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:	June 10, 2024
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Product Name:	Auvi-Q (epinephrine injection, USP), for intramuscular or subcutaneous use
Pediatric Labeling Approval Date:	November 17, 2017
Application Type/Number:	NDA 201739
Applicant:	Kaleo, Inc.
TTT Record ID:	2024-8739

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Auvi-Q (epinephrine injection, USP) for intermuscular or subcutaneous use in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Auvi-Q in pediatric patients.

Auvi-Q (epinephrine injection, USP) for intermuscular or subcutaneous use is a non-selective α- and β-adrenergic receptor agonist indicated in the emergency treatment of Type I allergic reactions including anaphylaxis. Auvi-Q was first approved in the United States on August 10, 2012. At initial approval, Auvi-Q was indicated for use in pediatric patients at a dosage appropriate to body weight. It was available as an auto-injector in two strengths: 0.3 mg and 0.15 mg.

On November 17, 2017, FDA approved a supplemental new drug application (sNDA 201739/S-008) for a new 0.1 mg dosage strength and labeling revisions to the 0.15 mg and 0.3 mg Auvi-Q presentations. Approval of the 0.1 mg dosage strength triggered PREA as it represented a new dosing regimen that could be used in pediatric patients who weigh between 7.5 and 15 kg, corresponding with children aged 1-3 years.

This pediatric postmarketing safety review was prompted by the pediatric labeling on November 17, 2017, that reflected approval of sNDA 201739/S-008. DPV has not previously performed a pediatric postmarketing pharmacovigilance review for Auvi-Q for the Pediatric Advisory Committee (PAC). However, DPV performed a review for another epinephrine product, Primatene Mist (aerosol for inhalation), on November 7, 2023. DPV's evaluation did not identify any new safety concerns and recommended continued routine monitoring for adverse events with Primatene Mist. DPV presented their evaluation to the PAC via webposting on December 21, 2023.

DPV reviewed all serious FAERS reports with Auvi-Q in pediatric patients less than 17 years of age through March 12, 2024. Of the 39 reports retrieved, DPV included 6 cases in the case series for discussion. The cases were received by FDA from 2014 through 2016 and described potential device failures and malfunctions. This time frame coincided with the voluntary recall for Auvi-Q from the market in October 2015 for quality product concerns. The Applicant resumed manufacturing and marketing of Auvi-Q in February 2017 after submitting supplemental applications to perform manufacturing changes for device reliability. There are no other serious pediatric FAERS reports describing device quality concerns for Auvi-Q after 2016.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with Auvi-Qin pediatric patients less than 17 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Auvi-Q (epinephrine injection, USP) for intermuscular or subcutaneous use in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Auvi-Q in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Auvi-Q (epinephrine injection, USP) for intermuscular or subcutaneous use is a non-selective α- and β-adrenergic receptor agonist indicated in the emergency treatment of Type I allergic reactions including anaphylaxis. Auvi-Q was first approved in the United States on August 10, 2012[a]. At initial approval, Auvi-Q was indicated for use in pediatric patients at a dosage appropriate to body weight. It was available as an auto-injector in two strengths: 0.3 mg and 0.15 mg.[1]

On November 17, 2017, FDA approved a supplemental new drug application (sNDA 201739/S-008) for a new 0.1 mg dosage strength and labeling revisions to the 0.15 mg and 0.3 mg Auvi-Q dosage strengths.[2] Approval of the 0.1 mg dosage strength triggered PREA as it represented a new dosing regimen that could be used in pediatric patients who weigh between 7.5 and 15 kg, corresponding with children aged 1-3 years. A summary of PREA required pediatric assessments is reproduced below from the sNDA 201739/S-008 Multidisciplinary Clinical Review:[3]

> An agreed iPSP[b], which was previously reviewed by the Pediatric Review Committee (PeRC), was submitted with the supplement. No clinical studies are/were needed. The iPSP included: 1) literature to support PK/PD modeling, which supports the use of a fixed dose of 0.1 mg for patients who weigh 7.5 to <15 kg, and 2) a sonographic study that supports the safety of the exposed needle length proposed for the new dosage strength, such that when the new dosage strength is administered as directed in the mid anterolateral thigh it will not hit bone (major safety risk). This information was submitted with the supplement, and the Division believes that this fulfills the PREA requirement for patients who weigh 7.5 kg and above, because the 0.1 mg dosage strength (along with the approved 0.15 mg and 0.3 mg dosage strengths) cover all of the pediatric weight/age range above 7.5 kg or 1 year of age.
>
> Since a standardized (fixed) dose is not appropriate for patients who weigh less than 7.5 kg, and since vial formulations of epinephrine that allow for appropriate weight based dosing are available, the Division recommends granting a waiver under PREA for patients who weigh less than 7.5 kg, corresponding to children who are less than approximately 1 year of age.
>
> The Division discussed the two supplements with PeRC on September 6, 2017. PeRC agreed with the Division's recommendations.

This pediatric postmarketing safety review was prompted by the pediatric labeling on November 17, 2017, that reflected approval of sNDA 201739/S-008. DPV has not previously performed a pediatric postmarketing pharmacovigilance review for Auvi-Q for the Pediatric Advisory Committee (PAC). However, DPV performed a review for another epinephrine product, Primatene Mist (aerosol for inhalation), on November 7,

[a] Initial FDA-approval for the first epinephrine medical drug product was in 1939.
[b] iPSP=Initial pediatric study plan

2023. DPV's evaluation did not identify any new safety concerns and recommended continued routine monitoring for adverse events with Primatene Mist. DPV presented their evaluation to the PAC via webposting on December 21, 2023.[4]

1.2 RELEVANT LABELED SAFETY INFORMATION

The Auvi-Q labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Auvi-Q labeling information, please refer to the full prescribing information.[5]

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- In conjunction with use, seek immediate medical or hospital care. (5.1)
- Do not inject intravenously, into buttock, or into digits, hands, or feet. (5.2)
- To minimize the risk of injection-related injury, instruct caregivers to hold the child's leg firmly in place and limit movement prior to and during injection when administering to young children or infants. (5.2)
- Rare cases of serious skin and soft tissue infections have been reported following epinephrine injection. Advise patients to seek medical care if they develop signs or symptoms of infection at the epinephrine injection site. (5.3)
- The presence of a sulfite in this product should not deter use. (5.4)
- Administer with caution in patients with heart disease; may aggravate angina pectoris or produce ventricular arrhythmias. (5.5)

----------ADVERSE REACTIONS----------
Adverse reactions to epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties. (6)

8.4 Pediatric

AUVI-Q may be administered to pediatric patients at a dosage appropriate to body weight [see Dosage and Administration (2)]. Clinical experience with the use of epinephrine suggests that the adverse reactions seen in children are similar in nature and extent to those both expected and reported in adults. Since the doses of epinephrine delivered from AUVI-Q are fixed, consider using other forms of injectable epinephrine if doses lower than 0.1 mg are deemed necessary.

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 13, 2024
Time period of search	All dates through March 12, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product name: Auvi-Q OR NDA: 201739
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, NDA=New Drug Application	

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 March 12, 2024, with Auvi-Q.

Table 2. Total Adult and Pediatric FAERS Reports[*] Received by FDA Through March 12, 2024, With Auvi-Q

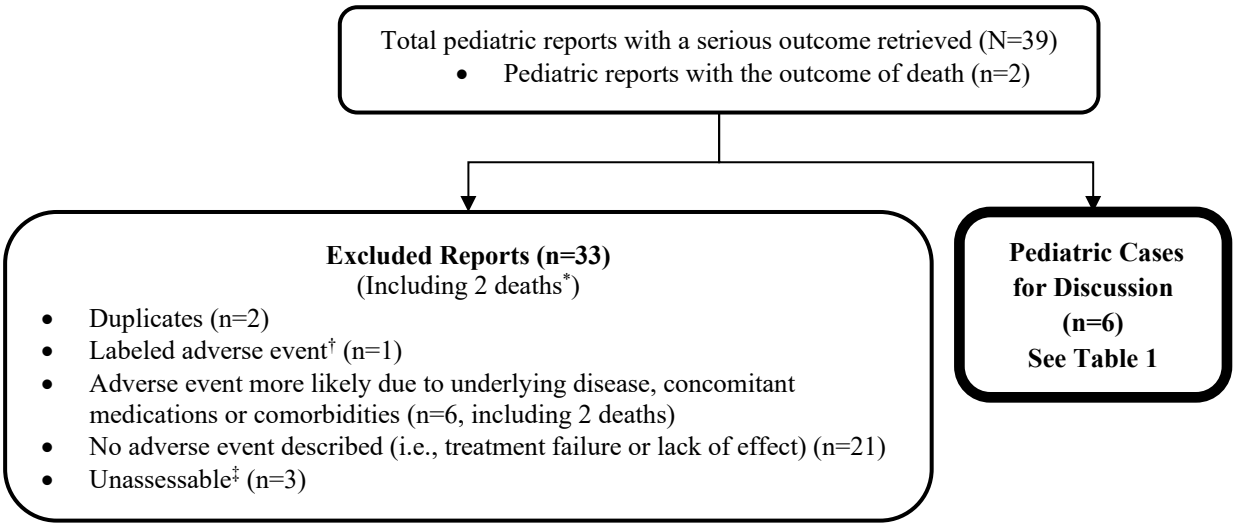
	All Reports (U.S.)	Serious[†] (U.S.)	Death (U.S.)
Adults (≥ 17 years)	273 (229)	100 (56)	13 (4)
Pediatrics (0 - < 17 years)	190[‡] (184)	39[‡] (33)	2[‡] (0)

* 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.
‡ See Figure 1. One additional report describing a pediatric death was identified among reports not reporting an age. This report is reflected in the counts of pediatric reports.

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 39 serious pediatric reports through March 12, 2024. We reviewed all FAERS pediatric reports with a serious outcome. We excluded 33 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 Serious Pediatric Cases With Auvi-Q



* Two excluded FAERS reports described fatal outcomes. One report described a neonate who died from immune reconstitution inflammatory syndrome (IRIS) after an unspecified infection. The second report described an adolescent with a history of asthma, celiac disease, and multiple food allergies who developed immediate and severe anaphylactic shock after exposure to an allergen-containing food and died despite intervention with oral steroids, intramuscular adrenaline, and cardiopulmonary resuscitation. Neither of the deaths were determined to be attributed to Auvi-Q.
† Labeled adverse event does not represent increased severity or frequency.
‡ Unassessable: The 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 report cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of Serious Non-Fatal Pediatric Cases (N=6)

Six cases reported potential device failures or malfunctions. The cases are summarized in **Table 3** below. See Appendix B for a full line listing of the case series.

Table 3. Summary of Serious Non-Fatal Pediatric Cases Received by FDA Through March 12, 2024, With Auvi-Q

FAERS Case	Age (Years)	Sex	FDA Received Year	Case Summary
10390688	9	F	2014	Device safety guard difficult to remove and "whole thing" fell apart when safety guard removed
10181907	6	M	2014	Needle did not come out of device
12327056	8	M	2016	Patient did not feel the Auvi-Q needle
11689698	6	M	2015	Auvi-Q dose was ineffective and parent suspects this was related to device problem noted with recent epinephrine recall
11693117	4	F	2015	Auvi-Q dose was ineffective and parent suspects this was related to device problem noted with recent epinephrine recall
11734846	4	M	2015	Auvi-Q device potentially functioning incorrectly with incorrect dosage
Abbreviations: F=female, M=male				

Reviewer comment: The Applicant voluntarily recalled all Auvi-Q 0.15 mg and 0.3 mg devices from hospitals, retailers, and consumers in October 2015 due to potential product quality concerns.[6] FDA subsequently opened a Tracked Safety Issue (TSI) for epinephrine autoinjectors. The Applicant performed a root cause analysis and submitted a Chemistry Manufacturing and Controls supplemental application to support manufacturing changes for device reliability. The Applicant resumed manufacturing and marketing of Auvi-Q in February 2017 and FDA closed the TSI.[7] There are no other serious pediatric FAERS reports describing device quality concerns for Auvi-Q after 2016.

4 DISCUSSION

DPV reviewed all serious FAERS reports with Auvi-Q in pediatric patients less than 17 years of age through March 12, 2024. Of the 39 reports retrieved, DPV included 6 cases in the case series for discussion. The cases were received by FDA from 2014 through 2016 and described potential device failures and malfunctions. This time frame coincided with the voluntary recall for Auvi-Q from the market for quality product concerns. The Applicant resumed manufacturing and marketing of Auvi-Q in February 2017 after submitting supplemental applications to perform manufacturing changes for device

reliability. There are no other serious pediatric FAERS reports describing device quality concerns for Auvi-Q after 2016.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with Auvi-Q in pediatric patients less than 17 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Auvi-Q (epinephrine injection, USP), for intramuscular or subcutaneous use. Bridgewater, NJ; Sanofi-Aventis U.S., LLC: August 2012.
2. Auvi-Q (epinephrine injection, USP), for intramuscular or subcutaneous use. Richmond, VA; Kaleo, Inc.: November 2017.
3. Starke PR. Multidisciplinary Review. NDA 201739, S-008, S-009. September 26, 2017.
4. Kim I. Pediatric Postmarketing Pharmacovigilance Review. November 7, 2023. Available at: www.fda.gov/media/175016/download
5. Auvi-Q (epinephrine injection, USP), for intramuscular or subcutaneous use. [Prescribing information]. Richmond, VA; Kaleo, Inc.: February 2024.
6. Sanofi. Press Release. October 30, 2015. Available at: www.news.sanofi.us/2015-10-28-Sanofi-US-Issues-Voluntary-Nationwide-Recall-of-Auvi-Q-Due-to-Potential-Inaccurate-Dosage-Delivery. Accessed May 7, 2024.
7. Seymour, S. Memorandum. NDA 201739. TSI 1553. August 14, 2017.

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.

7.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=6)

	Initial FDA Received Date	FAERS Case #	Ver-sion #	Manufacturer Control # or Central Triage Unit #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	5/19/2014	10181907	2	US-SA-2014SA024476	Periodic	6	M	USA	LT, OT
2	8/18/2014	10390688	1	US-SA-2014SA066537	Periodic	9	M	USA	OT
3	10/30/2015	11689698	1	621719	Direct	6	M	USA	LT, HO
4	11/2/2015	11693117	1	622139	Direct	4	F	USA	HO
5	11/12/2015	11734846	1	623466	Direct	4	M	USA	OT
6	5/2/2016	12327056	1	653087	Direct	8	M	USA	RI, LT, HO

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those that are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome.

Abbreviations: F=female, HO=hospitalization, LT=life-threatening, M=male, OT=other medically significant, RI=required intervention