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 6, 2022
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Product Names:	Corlanor (ivabradine)
Pediatric Labeling Approval Date:	April 22, 2019
Application Type/Number:	NDAs 209964 (Oral Solution), 206143 (Tablets)
Applicant:	Amgen, Inc.
TTT ID:	2022-19

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and the medical literature for Corlanor (ivabradine) in pediatric patients through and including age 17 years. The Division of Pharmacovigilance I (DPV-I) 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 ivabradine in pediatric patients.

Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated channel blocker. The tablet formulation (NDA 206143) was approved on April 15, 2015. At the time of approval, the safety and effectiveness in pediatric patients had not been established. Ivabradine oral solution (NDA 209964) was approved on April 22, 2019, which prompted this pediatric review. Both NDAs presently use the same U.S. Prescribing Information (USPI), and are indicated in adults and pediatric patients:

Adults

- To reduce the risk of hospitalization for worsening heart failure in adult patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

Pediatrics

- For the treatment of stable symptomatic heart failure due to dilated cardiomyopathy in pediatric patients ages 6 months and older, who are in sinus rhythm with an elevated heart rate.

A prior approval supplemental new drug application approved on May 13, 2019, provided for updates to the ivabradine (NDA 206143) USPI and Medication Guide and to harmonize with labeling for ivabradine oral solution.

We reviewed all FAERS reports coded with a serious outcome for ivabradine in the pediatric population (ages 0 - < 18 years) during the period from April 22, 2019, through June 26, 2022. We did not identify any cases for inclusion in our case series.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and the medical literature for Corlanor (ivabradine) in pediatric patients through age 17 years. The Division of Pharmacovigilance I (DPV-I) 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 ivabradine in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1]

Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated channel blocker. The tablet formulation (NDA 206143) was approved on April 15, 2015. At the time of approval, the safety and effectiveness in pediatric patients had not been established. Ivabradine oral solution (NDA 209964) was approved on April 22, 2019. Both NDAs presently use the same U.S. Prescribing Information (USPI), and are indicated in adults and pediatric patients:

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This review was prompted by the April 22, 2019, approval of ivabradine oral solution. A pediatric safety review for ivabradine has not previously been presented to the Pediatric Advisory Committee (PAC).

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The following provides a summary of safety information and information on use in pediatric patients excerpted from the HIGHLIGHTS OF PRESCRIBING INFORMATION section of the ivabradine labeling:

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

Adult and pediatric patients greater than 40 kg

Starting dose is 2.5 (pediatrics and vulnerable adults) or 5 mg twice daily with food. After 2 weeks of treatment, adjust dose based on heart rate. The maximum dose is 7.5 mg twice daily.

Pediatric Patients less than 40 kg

Starting dose is 0.05 mg/kg twice daily with food. Adjust dose at two-week intervals by 0.05 mg/kg based on heart rate. Maximum dose is 0.2 mg/kg (patients 6 months to less than 1 year old) or 0.3 mg/kg (patients 1 years old and older), up to a total of 7.5 mg twice daily.

---------- **CONTRAINDICATIONS** ----------

- Acute decompensated heart failure
- Clinically significant hypotension
- Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
- Clinically significant bradycardia
- Severe hepatic impairment
- Heart rate maintained exclusively by the pacemaker
- In combination with strong cytochrome CYP3A4 inhibitors

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

- Fetal toxicity: Females should use effective contraception.
- Monitor patients for atrial fibrillation.
- Monitor heart rate decreases and bradycardia symptoms during treatment.
- Not recommended in patients with 2nd degree AV block.

---------- **ADVERSE REACTIONS** ----------

Most common adverse reactions occurring in ≥ 1% of patients are bradycardia, hypertension, atrial fibrillation and luminous phenomena (phoshenes).

Additionally, the following provides a summary of safety information and information on use in pediatrics excerpted from the pertinent sections of the ivabradine labeling:

5.3 Bradycardia and Conduction Disturbances

Pediatric Patients
Bradycardia and first-degree heart block were observed in pediatric patients treated with Corlanor. Asymptomatic and symptomatic bradycardia were observed in 6.8% and 4.1% of pediatric patients treated with Corlanor, respectively. In the placebo treatment arm, 2.4% of pediatric patients had asymptomatic bradycardia, but none had symptomatic bradycardia. Bradycardia was managed through dose titration but did not result in study drug discontinuation [*see Dosage and Administration (2.2)*].

6.1 Clinical Trials Experience

Pediatric Patients with Heart Failure

The safety of Corlanor in pediatric patients 6 months to less than 18 years of age is based on a clinical trial [see Clinical Studies (14.2)] in symptomatic heart failure patients with dilated cardiomyopathy and elevated heart rate. This trial provides experience in 73 patients treated with Corlanor for a median duration of 397 days, and 42 patients given placebo. Bradycardia (symptomatic and asymptomatic) occurred at rates similar to those in adults. Phosphenes were observed in pediatric patients treated with Corlanor.

6.2 Postmarketing Experience

The following adverse reactions have been identified in adults during post-approval use of Corlanor: syncope, hypotension, torsade de pointes, ventricular fibrillation, ventricular tachycardia, angioedema, erythema, rash, pruritus, urticaria, vertigo, and diplopia, and visual impairment.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Corlanor may cause fetal harm, based on animal data. Advise females of reproductive potential to use effective contraception during Corlanor treatment.

8.4 Pediatric Use

The safety and effectiveness of Corlanor have been established in pediatric patients (age 6 months to less than 18 years old) and are supported by pharmacokinetic and pharmacodynamic trials and evidence from adequate and well-controlled trials of Corlanor in adult patients. The pediatric study included 116 patients in the following age groups: 17 patients in the 6 months to less than 12 months age group, 36 patients in the 1 year to less than 3 years age group, and 63 patients in the 3 years to less than 18 years age group [*see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.2)*].

The safety and efficacy of Corlanor have not been established in patients less than 6 months of age.

Animal Data

Ivabradine given orally to juvenile rats from postnatal day (PND) 7 until PND 77 at 7.5, 15 and 30 mg/kg/day did not affect postnatal (pre-weaning) development and reproductive performance (post-weaning development). Similar to adult animals, ivabradine decreased heart rate dose-dependently, and increased heart weights at the highest dose administered. Ivabradine also decreased white blood cell counts (lymphocytes) at the highest dose administered. The decrease in white blood cell counts partially reversed within a 3-week recovery period. Exposures in male and female rats at the No Observed Adverse Effect Level (NOAEL) of 7.5 mg/kg/day, was approximately 3 and 8-times, respectively, steady state exposure associated with the highest received maintenance doses across age groups in pediatric patients (based on AUCs).

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

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

Table 1. FAERS Search Strategy*	
Date of search	June 27, 2022
Time period of search	April 22, 2019†– June 26, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Product Selection: IVABRADINE (Active Moiety)
MedDRA search terms (Version 24.1)	All PTs
Age	0-17.999 years
* See Appendix A for a description of the FAERS database. † U.S. approval date for ivabradine oral solution Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

2.2 LITERATURE SEARCH STRATEGY

DPV-I searched the medical literature with the strategy described in Table 2.

Table 2. Literature Search Strategy*		
Database	Embase	PubMed
Date of search	June 21, 2022	
Search terms	'ivabradine'/exp	ivabradine
Limits	English, humans, neonate, infant, child, adolescent, case report	English, humans, child (birth-18 years)

3 RESULTS

3.1 FAERS AND THE MEDICAL LITERATURE

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from April 22, 2019, through June 26, 2022, with ivabradine.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From April 22, 2019†, through June 26, 2022, With Ivabradine			
	All reports (U.S.)	**Serious‡ (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	918 (187)	805 (78)	58 (5)
Pediatrics (0 - <18 years)	36 (12)	23‡ (3)	**7§** (1)
* May include duplicates and transplacental exposures, and have not been assessed for causality † U.S. approval date for ivabradine oral solution ‡ 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.			

§ Two additional reports of pediatric deaths were identified among reports not reporting an age. These two reports are reflected in the counts of pediatric reports.

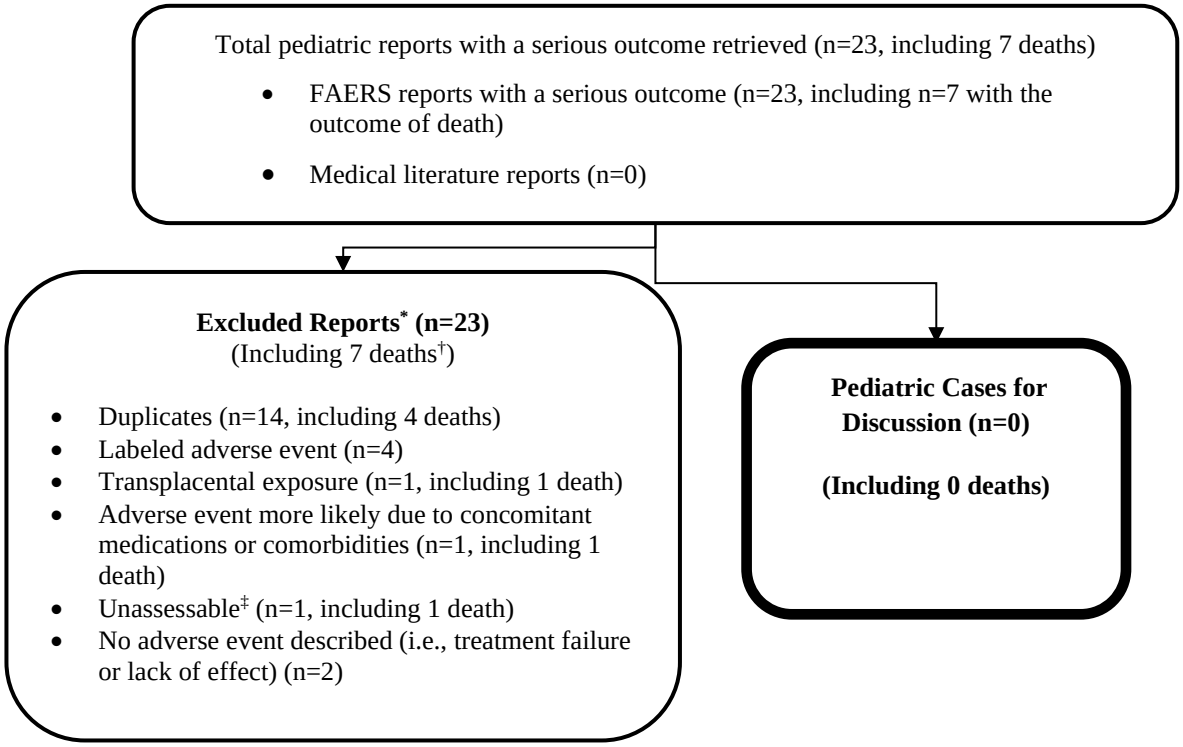
3.1.2 Selection of Serious Pediatric Cases in FAERS and the Medical Literature

Our FAERS search retrieved 23 serious pediatric reports from April 22, 2019, to June 26, 2022 with ivabradine. We reviewed all FAERS reports with a serious outcome. We excluded all reports from our case series for various reasons: duplicate reports, labeled adverse event, transplacental exposure, adverse event more likely due to concomitant medications or comorbidities, unassessable reports (reports that cannot be assessed for causality because there is insufficient information reported or the information is contradictory or information in the case cannot be supplemented or verified), and reports describing no adverse event. Notably, four pediatric reports described the use of ivabradine tablets, and the majority of the reports described off-label use.

DPV-I performed a literature search for additional case reports for adverse events with ivabradine in pediatric patient using the strategy delineated in Table 2. We identified no additional cases for inclusion in the case series.

Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with Ivabradine in FAERS and the Medical Literature



* DPV reviewed these reports, but they were excluded from further discussion for the reasons listed above.

† Seven reports described a fatal outcome. Of these, four reports were duplicates. One foreign fatal report described a 1-day-old premature female neonate with transplacental exposure to ivabradine who was born with multiple major congenital anomalies and died from complications of congenital anomalies.

Another domestic report described a female infant with a history of complex cyanotic congenital heart defect and two heart surgeries whose post-operative courses were complicated by multisystem dysfunction and refractory arrhythmia. The patient received ivabradine and multiple other antiarrhythmic agents to treat her arrhythmia; however, she continued to experience clinical decline, so the family elected to withdraw life support and she died. The last report was foreign and described a 16-year-old male who was status post cardiac transplantation with a complicated hospital course who received ivabradine for tachycardia and died due to an unknown cause.

‡ 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) or the information is contradictory, or information provided in the case cannot be supplemented or verified.

4 DISCUSSION

DPV-I reviewed all FAERS reports coded with a serious outcome for ivabradine in the pediatric population (ages 0 - < 18 years) during the period from April 22, 2019, through June 26, 2022. Of the 23 serious reports reviewed, no cases of interest were identified for discussion related to adverse events. No specific pattern of adverse events was noted. There are no new safety signals, no increased severity or frequency of any labeled adverse events, and no pediatric deaths that could definitively be attributed to ivabradine.

5 CONCLUSION

DPV-I did not identify any new pediatric safety concerns for ivabradine at this time.

6 RECOMMENDATION

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

7 REFERENCES

1. Corlanor (ivabradine) [package insert]. Thousand Oaks, CA: Amgen Inc. August 2021.
2. Corlanor (ivabradine) prior approval supplement. May 13, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/206143Orig1s007ltr.pdf. Accessed June 29, 2022.

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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