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 Postmarket Adverse Event Review

Date:	October 11, 2012
Reviewer(s):	Carolyn Volpe, Pharm. D. Division of Pharmacovigilance II Joseph M. Tonning, M.D., R.Ph., M.P.H. Division of Pharmacovigilance II
Team Leader(s):	Peter Diak, Pharm. D., M.P.H. Division of Pharmacovigilance II Ethan D. Hausman, MD Division of Pharmacovigilance I
(Deputy) Division Director(s):	Bindi Nikhar, M.D. Division of Pharmacovigilance II
Product Name(s):	Gadavist (gadobutrol)
Pediatric Labeling Change Date:	March 14, 2011
Application Type/Number:	NDA 201277
Applicant/Sponsor:	Bayer Healthcare
OSE RCM #:	2012-1804

TABLE OF CONTENTS

Executive Summary 1
1 Introduction 2
1.1 Product Formulations and Indications 2
1.2 Pediatric Filing History 2
1.3 Pediatric Labeling 3
2 Methods and Materials 3
2.1 AERS Search Strategy 3
3 Results 4
3.1 AERS Reports 4
3.2 Figure 2. Selection of Serious Pediatric AERS Cases 5
3.3 Descriptive Characteristics From Pediatric Case Series 5
4 Discussion of Serious Pediatric Case Series 6
4.1 Summary of pediatric deaths 6
4.2 Summary of serious pediatric adverse events (n =6) 7
5 Conclusions 9
6 Recommendations 9
7 References 9
8 Appendices 10
8.1 Appendix A. Gadavist Dosage and Administration Labeling 10
8.2 Appendix B. Standard Searches 11
8.3 Appendix C. Adverse Event Reporting System (AERS) 12
8.4 Appendix D. AERS ISR Numbers, AERS Case Numbers and Manufacturer Control Numbers 13

EXECUTIVE SUMMARY

In accordance with Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV) was asked to summarize postmarketing reports of adverse events associated with the use of Gadavist® (gadobutrol) in pediatric patients (0-16 years of age). The main focus of this review is pediatric reports of serious unlabeled adverse events with Gadavist® (gadobutrol).

Gadobutrol is a gadolinium-based contrast agent indicated 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. The product is available in the United States and Europe under the brand name Gadavist®.

The Adverse Event Reporting System (AERS) database was searched for all reports of adverse events (serious and non-serious) up to the "data lock" date of July 11, 2012. AERS contained 341 reports for gadobutrol. There were a total of 11 pediatric reports, including 6 serious reports, described briefly below. Pediatric reports represent approximately 3 % of the total (11/341). There were no reports of pediatric death.

The serious pediatric cases consisted of: one case of respiratory insufficiency (likely related to concomitant sedation and anesthesia); two cases of hypersensitivity-type reactions; and a fourth case with insufficient clinical information, which may have had an anaphylactic-type reaction, or pulmonary edema, likely related to concomitant medications. Hypersensitivity reactions are described in the current Warnings and Precautions section of the gadobutrol label. A fifth case reported miscellaneous symptoms that are labeled (e.g., feeling cold and paresthesia). The sixth case reported an overdose.

This pediatric review did not identify any new serious or unexpected unlabeled events with gadobutrol.

DPV will continue routine pharmacovigilance activities associated with gadobutrol.

1 INTRODUCTION

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Gadobutrol is a gadolinium-based contrast agent (GBCA) indicated for intravenous use in diagnostic 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. Gadobutrol is marketed in the United States under the trade name Gadavist®. Gadavist® injection contains 1 mmol gadobutrol/mL (equivalent to 604.72 mg gadobutrol/mL) and is available in vials and prefilled syringes.

1.2 PEDIATRIC FILING HISTORY

At the time of approval, on March 14, 2011, Gadavist® was approved for use in adults and children 2-17 years of age; however, the pediatric study of children 0-23 months had not been completed. The FDA deferred submission of the 0-23 months pediatric study requirement as reflected in the required pediatric post-marketing study components listed below.

Study 1743-1

- This study will provide nonclinical (animal) data to support the safety of Gadavist® in the 0-23 month pediatric age group. These data will be obtained from newborn to juvenile animals that model pediatric patients in this age group. The study will examine the safety of Gadavist® in these animals following a single dose and limited repeated dose administrations.

  - ❖ Final Protocol Submission: May, 2011
  - ❖ Study/Trial Completion: January, 2012
  - ❖ Final Report Submission: June, 2012

  Conclusions/Recommendations: (Protocol T6082538) "The findings are acceptable…. there was no evidence of toxicity at the administered repeated doses….The reviewer however notes the occurrence of renal tubular vacuolation, though resolved by the end of recovery period and the presence of atrophic clear cell tubules that was not completely reversed. While renal cortical tubular vacuolation and atrophic clear cell tubules have been commonly described in adult rodents administered intravenous GBCAs, the significance and clinical implications of these findings in neonate animals is yet to be determined. The findings of this repeated dose toxicity study in neonatal rats are in general, acceptable."

Study 1743-2

- This study will examine human subjects 0-23 months of age who are referred for an MRI exam with contrast. At least 40 patients will be evaluated in this study to characterize the pharmacokinetics and efficacy of Gadavist® in this age group.

- ❖ Final Protocol Submission: July, 2012
- ❖ Study/Trial Completion: March, 2014
- ❖ Final Report Submission: January, 2015

1.3 PEDIATRIC LABELING

The labeling for Gadavist® (gadobutrol) has the following information concerning the pediatric population:

Pediatric Use (Section 8.4 of the label)
"The pharmacokinetics, safety and efficacy of Gadavist at a single dose of 0.1 mmol/kg have been established in children 2 to 17 years of age. No dose adjustment according to age is necessary in this population. The safety and effectiveness of Gadavist have not been established in children below two years of age."

Pharmacokinetics (Section 12.3 of the label)
"The pharmacokinetics of Gadavist were evaluated based on a population pharmacokinetic analysis in 130 pediatric subjects aged 2 to 17 years. Subjects received a single intravenous dose of 0.1 mmol/kg of Gadavist. The median AUC (mmol·h/L), clearance (L/hr/kg) and elimination half-life (hrs) of gadobutrol was similar across the age range of 2 – 17 years. The median AUC of gadobutrol in children 2 – 6 years (n=45) was 0.8 mmol·h/L, 1.0 mmol·h/L in children 7 – 11 years (n=39), and 1.2 mmol·h/L in children 12 – 17 years (n=46). The median clearance of gadobutrol in children 2 – 6 years was 0.13 L/hr/kg, 0.1 L/hr/kg in children 7 – 11 years, and 0.09 L/hr/kg in children 12 – 17 years, and the median elimination half-life of gadobutrol in children 2 – 6 years was 1.75 hours, 1.61 hours in children 7 – 11 years, and 1.65 hours in children 12 – 17 years. Approximately 99% (median value) of the dose was recovered in urine within 6 hours."

2 METHODS AND MATERIALS

2.1 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) was searched with the strategy described in Table 1 (see Appendix B).

Table 1. AERS Search Strategy*	
Date of search	July 12, 2012
Time period of search	March 14, 2011^ - July 11, 2012
Product Terms	Active: gadobutrol Trade: Gadavist
<<insert other criteria>>	Refer to Appendix B

* See Appendix C for description of the AERS database.
^ US Approval date

3 RESULTS

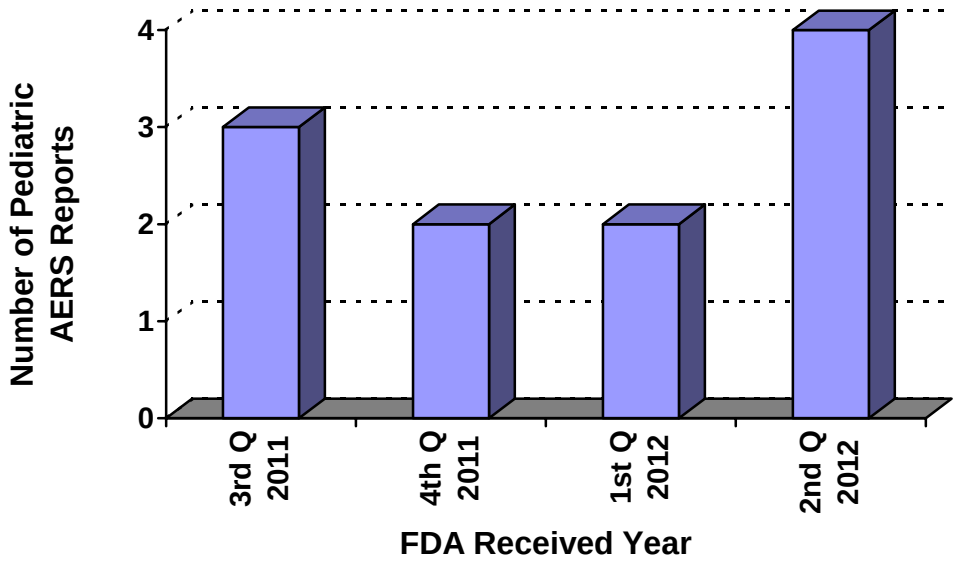
3.1 AERS REPORTS

Table 2. Total number of AERS reports* (March 14, 2011 to July 11, 2012)			
	All reports (US) ^	**Serious‡ (US)**	**Death (US)**
Adults (≥17 years)	182 (115)	91 (25)	5 (0)
Pediatrics (0-16 years)	11 (7)	5 (1)†	0
Age unknown (null values)	148 (139)	29 (20)†	0†
Total	341 (261)	125 (46)	5 (0)

* May include duplicates and have not been assessed for causality
^ US counts in parentheses
‡ Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.
† Also see Figure 2; one pediatric case identified.

Figure 1. Total Number of Pediatric Reports (including serious and non-serious) for gadobutrol, by year of FDA receipt (March 14, 2011 to July 11, 2012) (n=11)

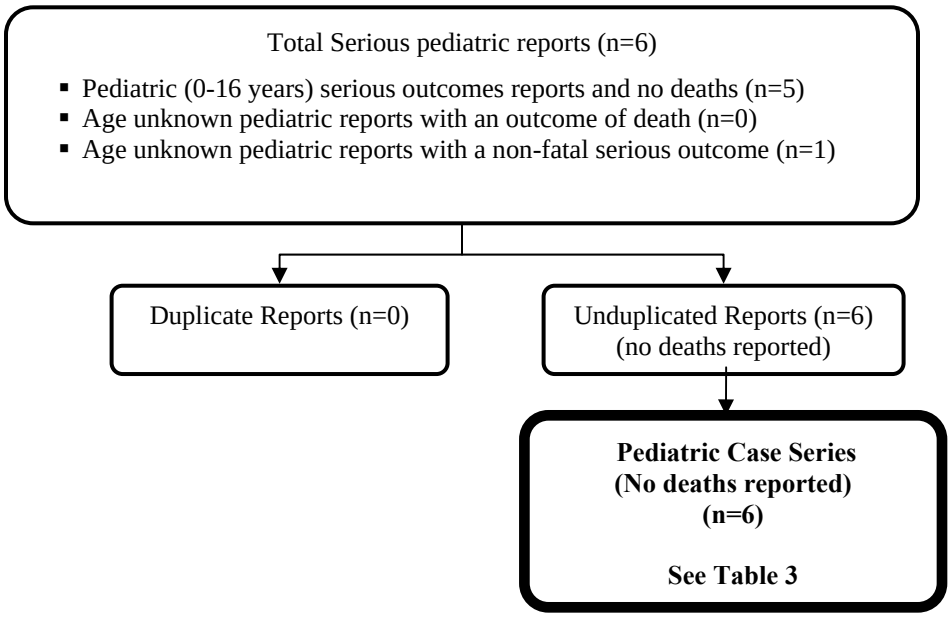
These numbers include data where age (0-16 years) is known and may contain duplicate reports.



In addition to reviewing pediatric reports with serious outcomes, we also reviewed all reports with the age unknown reporting an outcome of death or a non-fatal serious outcome to determine if the report concerned a pediatric patient. Of these age unknown reports, none reported an outcome of death and one reported a non-fatal serious outcome

which described a pediatric patient. **Figure 2** below summarizes the specific selection of cases to be reviewed in **Section 4**.

3.2 FIGURE 2. SELECTION OF SERIOUS PEDIATRIC AERS CASES



3.3 DESCRIPTIVE CHARACTERISTICS FROM PEDIATRIC CASE SERIES

Table 3 summarizes the six AERS cases from the Pediatric Case Series with gadobutrol.

Appendix D lists all the AERS case numbers, AERS ISR numbers and Manufacturer Control numbers for the Pediatric Case Series (i.e., reports of serious events).

Table 3. Descriptive characteristics of Pediatric Case Series (March 14, 2011 to July 11, 2012)		
	(N=6)	
Age (n=6)	1 month - <1 year	1
	1-2 years	2
	3-11 years	2
	12-16 years	1
Sex	Male	4
	Female	2
Country of reporter	United States	1
	Foreign	5
Report type	Expedited	4
	Periodic	2
Event date	2011	2
	2012	2
	Unknown	2
Dose (n=5)	Average dose	5 mLs
	Range	0.52 – 12 mLs
Indications	Contrast MRI of the:	
	Brain	3
	Abdomen	1
	Not specified	2
Serious Outcomes*	Life-threatening	2
	Hospitalized	3
	Other serious	5
Preferred Terms (PTs) reported*	Pulmonary oedema	2
	Respiratory failure	2
	The following PTs were reported once:	
	hypovolaemic shock; anaphylactic reaction; cardiovascular insufficiency; pyrexia; dyspnoea; throat tightness; oxygen saturation decreased; tachycardia; paraesthesia; feeling cold; chills; dizziness; blood pressure decreased	

* Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. A report may have more than one outcome or PT reported.

4 DISCUSSION OF SERIOUS PEDIATRIC CASE SERIES

4.1 SUMMARY OF PEDIATRIC DEATHS

There were no reports of pediatric deaths.

4.2 SUMMARY OF SERIOUS PEDIATRIC ADVERSE EVENTS (N =6)

There was one case of respiratory insufficiency, two cases of hypersensitivity-type reactions, and a fourth case with insufficient clinical information, which may have had an anaphylactic-type reaction, or pulmonary edema. A fifth case reported miscellaneous symptoms, e.g., feeling cold and paresthesia. The sixth case reported an overdose. In these 6 cases, patient age ranged from 6 weeks to 12 years.

Case summaries are provided below.

ISR # 8435340: A 6 week old male received gadobutrol as part of a phase 1, open-label, multi-center, pharmacokinetic and safety study of children in Germany. He received 0.52 mL of gadobutrol (0.1 mmol/kg, patient weight 5.13 kg) for a contrast enhanced MRI (unknown indication for MRI). He was intubated prior to receiving gadobutrol and for the entire MRI procedure. Concomitant medications during the procedure included sevoflurane, sufentanil citrate, rocuronium bromide, and propofol for anesthesia and sedation while intubated. His vital signs were monitored during the procedure. After the MRI, the patient was extubated after which he experienced *respiratory insufficiency with oxygen desaturation to <90*. He was re-intubated and recovered; the reporting clinicians ascribed the respiratory insufficiency to depressed respiratory drive due to anesthesia. The patient's medical history included pyelonephritis and concomitant medications included amoxicillin, ergocalciferol, electrolyte solutions, and furosemide. (German report received by the FDA on September 20, 2011.)

Comment: The respiratory insufficiency experienced by this patient is likely related to depressed respiratory drive due to concomitant sedation and anesthesia.

ISR # 8468898: An 11 year old female ICU patient received gadobutrol 6.5 mL (0.1 mL/kg, patient weight 65 kg) for a contrast enhanced MRI for an unknown MRI indication, and experienced ventilatory failure with *severe pulmonary edema* and *cardiovascular failure associated with hypovolemic shock*. The reporting clinicians attributed these events to presumed anaphylaxis. Her medical history included Hashimoto's encephalopathy, which required intubation during her stay in the ICU. Her concomitant ICU medications included unspecified antibiotics, propofol, and other unspecified sedatives prior to receiving gadobutrol. Treatment included prednisone and veno-venous extracorporeal life support (ECMO). She recovered on an unspecified date. (Canadian report received by the FDA on June 26, 2012.)

Comment: The anaphylaxis in this patient may be attributable to a variety of medications; however, the time course appears to suggest a reaction to gadobutrol. Gadavist is labeled for hypersensitivity reactions/anaphylaxis in the Warnings and Precautions sections of the label.

ISR # 8349007: A 7 year old male reported *throat constriction and difficulty breathing* at an unspecified time after receiving gadobutrol (unknown dose) for a contrast enhanced MRI of the brain. Treatment and outcome were not reported. No information was given

on the patient's medical history or concomitant medications. (US report received by the FDA on May 10, 2012.)

Comment: While there is insufficient clinical information, it appears that this patient may have had stridor and bronchospasm, i.e., a hypersensitivity-type reaction.

ISR # 7787594: A 2 year old male received gadobutrol 1.3 mL (0.1 mL/kg, patient weight 13 kg) for a contrast enhanced abdominal MRI. The patient received sevoflurane, isoflurane, and propofol for sedation and anesthesia during the procedure. After the patient received gadobutrol, he experienced *tachycardia* (heart rate = 150 beats per minute) and began to *desaturate*. At this time, chest imaging showed *pulmonary edema*. He was then ventilated and a second set of chest images was obtained. He continued to desaturate to < 60% and chest imaging showed that his lung fields were fluid filled. He recovered from the events. His medical history included hepatomegaly, splenomegaly, thrombocytopenia, and hemangioma. (Canadian report received by the FDA on September 29, 2011.)

*Comment: There is insufficient clinical information to distinguish whether this event represented anaphylaxis or 'flash pulmonary edema' which is a rare complication of anesthesia***.**

ISR #7763577: A 12 year old female reported *dizziness, shivering, bilateral tingling in hands and feet, and a sensation of coldness 10 minutes* after receiving gadobutrol for a contrast enhanced MRI of the brain. The gadobutrol dose was reported as 0.1mL/kg and her body weight was 49 kg. The symptoms persisted for 30 minutes and the patient received dimetindene, ranitidine, and prednisolone for treatment. She was monitored for 9 hours. No outcome was reported. No information was reported on the patient's medical history or concomitant medications. (German report received by the FDA on September 20, 2011.)

Comment: The terms reported in this case are all listed in the Adverse Reaction section of the gadobutrol label.

ISR # 7681858: A 1 year old male received *gadobutrol 12 mL* IV once for a contrast enhanced brain MRI for suspected delay in mental development. *He weighed 8 kg*, which resulted in *15 times the estimated labeled dose* of gadobutrol (0.1 mL/kg); however the product is not labeled for use in patients younger than 2 years old. He experienced a "*drop in blood pressure"* after receiving gadobutrol. No additional adverse effects were reported. He received hemodiafiltration in the ICU. On an unreported date, he recovered. The patient's medical history included suspected obliterative bronchiolitis, and his concomitant medications included albuterol and budesonide. (Portuguese report received by the FDA on August 13, 2011.)

Comment: This is a foreign report involving off-label use (<2 years of age). Gadobutrol is only available at a higher concentration (1 mmol/mL) compared to other GBCA's (0.5 mmol/mL). To prevent medication errors, the FDA-approved prescribing information for

gadobutrol includes a dosing table by body weight. See Appendix A for dosing table. This case was referred to Division of Medication Error and Prevention Analysis (DMEPA) for assessment; DMEPA will continue to monitor gadobutrol for reports of medication errors.

5 CONCLUSIONS

This pediatric review did not identify any new serious or unexpected unlabeled events with gadobutrol. As a result of this review, DPV does not recommend any pediatric labeling changes at this time.

6 RECOMMENDATIONS

DPV will continue routine monitoring of all adverse events with the use of gadobutrol in the pediatric population.

7 REFERENCES

Gadobutrol (Gadavist®) label
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201277s000lbl.pdf , accessed August 27, 2012.

Gadobutrol (Gadavist®) FDA approval letter
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/201277s000ltr.pdf , accessed August 27, 2012.

Propofol (Diprivan®) label
http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/019627s046lbl.pdf , accessed August 27, 2012.

8 APPENDICES

8.1 APPENDIX A. GADAVIST DOSAGE AND ADMINISTRATION LABELING

Gadavist is formulated at a higher concentration (1 mmol/mL) compared to certain other gadolinium based contrast agents, resulting in a lower volume of administration. Closely examine the table below to determine the volume to be administered.

2.1 Adults and Children (2 years and older)

The recommended dose of Gadavist is 0.1 mL/kg body weight (0.1 mmol/kg).

VOLUME OF GADAVIST INJECTION BY BODY WEIGHT		
BODY WEIGHT		**Volume to be administered, mL**
lb	**kg**	
22	10	1
33	15	1.5
44	20	2
55	25	2.5
66	30	3
77	35	3.5
88	40	4
99	45	4.5
110	50	5
132	60	6
154	70	7
176	80	8
198	90	9
220	100	10
242	110	11
264	120	12
286	130	13
308	140	14

8.2 APPENDIX B. STANDARD SEARCHES

A. Adults (17 yrs and above)
   1. All outcomes from approval date (no set criteria)
   2. Serious outcomes from approval date
   3. Death as an outcome from approval date

B. Ages 0-16 yrs ONLY
   1. Same as above 1-3

8.3 APPENDIX C. ADVERSE EVENT REPORTING SYSTEM (AERS)

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do 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 all adverse event reports that occur 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, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

8.4 APPENDIX D. AERS ISR NUMBERS, AERS CASE NUMBERS AND MANUFACTURER CONTROL NUMBERS

Table 4. AERS ISR numbers, Case numbers and Manufacturer control numbers		
AERS ISR Numbers	AERS Case numbers	Manufacturer control numbers
Serious Cases		
7681858	8057756	PT-BAYER-2011-062602
7763577	8145195	DE-BAYER-2011-086692
7787594	8142761	CA-BAYER-2011-087033
8349007	8554984	US-BAYER-2012-044639
8435340	8580562	DE-BAYER-2012-050018
8468898	8599635	CA-BAYER-2012-054545

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROLYN A VOLPE
10/11/2012

JOSEPH M TONNING
10/12/2012

PETER S DIAK
10/12/2012

ETHAN D HAUSMAN
10/12/2012

BINDI M NIKHAR
10/16/2012