

**One Year Post-Exclusivity  
Adverse Event Review:  
Terbinafine**

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**Background Drug Information**

- **Drug:** Lamisil® (terbinafine hydrochloride)
- **Therapeutic Category:** antifungal
- **Sponsor:** Novartis Pharmaceuticals Corporation
- **Original Market Approval:**
  - Topical cream Rx 1992; OTC 1999
  - Tablets 1996
  - Topical solution 1997
  - Topical gel 1998
  - Oral granules 9/28/2007
- **Pediatric Exclusivity Granted:** December 4, 2006

## Background Drug Information

### Indications

- **Oral granules:** Tinea capitis in patients 4 years and older
- **Tablets:** Onychomycosis in adults
- **Topical cream (OTC):** Tinea pedis, tinea cruris and tinea corporis in patients 12 and older
- **Topical solution:** Tinea versicolor in adults
- **Topical gel:** Tinea pedis, tinea cruris, tinea corporis, and tinea versicolor in adults

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## Background Drug Information

- Pediatric use accounts for ~ 2% of total dispensed oral terbinafine prescriptions.<sup>1</sup>
- No dispensed prescriptions for Lamisil® Oral Granules<sup>2</sup> in either adult or pediatric populations during the entire study period

<sup>1</sup>Source: Verispan Vector One®, National, Dec. 1, 2004 to Nov. 30, 2007  
Data Extracted 6/2008.

<sup>2</sup>Oral Granules approved September 28, 2007.

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## **Exclusivity Studies**

### **Lamisil® Oral Granules**

- One PK study (single and multiple dose) in 16 children, aged 4 to 8 years, with tinea capitis
  
- Two randomized, 6 week, active-controlled (griseofulvin) studies evaluating safety and efficacy in 1549 subjects, aged 4 to 12 years, with tinea capitis

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## **Exclusivity Studies Results**

### **Pharmacokinetic:**

- Systemic exposure showed high inter-individual variability.
- Systemic exposure in children was similar to adults.

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## Exclusivity Studies Results

### Efficacy:

- Terbinafine achieved superiority over griseofulvin in one of the two studies
- Subgroup analysis by species of fungal organism
  - For *T. tonsurans*, terbinafine was more efficacious than griseofulvin in both studies.
  - For *M. canis*, griseofulvin was more efficacious than terbinafine in both studies.
- U.S. frequency: *T. tonsurans* (90-96%), *M. canis* (1-5%)

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## Exclusivity Studies Results

### Safety:

#### Treatment related adverse events

Adverse event	Terbinafine	Griseofulvin
Vomiting	2%	2%
Upper abd. pain	1%	1%
Diarrhea	1%	1%
Headache	1%	1%
Nausea	1%	1%
Abd. pain	1%	0.2%

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## **Labeling**

Exclusivity studies resulted in:

- Approval of a new formulation (Lamisil® Oral Granules)
- Approval of a new indication (tinea capitis)
- Labeling with information on usage, dosing, adverse events, clinical pharmacology and clinical studies

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## **Labeling**

### **Warnings and Precautions**

**The following have been reported:**

- Cases of liver failure, some leading to death or liver transplant
- Severe neutropenia
- Stevens-Johnson syndrome and toxic epidermal necrolysis
- Lupus erythematosus

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## Labeling

### Adverse Reactions:

- Adverse events greater than 1% in pivotal trials include nasopharyngitis, headache, pyrexia, cough, vomiting, upper respiratory tract infection, upper abdominal pain and diarrhea.
- Adverse reactions seen during postapproval use include thrombocytopenia, agranulocytosis, pancytopenia, anemia, myalgia, rhabdomyolysis, acute pancreatitis, and hair loss.

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## Medication Errors – Name Confusion

- Pediatric exclusivity has not impacted the number of reported medication errors.
- Lamisil® confused primarily with Lamictal®
- Well documented error
- Interventions have been implemented
  - ✓ ISMP<sup>1</sup> – Confused Drug Names List
  - ✓ Extensive Educational Campaign
  - ✓ Rx Safety Advisor
- FDA will continue to monitor.

<sup>1</sup>Institute for Safe Medication Practices

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## Pediatric Adverse Events in 1-year Post Exclusivity Period

Crude Counts <sup>1</sup> of AERS Reports for All Sources from Date of Pediatric Exclusivity - 12/4/06 through 1/4/08			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs)	329 (91)	317 (83)	7 (1)
Pediatrics (0-16 yrs)	7 (4)	7 (4)	0(0)
Age unknown (Null Values)	94 (36)	88 (34)	3 (0)
<b>Total</b>	<b>430 (131)</b>	<b>412 (121)</b>	<b>10 (1)</b>

<sup>1</sup> May include duplicates

<sup>2</sup> Serious adverse drug experience, per (CFR 314.80), which includes death, life threatening, hospitalization, disability, congenital anomaly, and other serious (important medical events)

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## Pediatric Adverse Events Since Marketing Approval

Crude Counts <sup>1</sup> of AERS Reports for All Sources from Marketing Approval through January 4, 2008			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs)	4745 (2750)	4004 (2063)	144 (39)
Pediatrics (0-16 yrs)	84 (48)	80 (45)	1(0)
Age unknown (Null Values)	1576 (1281)	1051 (767)	30 (15)
<b>Total</b>	<b>6405 (4079)</b>	<b>5136 (2876)</b>	<b>175(54)</b>

<sup>1</sup> May include duplicates

<sup>2</sup> Serious adverse drug experience, per (CFR 314.80), which includes death, life threatening, hospitalization, disability, congenital anomaly, and other serious (important medical events)

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## **Pediatric Deaths**

### **One Death:**

- In utero exposure – Infant died. Was diagnosed with Trisomy 13. Not likely to be related to terbinafine exposure.

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## **Pediatric Serious Adverse Events Since Marketing Approval**

### **80 Crude Count Cases**

3 Duplicates

### **77 Unique Cases - 30 cases excluded:**

- 29 for various reasons [e.g., drug ineffective, medication errors, no temporal relationship]
- 1 miscoded age

### **47 Remaining Cases**

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## Serious Pediatric Adverse Events

### Skin reactions (N=16 cases) – labeled

- Skin rashes\*, erythema multiforme\*\*, Stevens-Johnson syndrome\*\*, toxic epidermal necrolysis, skin striae, hives, pruritus and alopecia

### Neurologic events (N=5 cases)

- Single reports of seizure or shaking spell, headache and neck pain, mental impairment, walking difficulty†, and somnolence
- Only headache is labeled.

\*One case required hospitalization

\*\*Required hospitalization

†May be related to skin rash

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## Serious Pediatric Adverse Events

### Gastrointestinal events (N=5 cases)

- Abdominal pain, vomiting, and diarrhea which are labeled events
- Hematochezia in a 3 y/o after 3 weeks of oral terbinafine, resolved after discontinuation – not labeled

### Hematologic events (N=3 cases)

- Leukopenia, thrombocytopenia/anemia, and neutropenia – all labeled events

### Musculoskeletal events (N=2 cases)

- Myalgia and rhabdomyolysis – labeled events

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## **Serious Pediatric Adverse Events**

### **Hepatic events** (N=2 cases) - labeled

- Fatigue and intense upper abdominal cramps
- Elevated bilirubin and alkaline phosphatase levels

### **Renal and Urinary events** (N=2) – unlabeled

- Single reports of nephrotic syndrome and incontinence

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## **Serious Pediatric Adverse Events**

### **Psychiatric events** (N=3 cases) – unlabeled

- 13 y/o developed depression, anxiety, insomnia, nausea, forgetfulness, and social withdrawal after 3 ½ weeks on oral terbinafine. Recovered after discontinuation. Concomitant medication – metoclopramide
- 16 y/o with history of depression (on escitalopram) and of Lyme disease, developed worsening depression and suicidal ideation after one month on oral terbinafine.
- 16 y/o with thoughts of self-harm after two months of oral terbinafine. Recovered after discontinuation.

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## **Serious Pediatric Adverse Events**

### **Other events (N=9 cases) – unlabeled**

#### **Oral terbinafine**

- 14 y/o - ALL 12 days after a 3 month course
- 13 y/o - ↑ carbamazepine level after one month - Resolved with adjustment of carbamazepine dose. Completed 3 months of terbinafine.
- 14 y/o - hypoglycemia after 4 weeks - Resolved without discontinuation of terbinafine.
- 5 y/o - chest pain and breast development after first dose
- 10 y/o - ecchymosis after 2 days

#### **Topical terbinafine**

- 4 events - no trend seen

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## **Summary 1: Terbinafine**

- No safety signals unique to the pediatric population identified since market approval
- Since 1992, three psychiatric events were found in the pediatric population. However, there was underlying illness or use of concomitant medications that confound the interpretation of causality.
- Exclusivity studies resulted in approval of a new formulation and a new indication.

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## Summary 2: Terbinafine

- This completes the one year post-exclusivity adverse event reporting for terbinafine.
- FDA will continue its ongoing safety monitoring for terbinafine.
- Does the Advisory Committee have any additional comments?

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