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Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date: September 19, 2017

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Product Name: Naftin (naftifine hydrochloride)

Pediatric Labeling Approval Dates: October 10, 2014 and November 11, 2016

Application Type/Number:

Dosage, Strength	NDA	ANDA
Cream, 1%	019599	205975
Cream, 2%	019599	206901, 206960
Gel, 1%	019356	N/A
Gel, 2%	204286	N/A

Applicant/Sponsor: NDA: Sebela Ireland Ltd
ANDAs: Taro, Tolmar

OSE RCM #: 2017-609

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports and drug utilization data for naftifine in pediatric patients (0 to <18 years old).

Naftifine is indicated for the topical treatment of tinea infections. Naftifine cream, 1% was initially approved by the FDA on February 29, 1988. It is currently available in the U.S. in 1% and 2% strengths, both as cream and gel formulations.

The pediatric labeling differs between the naftifine products. Naftifine cream, 1% and gel, 1% are not approved for use in the pediatric population. Naftifine cream, 2% is approved for interdigital tinea pedis and tinea cruris in patients ≥12 years of age and tinea corporis in patients ≥2 years of age. Naftifine gel, 2% is approved for interdigital tinea pedis in patients ≥12 years of age.

This PREA review was initiated by the following pediatric labeling changes for naftifine gel, 2% and cream, 2%. On October 10, 2014, the FDA extended the indication of naftifine gel, 2% for interdigital tinea pedis to pediatric patients ≥12 years of age. On October 10, 2014, the FDA also extended the indication of naftifine cream, 2% for interdigital tinea pedis and tinea cruris to pediatric patients ≥12 years of age. On November 11, 2016, the FDA extended the indication of naftifine cream, 2% for tinea corporis to pediatric patients ≥2 years of age.

The Division of Pharmacovigilance (DPV) identified two pediatric cases of naftifine cream, received by the FDA from February 29, 1988 to August 31, 2017 in the FDA Adverse Event Reporting System (FAERS) database. Both cases reported a serious outcome, but the adverse events were consistent with the known safety profile for naftifine. There were no new pediatric safety signals identified, no apparent increase in the severity or frequency of any labeled adverse events, and there were no pediatric deaths reported with naftifine.

Drug utilization for naftifine cream (brand and generic) and gel was assessed in the U.S. outpatient retail pharmacy setting from October 1, 2014 through July 31, 2017. Approximately 306,000 patients received a dispensed prescription for naftifine cream and gel for the review period. The pediatric population aged 0-17 years accounted for 5% of patients (15,190 patients) with a dispensed prescription for naftifine cream and gel. Patients aged 12-17 years accounted for 64% of pediatric patients and patients aged 0-11 years accounted for the remaining 36% of pediatric patients.

There is no evidence from these data that there are pediatric safety concerns with naftifine at this time. DPV recommends no labeling changes, and will continue to monitor adverse events associated with the use of naftifine.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Naftin (naftifine hydrochloride) is an allylamine antifungal approved for the topical treatment of tinea infections. Naftifine cream, 1% was initially approved by the FDA on February 29, 1988. It is currently available in the United States in 1% and 2% strengths, both as cream and gel formulations (see **Table 1.1.1**).

Table 1.1.1. Naftifine Approval Dates and Application Numbers		
Formulation and Strength	**Approval Date**	**NDA**
Naftifine cream, 1%	February 29, 1988	019599
Naftifine gel, 1%	June 18, 1990	019356
Naftifine cream, 2%	January 13, 2012	019599
Naftifine gel, 2%	June 27, 2013	204286

Table 1.1.2 shows the FDA-approved indications for each naftifine product. As shown in the table, the pediatric labeling differs between the naftifine products. Naftifine cream, 1% and gel, 1% are not approved for use in the pediatric population. Naftifine cream, 2% is approved for interdigital tinea pedis and tinea cruris in patients ≥12 years of age and tinea corporis in patients ≥2 years of age. Naftifine gel, 2% is approved for interdigital tinea pedis in patients ≥12 years of age.

Table 1.1.2. Naftifine Indications[1,2,3]	
Formulation	**Indication**
Naftifine cream, 1%	• Topical treatment of tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* • Pediatric indication: none
Naftifine gel, 1%	• Topical treatment of tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Epidermophyton floccosum* • Pediatric indication: none
Naftifine cream, 2%	• Treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton rubrum* • Pediatric indications: ≥12 years old: interdigital tinea pedis and tinea cruris ≥2 years old: tinea corporis
Naftifine gel, 2%	• Treatment of interdigital tinea pedis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* • Pediatric indication: ≥12 years old: interdigital tinea pedis

This Pediatric Research Equity Act (PREA) review was triggered by the following pediatric labeling changes for naftifine gel, 2% and cream, 2%.

- On October 10, 2014, the FDA extended the indication of naftifine gel, 2% for interdigital tinea pedis from adults (≥18 years of age) to pediatric patients ≥12 years of age. This was based on an open-label pediatric pharmacokinetics and safety trial in 22 pediatric subjects 12-17 years of age with interdigital tinea pedis who received naftifine gel, 2%. The incidence of adverse reactions in the pediatric population was similar to that observed in adult population.[1]

- On October 10, 2014, the FDA also extended the indication of naftifine cream, 2% for interdigital tinea pedis and tinea cruris from adults (≥18 years of age) to pediatric patients ≥12 years of age. This was based on an open-label pediatric pharmacokinetics and safety trial in 22 pediatric subjects 13-17 years of age with tinea pedis and tinea cruris who received naftifine cream, 2%. The incidence of adverse reactions in the pediatric population was similar to that observed in adult population.[2]

- On November 11, 2016, the FDA extended the indication of naftifine cream, 2% for tinea corporis from adult (≥18 years of age) to pediatric patients ≥2 years of age. The safety and efficacy was supported by a double-blind, vehicle-controlled, multi-center trial in 184 subjects (2 to <18 years of age) randomized to naftifine cream or vehicle. No new adverse reactions were identified in the trial. In addition, an open-label pharmacokinetics trial in 27 subjects 2 to <12 years of age provided information regarding the pharmacokinetics of naftifine following the topical application of naftifine cream, 2%.[2,4]

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The current approved labeling for naftifine provides the following safety information, excerpted from pertinent sections:[1,2,3]

CONTRAINDICATIONS

- **Cream, 1% and Gel, 1%:** *Naftin Cream and Gel, 1% are contraindicated in individuals who have shown hypersensitivity to any of their components.*
- **Cream, 2%:** *None*
- **Gel, 2%:** *None*

WARNINGS AND PRECAUTIONS

- **Cream, 1% and Gel, 1%:**
    - **Warnings:** *Naftin Cream and Gel, 1% are for topical use only and not for ophthalmic use.*
    - **Precautions:** *Naftin Cream and Gel, 1%, are for external use only. If irritation or sensitivity develops with the use of Naftin Cream or Gel, 1%, treatment should be discontinued and appropriate therapy instituted. Diagnosis of the disease should be confirmed either by direct microscopic examination of a mounting of infected*

tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

- **Cream, 2%:** *Discontinue treatment if redness or irritation develops with NAFTIN Cream use.*
- **Gel, 2%:** *If redness or irritation develops with the use of NAFTIN Gel treatment should be discontinued.*

ADVERSE REACTIONS

- **Cream, 1% and Gel, 1%:** *During clinical trials with Naftin Cream, 1%, the incidence of adverse reactions was as follows: burning/stinging (6%), dryness (3%), erythema (2%), itching (2%), local irritation (2%). During clinical trials with Naftin Gel, 1%, the incidence of adverse reactions was as follows: burning stinging (5.0%), itching (1.0%), erythema (0.5%), rash (0.5%), skin tenderness (0.5%).*
- **Cream, 2%:** *The most common adverse reaction (≥1%) is pruritus.*
- **Gel, 2%:** *The most common adverse reactions are application site reactions (2%).*

8.4 Pediatric Use

- **Cream, 1% and Gel, 1%:**
  Safety and effectiveness in pediatric patients have not been established.
- **Cream, 2%:**
  The safety and effectiveness of NAFTIN Cream have been established in pediatric patients age 12 and above with interdigital tinea pedis and tinea cruris and age 2 and above with tinea corporis [see Clinical Studies (14) and Clinical Pharmacology (12.3)].

  Use of NAFTIN Cream in these age groups is supported by evidence from adequate and well controlled studies in adults and children, with additional safety and PK data from two open label trials conducted in 49 pediatric subjects exposed to NAFTIN Cream [see Clinical Studies (14) and Clinical Pharmacology (12.3)].

  Safety and effectiveness of Naftin Cream in the treatment of tinea cruris and interdigital tinea pedis in pediatric patients less than 12 years of age have not been established.

  Safety and effectiveness of Naftin Cream in the treatment of tinea corporis in pediatric patients less than 2 years of age have not been established.
- **Gel, 2%:**
  The safety and effectiveness of NAFTIN Gel have been established in the age group 12-18 with interdigital tinea pedis. Use of NAFTIN Gel in this age group is supported by evidence from adequate and well controlled studies in adults with additional safety and PK data from an open label trial, conducted in 22 adolescents ≥12 years of age who were exposed to Naftin Gel at a dose of approximately 4 g/day [see Clinical Pharmacology (12.3)].

  Safety and effectiveness in pediatric patients <12 years of age have not been established.

1.3 PREVIOUS OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY POSTMARKETING SAFETY REVIEW

On June 17, 2015, the Office of Surveillance and Epidemiology and the Division of Dermatology and Dental Products (DDDP) in the Office of New Drugs performed a non-new molecular entity (non-NME) postmarket safety summary review for naftifine gel, 2% (NDA 204286). DPV evaluated five FAERS cases reported with naftifine gel, 2% since FDA approval on June 27, 2013. Additionally, DDDP reviewed the periodic safety reports submitted by the sponsor since approval. There were no pediatric cases reported with this product. No safety concerns were identified from this review.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see **Appendix A** for full database descriptions and limitations).

2.1.1 Determining Settings of Care

The QuintilesIMS National Sales Perspectives™ database was used to determine the various retail and non-retail channels of distribution for naftifine cream (brand and generic) and gel. Sales data for the period of October 2014 through June 2017 indicated that approximately 87% of packages were distributed to U.S. outpatient retail pharmacies; 10% were to non-retail settings; and 3% were to mail-order/specialty pharmacies.[5] As a result, only U.S. outpatient retail pharmacy utilization patterns were examined. Data from mail-order/specialty and non-retail settings were not included in this analysis.

2.1.2 Data Sources Used

The QuintilesIMS Total Patient Tracker™ (TPT) database was used to provide a national estimate of patients with a naftifine cream (brand and generic) and gel prescription dispensed from U.S. outpatient retail pharmacies from October 1, 2014 through July 31, 2017, cumulative.

2.2 RESULTS

2.2.1 Number of Patients

Table 2.2.1

National estimate of patients who received a prescription for naftifine from U.S. outpatient retail pharmacies, stratified by patient age (0-11, 12-17, 18+ yrs), October 2014 - July 2017

	Oct 2014 - Jul 2017	
	Patient Count	***Share***
naftifine cream† and gel	305,934	*100.0%*
Age 0-17 years	**15,190**	***5.0%***
Age 0-11 years	5,527	*36.4%*
Age 12-17 years	9,698	*63.6%*
Age 18+ years	290,061	*94.8%*
Unknown Age	1,242	*0.2%*

Source: QuintilesIMS, Total Patient Tracker. Oct 2014 - Feb 2017. Extracted April 2017. File:TPT 2017-
**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients 0-17 years of age include patients less than 18 years of age (17 years and 11 months). Subtotals may not sum exactly, due to rounding. Patients may have received multiple administrations of a drug during the study period and due to aging of patients during the study period, patients may be counted more than once across age groups. For this reason, summing is not advisable and will result in overestimates of patient counts.*
† Includes brand and generic products

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in **Table 3.1.1**. See **Appendix B** for a description of the FAERS database.

Table 3.1.1. FAERS Search Strategy

Date of Search	September 1, 2017
Time Period of Search	February 29, 1988* - August 31, 2017
Search Type	FBIS Quick Query
Product Terms	Product Active Ingredient: naftifine, naftifine hydrochloride
Search Parameters	All ages, all outcomes, worldwide

Abbreviation: FBIS = FAERS Business Intelligence Solution
* U.S. approval date of naftifine cream, 1%

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1. Total adult and pediatric FAERS reports* from February 29, 1988 to August 31, 2017 with naftifine

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	61 (57)	39 (35)	0 (0)
Pediatrics (0 - <18 years)	**4 (4)**	2 (2)	0 (0)

* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

3.2.2 Selection of Pediatric Cases in FAERS

We identified four pediatric reports in FAERS, received by the FDA between February 29, 1988 and August 31, 2017 (see **Table 3.2.1**). We excluded two cases that did not report any adverse events associated with naftifine. Therefore, we included two cases in the case series, summarized in **Sections 3.3 and 3.4.**

3.2.3 Characteristics of Pediatric Case Series

Appendix C lists the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the pediatric case series.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There were no pediatric deaths in the case series.

3.4 SUMMARY OF NON-FATAL PEDIATRIC ADVERSE EVENT CASES (N=2)

Two cases with a serious outcome of "other serious" reported dermatitis or contact dermatitis/hypersensitivity with the use of naftifine cream. The FDA received these cases in 1991 and 1993. The first case reported that diaper rash worsened after the use of naftifine cream in a 1-year-old female. The rash improved following the discontinuation of naftifine. In the second case, a 10-year-old male experienced "contact dermatitis" after using naftifine cream on his face. The outcome was unknown.

Reviewer's Comment: Based on the report dates, the naftifine products in these two cases concern the 1% cream (this was the only product available in the U.S. at the time). Naftifine cream, 1% is not indicated in pediatric patients; however, the labeling states to discontinue treatment if irritation or sensitivity develops with the use of naftifine cream (in the Precautions section). Additionally, the Adverse Reactions section of the labeling includes erythema and local irritation among other application site reactions such as burning/stinging and itching. Therefore, the events of dermatitis are consistent with the known safety profile for naftifine cream, 1%.

4 DISCUSSION

DPV identified two pediatric cases of naftifine, received by the FDA from February 29, 1988 to August 31, 2017 in the FAERS database. Both cases reported a serious outcome, but the adverse events were consistent with the known safety profile for naftifine. There were no new pediatric safety signals identified, no apparent increase in the severity or frequency of any labeled adverse events, and there were no pediatric deaths reported with naftifine.

Drug utilization for naftifine cream (brand and generic) and gel was assessed in the U.S. outpatient retail pharmacy setting. The pediatric population aged 0-17 years accounted for 5% of

patients with a dispensed prescription for naftifine cream (brand and generic) and gel from October 2014 through July 2017, the majority of whom were aged 12-17 years.

5 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with naftifine at this time.

6 RECOMMENDATIONS

DPV recommends no labeling changes, and will continue to monitor adverse events associated with the use of naftifine.

7 REFERENCES

1. Naftin (naftifine hydrochloride) gel, 2% [package insert]. Greensboro, NC: Merz Pharmaceuticals, LLC.; October 2014.

2. Naftin (naftifine hydrochloride) cream, 2% [package insert]. Greensboro, NC: Merz Pharmaceuticals, LLC.; November 2016.

3. Naftin (naftifine hydrochloride), 1% [package insert]. Greensboro, NC: Merz Pharmaceuticals, LLC.; April 2011.

4. Woitach A. Clinical review NDA 19599/S-013. Naftin (naftifine) cream, 2%, indication tinea corporis, pediatric patients ≥ 2 years. January 13, 2016.

5. QuintilesIMS, National Sales Perspectives™. October 2014-July 2017. Extracted August 2017. NSP 2017-609 Naftifine channels 8-22-17.xlsx

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS Vector One®: Total Patient Tracker (TPT)

TPT is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from United States retail pharmacies. Clients get access to all markets and can manipulate the period under study from 1 month to 1 year. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses the prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients, and multiple prescriptions fills, producing quick and reliable unique patient counts. Prescription coverage is 90%, has a sample of 50,400 pharmacies, and captures about 3.7 billion transactions annually. TPT is projected to the known universe.

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH NAFTIFINE (N=2)

FAERS Case #	Version Number	Manufacturer Control #
4784330	1	3910003
4968654	1	3920046

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/s/

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09/19/2017

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