Department of Health and Human Services
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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:	April 22, 2024
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Product Name:	Chantix (varenicline tartrate) tablets
Pediatric Labeling Approval Date:	February 22, 2019
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Applicant:	PF Prism C.V.
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Chantix (varenicline tartrate) tablets in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with varenicline tartrate in pediatric patients.

Chantix (varenicline tartrate) tablet is a nicotinic receptor partial agonist and was initially approved in the U.S. on May 10, 2006. Varenicline tartrate tablet is currently indicated for use as an aid to smoking cessation treatment in adults and is not approved for a pediatric indication.

This pediatric postmarketing safety review was stimulated by the pediatric labeling on February 22, 2019, that stated varenicline tartrate is not recommended for use in pediatric patients 16 years or younger because its efficacy in this population was not demonstrated.

DPV reviewed all U.S. serious FAERS reports with varenicline tartrate in pediatric patients less than 18 years of age from February 19, 2013, through March 11, 2024, and identified four reports; however, all reports were excluded from further discussion.

DPV did not identify any new pediatric safety concerns for varenicline at this time and will continue routine pharmacovigilance monitoring for varenicline tartrate.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Chantix (varenicline tartrate) tablets in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with varenicline tartrate in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Chantix (varenicline tartrate) tablet is a nicotinic receptor partial agonist and was initially approved in the U.S. on May 10, 2006. Varenicline tartrate tablet is currently indicated for use as an aid to smoking cessation treatment in adults and is not approved for a pediatric indication.[1]

This pediatric postmarketing safety review was stimulated by the pediatric labeling on February 22, 2019, that stated varenicline tartrate is not recommended for use in pediatric patients 16 years or younger because its efficacy in this population was not demonstrated.[2]

On June 28, 2013, the Office of Surveillance and Epidemiology (OSE) completed a review of postmarketing adverse event reports with a serious outcome for varenicline tartrate in pediatric patients. OSE's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with varenicline tartrate.[3] On September 19, 2013, OSE's evaluation was presented to the Pediatric Advisory Committee (PAC).

1.2 RELEVANT LABELED SAFETY INFORMATION

The varenicline tartrate tablet labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection.[1] For additional varenicline tartrate tablet labeling information, please refer to the full prescribing information.

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

- Neuropsychiatric Adverse Events: Postmarketing reports of serious or clinically significant neuropsychiatric adverse events have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Observe patients attempting to quit smoking with CHANTIX for the occurrence of such symptoms and instruct them to discontinue CHANTIX and contact a healthcare provider if they experience such adverse events. (5.1)
- Seizures: New or worsening seizures have been observed in patients taking CHANTIX. CHANTIX should be used cautiously in patients with a history of seizures or other factors that can lower the seizure threshold. (5.2)
- Interaction with Alcohol: Increased effects of alcohol have been reported. Instruct patients to reduce the amount of alcohol they consume until they know whether CHANTIX affects them. (5.3)
- Accidental Injury: Accidental injuries (e.g., traffic accidents) have been reported. Instruct patients to use caution driving or operating machinery until they know how CHANTIX may affect them. (5.4)

- Cardiovascular Events: Patients with underlying cardiovascular (CV) disease may be at increased risk of CV events; however, these concerns must be balanced with the health benefits of smoking cessation. Instruct patients to notify their healthcare providers of new or worsening CV symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction (MI) or stroke. (5.5 and 6.1)
- Somnambulism: Cases of somnambulism have been reported in patients taking CHANTIX. Some cases described harmful behavior to self, others, or property. Instruct patients to discontinue CHANTIX and notify their healthcare provider if they experience somnambulism. (5.6 and 6.2)
- Angioedema and Hypersensitivity Reactions: Such reactions, including angioedema, infrequently life-threatening, have been reported. Instruct patients to discontinue CHANTIX and immediately seek medical care if symptoms occur. (5.7 and 6.2)
- Serious Skin Reactions: Rare, potentially life-threatening skin reactions have been reported. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately at first appearance of skin rash with mucosal lesions. (5.8 and 6.2)
- Nausea: Nausea is the most common adverse reaction (up to 30% incidence rate). Dose reduction may be helpful. (5.9)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (e.g., vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting. (6)

8.4 Pediatric Use

CHANTIX is not recommended for use in pediatric patients 16 years of age or younger because its efficacy in this population was not demonstrated.

Single and multiple-dose pharmacokinetics of varenicline have been investigated in pediatric patients aged 12 to 17 years old (inclusive) and were approximately dose proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight >55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When 0.5 mg BID was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that noted in the adult population.

The efficacy and safety of varenicline was evaluated in a randomized, double-blind, placebo-controlled study of 312 patients aged 12 to 19 years, who smoked an average of at least 5 cigarettes per day during the 30 days prior to recruitment, had a score of at least 4 on the Fagerstrom Test for Nicotine Dependence scale, and at least one previous failed quit attempt. Patients were stratified by age (12 to 16 years of age, n = 216 and 17 to 19 years of age, n = 96) and by body weight (≤55 kg and >55 kg). Patients were randomized to one of two doses of varenicline, adjusted by weight to provide plasma levels in the efficacious range (based on adult studies) and placebo. Patients received treatment for 12 weeks, followed by a non-treatment period of 40 weeks, along with age-appropriate counseling throughout the study. Results from this study showed that varenicline, at either dose studied, did not improve continuous abstinence rates at weeks 9 through 12 of treatment compared with placebo in subjects 12 to 19 years of age. The varenicline safety profile in this study was consistent with that observed in adult studies.

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	March 12, 2024
Time period of search	February 19, 2013[†] - March 11, 2024

Table 1. FAERS Search Strategy*	
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient: Varenicline, Varenicline Tartrate
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database † Data lock date of most recent pediatric postmarketing pharmacovigilance review Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

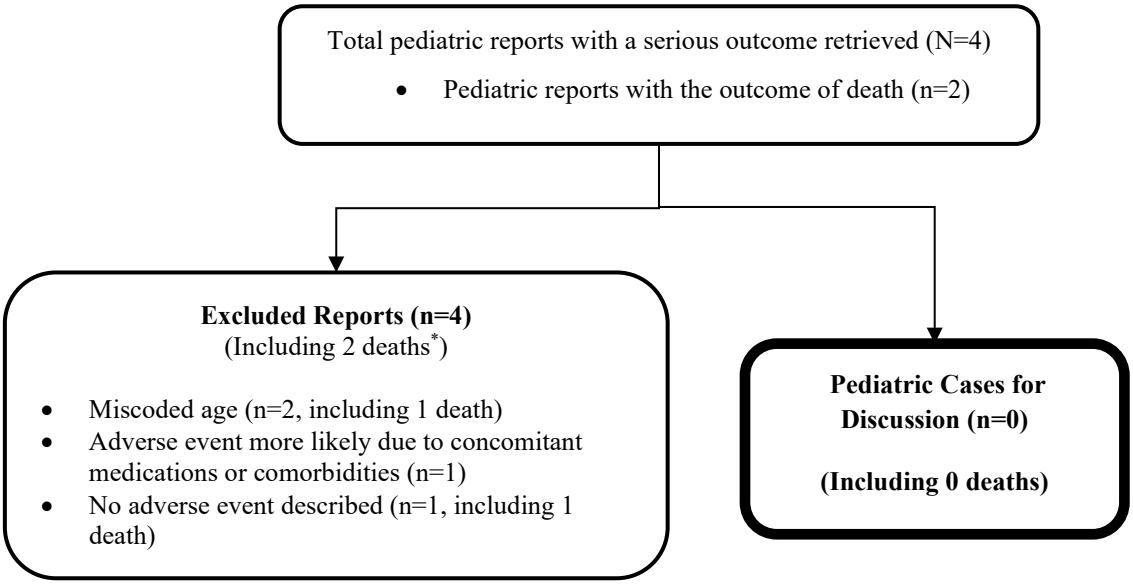
Table 2 presents the number of adult and pediatric FAERS reports from February 19, 2013, through March 11, 2024, with varenicline tartrate.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From February 19, 2013 through March 11, 2024, With Varenicline Tartrate			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	13,020 (10,897)	5,368 (3,283)	255 (173)
Pediatrics (0 - < 18 years)	15 (8)	11 (4)	2 (2)
* 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 U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved four U.S. serious pediatric reports from February 19, 2013, through March 11, 2024. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all four reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of U.S. Serious Pediatric Cases With Varenicline Tartrate



* Two excluded U.S. FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to varenicline. One report involved a 16-year-old that was a victim of homicide per the death certificate. The other death report had a miscoded age that did not involve a pediatric patient.

3.1.3 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

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

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with varenicline in pediatric patients less than 18 years of age from February 19, 2013, through March 11, 2024, and identified four reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with varenicline tartrate in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for varenicline tartrate at this time and will continue routine pharmacovigilance monitoring for varenicline tartrate.

6 REFERENCES

1. Chantix® (varenicline tartrate) tablets [Prescribing Information]. New York, NY: Pfizer Inc.; February 2019.
2. Afshar M. NDA/BLA Multi-Disciplinary Review and Evaluation for NDA 021928 / S-048 Chantix® (Varenicline tartrate). February 2019. https://www.fda.gov/media/124220/download?attachment
3. Pollock M, Mathew J, Gilbert J, Diak P, Mehta H, Bezabeh S, Chen M, Governale L. FDA Office of Surveillance and Epidemiology - Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review- Chantix (varenicline tartrate). 2013. https://wayback.archive-it.org/7993/20170113232446/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM367030.pdf

7 APPENDICES

7.1 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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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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