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

Pediatric Postmarketing Pharmacovigilance Review

Date:	January 5, 2018
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Product Names:	Gadavist (*gadobutrol*) Eovist (Primovist; *gadoxetate disodium*)
Pediatric Labeling Approval Dates:	March 14, 2011 (Gadavist, original approval) December 29, 2014 (Gadavist) March 27, 2015 (Eovist) April 27, 2016 (Gadavist)
Application Type/Number:	NDA 201277 NDA 22090
Applicant/Sponsor:	Bayer Healthcare Pharmaceuticals, Inc.
Tracked Safety Issues:	TSI 0144 Nephrogenic systemic fibrosis (active) TSI 1427 Brain and body deposition of gadolinium (active) TSI 1799 Exposure during pregnancy (ongoing)
OSE RCM #:	2017-1970

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for the gadolinium-based contrast agents (GBCAs) Gadavist (gadobutrol) and Eovist (gadoxetate disodium) in pediatric patients.

Gadavist was first approved in 2011 and is indicated for magnetic resonance imaging (MRI) of the brain (2011 in patients aged 2 years and older, 2014 in patients from term neonates to adults), malignant breast disease (2014), and supra-aortic or renal artery disease (2016). The approved pediatric indications include term neonates and are to 1) detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system and 2) to evaluate known or suspected supra-aortic or renal artery disease.

Eovist was first approved in 2008 and is indicated for use in MRI of the liver to detect and characterize lesions in patients with known or suspected focal liver disease. The approved pediatric labeling change in 2015 consisted of the removal of any reference to age in the indications and addition of a description of the limited data in pediatric patients under USE IN SPECIFIC POPULATIONS. Pediatric labeling states that no dose adjustment is needed in pediatric patients.

We reviewed all serious FDA Adverse Event Reporting System (FAERS) reports with Gadavist and Eovist in the pediatric population (ages 0 - < 17 years) received by FDA from July 1, 2012 through August 31, 2017. Twenty-nine Gadavist cases and one Eovist case were included in our case series. Overall, there were no new safety signals, no increased severity or reporting frequency of any labeled adverse events, and no deaths directly associated with Gadavist or Eovist. The majority of reports described adverse events that were likely hypersensitivity reactions, for which both drugs have a warning. One serious and unlabeled adverse event, a case of panic attack, was included in the Gadavist case series.

There is no evidence from these data that there are new pediatric safety concerns with these drugs at this time. DPV recommends no regulatory action at this time and will continue to monitor adverse events associated with the use of Gadavist and Eovist.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Gadavist (gadobutrol) and Eovist (gadoxetate disodium) are available as sterile solutions for injection and are administered intravenously. Structurally, Gadavist is a macrocyclic gadolinium-based contrast agent (GBCA), and Eovist is a linear GBCA.

Gadavist was first approved in March 2011 for intravenous use in diagnostic magnetic resonance imaging (MRI) in adults and children 2 years of age and older to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system. Approval included a Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) to study at least 40 patients 0 to 23 months of age who were referred for an MRI with contrast to characterize the pharmacokinetics and efficacy of Gadavist for central nervous system MRI in these patients. Safety studies in neonatal animals were required before the clinical study was undertaken. In June 2014, Bayer submitted the clinical study results with an efficacy supplement for use in ages from birth to 2 years.

In December 2014, Gadavist's brain imaging indication was extended from ages 2 years and older down to term neonates on the basis of the completed PMR (NDA 201277/s008). One patient among the 44 enrolled patients aged 0 to 23 months experienced emesis, a labeled adverse event.

In April 2016, the indication of magnetic resonance angiography (MRA) for known or suspected supra-aortic or renal artery disease in term neonates and up was approved for Gadavist (s011) on the basis of extrapolation of safety and efficacy from adults.

Gadavist was presented at the March 13, 2013 meeting of the Pediatric Advisory Committee. The postmarket adverse event review for that meeting was triggered by the original approval of Gadavist in patients aged 2 years and older. The pediatric review did not identify any new serious or unexpected events with gadobutrol.[a] The committee recommended continued routine adverse event monitoring.

Eovist was approved July 3, 2008, with a PREA PMR to conduct "An observational study of the administration of Eovist in pediatric patients who are referred for a routine contrast enhanced liver MRI because of suspected or known focal liver lesions." This study was to enroll subjects aged 2 months to 18 years and obtain evaluable safety and imaging data from at least 50 subjects. Clinical studies in patients less than 2 months old were deferred until the sponsor provided nonclinical data to support safety in this age group, after which, 10 patients were to be enrolled in a clinical study. In November 2013, the sponsor submitted data from the observational study

[a] Volpe C. NDA 201277. Pediatric Postmarket Adverse Event Review. RCM 2012-1804. Finalized October 16, 2012.

in patients aged 2 months to 18 years. In March 2015, FDA released Bayer from the PMR clinical study in ages 0 to 2 months because of difficulty enrolling patients. Also, in March 2015, labeling was approved that removed mention of age in the indication, and results of the observational study in patients aged 2 months to 18 years were added to the *Pediatric Use* subsection of USE IN SPECIFIC POPULATIONS.

In August 2017, the Division of Pharmacovigilance (DPV) completed a review of all adverse events in the FDA Adverse Event Reporting System (FAERS) and the medical literature in patients aged 0 to under 2 years with all GBCAs, in response to a consult request from the Division of Medical Imaging Products (DMIP).[b] The primary purpose of the review was to identify any reports of QT prolongation with Multihance (gadobenate dimeglumine), but the review was expanded because of the general lack of safety data with GBCAs in this age group. The final FAERS case series of all reported adverse events included no cases with Eovist and seven cases with Gadavist, four of which meet inclusion criteria (serious outcome, received between July 1, 2012 and August 31, 2017) and are in this pediatric review. That review did not identify any new safety concerns and concluded, "The FAERS database and the medical literature contain a paucity of information on the apparent general safety of GBCA use in children younger than 2 years old,…"

The Medical Imaging Advisory Committee (MIDAC) met on September 8, 2017 and discussed the potential risks of gadolinium retention in the brain and other body organs in patients receiving GBCAs for MRI procedures. Regarding postmarket safety, FDA presented FAERS and literature reports of adverse events in patients with laboratory or MRI evidence of retained gadolinium in patients of all ages and for all GBCAs. The literature reports did not include any individual pediatric cases of adverse events associated with gadolinium retention. Of the 39 FAERS cases, 2 cases were in pediatric patients. The two pediatric cases included a 7-year-old, who received 19 administrations of an unspecified linear GBCA for central nervous system neoplasm monitoring, but reported no clinical effects, and an 8-year-old who received Magnevist (gadopentetate dimeglumine) for an MRI of the brain, head, and neck for an unknown indication. The 8-year-old patient experienced a rash that persisted for 8 weeks, which was treated with antibiotics and steroids. Gadolinium was found in his urine and he was treated with intravenous ethylenediaminetetraacetic acid (EDTA). The number of GBCA administrations and the outcome of EDTA administration are unknown for this patient. Although the GBCA received by the 7-year-old was not specified, because it is linear and was used to monitor CNS neoplasm, we can conclude that is was not likely to have been Gadavist, which is macrocyclic, or Eovist, which is selectively taken up by hepatocytes.

[b]Mundkur M. NDA 021357, NDA 021358. Multihance: Adverse events in pediatric patients aged 0 to < 2 years. RCM 2017-1367. Finalized August 15, 2017.

In their discussions, the MIDAC generally agreed that:

- Gadolinium appears to persist in the brain and other tissues longer than originally thought.
- Available FAERS and literature data are insufficient to establish a causal relationship between gadolinium retention and reported adverse events.
- FDA should consider asking GBCA sponsors to perform studies to assess:
    - The risks of gadolinium retention
    - The relationship between symptoms and signs in patients with normal renal function and gadolinium retention
    - Patient factors that may predispose patients to increased risk of gadolinium retention
- The prescribing information for GBCAs as a class should be revised to include:
    - A warning for retention for all GBCAs, with greater retention of all or some of the linear GBCAs compared to the macrocyclic GBCAs
    - Risk minimization steps for specific patient populations (e.g., pediatric patients, pregnant patients)

Subsequent to the MIDAC meeting, on December 19, 2017, FDA issued a Drug Safety Communication (DSC) update announcing the requirement of new warnings in labeling of all GBCAs, a new Medication Guide, and human and animal studies to further assess the safety of GBCAs to be conducted by the GBCA manufacturers.[c] The DSC advises patients to read the Medication Guide that is to be provided to them by their health care professional before administering a GBCA. The DSC advises health care professionals to consider the retention characteristics of each GBCA when choosing a GBCA for patients who may be at higher risk for gadolinium retention, such as patients requiring multiple lifetime doses, pregnant women, children, and patients with inflammatory conditions. In addition, the DSC advises health care professionals to minimize repeated GBCA imaging studies when possible, particularly closely spaced MRI studies.

Retention and adverse effects of GBCAs are the focus of research and monitoring in all age groups for the foreseeable future. As mentioned in the recent DSC, findings will be communicated through labeling changes and other FDA communications.

[c] FDA Drug Safety Communication: FDA warns that gadolinium-based contrast agents (GBCAs) are retained in the body; requires new class warnings. Issued on December 19, 2017. Accessed December 22, 2017. Retrieved from https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

Labeling information is from Gadavist labeling approved April 2016 and Eovist labeling approved March 2015. Information is identical in both labels unless noted.

Boxed Warning

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- The risk for NSF appears highest among patients with:
  Chronic, severe kidney disease (GFR < 30 mL/min/1.73m2), or
  Acute kidney injury.

- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.

- For patients at highest risk for NSF, do not exceed the recommended [GBCA] dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration

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

History of severe hypersensitivity reaction to [GBCA]

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

Nephrogenic Systemic Fibrosis has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeated dosing appears to increase the risk.

Gadavist - Anaphylactic and other hypersensitivity reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, have occurred. Monitor patients closely during and after administration of Gadavist.

Eovist - Hypersensitivity: anaphylactoid/hypersensitivity reactions with cardiovascular, respiratory and cutaneous manifestations, ranging from mild to severe reactions including shock can occur. Monitor patients closely for need of emergency cardiorespiratory support

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

Gadavist - Most common adverse reactions (incidence ≥ 0.5%) are headache, nausea, and dizziness

Eovist - Most common adverse reactions (incidence ≥ 0.5%) are nausea, headache, feeling hot, dizziness, and back pain

----------USE IN SPECIFIC POPULATIONS----------

Gadavist *Pediatric Use*

The safety and effectiveness of Gadavist have been established in pediatric patients born at 37 weeks gestation or later based on imaging and pharmacokinetic data in 138 patients ages 2 to 17 years and 44 patients ages 0 to less than 2 years and extrapolation from adult data. The frequency, type, and severity of adverse reactions in pediatric patients were similar to adverse reactions in adults [see Adverse Reactions]. No dose adjustment according to age is necessary in pediatric patients. The safety and effectiveness of Gadavist have not been established in premature infants.

…Pharmacokinetic studies suggest that clearance of Gadavist is similar in pediatric patients and adults, including pediatric patients age younger than 2 years.... Normal estimated GFR (eGFR) is around 30 mL/min/1.73m^2 at birth and increases to mature levels around 1 year of age, reflecting growth in both glomerular function and relative body surface area. Clinical studies in pediatric patients younger than 1 year of age have been conducted in patients with the following minimum eGFR: 31 mL/min/1.73m^2 (age 2 to 7 days), 38 mL/min/1.73m^2 (age 8 to 28 days), 62 mL/min/1.73m^2 (age 1 to 6 months), and 83 mL/min/1.73m^2 (age 6 to 12 months).

Eovist *Pediatric Use*

Adequate and well-controlled studies of EOVIST in pediatric patients have not been conducted. An observational study with EOVIST was performed in 52 patients (aged > 2 months and < 18 years) referred for evaluation of suspected or known focal liver lesions. EOVIST improved border delineation and increased contrast of the primary lesion in the majority of patients when compared to non-contrast images. No safety issues were identified.

No dose adjustment according to age is necessary in pediatric patients. The safety and effectiveness of EOVIST have not been established in premature infants.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FAERS Search Strategy

DPV searched FAERS with the strategy described in **Table 1**. See **Appendix A** for a description of the FAERS database.

Table 1. FAERS Search Strategy	
Date of Search	November 6, 2017
Time Period of Search	July 1, 2012* - August 31, 2017
Search Type	FBIS Quick Query
Product Names	Product active ingredients: gadobutrol, gadoxetate disodium
Search Parameters	All ages, all outcomes, worldwide

* July 1, 2012 was selected to capture all reports received by FDA since the October 2012 pediatric adverse event review for Gadavist.

We searched the FAERS database for all reports of Gadavist or Eovist received from July 1, 2012 to August 31, 2017. July 11, 2012 was the end date of the FAERS search for the previous DPV pediatric review of Gadavist, and Eovist was indicated only for adults until March 2015. This review is focused on cases with serious outcomes in pediatric patients.

We reviewed all FAERS pediatric reports with a serious outcome. We included reports in our case series unless the serious adverse event was attributable to co-morbid diseases or concomitant medications, occurred prior to GBCA exposure, no adverse clinical events were reported, or adults were miscoded as pediatric patients.

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from July 1, 2012 to August 31, 2017 with Gadavist and Eovist.

Table 2. Total Adult and Pediatric FAERS Reports* July 1, 2012 to August 31, 2017 with Gadavist and Eovist

Gadavist			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	1571 (1275)	628 (350)	36 (24)
Pediatrics (0 - <17 years)	75 (65)	**35‡ (26)**	1 (1)

Eovist			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	118 (60)	78 (21)	13 (2)
Pediatrics (0 - <17 years)	3 (2)	**2 (1)**	1 (0)

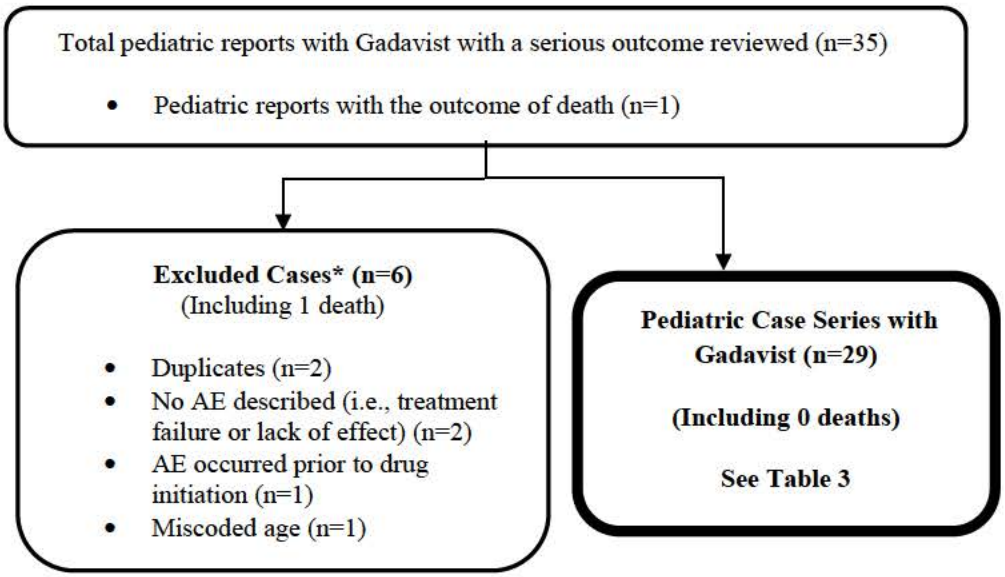
* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.
‡See **Figure 1**

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 35 pediatric reports with Gadavist that reported a serious outcome from July 1, 2012 through August 31, 2017. In the single report of death with Gadavist, the age is given as 0 days but the narrative says, "…he immediately felt burning in his pelvic region," which a neonate could not have conveyed, so this case was excluded. Our pediatric case series included 29 cases, including 0 deaths. **Figure 1** presents the specific selection of Gadavist cases summarized in **Sections 2.2.3** and **2.2.5.**

We identified two pediatric reports with Eovist that reported a serious outcome from July 1, 2012 through August 31, 2017. In one of the cases, death was the only reported adverse clinical event, but the death occurred an unspecified time after Eovist use and was attributed to metastatic cancer and the generally poor condition of the patient, so this case was excluded. The included serious case is summarized in **Section 2.2.6**.

Figure 1. Selection of Serious Pediatric Cases with Gadavist



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

2.2.3 Characteristics of Pediatric Case Series

Appendix B lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series with Gadavist and Eovist. This review includes one case with a serious outcome in a pediatric patient with Eovist, which is described in **Section 2.2.6**.

Figure 2 and **Table 3** summarize the 29 FAERS cases reporting a serious outcome in pediatric patients with Gadavist received by FDA from July 1, 2012 through August 31, 2017.

Figure 2. Serious Pediatric Cases for Gadavist by Year of FDA Receipt (n=29)

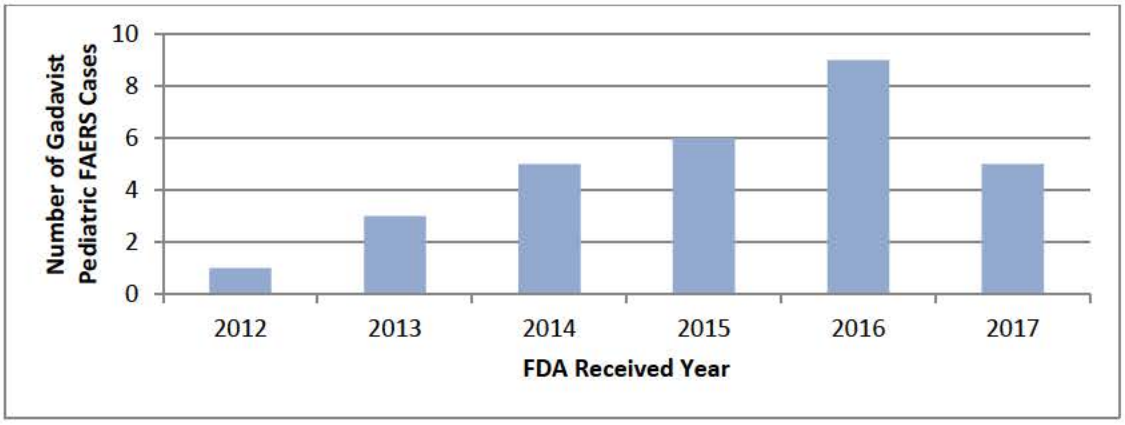


Table 3. Characteristics of the FAERS Pediatric Case Series with Gadavist received by FDA between July 1, 2012 through August 31, 2017 (N=29)		
Age	1 month - <2 years	4
	2- < 6 years	2
	6- <12 years	8
	12- < 17 years	15
Sex	Male	12
	Female	13
	Unknown	4
Country	United States	21
	Foreign	8
Reported Reason for Use	Brain MRI	12
	Arthrogram	3
	Angiogram	2
	Knee MRI	1
	Crohn's disease	1
	Computerized tomogram	1
	Unknown	9
Serious Outcome*	Life-threatening	7
	Hospitalization	11
	Other serious	17

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.

2.2.4 Summary of Fatal Pediatric Cases (N=0)

We did not include any fatal pediatric adverse event cases in our case series.

2.2.5 Summary of Non-Fatal Pediatric Serious Cases with Gadavist (N=29)

We identified 29 FAERS cases with Gadavist in the pediatric population reporting a non-fatal serious outcome, including 21 from the U.S. We identified no events of interest in the pediatric population with Gadavist that are serious and unlabeled.

Of the 29 FAERS cases, the adverse events in 26 cases are consistent with labeled hypersensitivity reactions. Anaphylactic reaction or shock was reported in 4 cases, and the remaining 22 cases reported one or more of the following: cutaneous reactions such as urticaria or erythema (12), respiratory events such as dyspnea or respiratory distress (11), edema of the face or upper respiratory tract (10), and chest pain (1).

The three cases that may not be hypersensitivity reactions report nausea and vomiting (labeled), a panic attack (unlabeled), and cardiac arrest (labeled). The case of cardiac arrest was not medically confirmed and is described below.

FAERS Case #10579315, MCN US-BAYER-2014-162373, Expedited, 2014
This case was reported by the patient's parent. A 4-month-old male received 0.5 mL Gadavist for a brain MRI because his eyes were deviating. The patient "seemed normal" after the procedure and was taken home. The next day, the patient "went into cardiac arrest" and had pale skin and blue lips. He vomited milk and a brown substance. The parents administered CPR and took the patient to the hospital where CPR was continued. The patient was placed on a ventilator but remained in a coma at the time of the report, 4 months later. The parent reports that the physician thought the adverse events may have been an allergic reaction to Gadavist. No information on medical history or MRI results was provided.

2.2.6 Summary of Non-Fatal Pediatric Serious Cases with Eovist (N=1)

We identified one U.S. FAERS case with Eovist in the pediatric population reporting a non-fatal serious outcome. The single serious case with Eovist was anaphylactic reaction, a labeled event. We identified no events of interest in the pediatric population with Eovist that are serious and unlabeled.

3 DISCUSSION

There were no new safety signals, no increased severity or reporting frequency of any labeled adverse events, and no deaths directly associated with Gadavist or Eovist reported among the 29 Gadavist cases and 1 Eovist case included in our case series. The majority of cases described signs and symptoms of hypersensitivity reactions, for which both GBCAs carry a warning. The unlabeled adverse event of panic attack is difficult to attribute to Gadavist. Panic attack may be intrinsic to the patient or could be related to the patient's anxiety of the MRI procedure. One case reported cardiac arrest in a 4-month-old the day after Gadavist administration. However, all of the information was provided by a parent months after the initial adverse event. The only health professional analysis is the parent's report that the doctor thinks an allergic reaction may have been the cause, in which case, the adverse event is labeled. We did not identify any new cases of adverse events attributed to gadolinium retention in pediatric patients.

4 CONCLUSION

There is no evidence from these data that there are new pediatric safety concerns with Gadavist or Eovist at this time.

5 RECOMMENDATIONS

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

6 APPENDICES

6.1 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 the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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.

6.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH GADAVIST (N=29) AND EOVIST (N=1)

FAERS Line Listing of Pediatric Cases for the Pediatric Case Series with Gadavist (N=29) and Eovist (N=1)									
Gadavist									
Case	**Initial FDA Received Date**	**FAERS Case #**	**Version #**	**Manufacturer Control #**	**Case Type**	**Age (years)**	**Sex**	**Country**	**Serious Outcome(s)***
1	7/31/2012	8694418	1	US-BAYER-2012-075753	Expedited (15-Day)	1.9	NULL	USA	HO
2	7/9/2013	9390992	3	US-BAYER-2013-080108	Non-Expedited	0.5	MALE	USA	HO, LT
3	10/9/2013	9610311	2	US-BAYER-2013-121474	Expedited (15-Day)	15	MALE	USA	OT
4	11/26/2013	9710645	2	US-BAYER-2013-140362	Non-Expedited	16	MALE	USA	HO, OT
5	6/13/2014	10235700	4	US-BAYER-2014-088769	Expedited (15-Day)	16	FEMALE	USA	OT
6	8/7/2014	10369062	1	US-BAYER-2014-114688	Non-Expedited	16	FEMALE	USA	OT
7	8/8/2014	10371959	1	KR-BAYER-2014-115146	Expedited (15-Day)	5	MALE	KOR	HO, LT
8	11/12/2014	10579315	1	US-BAYER-2014-162373	Expedited (15-Day)	0.3	MALE	USA	HO, LT
9	12/2/2014	10619988	2	DE-BAYER-2014-165092	Expedited (15-Day)	5	FEMALE	DEU	OT
10	1/23/2015	10732245	1	US-BAYER-2015-006653	Non-Expedited	11	MALE	USA	OT
11	3/20/2015	10935825	2	GB-BAYER-2015-037941	Expedited (15-Day)	16	FEMALE	GBR	LT, OT

FAERS Line Listing of Pediatric Cases for the Pediatric Case Series with Gadavist (N=29) and Eovist (N=1)									
Gadavist									
Case	**Initial FDA Received Date**	**FAERS Case #**	**Version #**	**Manufacturer Control #**	**Case Type**	**Age (years)**	**Sex**	**Country**	**Serious Outcome(s)***
12	5/13/2015	11110226	1	GR-BAYER-2015-202752	Non-Expedited	15	FEMALE	GRC	HO
13	6/29/2015	11225642	1	US-BAYER-2015-367594	Non-Expedited	14	FEMALE	USA	OT
14	7/27/2015	11311561	2	US-BAYER-2015-386474	Non-Expedited	10	MALE	USA	HO
15	10/1/2015	11583432	2	US-BAYER-2015-430417	Expedited (15-Day)	0.8	FEMALE	USA	LT
16	1/13/2016	11912950	2	US-BAYER-2016-006596	Expedited (15-Day)	7	MALE	USA	OT
17	1/29/2016	11978256	1	JP-BAYER-2016-012050	Expedited (15-Day)	16	FEMALE	JPN	LT
18	3/24/2016	12208361	2	US-BAYER-2016-056574	Expedited (15-Day)	13	MALE	USA	OT
19	3/31/2016	12225452	2	US-BAYER-2016-061221	Expedited (15-Day)	16	FEMALE	USA	HO
20	7/18/2016	12566723	1	AT-BAYER-2016-139648	Expedited (15-Day)	14	MALE	AUT	HO
21	8/4/2016	12623258	1	CA-BAYER-2016-150422	Expedited (15-Day)	9	FEMALE	CAN	OT
22	9/12/2016	12736172	2	US-BAYER-2016-176396	Expedited (15-Day)	12	FEMALE	USA	OT
23	9/19/2016	12758873	2	GB-BAYER-2016-152143	Expedited (15-Day)	13	MALE	GBR	HO, LT

FAERS Line Listing of Pediatric Cases for the Pediatric Case Series with Gadavist (N=29) and Eovist (N=1)									
Gadavist									
Case	**Initial FDA Received Date**	**FAERS Case #**	**Version #**	**Manufacturer Control #**	**Case Type**	**Age (years)**	**Sex**	**Country**	**Serious Outcome(s)***
24	11/21/2016	12960733	1	US-BAYER-2016-219775	Expedited (15-Day)	10	NULL	USA	OT
25	1/20/2017	13134916	2	US-BAYER-2017-011752	Expedited (15-Day)	8	NULL	USA	OT
26	1/24/2017	13143703	3	US-BAYER-2017-011906	Non-Expedited	13	NULL	USA	OT
27	1/24/2017	13143765	4	US-BAYER-2017-012854	Expedited (15-Day)	15	FEMALE	USA	OT
28	3/10/2017	13321198	2	US-BAYER-2017-046930	Expedited (15-Day)	6	MALE	USA	HO
29	6/1/2017	13602552	3	US-BAYER-2017-102657	Expedited (15-Day)	11	FEMALE	USA	OT
Eovist									
1	9/18/2012	8791901	4	US-BAYER-2012-095466	Expedited (15-Day)	9	MALE	USA	HO, OT

*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, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. A report may have more than one serious outcome.
Abbreviations (country): AUT=Austria, CAN=Canada, DEU=Germany, ESP=Spain, GBR=Great Britain, GRC=Greece, JPN=Japan, KOR=Korea, USA=United States
Abbreviations: HO=Hospitalization, LT= Life-threatening, OT=Other medically significant

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/s/

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01/05/2018

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