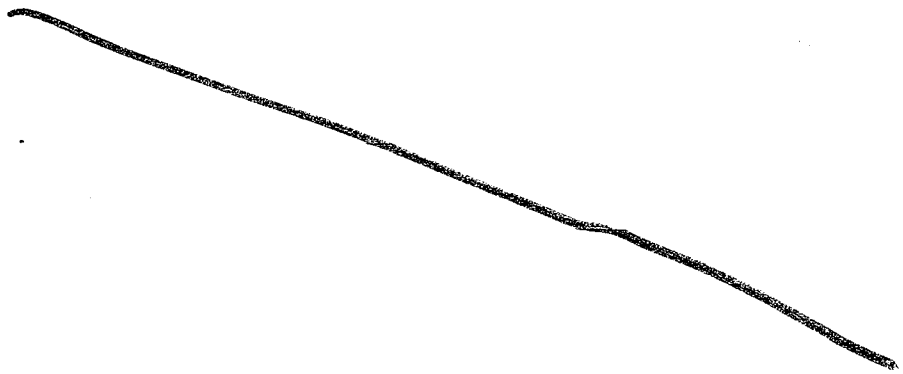
2.6.4 What bioanalytical methods are used to assess concentrations and were they adequately validated?

Terbinafine was determined in human plasma by LC/-MS/MS. The assay was validated for accuracy, precision, sensitivity, linearity and specificity as shown in the table below.

**Table 11: Analytical Method and Validation:**

| | |
|---|---|
| **Method** | LC/MS/MS |
| **Compound** | Terbinafine |
| **Internal Standard** | [redacted] |
| **Matrix** | Plasma |
| **Accuracy (% Bias)**<br>***Within-Day***<br><br>***Between-Day*** | <br>-5.3 to 5.5 (Calibration standards)<br><br>2.8 to 7.8 (QC standards) |
| **Precision (% CV)**<br>***Within-Day***<br><br>***Between-Day*** | <br>2.7 % to 7.1 % (Calibration standards)<br><br>5.3 % to 7.6 % (QC Standards) |
| **Standard curve range** | 1 ng/mL to 500 ng/mL ($r^2 \geq 0.997$) |
| **Sensitivity (LOQ)** | 1 ng/mL |
| **Selectivity** | There was no interference due to endogenous peaks in human plasma observed at the retention times of terbinafine and its internal standard. |
| **Stability** | Stable when stored in human plasma at -20°C for 9 months. |
| **Conclusion** | **The analytical method validation is acceptable** |

# 3 Detailed Labeling Recommendations



# 16 Page(s) Withheld

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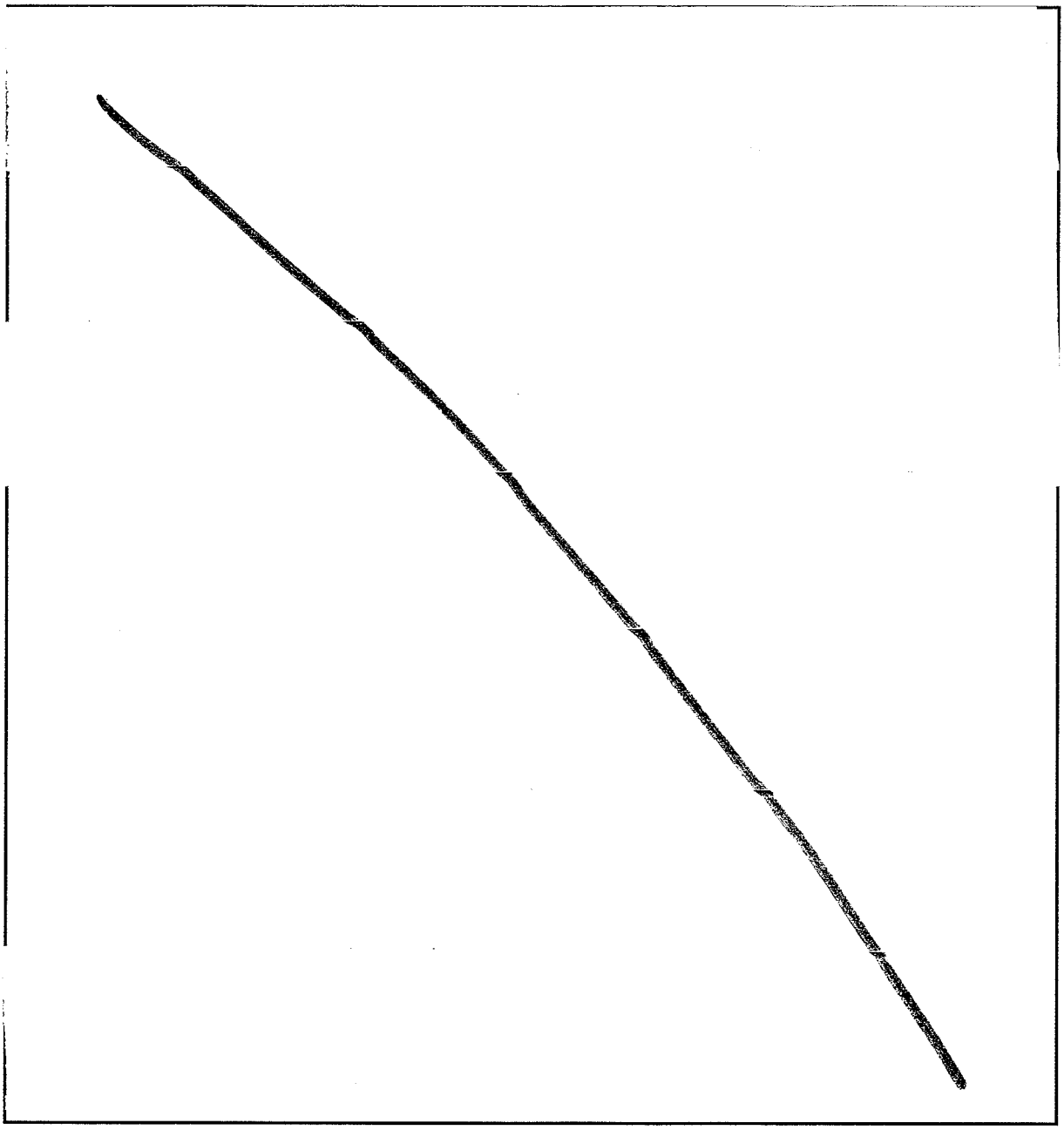
__✓__ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-_____*



## 4.2. Individual Study Reviews

**Studies in Patients**

**Study # C2101**
**Title of study:** An open-label, multiple-dose study to evaluate the pharmacokinetics of Terbinafine Hydrochloride Mini-tablets in children 4-8 years of age with tinea capitis
**Investigator:**

**Analytical Site:** [redacted] (Bioanalyst), Bioanalytics and Pharmacokinetics, Novartis Pharma S.A.S., 2/4 rue Lionel Terray, 92500 Rueil-Malmaison, France
**Study period:** First patient dosed 22-Oct-03 and Last patient completed 03-Dec-03
Plasma Sample Analysis: 04-Dec-2003 to 08-Jan-2004
**Objectives:**
Primary objective
• To evaluate the pharmacokinetics of terbinafine in children 4 to 8 years of age with tinea capitis after administration of Terbinafine Hydrochloride Mini-tablets
Secondary objective
• To determine the safety and tolerability of Terbinafine Hydrochloride Mini-tablets in children 4 to 8 years of age with tinea capitis
**Study Design:** This was an open-labeled, multiple-dose study, in which each patient with tinea capitis infection (regardless of causative organism - Trichophyton or Microsporum), received terbinafine hydrochloride mini-tablets once daily for 42 days.
**Study Population:** Sixteen (16) patients were planned for enrollment, 16 patients were randomized and 16 patients completed the study. ***Criteria for inclusion:*** Male and female patients, aged 4-8 years (inclusive), with a diagnosis of tinea capitis, but otherwise healthy. Patients confirmed the clinical diagnosis of tinea capitis by direct microscopic examination of infected host tissue and isolation of dermatophytic pathogen culture. Tinea capitis was also confirmed by positive culture for Trichophyton or Microsporum species. Samples were obtained from patients at Screening and were sent to an independent laboratory for evaluation. Patients were entered into the study prior to obtaining the culture result. However, if a negative culture was obtained and the patient was responding to treatment (in the Investigator's opinion), the study drug treatment was continued until Day 42. All PK sampling for such patients occurred as described in the study synopsis.
**Investigational drug (s):** Terbinafine Hydrochloride Mini-tablets in unit dose bottles:
30 Terbinafine Hydrochloride Mini-tablets x one unit dose bottle = 125mg
45 Terbinafine Hydrochloride Mini-tablets x one unit dose bottle = 187.5mg
60 Terbinafine Hydrochloride Mini-tablets x one unit dose bottle = 250mg
**Drug administration:** Patients received one of the following doses based on weight:
Patients < 25 kg received 125 mg q.d. [5-8 mg/kg] (Batch X208 0803)
Patients 25 to 35 kg received 187.5 mg q.d [5-7.5 mg/kg] (Batch X209 0803)
Patients > 35 kg received 250 mg q.d. [5-7.5 mg/kg] (Batch X210 0803)
Patients took the assigned Minitablet dose (depending on body weight) once a day in the morning with pudding followed by water. On Day 1, study medication was administered by the study center personnel in the morning with pudding. One teaspoon or tablespoon of vanilla pudding was filled in a small plastic cup and the mini-tablets were carefully sprinkled on the pudding immediately before administration. Patients were allowed to drink 120 mL of water. All patients fasted for at least 1 hour following study drug administration. Patients were instructed not to chew the medication, but to swallow it whole. The investigator or staff instructed the parent/guardian to put the Mini-tablets into 1 teaspoon of pudding, administer to the patient, and then follow this with water. Caretakers were instructed to provide study medication to patients at the same time each day. Patients took their study medication at the clinic on visit days (Days 21 and 42).
**Duration of Treatment:** Study drug was administered for 42 days q.d. in the morning.

**Pharmacokinetics Sampling:** Blood collection [600 µL blood per sample, Na EDTA tubes (plasma)]: Days 1 and 42 at predose, 0.5, 1, 2, 4, 6, 12 and 24 hours postdose; Day 21 at predose only. All samples were processed and kept frozen at < -18°C pending analysis at Novartis.
**Analytical Methods:** Terbinafine concentrations in plasma were determined by HPLC-MS method; LLOQ at 1 ng/mL.
**Pharmacokinetic and Statistical Analysis:** PK parameters for terbinafine: tmax, Cmax, Cmax/Dose, Cmin, AUC0-24h, AUC0-24h/Dose CLss/F, effective t½ from accumulation and accumulation ratio on Day 42, t1/2 apparent elimination half-life based on apparent plasma elimination rate constant λz. PK evaluations in plasma: Non-compartmental analysis. Descriptive statistics of the PK parameters include arithmetic and geometric mean, SD, CV, minimum, maximum and median. Pediatric PK data were compared to historic PK data in adults from two studies [SFP-101] [redacted] (1997)] and [SF0056 [redacted] (1995)] in a separate report and in a population PK analysis.

**Results:**
**Study Population:** Sixteen (16) patients were randomized and 16 patients completed the study; there were no study discontinuations.
**Demographics:** Distribution of patients by age was as follows: 4 years (1), 5 years (9), 6 years (1), 7 years (3) and 8 years (2).

**Table 7-1 Summary of demographic information**

| | SFO327 | SFO327 | SFO327 |
|---|---|---|---|
| Dose | 125 mg | 187.5 mg | 250 mg |
| Weight group | < 25 kg | 25 to 35 kg | > 35 kg |
| | N = 11 | N =4 | N = 1 |
| Age (years) | | | |
| mean ± SD | 5.36 ± 1.12 | 6.5 ± 1.29 | 7.0 |
| range | 4 - 8 | 5 - 8 | 7 |
| median | 5.0 | 6.5 | 7.0 |
| Sex | | | |
| Male | 9 (81.8 %) | 3 (75 %) | 1 (100%) |
| Female | 2 (18.2 %) | 1 (25%) | |
| Race | | | |
| Caucasian | 4 (36.4 %) | | |
| Black | 7 (63.6 %) | 4 (100%) | 1 (100%) |
| BMI ($kg/m^2$) | | | |
| mean ± SD | 15.83 ± 1.35 | 20.38 ± 5.36 | 20.3 |
| range | 12.8 – 18.1 | 16.4 – 28 | 20.3 |
| median | 15.9 | 18.55 | 20.3 |

| Height (cm) ++ | | | |
|---|---|---|---|
| n | 11 | 4 | 1 |
| mean | 113.27 | 126.50 | 137.00 |
| SD | 11.05 | 16.01 | |
| minimum | 94.00 | 108.00 | 137.00 |
| median | 117.00 | 125.50 | 137.00 |
| maximum | 127.00 | 147.00 | 137.00 |

| Weight (kg) ++ | | | |
|---|---|---|---|
| n | 11 | 4 | 1 |
| mean | 20.35 | 31.68 | 38.20 |
| SD | 3.20 | 3.42 | |
| minimum | 14.10 | 27.30 | 38.20 |
| median | 21.80 | 31.95 | 38.20 |
| maximum | 23.60 | 35.50 | 38.20 |

**Baseline Tests for Dermatophyte:** All patients had a positive KOH examination for dermatophyte infection at screening, as required for inclusion in the study. The results of the dermatophyte culture were obtained while the study was ongoing. Four (4) patients tested positive for *Trichophyton tonsurans* and 9 were positive for *Microsporum canis*. Specimens from 3 patients were not positive for either *Trichophyton* or *Microsporum*. In 2 of these patients (**5103 and 5107**), the infective agent was identified as *Cladosporium sp.*; the infective agent was not identified for patient **5116**.

*Reviewer's Comments: Medical Officer said these 3 patients being included in this study was OK and it is not considered to be a significant protocol violation for the purposes of this study.*

**Pharmacokinetics:**
Plasma Concentration-Time Profiles:

**Figure 7-1** **Mean (+ or - SD) terbinafine plasma concentrations (ng/mL) in children (N=11) with T. capitis after single and repeated oral doses of 125 mg of terbinafine given once daily as minitablets**

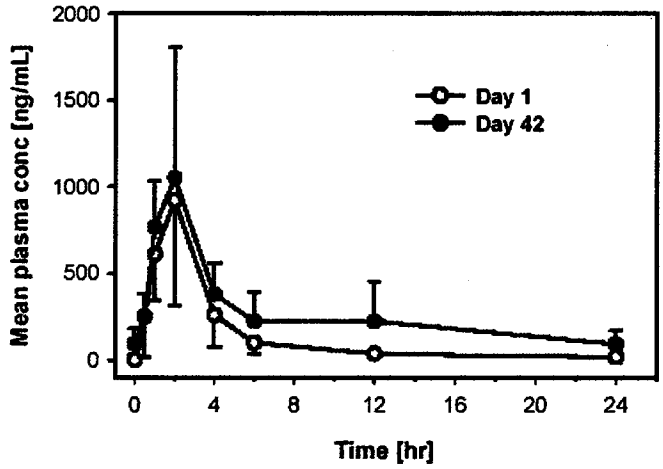


Figure 7-2 **Mean (+or - SD) terbinafine plasma concentrations (ng/mL) in children (N=4) with T. capitis after single and repeated oral doses of 187.5 mg of terbinafine given once daily as minitablets**

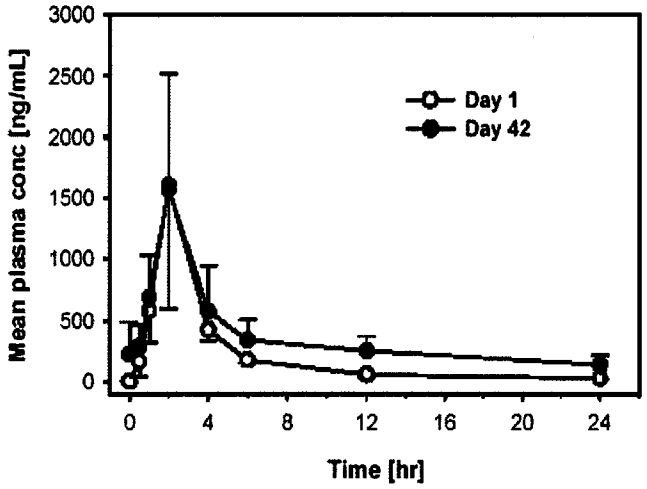



Figure 7-3 **Plasma concentrations of terbinafine (ng/mL) in one child with T. capitis after single and repeated oral doses of 250 mg of terbinafine given once daily as minitablets**

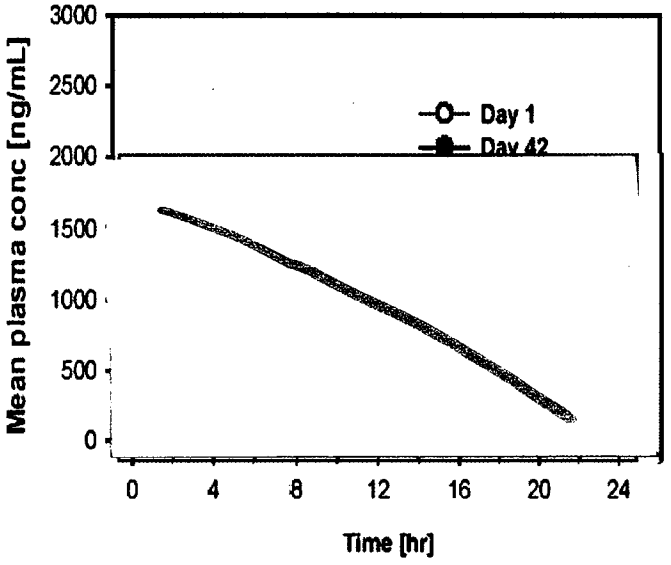


**Table 7-4** **Mean pharmacokinetic variables of terbinafine in plasma in children with T. capitis**

| Dose/Day | | Body weight (kg) | $t_{max}$ (hr) | $C_{max}$ (ng/mL) | $AUC_{0-24}$ (hr*ng/mL) | R | $t_{1/2,eff}$ (hr) | $CL_{ss}/F$ (L/hr) |
|---|---|---|---|---|---|---|---|---|
| 125mg | N | 11 | 11 | 11 | 11 | - | - | - |
| Day 1 | **Mean** | 20.3 | **1.8** | **971** | **3311** | - | - | - |
| | SD | 3.2 | 0.5 | 585 | 1605 | - | - | - |
| | Min | 14.3 | 0.5 | 306 | 1476 | - | - | - |
| | **Median** | 21.8 | **2.0** | **770** | **3201** | - | - | - |
| | Max | 23.6 | 2.0 | 2300 | 6973 | - | - | - |
| | CV% | 15.5 | 29.0 | 60 | 48 | - | - | - |
| 125mg | N | 11 | 11 | 11 | 11 | 11 | 10 | 11 |
| Day 42 | **Mean** | 20.5 | **2.5** | **1118** | **6513** | **2.1** | **26.7** | **25.4** |
| | SD | 3.1 | 3.2 | 713 | 4074 | 0.9 | 13.8 | 12.6 |
| | Min | 14.5 | 1.0 | 473 | 2474 | 0.9 | 7.9 | 8.4 |
| | **Median** | 22.3 | **2.0** | **923** | **4975** | **1.8** | **24.3** | **25.1** |
| | Max | 23.6 | 12.0 | 3130 | 14917 | 3.6 | 50.6 | 50.5 |
| | CV% | 15.3 | 130.6 | 64 | 63 | 44.3 | 51.5 | 49.5 |
| 187.5mg | N | 4 | 4 | 4 | 4 | - | - | - |
| Day 1 | **Mean** | 31.7 | **2.0** | **1602** | **5109** | - | - | - |
| | SD | 3.6 | 0.0 | 1010 | 1860 | - | - | - |
| | Min | 27.0 | 2.0 | 938 | 3764 | - | - | - |
| | **Median** | 32.1 | **2.0** | **1190** | **4440** | - | - | - |
| | Max | 35.6 | 2.0 | 3090 | 7791 | - | - | - |
| | CV% | 11.3 | 0.0 | 63 | 36 | - | - | - |
| 187.5mg | N | 4 | 4 | 4 | 4 | 4 | 3 | 4 |
| Day 42 | **Mean** | 31.6 | **2.0** | **1575** | **8653** | **1.9** | **30.5** | **27.1** |
| | SD | 3.8 | 0.0 | 942 | 4412 | 1.0 | 9.3 | 15.4 |
| | Min | 26.8 | 2.0 | 761 | 3868 | 0.5 | 20.5 | 13.2 |
| | **Median** | 32.1 | **2.0** | **1315** | **8274** | **2.1** | **32.2** | **23.4** |
| | Max | 35.5 | 2.0 | 2910 | 14197 | 2.9 | 39.0 | 48.5 |
| | CV% | 12.0 | 0.4 | 60 | 51 | 54.6 | 30.5 | 56.8 |
| 250mg | N | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Day 1 | | 37.7 | 2.0 | 1370 | 5253 | - | - | - |
| Day 42 | | 38.6 | 2.0 | 544 | 4154 | 0.8 | - | 60.2 |

Inter-individual variability of $C_{max}$ and $AUC_{0-24}$ values of terbinafine were high, which is reflected by coefficient of variation values between 36% and 64%.

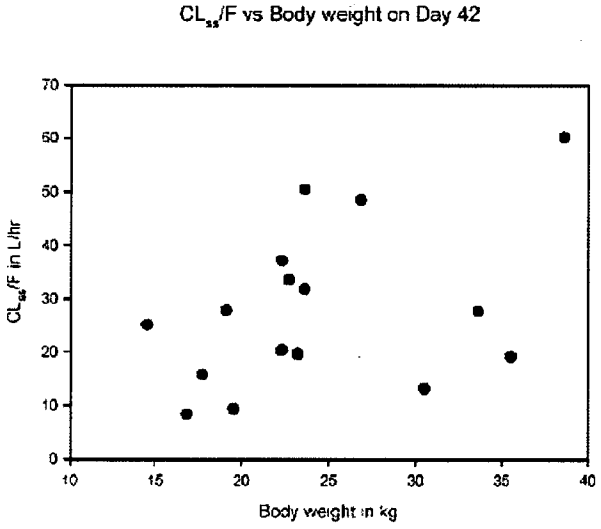
Means as well as median values of $C_{max}$ and $AUC_{0-24}$ were higher in the 187.5 mg group than in the 125 mg group, both on Day 1 and Day 42. However, on Day 42 the individual values of both parameters in the 187.5 mg dose group were within the ranges of values observed in the 125 mg dose group. After repeated administration (Day 42), mean $AUC_{0-24}$ values were generally higher than after the first dose (Day 1), with the mean accumulation ratio being 2.1 and 1.9 for the 125 mg and 187.5 mg doses, respectively.

The only patient who received a 250 mg dose showed a lower $AUC_{0-24}$ on Day 42 than on Day 1. This was also true for one patient in each of the other dose groups (125 mg and 187.5 mg) and is thought to reflect intra-subject variability.

Mean $C_{max}$ values were slightly higher on Day 42 compared to Day 1 in the 125 mg dose group (ratio of mean Day 42/mean Day 1 = 1.15). In the 187.5 mg dose group mean $C_{max}$ values were similar on Day 1 and Day 42 (ratio of mean Day 42/mean Day 1 = 0.98).
The time of maximum concentration ($T_{max}$) stayed constant over the dosing period with a median value of 2 hours in all dose groups. The individual values of the effective half-life of terbinafine determined from the accumulation in plasma on Day 42 as compared to Day 1 were between 7.9 and 50.6 hours. The arithmetic mean was 26.7 hours in the 125 mg dose group and 30.5 hours in the 187.5 mg dose group.

From $AUC_{0-24}$ on Day 42, the apparent plasma clearance of terbinafine was calculated at steady state ($CL_{ss}/F$). The individual $CL_{ss}/F$ values in the 125 mg and 187.5 mg dose groups ranged between 8.4 and 50.5 L/hr. The arithmetic mean was 25.4 L/hr for the 125 mg dose group and 27.1 L/hr for the 187.5 mg dose group. The patient receiving the 250 mg dose exhibited a high apparent clearance of 60.2 L/hr. Based on a a plot of $CL_{ss}/F$ vs. body weight (see Figure 7-8), a trend of increasing clearance with increasing body weight was observed.

**Figure 7-8** **Individual apparent terbinafine plasma clearance calculated on Day 42 vs body weight on Day 42 in children with T. capitis after daily oral doses of either 125 mg (N=11), 187.5 mg (N=4) or 250 mg N=1) of terbinafine given as minitablets**




Attainment of Steady State:
Blood samples were also collected on Day 21 before the daily dose (time = 0 hr, see Table 7-5). Eight (8) of the 16 patients had Day 42 trough concentrations which were higher than on Day 21, whereas the opposite (i.e., lower concentrations on Day 42 than on Day 21) was observed for the

other 8 patients. The mean ratio of the 0-hour concentrations measured on Day 42 vs. Day 21 was close to 1, indicating that on average patients were at steady state between Days 21 and 42.

**Table 7-5 Mean plasma terbinafine concentrations (ng/mL) measured before oral administration of the daily dose of terbinafine in children with T. capitis**

| Dose (mg) | | Day | | Ratio Day 42/Day 21 |
|---|---|---|---|---|
| | | 21 | 42 | |
| 125 | N | 11 | 11 | 11 |
| | Mean | 148.0 | 92.3 | **1.005** |
| | SD | 268.5 | 88.4 | 0.528 |
| | Min | 2.36 | 1.63 | 0.24 |
| | Median | 74.3 | 68.8 | **1.08** |
| | Max | 939.0 | 260.0 | 1.81 |
| | CV% | 181.5 | 95.8 | 52.5 |
| 187.50 | N | 4 | 4 | 4 |
| | Mean | 235.3 | 222.9 | **0.915** |
| | SD | 198.3 | 263.4 | 0.842 |
| | Min | 61.3 | 27.0 | 0.38 |
| | Median | 191.5 | 130.3 | **0.55** |
| | Max | 497.0 | 604.0 | 2.16 |
| | CV% | 84.2 | 118.2 | 92.1 |
| 250.00 | Patient 5103 | [redacted] | | 0.457 |

*Reviewer's Comments: When one takes the high variability into account, the data is considered to suggest that on average the patients were at SS between days 21 and 42. This is similar to what was observed in the second pediatric study (W352) that investigated the PK of terbinafine in children aged 4-8 years old with T. Capitis.*

**Comparison of the pharmacokinetics between children and adults**

An extensive descriptive comparison of the pharmacokinetics of terbinafine in children compared to adults is provided in ( [redacted] 2004) and can be summarized as follows:

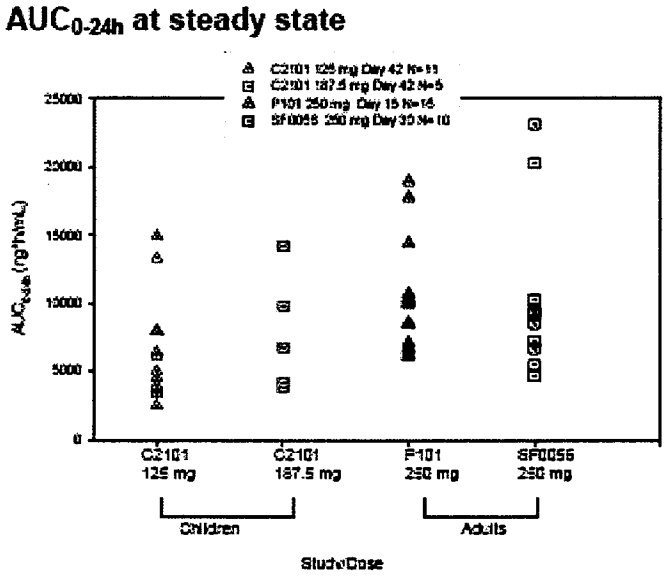
A comparison of the pharmacokinetic variables measured at state steady (Day 42) in these children with historic data from adult healthy volunteers was evaluated. The variables observed in children after daily oral doses of 125 and 187.5 mg are well within the range of values observed in adults after daily oral doses of 250 mg. At steady state mean accumulation ratio and mean effective half-life were similar in children and adults. Due to the design of this study in children neither the elimination rate constant nor the volume of distribution could be estimated. There are also no data on whether bioavailability of terbinafine in children and adults is similar. Therefore, the present data do not allow one to define any underlying differences in the pharmacokinetics of terbinafine between children and adults. However, from a plot of AUC versus dose in mg/kg it was evident that children need a higher dose in mg per kg body weight to reach a similar exposure to terbinafine as in adults. With the weight classes and doses of terbinafine proposed for children (i.e., <25 kg receive 125 mg qd, 25-35 kg receive 187.5 mg qd, > 35 kg receive 250 kg qd) the systemic exposure to terbinafine was shown not to exceed the exposure in adults.

**Table 11-1 Pharmacokinetic variables of terbinafine in plasma of children and adults at steady state. Mean +/- SD, median for tmax**

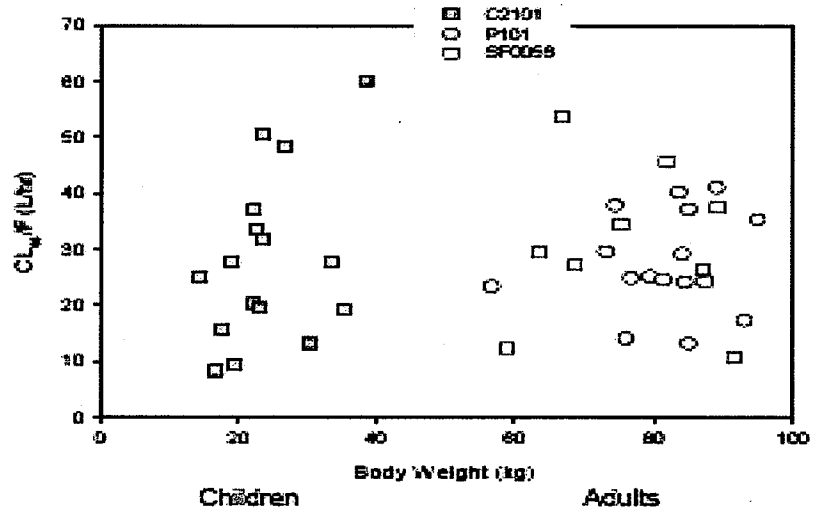
| Dose mg | Day/Study | N | Body_Weight (kg) | tmax (hr) | Cmax (ng/mL) | AUC0-24 (hr*ng/mL) | CLss/F (L/hr) | R | t1/2,eff (hr) |
|---|---|---|---|---|---|---|---|---|---|
| **Children** | | | | | | | | | |
| 125 | 42/C2101 | 11 | 20.5±3.1 | 2.0 | 1118±713 | 6513±4074 | 25.4±12.6 | 2.1±0.9 | 26.7±15.1 b |
| 187.5 | 42/C2101 | 4 | 31.6±3.8 | 2.0 | 1575±942 | 8653±4412 | 27.1±15.4 | 1.9±1.0 | 30.5±9.3 c |
| 250 | 42/C2101 | 1 | 38.6 | 2.0 | 544 | 4154 | 60.2 | 0.8 | nc |
| All doses | 42/C2101 | 16 | 24.4±6.9 | - | - | - | 28.0±15.1 | 1.9±0.9 | 27.6±13.8 d |
| **Adults** | | | | | | | | | |
| 250 | 15/P101 | 15 | 81.2±9.3a | 2.7 | 1740±714 | 10128±4009 | 27.8±9.1 | - | - |
| 250 | 30/SF0056 | 10 | 77.1±11.9a | 1.0 | 1700±767 | 10481±6202 | 30.2±13.4 | 2.26±0.53 | 28.4±9.1 |

a at baseline b N=10 c N=3 d N=13 nc = not calculated

**Figure 12-2 Individual $AUC_{0\text{-}24h}$ and $CL_{ss}/F$ values in children measured in study C2101 compared to historic data in adults at steady state**



$CL_{ss}/F$




**Applicant's Discussion:** The pharmacokinetics of terbinafine in this pediatric population receiving mini-tablets was characterized by a significant degree of inter-subject variability. As a result a weak and insignificant relationship between weight-normalized dose (range: 5.3 to 8.7 mg/kg) and exposure was observed. Overall, exposure estimates increased between 8% ($C_{max}$/Dose) and 82% ($AUC_{0-24}$/Dose), see in the pediatric subjects between first dose and steady-state. The degree of variability noted in the estimates of exposure at steady state was comparable to that observed after a single dose. Similarly, the extent of accumulation observed between individuals was highly variable.

Due to the design of this study (blood collection up to 24 hours after dosing) and the pharmacokinetic characteristics of terbinafine, a meaningful elimination half-life could not be determined by linear regression analysis of the semilogarithmic plasma concentration-time profiles of terbinafine on Day 1 and Day 42. Apparent elimination half-lives calculated from plasma concentrations between 4 or 6 hours and 24 hours after dosing were on average about 2-fold lower than the effective half-lives indicating that these apparent half-lives are not characterizing the elimination kinetics of terbinafine and cannot be used for prediction of steady-state.

**Applicant's Conclusions**

- Terbinafine hydrochloride mini-tablets, administered once daily for 42 days at the weight dependent doses used in this study (< 25 kg, 125 mg; 25-35 kg, 187.5 mg; > 35 kg, 250 mg), were safe and well-tolerated in children aged 4-8 years with tinea capitis.
- Once daily oral dosing of terbinafine in children with tinea capitis resulted in ~two-fold increase of systemic exposure to terbinafine as characterized by $AUC_{0-24}$, after 42 days compared to that following the first dose.
- Accumulation was similar in the 125 mg and the 187.5 mg dose groups.

- The mean effective half-life of terbinafine calculated from the observed accumulation was about 27 to 31 hours.
- On average, plasma concentrations of terbinafine ($C_{max}$ and $AUC_{0-24}$) tended to be higher in the 187.5 mg dose group than in the 125 mg dose group.
- The apparent plasma clearance of terbinafine at steady state was similar in the 125 mg and 187.5 mg dose groups and amounted to 25 to 27 L/hr on average.
- The comparison of the results in children with data in adults revealed that children need higher doses in mg per kg body weight to reach a similar exposure ($AUC_{0-24h}$) to terbinafine as adults.
- With the weight classes and doses of terbinafine proposed for children (i.e., <25 kg to receive 125 mg q.d, 25-35 kg to receive 187.5 mg q.d, > 35 kg to receive 250 kg q.d) the systemic exposure to terbinafine was shown not to exceed the exposure in adults.

**Analytical Method and Validation:**

| | |
|---|---|
| **Method** | LC/MS/MS |
| **Compound** | Terbinafine |
| **Internal Standard** | [redacted] |
| **Matrix** | Plasma |
| **Accuracy (% Bias)**<br>***Within-Day***<br><br>***Between-Day*** | <br>-5.3% to 5.5% (Calibration standards)<br><br>2.8 %% (QC standards) |
| **Precision (% CV)**<br>***Within-Day***<br><br>***Between-Day*** | <br>2.7 % to 7.1 % (Calibration standards)<br><br>5.3 % to 7.6 % (QC Standards) |
| **Standard curve range** | 1 ng/mL to 500 ng/mL ($r^2 \geq 0.997$) |
| **Sensitivity (LOQ)** | 1 ng/mL |
| **Selectivity** | There was no interference due to endogenous peaks in human plasma observed at the retention times of terbinafine and its Internal standard. |
| **Stability** | Stable in plasma plasma for stored at -20°C for 9 months. Based on internal report 0303-208 provided that used HPLC with UV detection method, the accuracy of the oldest sample was within a range of 80 to 120 % over a period of 9 months. |
| **Conclusion** | **The analytical method validation is acceptable** |

*Reviewer's Comments:*

*One additional QC sample was prepared (800 ng/mL) and analyzed in duplicate after a 4-fold and 7-fold dilution (Accuracy=0.7 % to 3.1% and Precision=5.4 % to 5.9 % was acceptable) in the routine analysis. Two additional CS (1000 ng/mL and 2500 ng/mL (Precision =4.7 and 2.7 % respectively, Accuracy = -0.9 and 0.1 respectively) were included in the validation method.*

*One additional QC sample of 2500 ng/mL (Precision = 7.6 % and Accuracy = 7.8) was also included in the validation method.*

**Studies in Healthy Volunteers**

**Study #C2303**

**Title of study:** A randomized, open-label, single dose, three-period, crossover study to evaluate the relative bioavailability of 250 mg terbinafine given orally either as one 250 mg Lamisil tablet (MF), two 125 mg Lamisil tablets (MF) or as sixty mini-tablets in healthy subjects.
**Investigator(s):** [redacted]

**Study Period:** First subject dosed 14-Oct-2003, Last subject completed 05-Dec-2003
**Objectives:** To evaluate the relative oral bioavailability of 250 mg terbinafine when given as 60 mini-tablets compared to one 250-mg Lamisil® tablet or two 125-mg Lamisil® tablets.
**Study Design:** This was a randomized, open-label, single dose, three period crossover study conducted in 24 (12 male and 12 female) subjects.
**Treatments:** Each subject was randomized to one of three treatment sequences. Treatment periods were separated by a fourteen (14) day wash-out period, and 8 subjects were allocated to each of the three treatment sequences (i.e. ABC, BCA, CAB). The dose of terbinafine was 250 mg for all treatments.
Treatment A: 1 x 250 mg Lamisil® tablet (Batch No. C3FO2961)
Treatment B: 2 x 125 mg Lamisil® tablet (Batch No. X2620902)
Treatment C: 60 x 4.167 mg terbinafine mini-tablets (Batch No. X2100803)
Tablets were administered by the study center personnel with 200 mL of water after at least a 10-hour fast. Subjects were instructed not to chew the medication, but to swallow it whole. After taking the medication, subjects were instructed to rest quietly in the upright position for the next 4 hours.
The mini-tablets were administered with 15 mL of a vanilla pudding [redacted]. The pudding was in a small plastic cup and the mini-tablets sprinkled on the pudding immediately before administration. The subjects were to spoon out the pudding and the investigator would verify that the mini-tablet container was empty. In addition the subject was to be given 200 mL of water.
*Reviewer's Comments: Applicant stated that for subject #'s 5015, 5016 and 5021, the tablets were administered by the method described above, but with yogurt and not vanilla pudding.*
**Duration of Treatment:** Each subject received three single oral dose treatments in separate periods.
**Pharmacokinetic Sampling:** Blood samples for pharmacokinetic evaluation were collected in each study period (1.2 mL in EDTA tubes) at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours post-dose.
**Analytical Methods:** Plasma concentrations were determined by means of LC-MS/MS with a limit of quantitation (LOQ) of 1ng/mL.
**Pharmacokinetic Analysis and Statistical Methods:** Demographic, safety variables and pharmacokinetic parameters, including AUC0-tlast, AUC0-∞, Cmax, tmax, t½, were summarized by treatment. Descriptive statistics were provided. Cmax, AUC0-tlast and AUC0-∞ were considered the primary pharmacokinetic parameters in the evaluation of relative bioavailability (BA). Analysis of variance (ANOVA) was performed on the log-transformed

AUC0-tlast, AUC0-∞, and Cmax data to compare the terbinafine bioavailability between the Test (60 mini-tablets) and Reference treatments (two 125 mg tablets and one 250 mg tablet). The ANOVA model included sequence, subject within sequence, treatment, and period as factors. Point estimate of test-reference ratio, and the associated 90% confidence intervals (CI) for the ratio of treatment means were calculated and reported.

**Pharmacogenetic Evaluations:** Ten (10) of the 24 subjects agreed to the collection of a single pharmacogenetic blood sample (18 mL blood in EDTA tubes). The samples were taken pre-dose in period 1.

*Reviewer's Comments: The applicant stated that the pharmacogenetic samples had not yet been analyzed at the time this report was submitted.*

**Results:** The terbinafine pharmacokinetic variables, together with the results of the analysis of variance (ANOVA) for Cmax, AUC0-tlast and AUC0-∞ of terbinafine, are summarized in Table 3-1. Mean concentration-time profiles of terbinafine for the three treatments are comparatively shown in Figure 3-1 (i.e. mini-tablets vs. 250 mg tablet and mini-tablets vs. 2 x 125 mg tablets). The mini-tablets containing 250 mg terbinafine were shown to be bioequivalent to the 250 mg Lamisil tablet and to two 125-mg Lamisil tablets in terms of peak and total exposure to terbinafine in plasma, as measured by Cmax, AUC0-tlast and AUC0-∞. For both comparisons, i.e. mini-tablets vs. 250 mg tablet and mini-tablets vs. 2 x 125 mg tablets, the ratios of the geometric means for Cmax, AUC0-tlast and AUC0-∞ were close to unity (0.95 to 1.04) and the 90% confidence intervals (CI) were all contained within the bioequivalence range of 0.8 to 1.25.

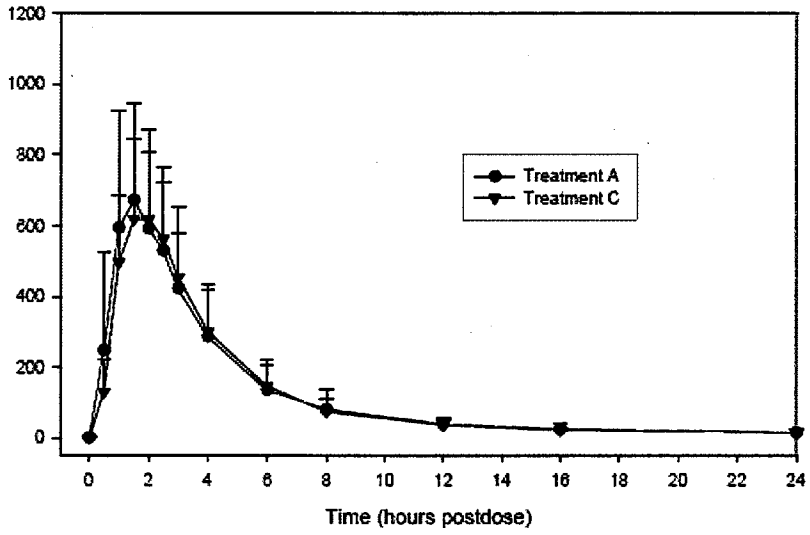
| **Table 3-1** | **Terbinafine pharmacokinetic parameters in plasma** | | | | |
|---|---|---|---|---|---|
| **Parameters** | **C** | **A** | **B** | **Ratio C/A*** | **Ratio C/B*** |
| | **60 mini-tablets (n=24)** | **one 250 mg tablet (n=24)** | **two 125 mg tablets (n=24)** | **(90% CI)** | **(90% CI)** |
| **tmax [hr]** | 1.75 | 1.50 | 1.50 | - | - |
| | [1.00 – 3.00] | [1.00 – 3.00] | [1.00 – 4.00] | | |
| **Cmax [ng/mL]** | 690 ± 242 | 745 ± 295 | 742 ± 307 | 0.95 | 0.98 |
| | (653) | (690) | (668) | (0.82 - 1.09) | (0.85 – 1.13) |
| **AUC0-tlast [ [ng*hr/mL]** | 3508 ± 1173 | 3577 ± 1379 | 3582 ± 1326 | 1.01 | 1.00 |
| | (3344) | (3322) | (3328) | (0.94 – 1.08) | (0.93 – 1.08) |
| **AUC0-∞ [ng*hr/mL]** | 3850 ± 1510 (3611) (n=20) | 3662 ± 1680 (3329) (n=16) | 3979 ±1363 (3717) (n=20) | 1.04 (0.95 – 1.14) | 1.04 (0.96 – 1.13) |
| **t1/2 [hr]** | 41.0 ± 11.5 | 38.3 ± 5.8 | 40.7 ± 8.3 | - | - |
| | (39.5) (n=20) | (37.9) (n=16) | (39.9) (n=20) | | |

Values are median [range] for tmax and mean ± SD (geometric mean) for other parameters

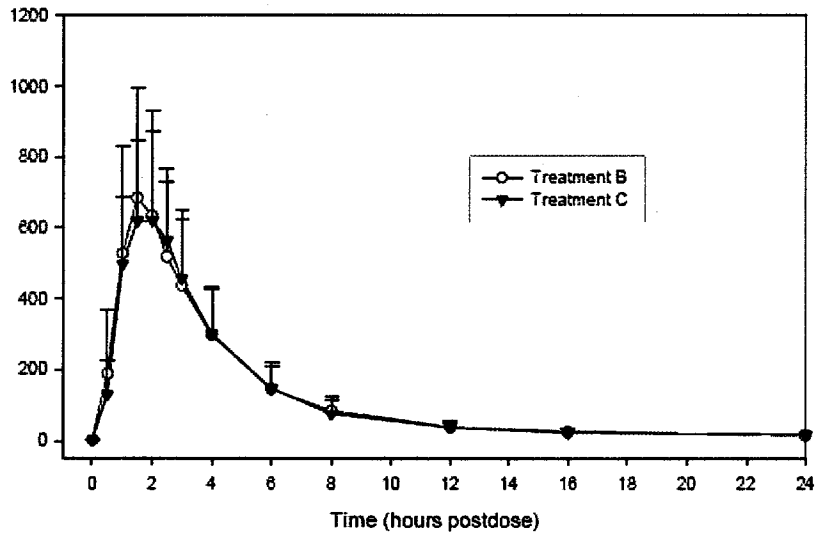
*Ratio is test/reference ratio of geometric means and 90% confidence interval from ANOVA (Appendix 6, Table 1)

No statistical evaluation was performed for tmax and t1/2

**Figure 3-1 Mean terbinafine (SFO327) plasma concentration (+ SD) profiles for treatments A (•) 250 mg tablet, B (○) 2 x 125 mg tablet and C (▼) 60 mini-tablets, linear view 0 – 24 hours time period, Comparison of C (mini-tablets, N=24) vs. A (250 mg tablet (N=23-24)**




**Comparison of C (mini-tablets, N=24) vs. B (2 x 125 mg tablets (N=24)**




**Applicant's Conclusions:**

Bioequivalence between terbinafine mini-tablets corresponding to 250 mg of terbinafine and one 250 mg Lamisil® tablet or two 125 mg Lamisil® tablets was established in this study, based on $C_{max}$, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$ of terbinafine in plasma

**Relative bioavailability and food effect study after single oral dose (175 mg) of a new oral formulation** [redacted] (not TBMF or strength, therefore only a summary of the studies is provided.)

The effect of food intake on the bioavailability of the new oral form [redacted] was investigated in study [L2306 and L2104]. Studies L2104 and L2306 showed that

the influence of a high-fat meal on the exposure to terbinafine is less pronounced under multiple dose conditions as compared to the food effect on [redacted] after a single dose (increase in AUC of 23% after repeated dose compared to 42% increase after single dose).

In the single dose study [L2104] that investigated the effect of food on the absorption of terbinafine from Lamisil [redacted] (2x175-mg [redacted]), systemic exposure of terbinafine increased when taken with food compared to the fasting state (42% increase in area under the curve and 24% increase in $C_{max}$ based on ratios of geometric means). Median $T_{max}$ was delayed by 1 hour (3 hr in fed state vs. 2 hr in fasting state)
In study [L2306] the effect of food intake on the bioavailability of the new dosage form after multiple dosing of Lamisil®, [redacted] (2x175-mg [redacted]) was investigated. The results demonstrated an increase in the overall exposure to terbinafine when taken with food compared to fasting (23% increase in $AUC_{0-24}$ and $C_{max}$ based on ratios of geometric means). Median $T_{max}$ was delayed by 1.5 hours (4.0 hr in fed state vs. 2.5 hr in the fasting state).

The applicant stated that the effect of food on [redacted] is in agreement with what was previously observed for Lamisil tablets. Previous food-effect studies (included in the original NDA 20- 539, studies SFP-101 and W404) with Lamisil tablets (250 mg) also showed a statistically significant increase in bioavailability of terbinafine. In a single dose study (SF W404), AUC was increased by 42%. In the previous multiple dose study with tablets (SFP-101) $AUC_{0-24h}$ was increased by 19%, and $C_{max}$ by 20% (based on geometric means) when Lamisil was taken with food, and absorption was delayed by about 30% ($T_{max}$) in the fed state. Thus, the food effect was also less pronounced after repeated oral doses compared to a single oral dose of Lamisil tablet (increase of AUC by 19% after repeated dose compared to 42% increase after single dose).

Despite the large variability associated with PK parameters (on average CV around 40%), terbinafine has a good margin of safety as demonstrated with Lamisil Tablets in a multiple dose PK Study P151 up to doses of 1500 mg, in a single dose study W401 up to 750 mg and in clinical safety and efficacy trials up to 500 mg. In light of this and the smaller effect of food after repeated dosing, the effect of food on Lamisil Tablets was considered clinically not significant. As the food effect on mini-tablets was shown to be similar to that on tablets, both after single and repeated dosing, it is considered as clinically not relevant at therapeutic dose regimens of terbinafine mini-tablets.

Though all these studies were performed in healthy adult subjects, it is considered that these results can similarly be applied to the target patient population, i.e. children 4 to 12 years of age. As the change in bioavailability related to the mode of administration (with or without food) is considered of no relevance for the clinical practice, no special recommendation on drug intake in relation to meals will be given. In addition the mini-tablets, for ease of administration, were given together with pudding in both the pharmacokinetic studies and the clinical trials.

**Drug-Drug Interaction Studies:**

**Drug Interaction Study with Fluconazole (0152)**

Because of the potential combination antifungal therapy for the treatment of systemic fungal infections, the interaction between fluconazole and terbinafine was investigated.

*Title: A randomized, open-label, single-dose, three-period crossover study to assess the pharmacokinetic interaction of Lamisil with fluconazole in healthy subjects*

In Study 0152, each subject (n=18 Male Caucasian Subjects, aged 19 to 42 years with a mean (SD) weight and height of 72 (7) [range = 60-83.8) kg and 177 (6) [range = 167-187] cm) received single administrations of the following treatments separated by a 7-day washout: 750 mg of Lamisil® (terbinafine), 100 mg Diflucan® (fluconazole), 750 mg Lamisil® + 100 mg Diflucan® in a Latin Square design (i.e. two 3 × 3 Latin Squares (3 periods, 6 sequence crossover design). Subjects ingested the study medication with 240 mLs of water following a 10 hour fast. Blood samples for pharmacokinetic evaluations of terbinafine, desmethylterbinafine and fluconazole were collected at the following times: 0-hour, 0.67, 1.33, 2h, 2.67, 3, 4, 6, 12, 24, 48, 96, 144 and 168 hours after dosing.

Plasma concentrations of terbinafine and desmethylterbinafine were determined by HPLC/UV method. The LOQ for terbinafine and desmethylterbinafine in plasma was 4 ng/mL and the standard curve range was 4 to 5000 ng/mL, Precision (% CV) ranged from 1.0-9.9 % and accuracy ranged from -11.5 to 4.0 %. Plasma concentrations of fluconazole were determined by HPLC/UV method. The LOQ for fluconazole in plasma was 0.05 mcg/mL and the standard curve range was 0.05 to 10 mcg/mL. Precision (% CV) ranged from 1.76-6.09 % and accuracy ranged from -1.32 to -0.67 %.

The mean terbinafine $C_{max}$ and $AUC_{0\text{-tlast}}$ were increased by 52% (from 2580 ± 807 ng/mL to 3935 ± 1170 ng/mL) and 69% (from 16199 ± 5579 ng·h/mL to 27404 ± 6705 ng·h/mL), respectively, after concomitant administration with fluconazole than when Lamisil was administered alone ($p<0.05$). The clearance after oral administration (Cl/F) was decreased significantly from 803 L/min to 467 L/min after concurrent administration with fluconazole, reflecting the observed increase in $AUC_{0\text{-tlast}}$.

A 28% decrease in the mean $C_{max}$ of the major terbinafine metabolite, desmethylterbinafine, was observed. The metabolite $t_{1/2}$ also was significantly increased (by 13%) compared to administration of Lamisil® alone, indicating that fluconazole may inhibit metabolism of the metabolite as well as the parent compound. No statistically significant differences were noted for $AUC_{0\text{-tlast}}$ or $AUC_{0\text{-}\infty}$ for the metabolite.

Fluconazole concentrations were nearly identical alone and after co-administration with Lamisil® (Table 2-1). The pharmacokinetic parameters of fluconazole in this study were similar to those reported in the literature.

**Table 2-1 Mean (SD) Pharmacokinetic parameters of terbinafine, desmethylterbinafine and fluconazole following a single oral dose of 750 mg of Lamisil or a single oral dose of 100 mg of fluconazole alone or in combination (N=18)**

| Parameter | Terbinafine | | Desmethylterbinafine | | Fluconazole | |
|---|---|---|---|---|---|---|
| | Alone | Combination | Alone | Combination | Alone | Combination |
| AUC0-tlast (ng*hr/mL) (µg*hr/mL)1 | 16199 (5579) | 27404* (6705) | 21683 (8125) | 22127 (6069) | 91.2 (15.7) | 89.5 (14.1) |
| AUC0-inf (ng*hr/mL) (µg*hr/mL)1 | 17567 (6330) | 29280* (7183) | 22487 (8610) | 23568 (6753) | 95.4 (17.1) | 93.6 (15.6) |
| Cmax (ng/mL) (µg/mL)1 | 2580 (807) | 3935* (1170) | 2220 (586) | 1600* (334) | 2.08 (0.41) | 2.00 (0.21) |
| tmax (hr) | 2.30 (0.55) | 2.26 (0.59) | 2.37 (0.54) | 2.54 (0.46) | 2.26 (2.57) | 1.83 (0.59) |
| t1/2 (hr) | 62.1 (15.2) | 55.7 (13.3) | 40.6 (6.88) | 46.1* (14.0) | 34.7 (5.09) | 34.4 (5.93) |
| CL/F (mL/min) | 803 (301) | 467* (196) | 629 (233) | 585 (229) | 17.9 (2.8) | 18.2 (2.9) |

*Difference compared to "treatment alone" is statistically significant at $p<0.05$ 1 terbinafine and desmethylterbinafine in ng; fluconazole in µg

Source: [CSFO3270152, Post-text Table 3], [CSFO3270152, Post-text Table 5], [CSFO3270152, Post-text Table

## Applicant's Conclusions:

1. Single 750 mg doses of Lamisil administered alone and in combination with 100 mg doses of fluconazole to 18 healthy subjects were safe and well tolerated.

2. A single oral dose of fluconazole increased terbinafine $C_{max}$ (52%), $AUC_{(0-t)}$ (69%), and $AUC_{(0-\infty)}$ (67%), and decreased desmethylterbinafine $C_{max}$ (28%) to a statistically significant degree. Concomitant therapy may require a dosage adjustment.

3. A concurrent single dose of Lamisil with fluconazole does not alter fluconazole pharmacokinetics.

*Reviewer's Comments: Applicant has proposed to include the increase in Cmax and AUC of terbinafine with fluconazole in the label. However, applicant did not propose to include the statement* [redacted] *I will propose that this be included and let the applicant provide an explanation of why they do not believe it should be included. Applicant may also include information* [redacted]

## Drug Interaction Study with Cotrimoxazole DS (0153)

*Title: A randomized, open-label, single-dose, three-period crossover study to assess the pharmacokinetic interaction of Lamisil with Cotrimoxazole DS in healthy subjects*

Cotrimoxazole DS (trimethoprim 160 mg / sulfamethoxazole 800 mg) and terbinafine do not share major enzymatic biotransformation pathways and, therefore, a metabolic drug interaction was not anticipated. Trimethoprim is primarily (80%) excreted unchanged in the urine with minor contribution by hydroxylation and oxide formation. Sulfamethoxazole primarily undergoes N-acetylation as well as formation of the glucuronide conjugate. However, a renal-based elimination mechanism of a drug interaction could not be ruled out. Additionally, cotrimoxazole DS is often prescribed to immunocompromised patients for the treatment or prophylaxis of opportunistic infections. Because fungal infections are also common in this patient population, the potential drug interaction between cotrimoxazole DS and terbinafine was investigated.

In Study 153, each subject (n=18, 9 Males and 9 females, 17 Caucasian subjects and 1 Black subject, aged 19 to 33 years old [mean(SD) = 24.2 (3.15) years with a mean (SD) weight and height of 65 (11.7) [range = 60-83.8) kg and 171.5 (8.5) [range = 167-187] cm)) received the following treatments separated by a 7-day washout: 750 mg of Lamisil® (terbinafine), cotrimoxazole DS, 750 mg Lamisil® + cotrimoxazole DS in a Latin Square design i.e. two 3 × 3 Latin Squares (3 period, 6 sequence, with each subject as his control and to allow for assessment of carry-over effects). One subject did not complete all 3 treatment periods (withdrawn from the study due to dyspepsia and nausea (1/2 hr after dosage administration) and vomiting (1 hour after Period 1 study drug administration) and was excluded from the PK evaluation.
Subjects ingested the study medication with 240 mLs of water following a 10 hour fast. Blood samples for pharmacokinetic evaluations of terbinafine and desmethylterbinafine were collected at the following times: 0-hour, 0.67, 1.33, 2, 2.67, 3, 4, 6, 12, 24, 48, 96, 144 and 168 hours after dosing of Lamisil ® tablets. Blood samples were only collected for up to 48 hours post-dosing of Cotrimoxazole DS for trimethoprim and sulfamethoxazole.

Plasma concentrations of terbinafine and desmethylterbinafine were determined by HPLC/UV method. The LOQ for terbinafine and desmethylterbinafine in plasma was 4 ng/mL and the standard curve range was 4 to 5000 ng/mL, Precision (% CV) ranged from 2.1-10.4 % and accuracy ranged from -4.9 to 9.8 %. Plasma concentrations of trimethoprim and sulfamethoxazole were determined by HPLC/UV method. The standard curve range for trimethoprim and sulfamethoxazole was 0.05 to 4.0 mcg/mL and 0.5 to 40 mcg/mL, respectively. Precision (% CV) ranged from 5.06 to 9.33 and 3.51 to 8.03 % respectively and, accuracy ranged from -1.13 to 6.35 %. and -3.41 to 3.86 %, respectively.

The pharmacokinetics of terbinafine and desmethylterbinafine were unaffected by co administration with cotrimoxazole DS (Table 2-2). No statistically significant differences in $AUC_{0-\infty}$, $C_{max}$ or $t_{1/2}$ of terbinafine were observed after co-administration. Accordingly, no statistically significant differences for $AUC_{0-\infty}$ and $C_{max}$ were observed for sulfamethoxazole or trimethoprim (Table 2-3).

**Table 2-2** **Mean (SD) pharmacokinetic parameters of terbinafine and desmethylterbinafine following a single oral dose of 750 mg of Lamisil alone or with concomitant administration of Cotrimoxazole DS (N=17)**

| Parameter | Terbinafine | | Desmethylterbinafine | |
|---|---|---|---|---|
| | Alone | Combination | Alone | Combination |
| $AUC_{0\text{-}inf}$ (ng*hr/mL) | 21981 (5553) | 21093 (4389) | 22057 (5007) | 20402 (5236) |
| $C_{max}$ (ng/mL) | 3230 (904) | 2992 (944) | 2204 (532) | 1998 (507) |
| $t_{max}$ (hr) median | 2.67 | 2.67 | 2.0 | 2.67 |
| $t_{1/2}$ (hr) | 60.3 (13.8) | 58.3 (10.2) | 40.5 (9.38) | 41.0 (9.29) |

**Mean Pharmacokinetic Parameters Of Trimethoprim Following A Single Oral Dose Of Cotrimoxazole DS Alone Or With Concomitant Administration Of Lamisil®**

| Treatment | Lamisil® + Cotrimoxazole DS | Cotrimoxazole DS alone |
|---|---|---|
| Parameter | Arithmetic Mean ± SD<br>Geometric Mean<br>(Range)<br>N = 17 | |
| $AUC_{0-\infty}$ (ng•hr/mL) | 25.5 ± 6.76<br>24.7<br>(14.9 - 41.9) | 24.5 ± 7.18<br>23.6<br>(12.3 - 41.2) |
| $C_{max}$ (ng/mL) | 1.63 ± 0.41<br>1.58<br>(0.99 - 2.46) | 1.68 ± 0.43<br>1.62<br>(0.70 - 2.48) |
| $t_{max}$ (hr)* | 2.00<br>(0.67 - 6.00) | 2.00<br>(0.67 - 2.67) |
| $t_{½}$ (hr) | 10.1 ± 1.28<br>10.0<br>(8.30 - 12.4) | 9.41 ± 1.61<br>9.27<br>(5.74 - 12.3) |

**Mean Pharmacokinetic Parameters Of Sulfamethoxazole Following A Single Oral Dose Of Cotrimoxazole DS Alone Or With Concomitant Administration Of Lamisil®**

| Treatment | Lamisil® + Cotrimoxazole DS | Cotrimoxazole DS alone |
|---|---|---|
| Parameter | Arithmetic Mean ± SD<br>Geometric Mean<br>(Range)<br>N = 17 | |
| $AUC_{0-\infty}$ (ng•hr/mL) | 788 ± 198<br>766<br>(461 - 1255) | 768 ± 173<br>751<br>(565 - 1174) |
| $C_{max}$ (ng/mL) | 44.1 ± 11.1<br>42.9<br>(26.5 - 76.5) | 46.5 ± 13.7<br>44.9<br>(29.4 - 85.9) |
| $t_{max}$ (hr)* | 4.00<br>(2.67 - 6.00) | 3.00<br>(2.67 - 12.0) |
| $t_{½}$ (hr) | 9.68 ± 1.03<br>9.62<br>(8.14 - 11.9) | 9.36 ± 1.01<br>9.31<br>(8.05 - 11.3) |

**Drug Interaction Study with Zidovudine (ZDV) (0154)**

Because of the relatively high occurrence of opportunistic fungal disease in patients with HIV disease, the possible drug interaction between ZDV and terbinafine was investigated due to their potential co-administration in larger trials,

*Title: A randomized, open-label, single-dose, three-period crossover study to assess the pharmacokinetic interaction of lamisil with Zidovudine in healthy subjects*

In Study 0154, each subject (n=18, 14 males and 4 females, 17 Caucasians and 1 Black, (mean (SD) Age, Height and Weight were 24 (3) years [range = 19-31], 175 (9) cm [range = 160-191] and 69 (9) kg [range = 52.4-86.20], respectively) received single administrations of the following treatments separated by a 7-day washout: 750 mg Lamisil®, 200 mg zidovudine and 750 mg Lamisil® + 200 mg zidovudine in a Latin Square design (i.e. two 3 × 3 Latin squares). Subjects ingested the study medication with 240 mL of water after having fasted for 10 hours. One subject (# 1008) was excluded from the study prior to period 2 administration due to an episode of vomiting and nausea during the previous night. This subject was not included in the PK evaluation.
Blood samples for pharmacokinetic evaluations of terbinafine and desmethylterbinafine were collected at the following times: 0-hour, 0.67, 1.33, 2, 2.67, 3, 4, 6, 12, 24, 48, 96, 144 and 168 hours after dosing of lamisil ® tablets. Blood samples for pharmacokinetic evaluations of zidovudine were collected at the following times: 0-hour, 0.17, 033, 0.67, 1.0, 1.33, 2, 3, 4, 6 and 10 hours post-dose.

Plasma concentrations of terbinafine and desmethylterbinafine were determined by HPLC/UV method. The LOQ for terbinafine and desmethylterbinafine in plasma was 5 and 4 ng/mL and the standard curve range was 4 to 5000 ng/mL, Precision (% CV) ranged from 1.9 to 7.9 % (terbinafine) and 2.1 to 6.1 (desmethylterbinafine) and accuracy ranged from 1.8 to 9.6 % (terbinafine) and -2.8 to 2.6 (desmethylterbinafine). Plasma concentrations of Zidovudine were determined by radioimmunoassay. The standard curve range for zidovudine was 6.4 to250 ng/mL. Precision (% CV) ranged from 9.5 to 12.5 % and, accuracy ranged from -0.733 to 9.91%.

*Reviewer's Comments: For terbinafine an LOQ of 4 ng/mL had a precision of 23.87 % and an accuracy of -6.86 %. The high CV % was due to the inclusion of one sample run on June 4th, 1996. If this run is excluded the CV% for N=5 is 9.57 %. The applicant decided to change the LOQ to 5 ng/mL because this gave a better precision (7.89 %) and accuracy (1.79 %).*

The pharmacokinetics of terbinafine and desmethylterbinafine were unaffected by co administration with zidovudine. No statistically significant differences in any pharmacokinetic parameters for terbinafine or desmethylterbinafine were observed. However, the pharmacokinetic parameters of zidovudine were statistically different after co-administration. The mean $AUC_{0-\infty}$ of zidovudine increased by 15%, $C_{max}$ decreased by 25%, $t_{max}$ was prolonged by 41%, CL/F decreased by 15% and V/F decreased by 17%. The 15% increase in AUC was considered not to pose a safety concern because it is the minor metabolite of ZDV, AMT, which has been implicated with the bone marrow suppression associated with ZDV (check AZT label).

*Reviewer's Comments: In addition, the statistically significant differences in AUC may not pose a safety concern because the 90 % CI for log transformed AUC inf (111%-121%) were within 80%-125 % BE criteria. However, for Cmax, the 90% CI was 67%-90% which was outside the 80-125 % BE criteria suggesting that efficacy may be a concern when zidovudine is administered with lamisi, but a relationship between efficacy and Cmax has not been established so this may not be clinically relevant.*

**Table 2-4 Mean (SD) Pharmacokinetic parameters of terbinafine, desmethylterbinafine and zidovudine following a single oral dose of 750 mg of Lamisil or a single oral dose of 200 mg of zidovudine alone or in combination (N=17)**

| Parameter | Terbinafine | | Desmethylterbinafine | | Zidovudine | |
|---|---|---|---|---|---|---|
| | Alone | Combination | Alone | Combination | Alone | Combination |
| AUC0-inf (ng*hr/mL) | 18425 (7910) | 18346 (6602) | 18816 (7240) | 18738 (6725) | 1334 (358) | 1531* (341) |
| Cmax (ng/mL) | 2772 (981) | 2795 (840) | 1916 (578) | 1861 (497) | 1209 (555) | 910* (401) |
| tmax (hr) | 2.22 (0.75) | 2.26 (0.71) | 2.37 (0.62) | 2.49 (0.59) | 0.82 (0.47) | 1.16* (0.46) |
| t1/2 (hr) | 57.3 (13.8) | 56.4 (13.8) | 38.5 (9.01) | 38.6 (8.37) | 1.22 (0.34) | 1.18 (0.39) |
| CL/F (mL/min) | 809 (362) | 793 (353) | 781 (360) | 754 281) | 2673 (723) | 2281* (511) |
| V/F (L) | 3836 (1486) | 3667 (1283) | 2580 (1246) | 2575 (1256) | 275 (79) | 229* (74) |

**Difference compared to "treatment alone" is statistically significant at p<0.05

| Treatments | 200 mg Zidovudine alone | 200 mg Zidovudine + 750 mg Lamisil |
|---|---|---|
| Parameters | Arithmetic Mean ± SD<br>Geometric Mean<br>(Range)<br>N = 17 | |
| $AUC_{0-\infty}$ (ng•hr/mL) | 1334 ± 358<br>1290<br>(816 - 1998) | 1531 ± 341<br>1496<br>(982 - 2190) |
| $C_{max}$ (ng/mL) | 1209 ± 555<br>1093<br>(393 - 2407) | 910 ± 401<br>843<br>(444 - 2055) |
| $t_{max}$ (hr) | 0.82 ± 0.47<br>0.7<br>(0.33 - 2.00) | 1.16 ± 0.46<br>1.08<br>(0.67 - 2.00) |
| $t_{½}$ (hr) | 1.22 ± 0.34<br>1.18<br>(0.92 - 1.94) | 1.18 ± 0.39<br>1.13<br>(0.82 - 2.04) |
| CL/f (mL/min) | 2673 ± 723<br>2584<br>(1668 - 4084) | 2281 ± 511<br>2229<br>(1522 - 3396) |
| V/f (L) | 275 ± 79<br>264<br>(147 - 413) | 229 ± 74<br>218<br>(110 - 365) |

**Drug Interaction Study with Theophylline (0156)**

Theophylline is classified as a drug with a narrow therapeutic index. In general, concentrations below 10 ng/mL may be ineffective while concentrations above 20 ng/mL are more likely to produce toxicity. At normally therapeutic doses, inhibition of theophylline metabolism may **produce increases in plasma theophylline concentrations within the 'toxic' range. Because** terbinafine and theophylline may share the same routes of elimination, the potential for a metabolic drug interaction was investigated.

*Title: A randomized, open-label, single-dose, three-period crossover study to assess the pharmacokinetic interaction of lamisil with Theophylline in healthy subjects*

In Study 0156, each subject (n=18, 10 females and 8 males ages from 19 to 42 years (mean (sd) = 26.2 (4.1) years, with a mean (sd) weight and height of 65.4 (9.6) kg and 172.4 (9.9) cm), received single administration of the following treatments separated by a 7-day washout: 250 mg Lamisil® alone, 375 mg theophylline alone or 250 mg Lamisil®+ 375 theophylline in a Latin Square design (3 period, 6 sequence study).
Subjects ingested the study medication with 240 mL of water after having fasted for 10 hours.

Blood samples for pharmacokinetic evaluations of terbinafine and desmethylterbinafine were collected at the following times: 0-hour, 0.67, 1.33, 2, 2.67, 3, 4, 6, 12, 24, 48, 96, 144 and 168 hours after dosing of lamisil ® tablets. Blood samples for pharmacokinetic evaluations of theophylline were collected at the following times: 0-hour, 033, 0.67, 1.0, 1.33, 2, 2.67, 3, 4, 6 12, 24, 48 and 96 h post-dose.

Plasma concentrations of terbinafine were determined by HPLC/UV method after liquid-liquid extraction. The LOQ for terbinafine in plasma was 10 ng/mL and the standard curve range was 10 to 1500 ng/mL, Precision (% CV) ranged from 5.6 to 12.1 % (terbinafine) and accuracy ranged from 0.1 to 5.2 % (terbinafine). Plasma concentrations of Theophylline were determined by HPLC with UV detection. The LOQ was 0.1 mcg/mL. The standard curve range for theophylline was 0.1 to 20 mcg/mL. Precision (% CV) ranged from 0.9 to 2.5 % and, accuracy ranged from -3.0 to 10.0 %.

The pharmacokinetics of theophylline after co-administration with Lamisil® demonstrated a statistically significant decrease in the mean CL/F of theophylline by 8.5%, although, no differences in the mean $AUC_{0-\infty}$, $C_{max}$ or $t_{1/2}$ was evident.

After co-administration with theophylline, the mean $AUC_{0-\infty}$ and $C_{max}$ of terbinafine were increased by 17.6 % and 23.4 %, respectively; only the difference in the $AUC_{0-\infty}$ was statistically significant. These differences in the pharmacokinetics of terbinafine after concurrent administration of terbinafine and theophylline are not considered to be clinically meaningful due to the wide safety margin of terbinafine (Table 2-5).
Although theophylline and terbinafine may share the same metabolic pathways, no clinically significant interaction was noted in this study.

*Reviewer's Comments: The difference in the Cmax arithmetic mean was not statistically significant, however, that of the geometric mean was statistically significant. However, the 90 % CI's were outside the BE range of 80-125 % (for AUC=1.1%-1.4% and for Cmax =1.06%-1.48%).*

**Table 2-5** **Mean (SD) pharmacokinetic parameters of terbinafine and theophylline following a single oral dose of 250 mg Lamisil or 37[illegible] of theophylline taken alone or in combination (N=18)**

| Parameter | Terbinafine | | Theophylline | |
|---|---|---|---|---|
| | Alone | Combination | Alone | Combination |
| $AUC_{0\text{-}inf}$ (ng*hr/mL) (µg*hr/mL)[1] | 4933 (3066) | 5800* (2625) | 168.5 (45.9) | 181.7 (45.4) |
| $C_{max}$ (ng/mL) (µg/mL)[1] | 1064 (515) | 1312 (599) | 13.1 (2.4) | 13.2 (2.2) |
| $t_{max}$ (hr) median | 1.33 | 1.33 | 1.0 | 1.33 |
| $t_{1/2}$ (hr) | 24.3 (32.9) | 22.1 (22.0) | 8.55 (3.08) | 9.37 (3.28) |
| CL/F (mL/min) | 1132 (614) | 866* (383) | 32.0 (9.5) | 29.3* 7.8) |

[1] terbinafine in ng; theophylline in µg
*Difference compared to "treatment alone" is statisticallly significant at p<0.05

| Analyte | Terbinafine | | | |
|---|---|---|---|---|
| Pharmacokinetic Parameter | $AUC_{0-\infty}$ (ng*hr/mL) | $C_{max}$ (ng/mL) | $t_{½}$ (hr) | CL/f (mL/min) |
| % Difference[1] | | | | |
| Arithmetic Mean | 17.6 | 23.4 | -8.6 | -23.5 |
| Geometric Mean | 24.7 | 25.0 | 25.5 | -19.8 |
| Significance (p value)[2] | | | | |
| Arithmetic Mean | 0.0210 | 0.1346 | 0.6894 | 0.0091 |
| Geometric Mean | 0.0036 | 0.0352 | 0.1720 | 0.0036 |
| Conventional 90% CI (Range) | | | | |
| Arithmetic Mean | (1.06, 1.30) | (0.97, 1.49) | (0.53, 1.29) | (0.63, 0.90) |
| Geometric Mean | (1.11, 1.40) | (1.06, 1.48) | (0.95, 1.66) | (0.72, 0.90) |

| Analyte | Theophylline | | | |
|---|---|---|---|---|
| Pharmacokinetic Parameter | $AUC_{0-\infty}$ (µg*hr/mL) | $C_{max}$ (µg/mL) | $t_{½}$ (hr) | CL/f (mL/min) |
| % Difference[1] | | | | |
| Arithmetic Mean | 7.8 | 0.8 | 9.6 | -8.5 |
| Geometric Mean | 8.5 | 1.0 | 9.3 | -7.8 |
| Significance (p value)[2] | | | | |
| Arithmetic Mean | 0.0725 | 0.8066 | 0.3774 | 0.0262 |
| Geometric Mean | 0.0383 | 0.7666 | 0.2881 | 0.0383 |
| Conventional 90% CI (Range) | | | | |
| Arithmetic Mean | (1.01, 1.17) | (0.95, 1.06) | (0.92, 1.24) | (0.84, 0.97) |
| Geometric Mean | (1.02, 1.18) | (0.95, 1.07) | (0.95, 1.23) | (0.85, 0.98) |

[1]% Difference in Arithmetic Means = [(Mean of Combination - Mean of Single Compound)/(Mean of Single Compound)] x 100%
% Difference in Geometric Means = [(Geometric Mean of Combination - Geometric Mean of Single Compound)/(Geometric Mean of Single Compound)] x 100%
[2] Statistically significant at $p < 0.05$.

*Reviewer's Comments: The increase in the AUC of Lamisil when given in combination with terbinafine may not be clinically relevant because the range of AUC's when given in combination (2406-11327hr*ng/mL) is comparable to that obtained when given alone. The increase in Cmax may not pose a safety concern because the range of Cmax obtained (681-2929 ng/mL) following administration in combination with lamisil is still within the range obtained in the other 3 drug-drug interaction studies in which 3 X the dose (i.e. 750 mg) was administered. The applicant stated that this 750 mg dose did not result in any significant toxicity.*

## 4.3 Consult Reviews (including Pharmacometric Reviews)

**Office of Clinical Pharmacology and Biopharmaceutics Pharmacometrics Review**

| | |
|---|---|
| **NDA** | **22-071** |
| **Volume:** | **Report Number RANVR050-051** |
| **Compound:** | **Terbinafine HCl Mini-tablets 125 mg and 187.5 mg** |
| **Indication:** | **Treatment of Tinea Capitis** |
| **Submission Dates:** | **September 8th, 2006 and December 4th, 2006** |
| **Sponsor:** | **Novartis Pharmaceuticals, East Hanover, NJ** |
| **Pharmacometrics Reviewer:** | **Abi Adebowale, Ph.D./Atul Bhattaram, Ph.D.** |
| **Pharmacometrics Team leader:** | **Yaning Wang, Ph.D.** |



### Executive Summary

The applicant performed a population pharmacokinetic (PK) analysis to evaluate the PK of terbinafine in pediatric patients (with tinea capitis) and healthy adult subjects. The influence of covariates (or prognostic factors) on the population PK parameters was also assessed. The pharmacokinetics of terbinafine between children and adults were then compared. Clearance (CL/F) of terbinafine was found to be dependent on body weight in a nonlinear manner, with an exponential scaling factor of 0.34 for body weight. For a typical child of 25 kg CL/F was predicted to be 19 L/h and for a typical adult of 70 kg body weight it was predicted to be 26.9 L/h.

We have the following labeling recommendations ("additions" are in bold italics and "deletions" are strikethroughs) for the proposed label (shown below) that was based on the above analysis:

*Pediatrics*

...A population pharmacokinetic evaluation found that clearance (CL/F) of terbinafine is dependent on body weight in a nonlinear manner. For a typical child of 25 kg CL/F ~~is~~ ***was*** predicted to be 19 L/h and for a typical adult of 70 kg body weight ~~is~~ ***it was predicted to be*** 27 L/h.

**Introduction**

Terbinafine is an antifungal agent that is being investigated for the treatment of tinea capitis in children (aged 4-12 years old). Numerous studies that have characterized the pharmacokinetics (PK) of terbinafine in adults have been conducted previously. Terbinafine is eliminated in a multi-phasic manner with an initial distribution half-life ($t_{1/2, \alpha}$) of approximately 1 hour, and an accumulation half-life ($t_{1/2, \beta}$) of approximately 25-30 hours. In addition, a terminal elimination $t_{1/2}$ of terbinafine of 400 hours has been described after administration of 250 mg doses of Lamisil® for 4 weeks. This half-life was determined from a three-compartment open model and most likely reflects the slow redistribution from tissue compartments into plasma.

**Objectives:**

The objectives of this analysis were to:
a) Define the pharmacokinetics (PK) of terbinafine in pediatric patients with tinea capitis, with particular reference to a model previously determined on a subset of the data.
b) Define the population pharmacokinetic (PPK) parameters and their associated precision and variability.
c) Estimate the inter-individual variability in the structural model parameters and residual variability between the model-predicted and observed concentrations.
d) Assess the influence of covariates (e.g., age, body weight) on the population PK parameters to identify sub-populations with altered pharmacokinetics (CL/F) and thereby compare the pharmacokinetics in adults and children.

**Study Design:**

Terbinafine plasma concentration data from 5 studies in healthy volunteers and patients were used for the PK analysis.

**Study W352**

This was an open-labeled, multiple-dose study, where each patient was to receive terbinafine ***tablets*** once daily for either 28 or 42 days, depending upon the type of tinea capitis infection. A total of 22 pediatric patients (3 - 8 years of age) with tinea capitis completed this study.

The dose administered was based on body weight as follows: <25 kg received a 125-mg dose (1 tablet), 25 to 35 kg received a 187.5 mg-dose (1 1/2 tablets), >35 kg received a 250 mg-dose (2 tablets).

*Trichophyton* infections: Terbinafine treatment was to occur for 28 days once daily in the morning. This was however changed during the study to 42 days for all types of patients by a study amendment.
*Microsporum* infections: Terbinafine treatment was for 6 weeks (Days 1-42).

Patients had PK blood samples taken after the first dose of terbinafine on Day 1 (0, 0.5, 1, 2, 4, 6, 12, and 24 hours post-dose). They returned to the clinic (prior to drug administration) on Day 14 (or Day 21) to provide a pre-dose PK blood sample. On Day 28 (or Day 42), PK sampling occurred from pre-dose to 24 hours post-dose (0, 0.5, 1, 2, 4, 6, 12, and 24 hours).

**Study C2101**

This was an open-label, multiple-dose study, where each patient was to receive terbinafine ***mini-tablets*** once daily or 42 days, for tinea capitis infection. A total of 16 pediatric patients (aged 4 - 8 years) with tinea capitis completed this study.

Patients received their dose as ***mini-tablets*** based on body weight as follows: <25 kg received a 125-mg dose, 25 to 35 kg received a 187.5-mg dose, and >35 kg received a 250-mg dose. Terbinafine treatment was for 42 days q.d. in the morning for both *Trichophyton* and *Microsporum* infections. Patients had PK blood samples taken after the first dose of terbinafine on Day 1 (0, 0.5, 1, 2, 4, 6, 12, and 24 hours post-dose). They returned to the clinic (prior to drug administration) on Day 21 to provide a pre-dose PK blood sample. On Day 42, PK sampling occurred as follows: (0, 0.5, 1, 2, 4, 6, 12, and 24 hours post-dose).

**Study T201**

This was a randomized, double-blind, 3-arm, parallel group, dose-ranging, multicenter study in 40 pediatric patients (aged 4-12 years) with tinea capitis due to the infection of the *Trichophyton* species. Patients received a daily oral terbinafine tablets. The dose was based on body weight: <20 kg = 62.5 mg/day, 20-40 kg = 125 mg/day, >40 kg = 250 mg/day. Doses were given as one half 125-mg tablet, one 125-mg tablet or one 250-mg tablet, respectively.
Patients were randomized to one of the following treatments:

**Table 1. Study Design**

| **Pretreatment Phase** | | **Treatment Phase** | **Post treatment** |
|---|---|---|---|
| **Screening** | **Baseline** | | **Follow-up Phase** |
| Day -21 to Day -3 | Day 0<br>Randomization | Lamisil for 1w then Placebo for 3w<br>Lamisil for 2w then Placebo for 2w<br>Lamisil for 4w | 8w<br>8w<br>8w |

The total study duration was 12-13 weeks. In a subset of patients blood was sampled 1 and 3 hr post dose on Day 1 (i.e., after the first dose), immediately pre-dose and 2 to 4 hr post dose at visits on Weeks 1, 2 and 4.

**Study P101**

This was an open-label, multiple-dose, crossover study to evaluate the effect of food on the bioavailability of Lamisil® in healthy elderly versus young volunteers. Thirty subjects were assigned to 2 age groups (N=15 per group): elderly (age range 60-80 years) and young adults (age range 19-33 years). Subjects in each treatment group were randomized to a sequence of food conditions. Subjects randomized to sequence 1 received Lamisil (one 250-mg tablet) with

food on Day 8 (Period 1) and then received Lamisil in the fasted state on Day 15 (Period 2). Subject randomized to sequence 2 received Lamisil fasted (Day 8) and fed (Day 15). All subjects began taking Lamisil (250 mg tablets) daily on Day 1 (with food) and continued taking Lamisil each morning up to Day 15. Pharmacokinetic sampling was performed on Days 8 and 9 (end of Period 1) and Days 15 and 16 (end of Period 2).

On Day 15 blood samples were collected at the following time points: pre-dose and 0.67, 1.3, 2, 2.7, 3.3, 4, 6, 8, 12, 16, 24, 48, 72, 96, 168 and 336 hr post-dose. Additional pre-dose samples were collected on Days 13 and 14 to assess drug accumulation.
For the purpose of this analysis, all PK profiles measured in young adults on Day 15 regardless of whether Lamisil was taken fasted or with food were used. This appears justified as this study had demonstrated that food has only a minor effect on bioavailability of terbinafine after multiple dosing which was considered to be clinically not relevant.

**Study SF0056**
This was an open-label, randomized, parallel group multiple-dose pharmacokinetic study in 20 healthy male subjects 18 – 45 years of age. The subjects were assigned to one of two treatment groups (either one 125-mg or one 250-mg Lamisil® tablet; 10 subjects per group) according to a randomization list. Single-dose and multi-dose pharmacokinetics of terbinafine were determined.

On Day 1, 16 and 30, blood samples were collected pre-dose and 15, 30, 45 minutes, and 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 16, 24, 28, 32, 36 and 48 hours post-dose. Beginning on Day 3 and continuing until Day 30 (28 consecutive days) Lamisil® tablets were administered once daily. On days with pharmacokinetic profiling the tablets were given after an overnight fast of at least 10 hours. Pre-dose samples were collected on Days 6, 9, 12, 21, 24, and 27. In addition blood was collected after the last dose during the wash-out period, on Day 31 at 4, 8, 12 and 24 hours (= 28, 32, 36, 48 hours post the last dose), on Day 32 at 4, 8 and 12 hours (= 52, 56, and 60 hours post the last dose) and on Days 33, 36, 44, 48, 52, 56, 60, 67, 74, 80 and 90 in the morning.

**Pharmacokinetic Sample Analysis**
In studies W352, C2101 and T201 terbinafine and its internal standard were determined in plasma by [redacted] analysis. The lower limit of quantification for the method was 1 ng/mL.

In studies P101 and SF0056, terbinafine in plasma was measured by an HPLC method with UV detection at 224 nm and a lower limit of quantification of 10 and 20 ng/mL respectively.

**Data:** The final dataset contained 2341 observations from 113 subjects.

**Table 2: Summary (median, range) of demographic characteristics by study of the patients used in the population pharmacokinetic analysis**

| | **Study W352 (N=22)** | **Study C2101 (N=16)** | **Study T201 (N=40)** | **Study P101 (N=15)** | **SF0056 (N=20)** |
|---|---|---|---|---|---|
| Age (yrs) | 5.5 (3-8) | 5 (4-8) | 6 (4-12) | 25 (19-33) | 25 (18-45) |
| Weight (kg) | 22.35 (18-31) | 22.75 (14.1-38.2) | 25.65 (15.4-68) | 83.6 (56.8-95) | 78.1 (59-91.6) |
| Height (cm) | 119.5 (104-156) | 118 (94-147) | 124 (100-155) | 170 (163-191) | 180 (162-193) |
| BMI ($kg/m^2$) | 15.49 (11.561-19.13) | 16.2 (12.8-28.03) | 16.7 (12.7-33.7) | 26.93 (18.98-31.65) | 24.2 (21.1-27.6) |

| | | | | | |
|---|---|---|---|---|---|
| Weight-adjusted dose (mg/kg) | 6.1 (5.21-7.5) | 5.73 (4.91-8.87) | 4.43 (3.13-6.25) | 2.99 (2.63-4.4) | 2.39 (1.37-4.24) |
| Sex (male/female) | 10/12 | 13/3 | 26/14 | 15/0 | 20/0 |
| Tablet type (1/2)* | 22/0 | 0/16 | 40/0 | 15/0 | 20/0 |

* 1=tablets, 2= mini-tablets

**Model Selection**

Selection of the Base Model

Development of the base structural model for PPK and covariate analysis was conducted using all available pharmacokinetic data. The first order (FO) method and first order conditional estimation method with interaction (FOCEI) were used throughout the present analysis. Three- and four-compartment models with first-order and zero-order input were tested. Due to problems with model stability and convergence, runs were executed with NONMEM V and VI beta.

Selection of the appropriate base PPK model was based on the following criteria:

- a significant reduction in the objective function value ($p<0.01$, 6.64 points) based on the Likelihood Ratio Test
- visual inspection of diagnostic plots, including PRED vs DV, IPRED vs DV,
- WRES vs TIME, and PRED, IPRED vs TIME
- model convergence with at least 2 significant digit

Selection of the Final Model

The selected base model was fitted, and the individual random effects (ETAs) were generated using the posterior conditional estimation technique (posthoc) of NONMEM.
The following covariates were examined: age, weight (WT), body mass index (BMI), height (HT), weight-adjusted dose (WAD), and tablet type (TAB). The following criteria were used to determine the final covariate model:

- During the screening process, all covariates were tested on CL and V. In addition, the TAB covariate was tested on the duration of zero-order input (D1). The significance of each covariate was tested individually.

The following evaluation criteria were used to determine the significance of the covariates tested:

- a covariate was retained in the model if, upon its removal, the objective function value increased by more than 10.83 ($p<0.001$) points using FOCEI
- visual inspection of diagnostic plots, including PRED vs DV, IPRED vs DV, WRES vs TIME, and PRED, IPRED vs TIME
- model convergence with at least 2 significant digits
- The least non-significant covariate was excluded from the model and the elimination steps repeated until all non-significant covariates are excluded and the final model was defined.

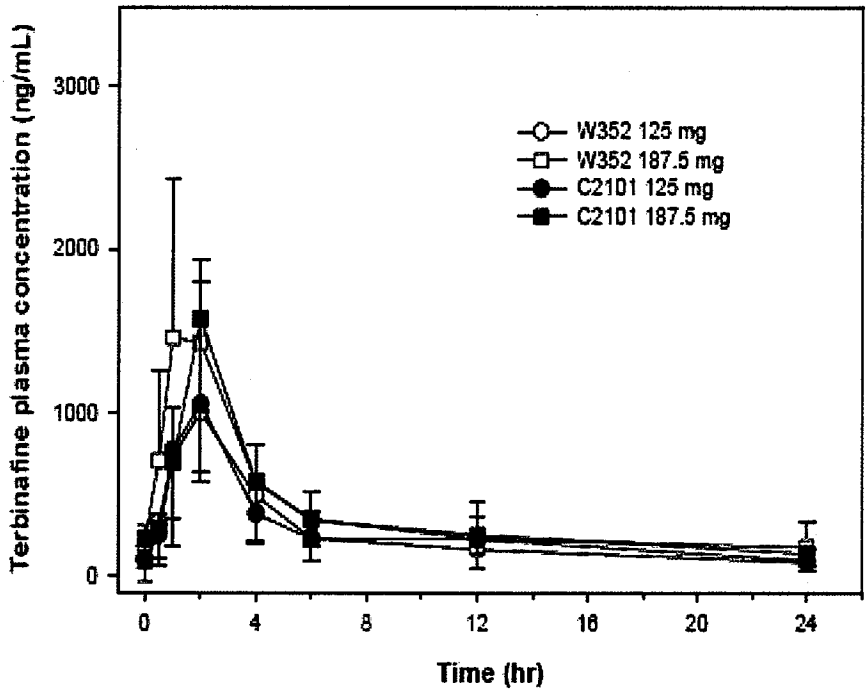
**Software**

Population pharmacokinetic models were built using a nonlinear mixed-effect population modeling approach with the NONMEM software (double precision, Version V, Level 1.1, and Version VI, beta). Models were run using the Compaq Fortran Compiler (Version 6.6b) on a personal computer, and Fortran g77 using Linux. The NONMEM interface software, PDx-Pop™, was used to run NONMEM. Goodness-of-fit diagnostic plots were prepared within S-Plus 2000 Professional Release.

## Results and Discussion

**Figure 1: Mean (+ or – SD) terbinafine plasma concentration-time profiles in children with T. capitis after oral doses of either 125 mg or 187.5 mg and in adults after oral doses of 250 mg of terbinafine, both at steady state**

Children 125 and 187.5 mg Day 28 or 42




Adults 250 mg Day 15 or 30

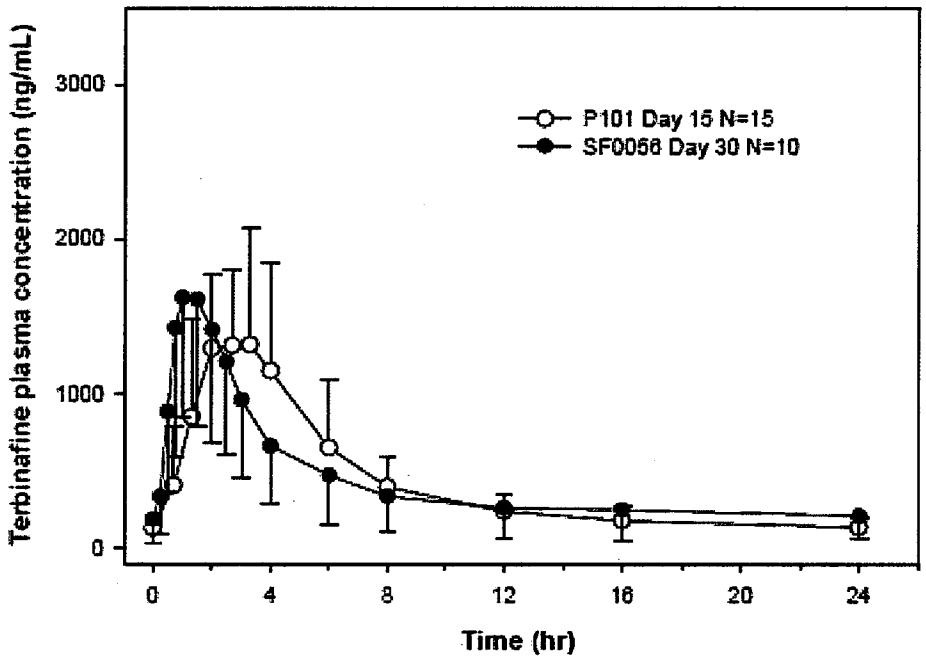
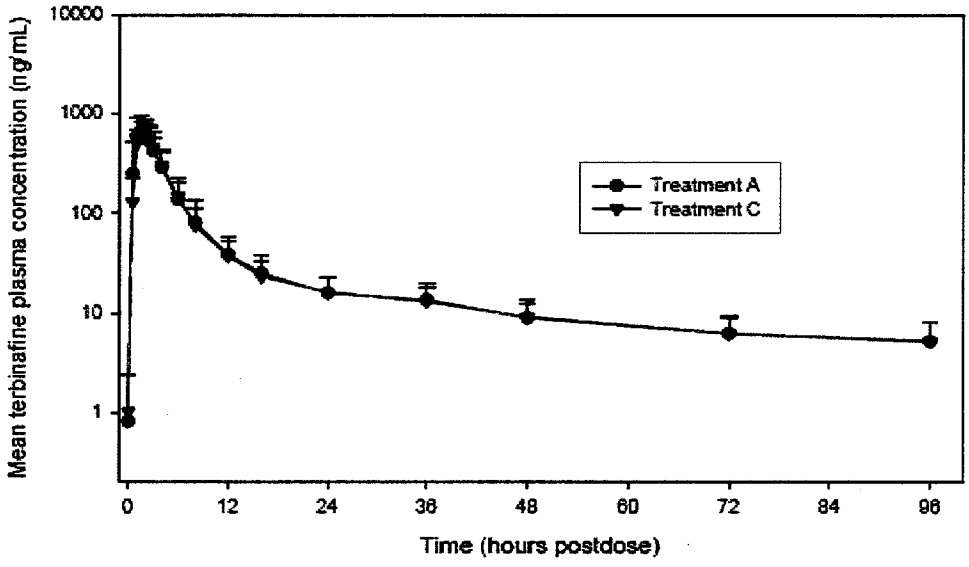



**Figure 2: Mean plasma terbinafine concentrations (+ SD) profiles (n=24) after single oral administration of 250 mg Lamisil to healthy subjects, semi logarithmic view.** Treatments: A: 250-mg Lamisil tablet (n=23-24), and C: sixty mini-tablets= 250 mg (n=24)



**Model and Model Selection:**

Base Model

The current analysis was able to discriminate between three- and four-compartment models in that the terminal phase of the concentration-time profile, shown in Figure 1 above was not well described by a three-compartment model (objective function value =22882.6). This, coupled with the lower objective function value (22827.77) for the four-compartment model, led to selecting this as the best structural model. The applicant stated that the longer sampling times for the additional studies included within the current data set were useful in defining the terminal phase for terbinafine in the fourth compartment in the current analysis.

The ADVAN5 subroutine, describing a four-compartment model with zero-order input, was used. The model was parameterized in terms of CL, V, duration of drug input, and rate constants describing the transfer between the four compartments. WT was included as a covariate on both CL and V. An exponential error model was used to estimate the interindividual variability on all structural parameters, except duration (D1) and the rate constant from compartment 4 to compartment 1 (K41). A term was included to estimate the correlation between the variance terms for CL and V.

In addition, the rate constants were constrained (DK31 and DK21) so that K31 (rate constant from compartment 3 to compartment 1) = K41 + DK31 > K41 and K21 (rate constant from compartment 2 to compartment 1) = K31 + DK21 > K31. Combined additive and proportional models were used to define the residual random error. A copy of the control stream describing the model is attached in the Appendix. The structure of the model is shown below:

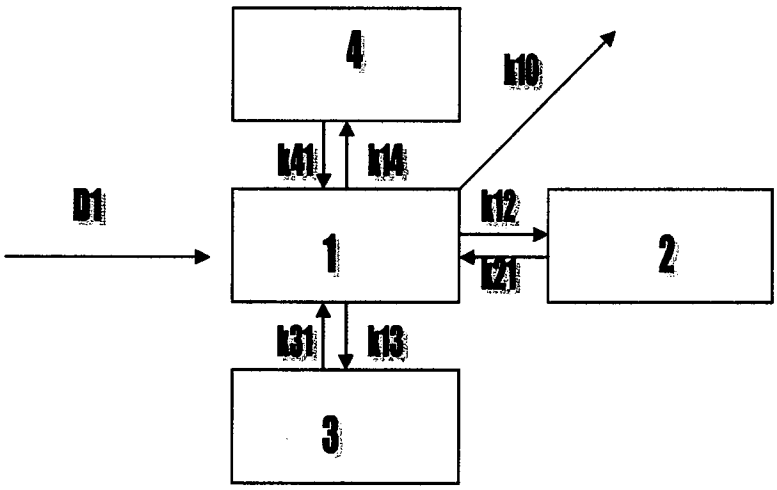



**Figure 3: Four-Compartment Model**

Parameter estimation results:

**Table 3. Base Population Pharmacokinetic Parameter Estimates (Run novfnlnovbp001_5)**

| Final Model Parameter Estimates | | |
|---|---|---|
| **Structural Model and Inter-individual Variance Parameters** | | |
| **Parameter [Units]** | **Typical Value (%RSE*)** | **Inter-individual %CV** (%RSE*)** |
| CL/F[a] [L/hr] | 22.8 | 58.5% |
| V/F[b] [L] | 107 | 51.5% |
| D1 [hr] | 1.74 | NE |
| K14 [$hr^{-1}$] | 0.0760 | 101% |
| K41[$hr^{-1}$] | 0.00265 | NE |
| K13 [$hr^{-1}$] | 0.0901 | 76.4% |
| DK31 [$hr^{-1}$] | 0.0138 | 30.5% |
| K12 [$hr^{-1}$] | 0.0754 | 91.5% |
| DK21 [$hr^{-1}$] | 0.211 | 19.2% |
| CL~WT[c] | 0.341 | |
| V~WT[d] | 0.300 | |
| $\rho_{CL,V}$ | | 0.691 |
| **Intra-individual, Residual Error** | | |
| **Parameter** | **Estimate (%RSE*)** | |
| $\sigma^2_{prop}$ | 0.109 | 33.0% |
| $\sigma^2_{add}$ | 9.41 | 3.07 ng/mL |

%RSE: percent relative standard error of the estimate = SE/parameter estimate * 100
**Inter-individual %CV = 100*sqrt($\omega_2$) for CL/F through V~WT; for $\rho_{CL,V}$ it is the estimate of $\rho_{CL,V}$ itself.
Abbreviations: CL/F = clearance, V/F = volume of central compartment, D1 = duration of drug input, K14/K41 = rate constants in/out 4th compartment, K13/K31 = rate constants in/out 3rd compartment, K12/K21 = rate constants in/out 2nd compartment, K31=K41+DK31, K21=K31+DK21. $\sigma_2$
prop = proportional component of the residual error mode, $\sigma_2$
add = additive component of the residual error model, NE = Not Estimated.
[a] 22.8 L/hr is the typical value of CL/F for a patient with a body weight of 42.81 kg
[b] 107 L is the typical value of V/F for a patient with a body weight of 42.81 kg
[c] exponential factor of WT on CL by the following equation: $CL/F = 22.8*(WT/42.81)^{0.341}$
[d] exponential factor of WT on V by the following equation: $V/F = 107*(WT/42.81)^{0.300}$

Goodness of fit:

**Figure 4. Population Mean Predictions versus Observed Plasma Concentrations (ng/mL) (Base Model)**

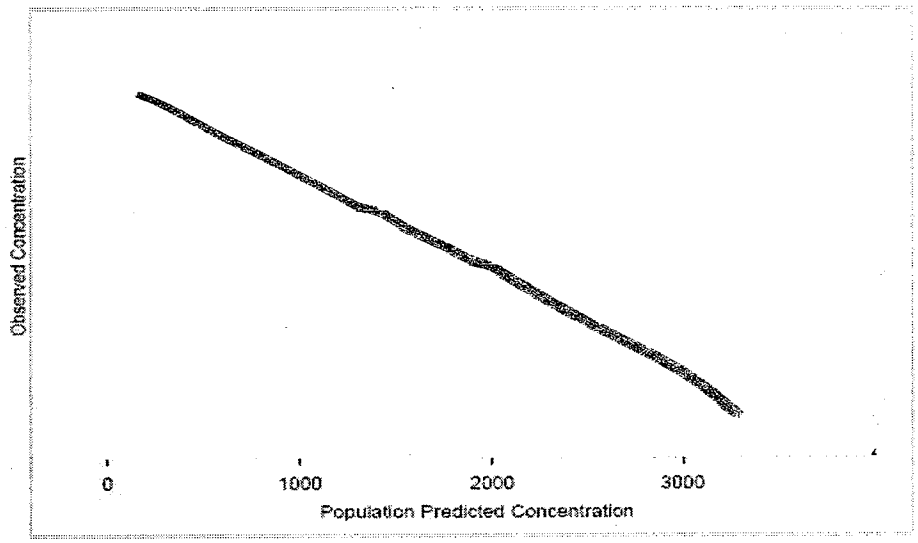
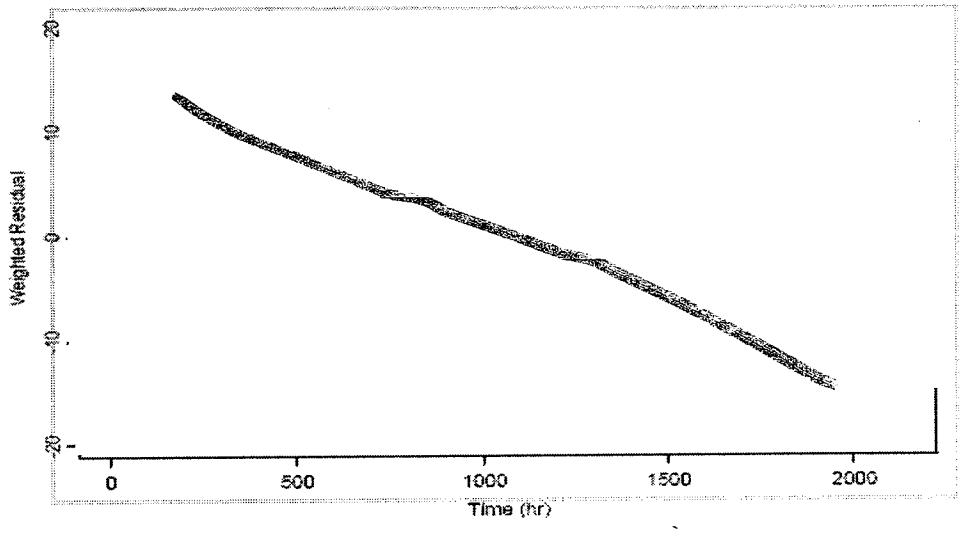



**Figure 5. Weighted Residuals versus Time (Base Model)**




Model Selection

Based on the diagnostic plots (PRED (population predicted concentrations) vs DV and IPRED (individual predicted concentrations) vs DV) of the base model there appeared to be some individuals with high observed concentrations that were not being well predicted by the model. In addition, the WRES vs TIME plot indicated that some concentrations at the end of the concentration time profile were slightly underpredicted by the model.

Prior to initiating the evaluation of the effect of covariates, alternative base models were investigated. This included duration estimated with and without interindividual variability, rate estimated with and without interindividual variability, and CL or V without WT. In addition, AGE and BMI were explored as alternatives to WT. Based on these runs the best base model was found to be a four-compartment model with zero-order input. The CL and V were both estimated as a function of patient WT. The alternative base models using AGE or BMI instead of WT did not demonstrate any improvement over the original base model.

Final Model

***Model description***

Following the identification of the base model, the effects of the covariates on parameters, CL, V, and D1 were explored. The possible effects of weight-adjusted dose (WAD), tablet type (TAB), sex (SEX) and height (HT) on CL and V and TAB on duration (D1) were included into the base model. Based on these analyses, the only covariate that resulted in a significant reduction of the objective function (ΔOFV ~30) was the effect of tablet type on the duration of drug input. There appeared to be little improvement in the PRED vs DV and IPRED vs DV plots. However, the WRES vs
TIME plot did appear to improve in that the underprediction of the observed concentrations at later time was slightly reduced. A copy of the control stream for the final model is included in the Appendix. Difficulty in obtaining the variance-covariance matrix for the parameter estimates suggested that the full model could be over-parameterized. Subsequent evaluation of the interindividual variance model suggested that the interindividual variances for DK21 and DK31 could be removed from the model (fixed to zero) with a change in the OFV of only ~3 units. The parameter estimates for the resulting final model are provided in Table 3.
Parameter estimation results:

**Table 4. Final population pharmacokinetic parameter estimates (Run novfnlnovbp037iwxs_5)**

| Final Model Parameter Estimates<br>Structural Model and Inter-individual Variance Parameters | | |
|---|---|---|
| **Parameter [Units]** | **Typical Value (%RSE*)** | **Inter-individual %CV** (%RSE*)** |
| CL/F[a] [L/hr] | 22.8 (9.17) | 58.2% (18.0) |
| V/F[b] [L] | 111 (8.10) | 50.4% (16.5) |
| D1 [hr] | 1.63 (2.86) | NE |
| K14 [$hr^{-1}$] | 0.0765 (17.9) | 96.5% (29.7) |
| K41 [$hr^{-1}$] | 0.00276 (23.6) | NE |
| K13 [$hr^{-1}$] | 0.0832 (18.6) | 79.9% (41.1) |
| DK31 [$hr^{-1}$] | 0.0143 (14.1) | NE |
| K12 [$hr^{-1}$] | 0.0643 (36.5) | 97.9% (46.6) |
| DK21 [$hr^{-1}$] | 0.189 (20.5) | NE |
| CL~WT[c] | 0.340 (38.5) | |
| V~WT[d] | 0.325 (40.6) | |
| D1~TAB[e] | 0.366 (23.2) | |
| $\rho_{CL,V}$ | | 0.685 (18.6) |
| **Intra-individual, Residual Error** | | |
| **Parameter** | **Estimate (%RSE*)** | |
| $\sigma^2_{prop}$ | 0.108 (1.99) | 32.9% |
| $\sigma^2_{add}$ | 9.49 (9.91) | 3.08 ng/mL |

* %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; for $\rho_{CL,V}$ it is the percent relative standard error of the corresponding estimated covariance between CL and V.
**Inter-individual %CV = 100*sqrt($\omega_2$) for CL/F through D1~TAB; for $\rho_{CL,V}$ it is the estimate of $\rho_{CL,V}$ itself.
Abbreviations: CL/F = clearance, V/F = volume of central compartment, D1 = duration of drug input, K14/K41 = rate constants in/out 4th compartment, K13/K31 = rate constants in/out 3rd compartment, K12/K21 = rate constants in/out 2nd compartment, K31=K41+DK31, K21=K31+DK21. $\sigma_2$
prop = proportional component of the residual error mode, $\sigma_2$
add =
additive component of the residual error model, NE = Not Estimated.
a 22.8 L/hr is the typical value of CL/F for a patient with a body weight of 42.81 kg
b 111 L is the typical value of V/F for a patient with a body weight of 42.81 kg
c exponential factor of WT on CL by the following equation: $CL/F = 22.8*(WT/42.81)^{0.340}$
dexponential factor of WT on V by the following equation: $V/F = 111*(WT/42.81)^{0.325}$
e relationhip between tablet type and duration; if TAB =1, D1=1.63+(TAB*0.366) =1.63+0.366=1.996; else D1=1.63

Goodness of fit:

**Figure 6. Population Mean Prediction versus Observed Plasma Concentrations (Final Model)**

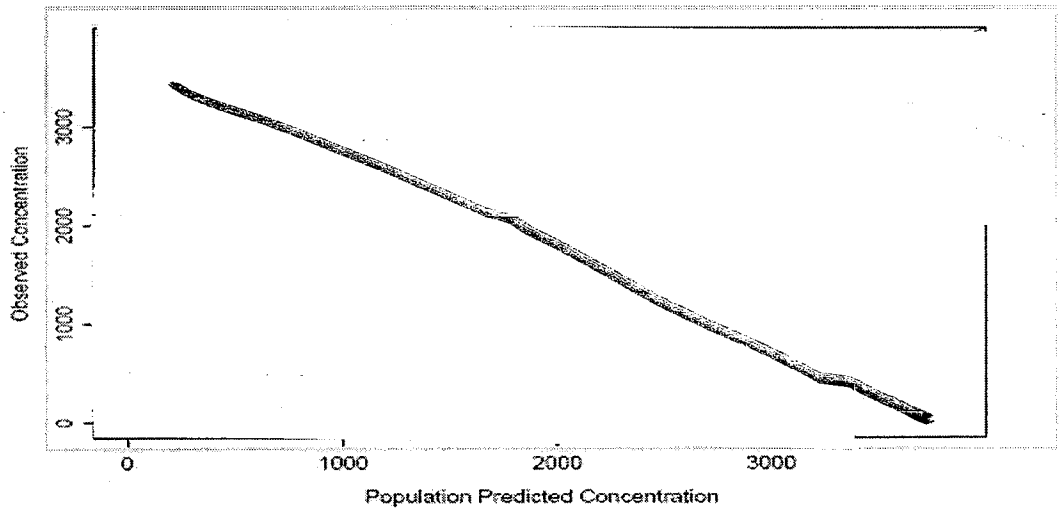
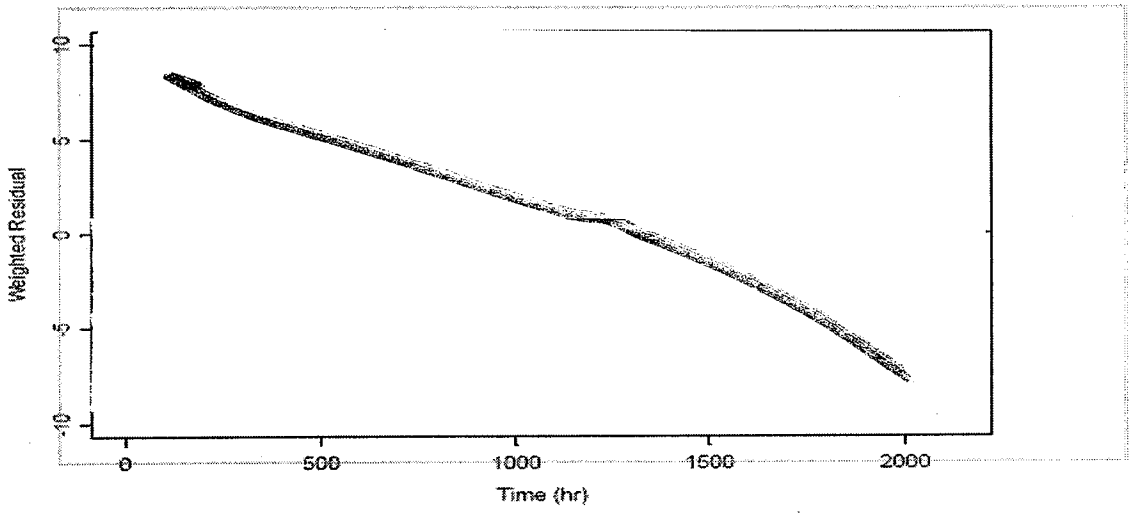



**Figure 7. Weighted Residuals versus Time after Dose (Final Model)**




**Discussion**

A PPK analysis was performed and was used to describe the PK of orally administered terbinafine in pediatric and adult patients. One hundred and thirteen patients from 5 studies were included in the analysis. Both single dose and multiple dose data were available for inclusion into the modeling.

A four-compartment model with zero-order input, parameterized in terms of CL/F, V/F (volume of the central compartment), duration of drug input, and rate constants describing the input and

output from the four compartments was the best among alternative models. Inter-individual variability could be defined for all parameters except duration of drug input and K41. Clearance and volume of the central compartment, calculated by the equations shown below, were 22.8 L/hr and 111 L, respectively, for patients with a median weight of 42.81 kg. For patients having the typical weight of 25 kg or 80 kg, clearance was calculated to be 19.0 and 28.2 L/hr respectively and volume of the central compartment was calculated to be 93.2 and 136 L respectively.

Over the weight range for patients included in this analysis (14.1 kg – 95 kg), CL/F ranged between 15.6 – 29.9 L/hr and V/F ranged between 77.4 L – 143.8 L.

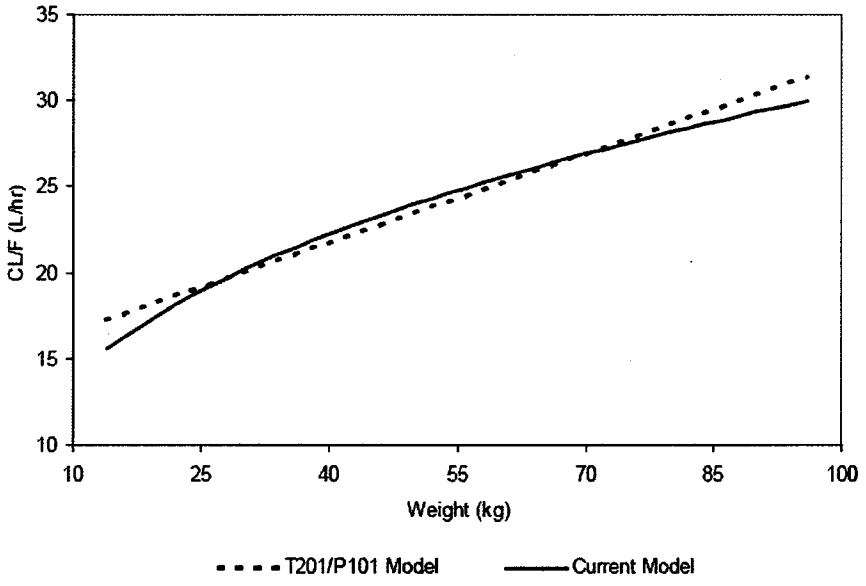
$CL/F = 22.8*(WT/42.81)^{0.340}$ [L/hr]

$V/F = 111*(WT/42.81)^{0.325}$ [L]

Tablet type was the only other covariate that had an impact on the PK of terbinafine. Differences between tablet types resulted in a longer duration of absorption for the minitablet, with duration being estimated as 2.00 hr for the minitablet and 1.6 hr for the conventional tablet. However, it should be noted that only 16 patients, under 10% of the patient database, provided data for this comparison.

The applicant stated that this analysis was generally consistent with previously conducted analysis using data from study # T201 and P101 (reference report is # DAD 00-01], that was deemed a four-compartment model with first-order input adequate to describe the PK of terbinafine in patients and healthy volunteers. In the graph below is a comparison of the current model and the T201/P101 model showing the effect of weight on CL/F.

**Figure 8. Effect of body weight on CL/F for the T201/P101 model versus the current model**



## Overall Conclusions

- A four-compartment model with zero-order input best described the PK of terbinafine. CL and V were estimated as a function of patient weight. To achieve a similar systemic exposure in children than in adults, the dose of terbinafine in children should be adjusted based on body-weight.
- The absorption from the minitablet was slightly (about 0.4 hr) prolonged when compared to the conventional tablet.
- The results of this analysis are consistent with in vitro and in vivo information available for terbinafine that have described its lipophilic characteristics and its large V, consistent with its distribution into skin and other tissues with a high lipid content.

## Recommendations

### Labeling

Applicant's Proposed Label:

*Pediatrics*

A population pharmacokinetic evaluation found that clearance (CL/F) of terbinafine is dependent on body weight in a nonlinear manner. For a typical child of 25 kg CL/F is predicted to be 19 L/h and for a typical adult of 70 kg body weight is 27 L/h.

We have the following labeling recommendations (**"additions" are in bold italics and "deletions"** are strikethroughs) for the proposed label:

*Pediatrics*

...**A population pharmacokinetic** evaluation found that clearance (CL/F) of terbinafine is dependent on body weight in a nonlinear manner. For a typical child of 25 kg CL/F ~~is~~ was predicted to be 19 L/h and for a typical adult of 70 kg body weight ~~is~~ it was predicted to be 27 L/h.

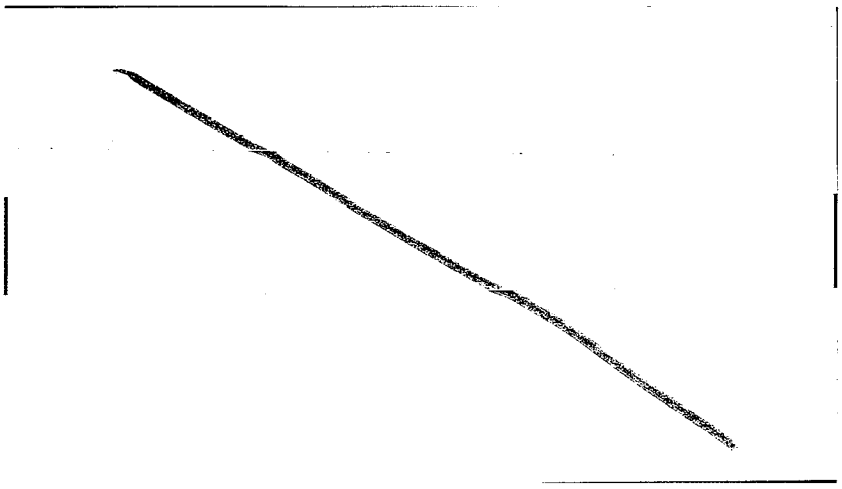
# 5 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-_____*



## 4.4 Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

*New Drug Application Filing and Review Form*

*General Information about the Submission*

| | Information | | Information |
|---|---|---|---|
| **NDA Number** | 22-071 | **Brand Name** | Lamisil ® Mini-Tablets |
| **OCPB Division (I, II, III)** | DCP3 | **Generic Name** | Terbinafine HCl |
| **Medical Division** | OND 540 | **Drug Class** | Antifungal |
| **OCPB Reviewer** | Abi Adebowale | **Indication(s)** | Treatment of Tinea Capitis in children (4-12 years of age) |
| **OCPB Acting Team Leader** | Sue-Chih Lee | **Dosage Form** | Mini-tablets 125 mg and 187.5 mg |
| **Letter Date** | September 8th, 2006 | **Dosing Regimen** | To be taken once a day for 6 weeks based upon body weight (< 25 kg (125 mg/day), 23-35 kg (187.5 mg/day and > 35 kg (250 mg/day)) |
| **Stamp Date** | September 8th, 2006 | **Route of Administration** | Oral |
| **Estimated Due Date of OCPB Review** | March 1st, 2007 | **Sponsor** | Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936 |
| **PDUFA Due Date** | July 8th, 2007 | **Priority Classification** | 5S |

| Division Due Date | April 1st, 2007 | **IND Number** | [redacted] and [redacted] Related NDAs: 20-192, 20-539, 20-749, 20-980, 21-124 |
|---|---|---|---|

*Clin. Pharm. and Biopharm. Information*

| | **"X" if included at filing** | **Number of studies submitted** | **Number of studies reviewed** | **Study Numbers If any** |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | X | | | |
| **Tabular Listing of All Human Studies** | X | | | |
| **HPK Summary** | X | | | |
| **Labeling** | X | | | |
| **Reference Bioanalytical and Analytical Methods** | X | 1 | | DMPK(US)R99-100 |
| **I. Clinical Pharmacology** | | 1 | | |
| **Mass balance:** | | 1 | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| Healthy Volunteers- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Patients-** | | | | |
| single dose: | | | | |
| multiple dose: | X | 2 | | SFO327CW352 and CSFO327C2101 (children aged 4-8 years old with T.Capititis) |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | 4 | | SFW 152, 153, 154 and 156 (using Lamisil tablets, not mini-tablets) |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | X | 1 | | RANVR050-051 Report used for dose selection for PK studies and Phase 3 studies |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | X | | | |

| | | | | |
|---|---|---|---|---|
| solution as reference: | | | | |
| alternate formulation as reference (IR): | X | 2 | | CSFO327L2104 (uses the 175 mg [redacted] and CSFO327C2303 |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | X | 2 | | CSFO327L2104 and SFO327L2306 |
| **Dissolution:** | X | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Other (in vitro percutaneous absorption study)** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | [redacted] 2004 (Expert statement on the two pediatric Studies) |
| **Total Number of Studies** | | 9 | | |

**Filability and QBR comments**

| Types and #'s of studies and supplementary information (literature review) are adequate to conduct a review | "X" if yes<br>X | Comments |
|---|---|---|
| Application filable? | X | Reasons if the application is not filable (or an attachment if applicable)<br>For example, is clinical formulation the same as the to-be-marketed one? |
| Comments sent to firm? | No | Comments have been sent to firm (or attachment included). FDA letter date if applicable. |
| **QBR questions (key issues to be considered)** | What is the PK of lamisil minitabs in the pediatric popluation?<br>How were the doses based on body weight selected?<br>Is the PK in pediatrics comparable to that of adults? If not do we recommend any dosage adjustment?<br>Do we need a PM consult? Yes<br>Was the TBMF used in the clinical trials? | |
| **Other comments or information not included above** | **PM consult sent on September 28th, 2006** | |
| **Primary reviewer Signature and Date** | **Abi Adebowale 09/28/06 (filing review), 04/27/07 (first draft of CP review)** | |
| **Secondary reviewer Signature and Date** | **Sue-Chih Lee** | |

CC: NDA 22-071, HFD-850 (P.Lee), HFD-540 (K. Bhatt), DCP 3 (D. Bashaw, S. Lee)

## Comments to be sent to the firm:

Please submit or direct us to the location of the following datasets to support the population analysis (RANVR050-051):

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation

model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

- A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
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Abi Adebowale
6/11/2007 06:04:46 PM
BIOPHARMACEUTICS

Sue Chih Lee
6/11/2007 07:20:32 PM
BIOPHARMACEUTICS