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Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	November 8, 2022
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Product Name:	Effient (prasugrel)
Pediatric Labeling Approval Date:	July 12, 2016
Application Type/Number:	NDA 022307
Applicant:	Cosette Pharmaceuticals, Inc.
TTT Record ID:	2022-2158

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Effient (prasugrel) in pediatric patients through age 17 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). This review focuses on serious unlabeled adverse events associated with prasugrel in pediatric patients.

The FDA approved prasugrel on July 10, 2009, and it is indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina or non-ST-elevation myocardial infarction (NSTEMI)
- Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI

On July 12, 2016, the prasugrel labeling was updated to reflect that safety and effectiveness had not been established in pediatric patients less than 18 years following a failed trial in pediatric patients aged 2 to <18 years. This review was prompted by the July 12, 2016, pediatric labeling change.

DPV reviewed all serious FAERS reports with prasugrel in the pediatric population (ages 0 – 17 years) from July 10, 2009, through September 27, 2022. We identified no cases reporting an unlabeled adverse event with prasugrel. We identified no new safety signals and no deaths associated with prasugrel.

DPV did not identify any new pediatric safety concerns for prasugrel at this time. DPV recommends no regulatory action at this time, and will continue to monitor all adverse events associated with the use of prasugrel.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and for Effient (prasugrel) in pediatric patients through age 17 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). This review focuses on serious unlabeled adverse events associated with prasugrel in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY [1,2]

Prasugrel is an orally bioavailable, third generation thienopyridine that inhibits platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelet sufaces. FDA first approved prasugrel on July 10, 2009, for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina or non-ST-elevation myocardial infarction (NSTEMI)
- Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI

On July 12, 2016, the prasugrel labeling was updated to reflect that safety and effectiveness had not been established in pediatric patients less than 18 years following a failed trial in pediatric patients aged 2 to <18 years. The pediatric labeling change reflected findings from four clinical trials evaluating prasugrel use to reduce the frequency and severity of vaso-occlusive crisis (VOC) in pediatric patients with sickle cell disease (SCD). The submission also included a population pharmacokinetic (PK) report that contained a summary of the final population PK model and exposure-response (E-R) analyses and two bioanalytical method validation reports.

This review was prompted by the July 12, 2016, pediatric labeling change. DPV has not previously presented prasugrel to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The prasugrel labeling contains the following safety information excerpted from the Highlights section of the product labeling and the Pediatric Use subsection. For further labeling information, please refer to the full prescribing information.

---------- INDICATIONS AND USAGE ----------
Effient is a P2Y12 platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina or non-ST-elevation myocardial infarction (NSTEMI) (1.1).
- Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI (1.1).

---------- DOSAGE AND ADMINISTRATION----------

- Initiate treatment with a single 60 mg oral loading dose (2).
- Continue at 10 mg once daily with or without food. Consider 5 mg once daily for patients <60 kg (2).
- Patients should also take aspirin (75 mg to 325 mg) daily (2).

---------- DOSAGE FORMS AND STRENGTHS----------

5 mg and 10 mg tablets (3)

---------- CONTRAINDICATIONS ----------

- Active pathological bleeding (4.1)
- Prior transient ischemic attack or stroke (4.2)
- Hypersensitivity to prasugrel or any component of the product (4.3)

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

- CABG-related bleeding: Risk increases in patients receiving Effient who undergo CABG (5.2).
- Discontinuation of Effient: Premature discontinuation increases risk of stent thrombosis, MI, and death (5.3).
- Thrombotic thrombocytopenic purpura (TTP): TTP has been reported with Effient (5.4).
- Hypersensitivity: Hypersensitivity including angioedema has been reported with Effient including in patients with a history of hypersensitivity reaction to other thienopyridines (5.5).

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

Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Opioids: Decreased exposure to prasugrel. Consider use of parenteral antiplatelet agent (7.3).

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

In a randomized, placebo-controlled trial, the primary objective of reducing the rate of vaso-occlusive crisis (painful crisis or acute chest syndrome) in pediatric patients, aged 2 to less than 18 years, with sickle cell anemia was not met.

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	September 28, 2022
Time period of search	July 10, 2009† - September 27, 2022
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product name: Effient Product active ingredient: Prasugrel Application: NDA 022307
MedDRA search terms (Version 25.0)	All PT terms

* See Appendix A for a description of the FAERS database.
† Approval date for Effient.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, NDA=New Drug Application 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 from July 10, 2009, to September 27, 2022, with prasugrel.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From July 10, 2009, to September 27, 2022, with Prasugrel			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	2884 (1508)	2717 (1354)	381 (164)
Pediatrics (0 < 18 years)	5 (0)	**5 (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 Serious Pediatric Cases in FAERS

Our FAERS search retrieved five reports of adverse events in pediatric patients with prasugrel from July 10, 2009, to September 27, 2002 coded with a serious outcome.

After hands-on review, all five serious pediatric reports with prasugrel were excluded from the case series as they all reported adverse events that are well described in the product labeling.

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 Serious Cases (N=0)

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

4 DISCUSSION

DPV reviewed all serious FAERS reports with prasugrel in the pediatric population (ages 0 – 17 years) from July 10, 2009, through September 27, 2022. We identified no cases reporting an unlabeled event with prasugrel. We identified no new safety signals and no deaths associated with prasugrel.

5 CONCLUSION

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

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of prasugrel.

7 REFERENCES

1. Effient (prasugrel) tablets [Prescribing Information]. Basking Ridge, NJ: Daiichi Sankjyo Company, Ltd; December 2020.
2. Ershler R. Clinical Review for Effient (prasugrel hydrochloride). June 2016. Available at: https://www.fda.gov/media/101254/download

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 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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