One Year Post-Exclusivity
Adverse Event Review:
Terbinafine

Pediatric Advisory Committee Meeting
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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
- **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):** Tines 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.¹

• No dispensed prescriptions for Lamisil® Oral Granules² in either adult or pediatric populations during the entire study period

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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

Exclusivity Studies Results

**Pharmacokinetic:**

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

Exclusivity Studies Results

Safety:
- Treatment related adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Terbinafine</th>
<th>Griseofulvin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Upper abd. pain</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Headache</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Abd. pain</td>
<td>1%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>
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

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
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.

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
  - ISMP1 – Confused Drug Names List
  - Extensive Educational Campaign
  - Rx Safety Advisor
- FDA will continue to monitor.

1Institute for Safe Medication Practices
Pediatric Adverse Events in 1-year Post Exclusivity Period

Crude Counts\(^1\) of AERS Reports for All Sources from Date of Pediatric Exclusivity - 12/4/06 through 1/4/08

<table>
<thead>
<tr>
<th></th>
<th>All reports (US)</th>
<th>Serious(^2) (US)</th>
<th>Death (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 17 yrs)</td>
<td>329 (91)</td>
<td>317 (83)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Pediatrics (0-16 yrs)</td>
<td>7 (4)</td>
<td>7 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Age unknown (Null Values)</td>
<td>94 (36)</td>
<td>88 (34)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>430 (131)</td>
<td>412 (121)</td>
<td>10 (1)</td>
</tr>
</tbody>
</table>

\(^1\) May include duplicates

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

Pediatric Adverse Events Since Marketing Approval

Crude Counts\(^1\) of AERS Reports for All Sources from Marketing Approval through January 4, 2008

<table>
<thead>
<tr>
<th></th>
<th>All reports (US)</th>
<th>Serious(^2) (US)</th>
<th>Death (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 17 yrs)</td>
<td>4745 (2750)</td>
<td>4004 (2063)</td>
<td>144 (39)</td>
</tr>
<tr>
<td>Pediatrics (0-16 yrs)</td>
<td>84 (48)</td>
<td>80 (45)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Age unknown (Null Values)</td>
<td>1576 (1281)</td>
<td>1051 (767)</td>
<td>30 (15)</td>
</tr>
<tr>
<td>Total</td>
<td>6405 (4079)</td>
<td>5136 (2876)</td>
<td>175 (54)</td>
</tr>
</tbody>
</table>

\(^1\) May include duplicates

\(^2\) Serious adverse drug experience, per (CFR 314.80), which includes death, life threatening, hospitalization, disability, congenital anomaly, and other serious (important medical events)
**Pediatric Deaths**

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

**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**
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

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
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

**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.
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

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.
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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