



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
DIVISION OF PHARMACOVIGILANCE

MEMORANDUM

DATE: October 21, 2008

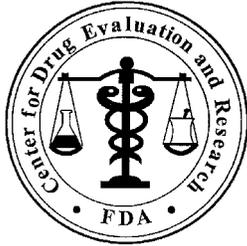
TO: Lisa L. Mathis MD, Associate Director
Pediatric and Maternal Health Staff (PMHS)
Office of New Drugs (OND), CDER
and
M. Dianne Murphy, MD, Director
Office of Pediatric Therapeutics (OPT), OC

FROM: Hyon J. Kwon, PharmD, MPH, Safety Evaluator/Acting Team Leader
Division of Pharmacovigilance I

THRU: Min Chu Chen, RPh, MS, Acting Director for
Mark Avigan, MD, CM, Director
Division of Pharmacovigilance I (DPV I)
Office of Surveillance and Epidemiology (OSE), CDER

SUBJECT: 1-year Pediatric Exclusivity Postmarketing Adverse Event Review

Attached is the amended 1-year Pediatric Exclusivity Postmarketing Adverse Event Review for terbinafine. The Tables 1 and 2 in sections 3.1 and 3.2 respectively were revised to include AERS reports with an outcome of other serious in the crude counts of serious reports.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: October 21, 2008

To: Lisa L. Mathis MD, Associate Director
Pediatric and Maternal Health Staff (PMHS)
Office of New Drugs (OND), CDER
and
M. Dianne Murphy, MD, Director
Office of Pediatric Therapeutics (OPT), OC

Through: Mark Avigan, MD, CM, Director
Division of Pharmacovigilance I (DPV I)
Office of Surveillance and Epidemiology (OSE), CDER

From: Hyon J. Kwon, PharmD, MPH, Safety Evaluator
Division of Pharmacovigilance I

Subject: 1-year Pediatric Exclusivity Postmarketing Adverse Event Review

Drug Name(s): Terbinafine (Lamisil®)

Pediatric Exclusivity Approval Date: December 4, 2006

Application Type/Number: NDA 22-071, 20-539, 20-192, 20-749, 20-846, 20-980

Applicant/sponsor: Novartis

OSE RCM #: 2008-701

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

CONTENTS

EXECUTIVE SUMMARY	1
1 BACKGROUND	1
1.1 Introduction (Product Formulations and Indications)	1
1.2 Pediatric labeling.....	2
2 METHODS AND MATERIALS.....	2
2.1 AERS Selection of Cases	2
3 AERS RESULTS for Terbinafine.....	3
3.1 Count of Reports: All sources- US and Foreign from marketing approval (Table 1)....	3
3.2 Count of Reports: All Sources- US and Foreign from Pediatric Exclusivity (Table 2). 4	
3.3 Characteristics of all serious pediatric cases (Table 3)	4
4 DISCUSSION/Summary Of Cases.....	5
4.1 Skin events (n=16)	5
4.2 Neurologic events (n=5).....	6
4.3 Gastrointestinal Events (n=5).....	7
4.4 Psychiatric events (n=3).....	7
4.5 Hematologic events (n=3)	8
4.6 Hepatic events (n=2).....	8
4.7 Renal & Urinary events (n=2).....	8
4.8 Musculoskeletal events (n=2)	8
4.9 Other events (n=9)	9
5 CONCLUSION.....	10
6 RECOMMENDATIONS.....	10
7 REFERENCE	10
APPENDIX	11

EXECUTIVE SUMMARY

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of terbinafine in pediatric patients. Up to the "data lock" date of January 4, 2008, AERS contained 6405 reports for terbinafine (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 1.3 % of the total (84/6405). The drug utilization data for oral terbinafine showed that the prescriptions in the pediatric population (ages ≤ 16 years) accounted for about 2% of total prescriptions (39,000/1.8 million) dispensed for oral terbinafine in the outpatient setting during the post-exclusivity 12-month period from December 1, 2006 through November 30, 2007.¹

DPV was asked to review and assess all serious adverse events occurring with the use of terbinafine in pediatric patients. We used an AERS data lock date of January 4, 2008, to allow time for reports received up to December 4, 2007, to be entered into AERS. Forty-seven post-marketing pediatric cases with serious outcomes were reported since approval through January 4, 2008. Of these, no deaths were observed, and six of 47 cases reported hospitalization, life-threatening, and/or disability outcome; these six cases included four cases of skin reactions, and one case each of leg pain and thrombocytopenia/anemia. The remaining 41 cases were considered serious because the reporter considered the event to be medically significant.

The majority of serious adverse events involved skin reactions (n=16), which are labeled events for terbinafine. Several unlabeled events with serious outcome were observed in the remaining cases, but an association appears to be unlikely between many of these events and terbinafine due to sparse number of reports for a particular reported event. These unlabeled events included neurologic events (one case each of seizure, mental impairment, walking difficulty, and somnolence), one GI event of hematochezia, and a case of nephrotic syndrome and incontinence; in addition, smattering of other unlabeled events were also noted (see section 4.9). However, there were three psychiatric events consisting of depression/suicidal ideation and self-harm (section 4.4), which may warrant further investigation.

We will further investigate all psychiatric events of depression, suicidal ideation, and self-harm reported with terbinafine, across all ages, to assess whether this may be a safety concern. In addition, we will continue routine monitoring of adverse events with the use of terbinafine in pediatric patients.

1 BACKGROUND

Terbinafine, an allylamine antifungal agent, is marketed in multiple topical and oral formulations, and a new formulation (oral granules) was approved on September 28, 2007 with an indication for treatment of tinea capitis in patients 4 years and older. Pediatric exclusivity was granted on December 4, 2006, based on two 6-week active-controlled, randomized safety and efficacy trials of terbinafine oral granules (dosed on body weight) compared to griseofulvin. The most commonly observed adverse events in these two trials were nasopharyngitis, headache, pyrexia, cough, vomiting, and upper respiratory tract infection.

1.1 INTRODUCTION (PRODUCT FORMULATIONS AND INDICATIONS)

Terbinafine is available in four formulations:

- Topical gel - FDA approved April 29, 1998 and is available as 1% gel
- Topical cream - FDA approved March 9, 1999 and is available as 1% cream
- Topical solution - FDA approved October 17, 1997 and is available as 1% solution

- Oral tablet - FDA approved May 10, 1996 and is available as 250 mg tablets
- Oral granules - FDA approved September 28, 2007 and is available as 125 mg and 187.5 mg oral granules

Terbinafine is indicated as follows:

- Topical gel is indicated for the topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur*, tinea pedis (athlete's foot), tinea corporis (ringworm) or tinea cruris (jock itch) due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum*.
- Topical cream is indicated for tinea pedis, tinea cruris, and tinea corporis
- Topical solution is indicated for the topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur*.
- Oral tablets are indicated for the treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium).
- Oral granules are indicated for the treatment of tinea capitis in patients four years of age and older.

1.2 PEDIATRIC LABELING

The safety and efficacy of terbinafine tablets and topical gel, cream, or solution have not been established in pediatric patients.

Terbinafine oral granules are indicated in pediatric patients four years of age and older for treatment of tinea capitis. The current labeling of oral granules contains *Warnings and Precautions* for hepatotoxicity, hematological, skin reactions, and lupus erythematosus.

2 METHODS AND MATERIALS

2.1 AERS SELECTION OF CASES

The AERS database was searched to obtain multiple crude count of reports of adverse events associated with the use of terbinafine, regardless of formulations (topical and oral), up to the data lock date of January 4, 2008. The results of these searches are shown in tables 1 and 2 in sections 3.1 and 3.2.

The PMHS requested review and assessment of all serious (fatal and non-fatal) adverse events, including hepatotoxicity, nephritis, eye symptoms, and neutropenia. In addition, it is a standard practice to review all pediatric adverse event reports received during the 1-year period following the approval of pediatric exclusivity in OSE BPCA review.

Thus, the AERS database was searched for 1) reports of all serious adverse events associated with terbinafine and 2) reports received during the 1-year period following the approval of pediatric exclusivity, regardless of formulations (topical and oral), up to the date lock date of January 4, 2008.

The search of all serious adverse events associated with terbinafine resulted in 80 reports, and 33 reports were excluded for the following reasons:

- Drug ineffective (n=9)
- Medication error (n=6); excluded since cases of medication error will be reviewed by DMEDP

- Event occurred 7 days to 3 months after discontinuation of terbinafine (n=6)
- Duplicates (n=3)
- Intentional drug misuse; an Australian report where ‘intentional drug misuse’ was coded because it was being used outside of approved pediatric age group in Australia (n=1)
- A patient in a blinded trial, which was not broken, so unknown if patient received terbinafine (n=1)
- In utero exposure and the baby died after being diagnosed with Trisomy 13; Trisomy 13 is a cytogenetic abnormality and not likely to be related to terbinafine exposure (n=1)
- Received transfusion from a donor who received terbinafine and experienced anaphylactic shock (n=1)
- Developed microcytic anemia and was diagnosed with heterozygous sickle cell alpha thalassemia (n=1)
- An adult case miscoded as pediatrics (n=1)
- Reported lip edema temporally associated with acetylsalicylic acid in a patient who has a history of allergy to acetylsalicylic acid (n=1)
- Follow-up reported that another unspecified diagnosis was established for the event (n=1)
- Overdose (n=1)

The resulting 47 cases are described in section 3.3.

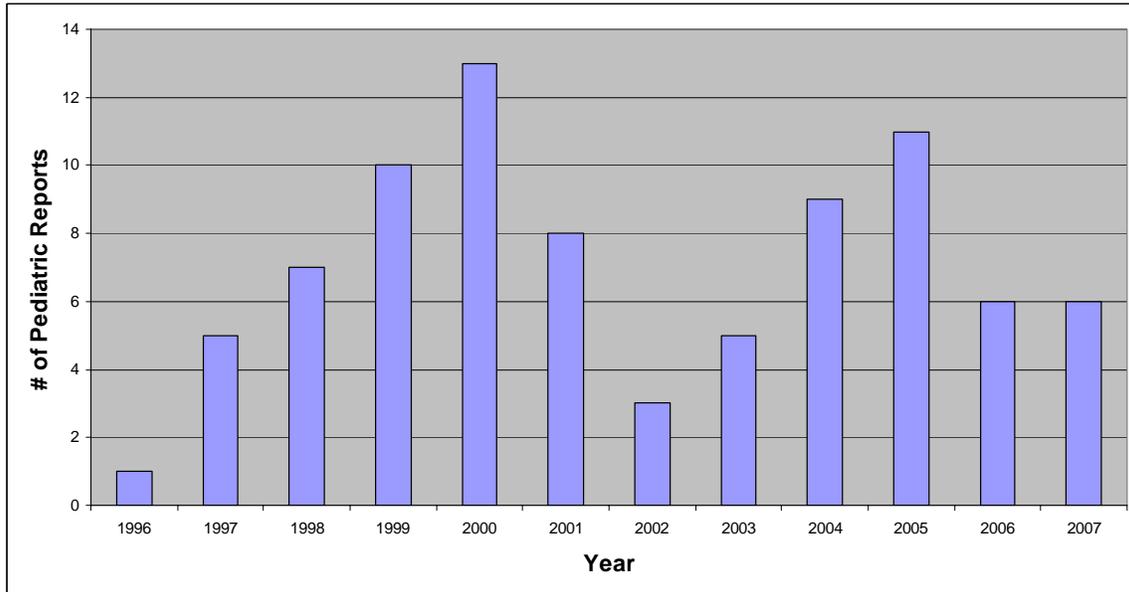
Seven reports were received during the 1-year period following the approval of pediatric exclusivity; since these seven reports were found to be in the search results of all serious adverse events associated with terbinafine, these will not be reviewed separately.

3 AERS RESULTS FOR TERBINAFINE

3.1 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM MARKETING APPROVAL (TABLE 1)

Table 1: Crude counts¹ of AERS Reports for All Sources from Marketing Approval through January 4, 2008 (US counts in parentheses)			
	All reports (US)	Serious ² (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)
Total	6405 (4079)	5136 (2876)	175 (54)
¹ May include duplicates			
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious.			

Figure 1: Reporting trend for pediatric reports from approval date to January 4, 2008:



3.2 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM PEDIATRIC EXCLUSIVITY (TABLE 2)

Table 2: Crude counts ¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted December 4, 2006 through January 4, 2008 (US counts in parentheses)			
	All reports (US)	Serious ² (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)
Total	430 (131)	412 (121)	10 (1)

¹ May include duplicates

² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, congenital anomaly, and other serious.

3.3 CHARACTERISTICS OF ALL SERIOUS PEDIATRIC CASES (TABLE 3)

Table 3 : Characteristics of all serious pediatric cases (from Marketing Approval through January 4, 2008) n=47	
Gender [n=46]	Male: 25 Female: 21
Age [n=47]	2-5 yrs: 10 6-11 yrs: 15

Table 3 : Characteristics of all serious pediatric cases (from Marketing Approval through January 4, 2008) n=47	
	12-16 yrs: 22 Mean 10 years; Median 10 years; Range 2 to 16 years
Origin [n=47]	US 24, Foreign 23
Event date (n=43)	1995 – 1, 1996 – 2, 1998 – 2, 1999 – 4, 2000 – 8, 2001 – 1, 2002 – 1, 2003 – 3, 2004 – 9, 2005 – 4, 2006 – 4, 2007 – 4
Reported route of administration [n=47]	Oral: 29 Topical: 16 Oral & topical: 2
Daily oral dose [n=26]	Average 204 mg, Median 250 mg, Range 62.5 to 250 mg
Time to event onset [n=36]	Average 19 days, Median 1 week Range: 1 day to 3 months
Indications [n= 44]	Onychomycosis 21 Tinea pedis 7 Ringworm 7 Tinea capitis 6 Fungal skin infection 1 “Chilblain” 1 Unspecified rash 1
Reporter [n=42]	Healthcare professional 24 Consumer 18
Outcomes [n=47] NOTE: more than one possible	Life-Threatening - 1, Hospitalization - 5 Disability -1, and Other Serious - 41

4 DISCUSSION/SUMMARY OF CASES

4.1 SKIN EVENTS (N= 16)

Seventeen cases reported skin reactions. These included skin rashes (n=9, some with blisters) and a case each of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), skin striae, hives, pruritus, and alopecia. Skin reactions (including SJS, TEN) are labeled events.

The ages ranged from 3 to 16 with a median of 11 years, and skin events occurred equally in females and males. Ten were US and 6 were foreign reports. Seven cases of skin reactions occurred with oral terbinafine, seven cases with topical therapy, and two cases received both oral and topical terbinafine therapy. The time to onset ranged from within a day of application to 3 months after initiation of terbinafine therapy, with a median of 4 days (n=13).

Three cases required hospitalization (SJS, EM, and one case of rash with blisters and pustules) and one case of skin striae was considered to be disabling; these four cases are summarized here as representative cases:

- ISR 1848333, foreign: A 6-year-old male received oral terbinafine (125 mg daily) for tinea capitis. Nine days later, he developed **erythema multiforme** with fever and somnolence. Terbinafine therapy was discontinued, and he was hospitalized. He improved subsequently.
- ISR 3219113, US: A 10-year-old male received oral terbinafine (250 mg daily) for an unspecified indication for seven days, and he developed a **rash with blisters** on his thighs

and groin. He was treated with oral prednisone, but his rash progressed to “generalized exanthematous pustular dermatosis”. He was hospitalized as the reaction was “progressive and widespread”, and the condition improved with intravenous corticosteroid therapy. Subsequently, he experienced “toxic desquamation” and required continuous high-dose prednisone therapy for several weeks. The final outcome was unknown.

- ISR 4080462, foreign: A 6-year-old female received oral terbinafine (125 mg every 2 days) and topical terbinafine twice daily for onychomycosis. Within 2 months, she was hospitalized and diagnosed with **Stevens-Johnson syndrome**. She received corticosteroid, neomycin, and loratadine. She improved initially, but the symptoms reappeared. She remained hospitalized at the time of report.
- ISR 4412762, foreign: A 16-year-old male received oral terbinafine (250 mg daily) for tinea pedis for about three months when he experienced **stretch marks** on his lumbar region. Terbinafine was discontinued and the patient improved slightly after massage. The reporter assessed the outcome of this case as ‘significant disability’.

In addition, one case of TEN was reported:

- ISR 5551688, US: A 12-year-old male received oral terbinafine (250 mg daily) for tinea capitis. Eight days later, he developed generalized erythroderma and skin peeling throughout the palms of his hands and bottoms of his feet. Terbinafine was discontinued. Biopsy showed drug-related neutrophilic dermatosis, and he was diagnosed with **toxic epidermal necrolysis**. He received oral prednisone and completely recovered.

4.2 NEUROLOGIC EVENTS (N=5)

Five neurologic events were reported. Except for one case of headache, which is a labeled event, the four other neurologic events are not labeled.

All five neurologic events are summarized:

- ISR 3137150, US: A 3-year-old (unknown gender) child experienced **seizure or shaking spell** after receiving topical terbinafine cream for ringworms. The outcome was unknown.
- ISR 3675031, US: A 6-year-old male experienced **headache and neck pain** after two applications of topical terbinafine cream for treatment of ringworm on his scalp.
- ISR 4506579, foreign: A 9-year-old female experienced **mental impairment** leading to inability to do mathematics after receiving five days of oral terbinafine (125 mg daily) for treatment of onychomycosis. After discontinuation of terbinafine, she recovered.
- ISR 5317619, foreign: A 6-year-old male experienced skin eruptions with cutaneous edema after receiving oral terbinafine (250 mg daily). He also presented with **walking difficulty** leading to emergency room visit. Skin eruptions were improving, and no other information was provided.
- ISR 4615054, US: A 12-year-old male received oral terbinafine (250 mg daily) for onychomycosis. After four weeks of therapy, he experienced **somnolence**. He completed six week course of terbinafine as directed. He continued to experience fatigue after discontinuation of terbinafine.

4.3 GASTROINTESTINAL EVENTS (N=5)

Five gastrointestinal events (GI) were reported with topical and oral terbinafine. The reported reactions included labeled events such as abdominal pain, vomiting, and diarrhea. One case of hematochezia was reported, which is not labeled.

All five GI events are summarized:

- ISR 3526072, US: A 7-year-old female used terbinafine cream topically twice daily for ringworm on her face. Four days later, she complained of **stomach ache**, which was relieved with Tylenol. She continued to use terbinafine cream.
- ISR 4602418, foreign: A 3-year-old male received oral terbinafine (62.5 mg daily) for treatment of onychomycosis. About three weeks later, he developed fresh **blood in stools**; after discontinuation of terbinafine, he recovered.
- ISR 4661700, foreign: An 11-year-old male received oral terbinafine (250 mg daily) for an unknown indication. Five days later, he complained of **stomach ache and vomited some blood**; after discontinuation of terbinafine and receiving an unspecified treatment for the event, he recovered.
- ISR 5248721, foreign: A 5-year-old female used terbinafine cream topically for a possible fungal skin infection. After using the cream, she became violently unwell with **severe diarrhea and vomiting**. Terbinafine cream was discontinued and the symptoms disappeared. She was rechallenged with terbinafine cream, and again experienced diarrhea and vomiting; she recovered after discontinuation of terbinafine.
- ISR 5090847, foreign: A 2-year-old female started topical terbinafine cream two to three times daily for treatment of ringworms. On the same day, she experienced **diarrhea, fever, lethargy**, and with continued use, experienced **vomiting and rash**. Terbinafine was discontinued two days later, and the condition was improving.

4.4 PSYCHIATRIC EVENTS (N=3)

Three psychiatric events were reported, which included depression/suicidal ideation and self-harm; these events are not labeled.

All three psychiatric events are summarized:

- ISR 3585671, foreign: A 13-year-old female received oral terbinafine (250 mg daily) for treatment of nail tinea. She received metoclopramide concomitantly. About 3.5 weeks later, she developed **depression, anxiety, insomnia, nausea, forgetfulness, and social withdrawal**; she recovered with discontinuation of terbinafine.
- ISR 4188753, US: A 16-year-old female received oral terbinafine (250 mg daily) for treatment of onychomycosis. Her past medical history included depression. Eleven days later, she experienced **worsening depression** initially, followed by **suicidal ideation** a month later. Terbinafine therapy was discontinued at the psychiatric event onset. Her escitalopram dose was doubled, and her depression improved. The reporting physician also reported that she was recently diagnosed with Lyme disease with ‘cerebral involvement’, and felt that this may have contributed to her depression symptoms.
- ISR 4865915, foreign: A 16-year-old male received oral terbinafine (250 mg daily) for onychomycosis. Two months later, he experienced **thoughts of self-harm**. Terbinafine was discontinued and he recovered completely.

4.5 HEMATOLOGIC EVENTS (N=3)

Three hematologic events, which are labeled, were reported and are summarized:

- ISR 3340356, US: A 12-year-old male experienced **leukopenia** [WBC of 2400/mm³] and possible upper respiratory tract infection after six weeks of therapy with oral terbinafine (250 mg daily) for treatment of onychomycosis. A year ago, he had received terbinafine without any side effects. Therapy with terbinafine was discontinued.
- ISR 4339411, foreign: An 8-year-old female received oral terbinafine (125 mg daily) for treatment of onychomycosis; her concomitant medications included topical bifonazole and tacrolimus therapies. Four weeks later, she was found to have **decreased platelet counts [54,000/mm³] and anemia**. She was hospitalized, and terbinafine therapy was discontinued; her event was considered life-threatening. Her bone marrow puncture showed **bone marrow hypoplasia**.
- ISR 5308094, US: An 8-year-old female received oral terbinafine (250 mg daily) for treatment of onychomycosis. About 2.5 months later, she developed **marrow suppression** which caused **neutropenia** [WBC 3100/mm³, ANC 1130/mm³]. Therapy with terbinafine was discontinued; four weeks later, her WBC returned to 6300/mm³ and ANC was 3430/mm³.

4.6 HEPATIC EVENTS (N=2)

Two hepatic events, which are labeled, were reported and are summarized:

- ISR 4366109, foreign: A 15-year-old male received oral terbinafine (250 mg daily) for two months for treatment of onychomycosis. He developed **fatigue and intense upper abdominal cramps** (unknown time to onset). He had hepatosplenomegaly and increased GPT level [35 U/L]; all other liver function tests were within normal limits. Serologic testing showed positive anti-Hbc and EBV IgG. His clinical symptoms were gradually resolving. The reporting physician suspected a hepatic damage of unknown etiology.
- ISR 4862148, US: A 12-year-old male received oral terbinafine (250 mg daily) for treatment of onychomycosis, despite elevated alkaline phosphatase at baseline [387 U/L]. Two months later, his **alkaline phosphatase level increased** to 418 U/L, and he had an **elevated bilirubin** [1.3 mg/dL, reference range 0.1-1.1]. Terbinafine was discontinued, and the alkaline phosphatase level was returning to baseline level [358 U/L].

4.7 RENAL & URINARY EVENTS (N=2)

Two renal & urinary events were reported; these are unlabeled events and are summarized:

- ISR 3097570, foreign: A 12-year-old female developed **nephrotic syndrome** 19 days after starting oral terbinafine therapy for nail fungal infection. She recovered after discontinuation of terbinafine therapy.
- ISR4330145, foreign: A 2-year-old female developed **incontinence** that coincided with starting oral terbinafine therapy for onychomycosis. No further information was provided.

4.8 MUSCULOSKELETAL EVENTS (N=2)

Two musculoskeletal events were reported and summarized below. Myalgia and rhabdomyolysis are labeled events.

- ISR 4352827, foreign: A 3-year-old female experienced **quadriceps pain** while receiving oral terbinafine therapy for onychomycosis. She was hospitalized for examinations. Terbinafine was discontinued, and the outcome was unknown.
- ISR 4994831, US: A 7-year-old male started therapy with oral terbinafine (125 mg daily) for tinea capitis and atomoxetine for his attention-deficit hyperactivity disorder on the same day. His concomitant medications included oxcarbazepine, levetiracetam, and amphetamine. Six days later, he developed **leg cramps and pain**, and was taken to the emergency room, where he was found to have **elevated CPK and AST levels** (1420 IU/L and 76 U/L, respectively). All of his medications were discontinued. He improved, and one week later his CPK and AST levels normalized (92 and 20 U/L, respectively). His concomitant medications were restarted without any further problem.

4.9 OTHER EVENTS (N=9)

Nine other events, which are unlabeled, were reported and are summarized:

- ISR 3356794, foreign: A 14-year-old male was treated with oral terbinafine (250 mg) for onychomycosis for almost 3 months. Twelve days after discontinuation of terbinafine, he was diagnosed with **acute lymphoblastic leukemia (ALL)**. The outcome was unknown and no other information was provided.
Comment: This case did not provide much further details; terbinafine is not known to cause malignancies, and since ALL primarily occurs in children, ALL is unlikely to be causally-related to terbinafine therapy.
- ISR 3602729, US: A 12-year-old male applied topical terbinafine solution to his neck for self-diagnosed ringworm, characterized by reddened circles and itching. Twelve minutes after application, the **condition worsened** and the area became irritated and tender. Terbinafine solution was discontinued and was switched to an alternative medicine (unspecified). His condition improved.
- ISR 3444240, US: A 13-year-old male was treated nine days with topical terbinafine cream twice daily for self-diagnosed athlete's foot, characterized by rash, peeling skin and itching in between the toes of both feet. Two to three days later, the **condition worsened** and became excoriated, and terbinafine was discontinued.
- ISR 5104998, US: A 13-year-old male applied topical terbinafine cream on both feet due to athlete's foot. Three to four days later, he developed **pain and swelling** on his toes and foot. A red discoloration was initially noted, which changed to purple as swelling worsened. He was seen at the emergency room, received ceftriaxone IV, and was discharged. His swelling improved and required no further treatment.
- ISR 4492517, foreign: A 5-year-old female received oral terbinafine (62.5 mg daily) for tinea capitis. After the first dose, she experienced **chest pain, and physical examination showed breast development**. Her treatment with terbinafine was continued for about 2.5 weeks.
- ISR 5212795, US: A 14-year-old male received oral terbinafine (250 mg daily) for onychomycosis. About 4 weeks later, his **glucose level decreased** to 48 mg/dl (baseline glucose level was 68 mg/dl); he was asymptomatic. A week later, follow-up glucose value was 79 mg/dl. His terbinafine therapy was continued.

Comment: His glucose level normalized with continued terbinafine therapy; thus, decreased glucose level appears to be unlikely related to terbinafine.

- ISR 3126359, US: A 13-year-old male received oral terbinafine (250 mg daily) for onychomycosis. His past medical history included seizure disorder and depression, and his concomitant medications included carbamazepine, fluoxetine, adapalene, and erythromycin. After one month of terbinafine therapy, he developed **increased carbamazepine level** (14.1). His carbamazepine dose was adjusted and his level returned to therapeutic level. He completed three months of terbinafine therapy.

Comment: Terbinafine is an inhibitor of CYP450 2D6 isozyme, and carbamazepine is mainly metabolized through CYP450 3A4; patient was also being treated with fluoxetine and erythromycin, which are CYP 3A4 inhibitors and therefore can increase plasma carbamazepine levels. Therefore, the event appears to be unlikely to be related to terbinafine therapy.

- ISR 4459734, foreign: A 4-year-old female was treated with topical terbinafine for “chilblain”. She experienced influenza before starting terbinafine therapy, and after an unknown time of using terbinafine, developed **tachycardia and delirium**. The outcome was unknown.
- ISR 4035862, foreign: A 10-year-old male experienced **ecchymosis** during the first two days of treatment with oral terbinafine (250 mg daily) for unspecified rash. No further information was available.

5 CONCLUSION

Forty-seven post-marketing pediatric cases with serious outcome were reported since approval through January 4, 2008. Of these, no deaths were observed, and six of 47 cases reported hospitalization, life-threatening, and/or disability outcome; these six cases included four cases of skin reactions, and one case each of leg pain and thrombocytopenia/anemia. The remaining 41 cases were considered serious because the reporter considered the event to be medically significant.

The majority of serious adverse events involved skin reactions (n=16), which are labeled events for terbinafine. Several unlabeled events with serious outcome were observed in the remaining cases, but an association appears to be unlikely between many of these events and terbinafine due to sparse number of reports for a particular reported event. These unlabeled events included neurologic events (one case each of seizure, mental impairment, walking difficulty, and somnolence), one GI event of hematochezia, and a case of nephrotic syndrome and incontinence; in addition, smattering of other unlabeled events were also noted (see section 4.9). However, there were three psychiatric events consisting of depression/suicidal ideation and self-harm (section 4.4), which may warrant further investigation.

6 RECOMMENDATIONS

We will further investigate all psychiatric events of depression, suicidal ideation, and self-harm reported with terbinafine, across all ages, to assess whether this may be a safety concern. In addition, we will continue routine monitoring of adverse events with the use of terbinafine in pediatric patients.

7 REFERENCE

1. Governale L. Lamisil® (terbinafine) tablets BPCA Drug Use Review. July 18, 2008.

APPENDIX

Standard Searches:

- A. Adults (17 yrs and above)
 - 1. All outcomes from approval date (no set criteria)
 - 2. Serious outcomes from AP date
 - 3. Death as an outcome from AP date
 - 4. All outcomes from PE date to present or any desired date
 - 5. Serious outcomes from PE date to present or any desired date
 - 6. Death as an outcome from PE date to present or any desired date

- B. Ages 0-16 yrs ONLY
 - 1. Same as above 1-6
 - 2. Retrieve case reports for hands-on review

Limitations of the Adverse Event Reporting System (AERS)

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

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

/s/

Hyon Kwon
10/21/2008 02:19:07 PM
DRUG SAFETY OFFICE REVIEWER

Min Chen
10/21/2008 02:28:29 PM
DRUG SAFETY OFFICE REVIEWER
Min Chen for Mark Avigan