

**Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pediatric Postmarketing Pharmacovigilance Review

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Product Name: Priftin® (Rifapentine)

**Pediatric Labeling
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Application Type/Number: NDA 021024

Applicant/Sponsor: Sanofi Aventis US

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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 for Priftin[®] (rifapentine) in pediatric patients.

Rifapentine was initially approved in 1998 and was indicated for the treatment of active pulmonary tuberculosis (TB) caused by *Mycobacterium tuberculosis*, in combination with one or more antituberculosis drugs. The approved pediatric labeling is for the treatment of active pulmonary TB caused by *M. tuberculosis* in children 12 years and older and for the treatment of latent tuberculosis infection (LTBI) caused by *M. tuberculosis* in combination with isoniazid in patients 2 years of age and older at high risk of progression to TB disease.

DPV searched the FDA Adverse Event Reporting System (FAERS) database for all reports of adverse events (serious and non-serious) from June 22, 1998 through May 31, 2017 with rifapentine. The FAERS database contained two pediatric cases for rifapentine; however, both cases described labeled adverse events and were also confounded by concomitant administration with isoniazid. No deaths directly associated with rifapentine were reported.

Based on current FAERS data, there is no evidence from these data that there are new pediatric safety concerns with rifapentine at this time. DPV recommends continued pharmacovigilance monitoring.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY¹⁻³

Priftin[®] (rifapentine) is a rifamycin antimycobacterial drug available as an oral tablet (150 mg). Rifapentine was initially approved in June 1998 and was indicated for the treatment of pulmonary TB caused by susceptible isolates of *Mycobacterium tuberculosis*, in combination with one or more antituberculosis drugs.

In May 2014, the sponsor submitted a supplement (NDA 021024 S011) to support the use of rifapentine, given weekly in combination with isoniazid for 12 weeks, in the treatment of LTBI in adults and children at least 2 years of age who are at high risk of progression to TB. The supplement was approved in November 2014.

For the treatment of LTBI, rifapentine should be administered in combination with isoniazid once-weekly for 12 weeks as directly observed therapy.

- Adults and children \geq 12 years: Rifapentine (based on weight, see Table 1.1) and isoniazid 15 mg/kg (900 mg maximum)

- Children 2 – 11 years: Rifapentine (based on weight, see Table 1.1.1) and isoniazid 25 mg/kg (900 mg maximum)

Weight Range	Rifapentine Dose	Number of Rifapentine Tablets
10 – 14 kg	300 mg	2
14.1 – 25 kg	450 mg	3
25.1 – 32 kg	600 mg	4
32.1 – 50 kg	750 mg	5
> 50 kg	900 mg	6

The Tuberculosis Trials Consortium (TBTC) Study 26 was the pivotal study to support the approval of rifapentine in children at least 2 years of age. The primary objective of TBTC Study 26 was to compare the effectiveness of a three-month regimen of weekly rifapentine and isoniazid (3RPT/INH) to the effectiveness of a nine-month regimen of daily INH (9INH) in preventing TB in high-risk tuberculin skin test reactors. The primary study endpoint was the development of culture-confirmed TB in adults and culture-confirmed or clinical TB in children at 33 months post enrollment. Similar effectiveness results were obtained in the TBTC Study 26 pediatric substudy that enrolled subjects 2 – 17 years of age. Treatment related adverse events leading to drug discontinuation were mainly hepatotoxicity in the 9INH arm and hypersensitivity in the 3RPT/INH arm. A higher proportion of subjects discontinued treatment due to treatment related adverse events in the 3RPT/INH arm despite the shorter duration of treatment. The severity grade of the adverse events that led to treatment discontinuation was similar in the two treatment arms.

Similar to the main study, a higher proportion of 9INH subjects in the pediatric substudy experienced at least one treatment emergent adverse event, likely reflecting the longer duration of therapy. Also similar to the main study, a higher proportion of 3RPT/INH subjects had an adverse event that was assessed as treatment related and discontinued therapy due to treatment related adverse event. There were no severe adverse events or deaths reported in the 3RPT/INH arm of the pediatric substudy. The proportion of subjects experiencing at least one adverse event was higher in the 2 – 11 age group compared to the 12 – 17 age group. In the pediatric substudy, seven subjects in the 9INH arm discontinued treatment due to an adverse event: asthenia (1), pregnancy (3), rash (2), and Kawasaki disease (1). The adverse events that led to discontinuation were judged treatment related in 3 subjects: asthenia (1) and rash (2). Nine subjects in the 3RPT/INH arm discontinued treatment due to an adverse event: flu-like illness (2), fatigue (1), drug intolerance (1), drug toxicity (2), decreased appetite (1), rash (1) and urticaria (1). The adverse events that led to drug discontinuation were judged as treatment related in 8 subjects: flulike illness (2), rash (1), urticaria (1), fatigue (1), vomiting (1), drug intolerance (1) and lip blisters (1).

There are no recently completed DPV reviews for rifapentine that have included pediatric cases. To our knowledge, there is no pending regulatory action involving new safety information for this drug in the pediatric population.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES²

The Priftin[®] (rifapentine) label includes the following information:

-----CONTRAINDICATIONS-----

Known hypersensitivity to any rifamycin

-----WARNINGS AND PRECAUTIONS-----

- Hepatotoxicity: Monitor for symptoms of liver injury and discontinue PRIFTIN if signs or symptoms or liver injury occur
- Hypersensitivity: Discontinue PRIFTIN if signs or symptoms of hypersensitivity reaction occur
- Relapse in the treatment of active pulmonary tuberculosis: Do not use as a once-weekly continuation phase regimen with isoniazid in HIV infected patients. Monitor for signs or symptoms of relapse in patients with cavitory lesions or bilateral disease
- Drug Interactions: May interact with drugs metabolized by CYP450
- Discoloration of body fluids: May permanently stain contact lenses or dentures red-orange
- *Clostridium difficile*-associated colitis: Evaluate if diarrhea occurs
- Porphyria: Avoid use in patients with porphyria

-----ADVERSE REACTIONS-----

The most common adverse reactions with regimen for active pulmonary tuberculosis (1% and greater) are anemia, lymphopenia, neutropenia, increased ALT, arthralgia, conjunctivitis, headache, vomiting, nausea, diarrhea, rash, pruritus, anorexia and lymphadenopathy. The most common adverse reaction (1% and greater) with the regimen for latent tuberculosis infection is hypersensitivity reaction.

-----DRUG INTERACTIONS-----

- Protease Inhibitors and Reverse Transcriptase Inhibitors
- Hormonal Contraceptives: Use another means of birth control
- May increase metabolism and decrease the activity of drugs metabolized by cytochrome P450 3A4 and 2C8/9. Dosage adjustments may be necessary if given concomitantly

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy	
Date of Search	June 4, 2017
Time Period of Search	June 22, 1998* - May 31, 2017
Search Type	FAERS Business Intelligence Solution (FBIS) Profile Query Product-Manufacturer Reporting Summary
Product Names	Product Name: Priftin Product Active Ingredient: Rifapentine
Search Parameters	All ages, all outcomes, worldwide
<i>*U.S. Approval date</i>	

3 RESULTS

3.1.1 Total number of FAERS reports by Age

Table 3.1.1 Total Adult and Pediatric FAERS Reports* from June 22, 1998* - May 31, 2017 with Rifapentine

	All reports (U.S.)	Serious[†] (U.S.)	Death (U.S.)
Adults (≥ 18 years)	61 (51)	57 (47)	2 (1)
Pediatrics (0 - <18 years)	2 (2)	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.

3.1.2 Selection of Pediatric Cases in FAERS

DPV identified two pediatric adverse event cases. No deaths were reported.

3.2 SUMMARY OF PEDIATRIC ADVERSE EVENT CASES (N=2)

FAERS Case Number **10282081 (version 1)**

Country United States
Manufacturer Control Number Direct Report
Initial FDA received date August 3, 2012

Case Narrative: A 17-year-old female (weight: 54.5 kg) with no known allergies and no preexisting conditions received rifapentine for LTBI. After receiving her first once weekly dose of isoniazid (900 mg) and rifapentine (900 mg), she experienced dizziness. After the second dose, which was administered one week later, dizziness continued. Treatment was stopped due to patient intolerance. The reporting health care professional did not provide the clinical outcome of the event or causality assessment.

Reviewer Comments: *The onset of dizziness after initiation of isoniazid and rifapentine supports a possible causal association. Isoniazid and rifapentine are both labeled for dizziness.*

FAERS Case Number **10282081 (version 1)**

Country United States
Manufacturer Control Number US-SA-2014SA032650
Initial FDA received date July 7, 2014

Case Narrative: A 14-year-old male (weight: 43.9 kg) received rifapentine for LTBI. Twenty-four hours after receiving isoniazid (700 mg), pyridoxine (50 mg), and rifapentine (750 mg), he experienced diffuse itching of the arms, angioedema of the eyes, swelling of the upper left arm, and redness and swelling at an injection site of a past bacille Calmette-Guerin (BCG) vaccination. Isoniazid, pyridoxine, and rifapentine were discontinued, he received an unspecified antihistamine, and he recovered over the next few days. The reporting physician did not provide a causality assessment.

Reviewer Comments: *The onset of events after initiation of isoniazid, pyridoxine, and rifapentine supports a possible causal association. Isoniazid and rifapentine are both labeled for hypersensitivity reactions; rifapentine is labeled for rash, pruritus, urticaria, and angioedema.*

4 DISCUSSION

Of the two adverse event cases reviewed in pediatric patients, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths directly associated with rifapentine.

5 CONCLUSION

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

6 RECOMMENDATIONS

DPV will continue pharmacovigilance monitoring for rifapentine.

7 REFERENCES

- 1) Development Resources for Medical, Statistical, and Clinical Pharmacology Reviews of Pediatric Studies Conducted under Section 505A and 505B of the Federal Food, Drug, and Cosmetic Act, as amended by the FDA Safety and Innovation Act of 2012 (FDASIA). Available at:
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- 3) Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, Hackman J, Hamilton CD, Menzies D, Kerrigan A, Weis SE, Weiner M, Wing D, Conde MB, Bozeman L, Horsburgh CR Jr, Chaisson RE; TB Trials Consortium PREVENT TB Study Team. *N Engl J Med*. 2011;365:2155-66.

8 APPENDICES

8.1 APPENDIX A. 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.

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/s/

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