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

Pediatric Postmarketing Pharmacovigilance Review

Date:	September 21, 2022
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Product Name:	Kerydin (tavaborole)
Pediatric Labeling Approval Date:	July 30, 2018
Application Type/Number:	NDA 204427/S-6
Applicant:	Pfizer, Inc.
TTT Record ID:	2022-785

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Kerydin (tavaborole) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on unlabeled adverse events associated with tavaborole in pediatric patients.

FDA approved tavaborole on July 7, 2014, for the topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*. On July 30, 2018, FDA expanded the tavaborole indication to include use in pediatric patients 6 years and older. This pediatric postmarketing pharmacovigilance review was prompted by the July 30, 2018, approval of tavaborole in pediatric patients aged 6 years and older. DPV has not previously presented tavaborole to the Pediatric Advisory Committee.

DPV reviewed all FAERS reports for tavaborole in the pediatric population (ages 0 through 16 years) for all dates through July 28, 2022. The FAERS search identified one nonserious report that contained insufficient information for a causality assessment. Consequently, there were no cases for inclusion in our case series for discussion. There were no safety signals, no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to tavaborole.

DPV will continue to monitor all adverse events associated with the use of tavaborole.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Kerydin (tavaborole) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with tavaborole in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

FDA approved tavaborole on July 7, 2014, for the topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*.[1] On July 30, 2018, FDA expanded the tavaborole indication to include use in pediatric patients 6 years and older.

Evidence of safety and effectiveness of tavaborole in pediatric patients relied on an open-label study to evaluate the safety, tolerability, and pharmacokinetics of Kerydin (tavaborole) topical solution, 5% in the treatment of onychomycosis of the toenail in pediatric subjects ages 6 to 16 years and 11 months.[2] A summary of the study design and findings are summarized below from the Kerydin (tavaborole) 5% solution Multi-Disciplinary Review and Evaluation.[3]

> "KERYDIN (tavaborole) topical solution, 5% was well tolerated at the application site and systemically. The majority AEs were assessed as unrelated to KERDIN, Events were generally self-limiting or resolved with standard medical intervention. No deaths, permanent discontinuations, temporary discontinuations, or dose reductions due to AEs were reported in this study. No trends for laboratory abnormalities were noted. The safety of KERYDIN in this pediatric population is similar to that reported in the two Phase 3 registration studies in 795 adult subjects treated with KERYDIN for onychomycosis.
>
> The pharmacokinetics of KERYDIN for onychomycosis was also investigated in 22 pediatric subjects 12 to 16 years of age with distal subungal onychomycosis involving at least 4 toenails (including 1 great toenail with at least 20% involvement) following once daily topical application of 5% solution of tavaborole to all ten toenails and 2 mm of skin surrounding each toenail for 29 days. The results of the PK are acceptable to determine efficacy extrapolation to pediatric subjects.
>
> In conclusion, the applicant has provided an acceptable clinical and pharmacokinetic study in pediatric subjects 6 years to 6 years and 11 months old to satisfy the Written Request and the PMR/PMC from the Agency. Pediatric exclusivity should be granted and the applicant can be released from their PMR/PMC requirement."

This pediatric postmarketing pharmacovigilance review was prompted by the July 30, 2018, approval of tavaborole in pediatric patients aged 6 years and older. DPV has not previously presented tavaborole to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Kerydin (tavaborole) labeling contains the following safety information excerpted from the Highlights section of the labeling. For further tavaborole labeling information, please refer to the full prescribing information.

---------- INDICATIONS AND USAGE----------
KERYDIN is an oxaborole antifungal indicated for the topical treatment of onychomycosis of the toenails due to Trichophyton rubrum or Trichophyton mentagrophytes. (1)
----------DOSAGE AND ADMINISTRATION ----------
- Apply KERYDIN to affected toenails once daily for 48 weeks. (2)
- KERYDIN should be applied to the entire toenail surface and under the tip of each toenail being treated. (2)
- For topical use only. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

---------- DOSAGE FORMS AND STRENGTHS----------
Solution, 5%. (3)
---------- CONTRAINDICATIONS ----------
None. (4)
---------- ADVERSE REACTIONS ----------
Common adverse reactions occurring in ≥1% in subjects treated with KERYDIN included application site exfoliation, ingrown toenail, application site erythema, and application site dermatitis. (6.1)

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	July 29, 2022
Time period of search	All reports through July 28, 2022
Search type	RxLogix PV Signal Quick Query
Product terms	PAI: Tavaborole
MedDRA search terms (Version 25)	All PT terms
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PAI=Product Active Ingredient, PT=Preferred Term	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports through July 28, 2022, with tavaborole.

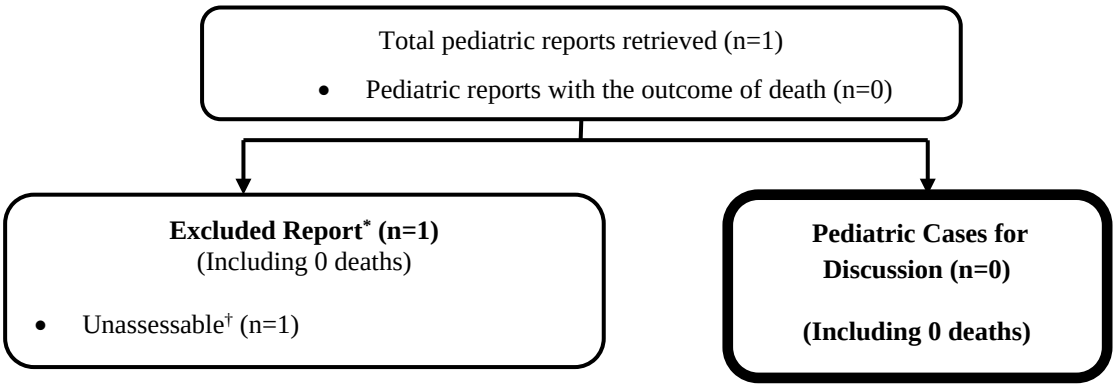
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through July 28, 2022, With Tavaborole			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	332 (331)	30 (30)	8 (8)
Pediatrics (0 - <17 years)	1 (1)	0 (0)	0 (0)
* May include duplicates and transplacental exposures, 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, or other serious important medical events.

3.1.2 Selection of Pediatric Cases in FAERS

The FAERS search retrieved one report with tavaborole through July 28, 2022. DPV reviewed the FAERS case and excluded it from further discussion due to it being an unassessable report. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Pediatric Cases with Tavaborole



* DPV reviewed this report, but the report was excluded from further discussion for the reason listed above.
† Unassessable: Report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the case cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for further discussion.

3.1.4 Summary of Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for further discussion.

4 DISCUSSION

DPV reviewed all FAERS reports for tavaborole in the pediatric population (ages 0 through 16 years) for all dates through July 28, 2022. The FAERS search identified one nonserious report that contained insufficient information for a causality assessment. Consequently, there were no cases for inclusion in our case series for discussion. There were no safety signals, no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to tavaborole.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for tavaborole at this time.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of tavaborole.

7 REFERENCES

1. Kerydin (tavaborole) [package insert]. New York, NY: Pfizer. July 2018.
2. An Open-label Study To Evaluate The Safety, Tolerability, And Pharmacokinetics Of Kerydin (Registered) (Tavaborole) Topical Solution, 5% In The Treatment Of Onychomycosis Of The Toenail In Pediatric Subjects Ages 6 To 16 Years And 11 Months. (2018) Retrieved from https://clinicaltrials.gov/ct2/show/NCT03405818?term=tavaborole&draw=3&rank=1. (Identification no. NCT03405818).
3. Kettl D. Kerydin (tavaborole) Multi-Disciplinary Review and Evaluation. February 2, 2018. Available at: https://www.fda.gov/media/115237/download. Accessed August 1, 2022.

8 APPENDICES

8.1 APPENDIX A. 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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council 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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