

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

<b>NDA</b>	<b>22-071</b>	<b>Submission Date(s)</b>	September 8 <sup>th</sup> , 2006, December 4 <sup>th</sup> , 2006, December 5 <sup>th</sup> , 2006 and March 20 <sup>th</sup> , 2007
<b>Brand Name</b>	Lamisil <sup>®</sup> Mini-tablets		
<b>Generic Name</b>	Terbinafine Hydrochloride		
<b>Reviewer</b>	Abimbola Adebawale, Ph.D.		
<b>Team Leader</b>	Sue-Chih Lee, Ph.D.		
<b>Pharmacometrics Reviewer</b>	Atul Bhattaram, Ph.D		
<b>Pharmacometrics Team Leader</b>	Yaning Wang, Ph.D.		
<b>OCP Division</b>	DCP 3		
<b>OND division</b>	HFD-540		
<b>Sponsor</b>	Novartis Pharmaceuticals Corporation, NJ 07936		
<b>Relevant IND(s)</b>	██████ and ██████		
<b>Submission Type; Code</b>	Pediatric Study Reports	3S	
<b>Formulation; Strength(s)</b>	Mini-tablets, 125 mg and 187.5 mg		
<b>Indication</b>	Treatment of Tinea Capitis		

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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
<b>AUC0-24 (hr*ng/mL)</b>	3311 (1605)	6513 (4074)	5109 (1860)	8653 (4412)	5253	4154
<b>Cmax (ng/mL)</b>	971 (585)	1118 (713)	1602 (1010)	1575 (942)	1370	544
<b>Tmax (hr)</b>	1.8 (0.5)	2.5 (3.2)	2.0 (0.0)	2.0 (0.0)	2.0	2.0
<b>T 1/2 effective (hr)</b>	*ND	26.7 (13.8)	ND	30.5 (9.3)	ND	ND
<b>Accumulation Ratio (R)**</b>	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 CL<sub>ss</sub>/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 CL<sub>ss</sub>/F of 60.2 L/hr.

**Comparison of the pharmacokinetics of terbinafine in children and adults:**

A comparison of the systemic exposure (AUC and C<sub>max</sub>) 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<sub>0-24</sub> was 30 to 50 % lower and median C<sub>max</sub> 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 mg 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, \_\_\_\_\_ in study [L2104] after a single dose and in study [L2306] after repeated doses of 350 mg \_\_\_\_\_ 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 ██████ 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 ██████████. Therefore the applicant’s extrapolation of the food effect data from this formulation to the mini-tablets ██████████ 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	<b>C<sub>max</sub> +52%;</b> <b>AUC +67%</b>
0153	Cotrimoxazole/ 160 mg trimethoprim 800 mg sulfamethoxazole	750 mg	PK not altered	PK not altered
0154	Zidovudine/200 mg	750 mg	<b>AUC +15%;</b> <b>T<sub>max</sub> +41%;</b> <b>C<sub>max</sub> -25%;</b> <b>CL/F -15%;</b> <b>V/F -17%</b>	PK not altered
0156	Theophylline/375 mg	250 mg	PK not altered	<b>C<sub>max</sub> +23%;</b> <b>AUC +18%;</b> <b>CL/F -23%</b>

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 C<sub>max</sub> 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 C<sub>max</sub> (52%), AUC (0-tlast) (69%), and AUC (0-∞) (67%), and decreased desmethylterbinafine C<sub>max</sub> (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:

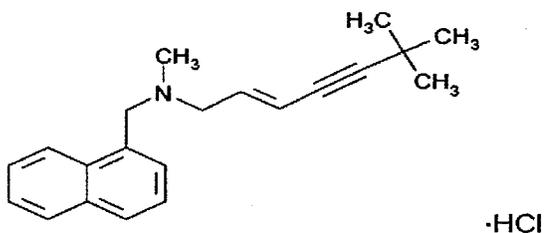
The relative bioavailability of the mini-tablets compared to the marketed tablets was investigated in study C2303. This was a randomized, open-label, single dose, three period crossover study conducted in 24 Caucasian (12 male and 12 female) adult healthy volunteers. The mini-tablets were administered 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 C<sub>max</sub>, AUC<sub>0-tlast</sub> and AUC<sub>0-∞</sub> 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?*



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-ynyl)-N-methyl-1-naphthalenemethanamine hydrochloride. The terbinafine free base and the hydrochloride have a molecular weight of ~~282.4~~ and 327.9, respectively. In this submission, all doses, concentrations and pharmacokinetic parameters are given in terms of terbinafine free base.