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Pediatric Postmarketing Pharmacovigilance

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Visipaque (iodixanol) injection 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) Pediatric Research Equity Act (PREA). This review focuses on serious adverse events associated with Visipaque (iodixanol) injection in pediatric patients.

The FDA approved Visipaque (iodixanol) injection on March 22, 1996 and it is indicated for use in both intra-arterial and intravenous radiologic procedures. The approved pediatric labeling is for intra-arterial digital subtraction angiography, peripheral arteriography, peripheral venography, coronary computed tomography angiography (CCTA) in patients 12 years and older and for angiocardiography, visceral arteriography, cerebral arteriography, excretory urography, and computed tomography (CT) imaging of the head and body in pediatric patients from birth to 17 years of age.

DPV reviewed all serious FAERS reports with Visipaque (iodixanol) injection in the pediatric population through <17 years of age during the period March 22, 1996 to March 13, 2019 and identified 16 foreign cases of serious adverse events (no U.S. cases retrieved in search), including 3 fatal cases. Of the fatal cases, one case described a neonate whose autopsy findings revealed underlying abnormal lymphatic permeability that may have predisposed the patient to increased drug resorption and contributed significantly to the fatal events. The remaining two death cases described an unwitnessed infant death and cardiorespiratory arrest following a seizure in an adolescent patient; both cases had insufficient information for causality assessment. Of the 13 serious non-fatal cases, 11 cases described adverse events consistent with known labeled adverse events (cardiovascular events (n=2), extravasation (n=2), and hypersensitivity (n=7)). The remaining two cases lacked information to characterize the adverse event; one case described transient aphasia that may represent the labeled event of transient contrast-induced encephalopathy and the other case described cholangitis in a patient who may have Alagille syndrome. All cases had limited clinical information to assess causality.

There is no evidence from these data that there are new pediatric safety concerns with Visipaque (iodixanol) injection at this time. DPV recommends no regulatory action and will continue to monitor adverse events associated with Visipaque (iodixanol) injection use.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Visipaque (iodixanol) injection 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) Pediatric Research Equity Act (PREA). This review focuses on serious adverse events associated with Visipaque (iodixanol) injection in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Visipaque (iodixanol) injection is an isosmolar, non-ionic, water-soluble iodinated radiographic contrast agent. Visipaque (iodixanol) injection was initially approved in two concentrations (270 mg and 320 mg iodine/mL) by the FDA as a single dose injection (NDA 20351) on March 22, 1996 for use in intra-arterial and intravenous radiologic procedures in adult and pediatric patients. The pharmacy bulk package (NDA 20808) was approved on August 29, 1997.

On February 27, 2015, FDA issued a postmarketing requirement (PMR) for the Sponsor to conduct an observational study of pediatric patients from birth to 3 years of age who are administered iodixanol for clinical evaluation, in order to assess their risk of developing hypothyroidism. The PMR study is currently ongoing.

The Sponsor submitted a Supplemental New Drug Application (sNDA) on October 5, 2016 seeking approval for a new indication for coronary computed tomography (CCTA) to assist diagnostic evaluation of patients with suspected coronary artery disease with the 320 mg iodine/mL formulation. The Sponsor requested a full waiver of the requirement to provide a pediatric assessment for the CCTA indication citing that obstructive coronary artery stenosis is due to atherosclerotic disease, which is largely a disease of adults. However, the Pediatric Review Committee (PeRC) recommended pediatric patients over 12 years of age be included for the CCTA indication because of the known use of CCTA in these patients with Kawasaki disease, the leading cause of acquired coronary disease in children. This recommendation is based on extrapolation of efficacy and safety data from adults as well as several small scale reports on imaging protocols and efficacy results for the use of CCTA in the older pediatric population with a history of Kawasaki disease.[1] One published study reported the successful performance of CCTA in 16 adolescents and young adults (age range of 13-17 years) with Kawasaki disease.[2] A second study demonstrated the ability of CCTA to detect coronary stenoses that were not visualized by other noninvasive imaging tests in 32 pediatric patients with Kawasaki disease (median age 12.9 years).[3] On April 4, 2017, FDA approved the use of Visipaque (iodixanol) injection for use in CCTA in adults and pediatric patients 12 to 18 years of age and waived the pediatric study requirement under the PREA for ages 0 to 11 years because studies would be impossible or highly impractical due to the very low prevalence of coronary artery stenosis in pediatric patients in this group.[4]

Visipaque (iodixanol) injection is currently approved for use for the following:[5]

Intra-arterial Procedures

Adults and pediatric patients 12 years of age and over:

- Intra-arterial digital subtraction angiography (270 and 320 mg iodine/mL)
- Angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography (320 mg iodine/mL)

Pediatric patients less than 12 years of age:

- Angiocardiography, cerebral arteriography, and visceral arteriography (320 mg iodine/mL)

Intravenous Procedures

Adults and pediatric patients 12 years of age and over:

- Computed tomography (CT) imaging of the head and body (270 and 320 mg iodine/mL)
- Excretory urography (270 and 320 mg iodine/mL)
- Peripheral venography (270 mg iodine/mL)
- Coronary computed tomography angiography (CCTA) to assist diagnostic evaluation of patients with suspected coronary artery disease (320 mg iodine/mL)

Pediatric patients less than 12 years of age:

- CT imaging of the head and body (270 mg iodine/mL)
- Excretory urography (270 mg iodine/mL)

This review was prompted by the sNDA approval of Visipaque (iodixanol) injection for use in CCTA to assist diagnostic evaluation of patients with suspected coronary artery disease on April 4, 2017. DPV has not presented Visipaque (iodixanol) injection before the Pediatric Advisory Committee (PAC) in the past.

1.2 SELECT LABELED SAFETY INFORMATION

Select safety information from the Visipaque (iodixanol) injection for oral suspension product label dated March 2019 is included below:[5]

WARNING: NOT FOR INTRATHECAL USE

Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema. (4, 5.1**)**

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

VISIPAQUE is contraindicated for Intrathecal use [see Warnings and Precautions (5.1)]

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

5.1 Risks Associated with Inadvertent Intrathecal Administration

VISIPAQUE is for intravascular use only and is contraindicated for intrathecal use [see Contraindications (4) *and* Dosage and Administration (2.1)]. Inadvertent Intrathecal administration can cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.

5.2 Hypersensitivity Reactions

VISIPAQUE can cause life-threatening or fatal hypersensitivity reactions including anaphylaxis. Manifestations include respiratory arrest, laryngospasm, bronchospasm, angioedema, and shock. Most severe reactions develop shortly after the start of

the injection (within 3 minutes), but reactions can occur up to hours later. There is an increased risk in patients with a history of a previous reaction to contrast agent, and known allergies (i.e., bronchial asthma, drug, or food allergies) or other hypersensitivities. Premedication with antihistamines or corticosteroids does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.
Obtain a history of allergy, hypersensitivity, or hypersensitivity reactions to iodinated contrast agents and always have emergency resuscitation equipment and trained personnel available prior to VISIPAQUE administration. Monitor all patients for hypersensitivity reactions.

5.3 Contrast Induced Acute Kidney Injury
Acute kidney injury, including renal failure, may occur after VISIPAQUE administration. Risk factors include: pre-existing renal impairment, dehydration, diabetes mellitus, congestive heart failure, advanced vascular disease, elderly age, concomitant use of nephrotoxic or diuretic medications, multiple myeloma / paraproteinaceous diseases, repetitive and/or large doses of an iodinated contrast agent.
Use the lowest necessary dose of VISIPAQUE in patients with renal impairment. Adequately hydrate patients prior to and following VISIPAQUE administration. Do not use laxatives, diuretics, or preparatory dehydration prior to VISIPAQUE administration.

5.4 Cardiovascular Adverse Reactions
Life-threatening or fatal cardiovascular reactions including hypotension, shock, cardiac arrest have occurred with the use of VISIPAQUE. Most deaths occur during injection or five to ten minutes later, with cardiovascular disease as the main aggravating factor. Cardiac decompensation, serious arrhythmias, and myocardial ischemia or infarction can occur during coronary arteriography and ventriculography.
Based upon clinical literature reported deaths from the administration of iodinated contrast agents range from 6.6 per million (0.00066%) to 1 in 10,000 (0.01%). Use the lowest necessary dose of VISIPAQUE in patients with congestive heart failure and always have emergency resuscitation equipment and trained personnel available. Monitor all patients for severe cardiovascular reactions.

5.5 Thromboembolic Events
Angiocardiography
Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke can occur during angiocardiography procedures with both ionic and nonionic contrast media. During these procedures, increased thrombosis and activation of the complement system occurs. Risk factors for thromboembolic events include: length of procedure, catheter and syringe material, underlying disease state, and concomitant medications.
To minimize thromboembolic events, use meticulous angiographic techniques, and minimize the length of the procedure. Avoid blood remaining in contact with syringes containing iodinated contrast agents, which increases the risk of clotting. Avoid angiocardiography in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

5.6 Extravasation and Injection Site Reactions
Extravasation of VISIPAQUE Injection may cause tissue necrosis and/or compartment syndrome, particularly in patients with severe arterial or venous disease. Ensure intravascular placement of catheters prior to injection. Monitor patients for extravasation and advise patients to seek medical care for progression of symptoms.

5.7 Thyroid Storm in Patients with Hyperthyroidism
Thyroid storm has occurred after the intravascular use of iodinated contrast agents in patients with hyperthyroidism, or with an autonomously functioning thyroid nodule. Evaluate the risk in such patients before use of VISIPAQUE.

5.8 Hypertensive Crisis in Patients with Pheochromocytoma
Hypertensive crisis has occurred after the use of iodinated contrast agents in patient with pheochromocytoma. Monitor patients when administering VISIPAQUE if pheochromocytoma or catecholamine-secreting paragangliomas are suspected. Inject the minimum amount of contrast necessary, assess the blood pressure throughout the procedure, and have measures for treatment of a hypertensive crisis readily available.

5.9 Sickle Cell Crisis in Patients with Sickle Cell Disease
Iodinated contrast agents when administered intravascularly may promote sickling in individuals who are homozygous for sickle cell disease. Hydrate patients prior to and following VISIPAQUE administration and use VISIPAQUE only if the necessary imaging information cannot be obtained with alternative imaging modalities.

5.10 Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions (SCAR) may develop from 1 hour to several weeks after intravascular contrast agent administration. These reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS). Reaction severity may increase and time to onset may decrease with repeat administration of contrast agents; prophylactic medications may not prevent or mitigate severe cutaneous adverse reactions. Avoid administering VISIPAQUE to patients with a history of a severe cutaneous adverse reaction to VISIPAQUE.

----------ADVERSE REACTIONS----------
The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risks Associated with Inadvertent Intrathecal Administration [see Warnings and Precautions (5.1)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.2)]
- Contrast Induced Kidney Injury [see Warnings and Precautions (5.3)]
- Cardiovascular Adverse Reactions [see Warnings and Precautions (5.4)]
- Thromboembolic Events [see Warnings and Precautions (5.5)]
- Severe Cutaneous Reactions [see Warnings and Precautions (5.10)]

8.4 Pediatric Use
The safety and efficacy of VISIPAQUE have been established in pediatric patients down to birth for angiocardiography, cerebral arteriography, visceral arteriography, CT imaging of the head and body, and excretory urography. The safety and efficacy of VISIPAQUE have also been established in pediatric patients 12 years and older for intra-arterial digital subtraction angiography, peripheral arteriography, peripheral venography and CCTA. Use of VISIPAQUE is supported by evidence from adequate and well controlled studies of VISIPAQUE in adults and additional safety data obtained in 459 pediatric patients. In general, the types of adverse reactions reported are similar to those of adults. A higher number of adverse events in patients less than 1 year of age compared to older patients were observed in a study of VISIPAQUE *[see Adverse Events (*6.3*)]*. The elimination of VISIPAQUE is slower in this age group *[see Clinical Pharmacology (*12.3*)]*.

Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been uncommonly reported following iodinated contrast media administration to pediatric patients, including infants. Some patients were treated for hypothyroidism *[See Adverse Reactions (*6.2*)]*.

Pediatric patients at higher risk of experiencing an adverse reaction during and after administration of any contrast agent may include those with asthma, hypersensitivity to other medication and/or allergens, cyanotic and acyanotic heart disease, congestive heart failure, or a serum creatinine greater than 1.5 mg/dL. Pediatric patients with immature renal function or dehydration may be at increased risk for adverse events due to slower elimination of iodinated contrast agents *[see Clinical Pharmacology (*12.3*)]*.

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 14, 2019
Time period of search	March 22, 1996† - March 13, 2019
Search type	*Quick Query*
Product terms	Product name: Visipaque Product active ingredient: iodixanol NDA: 20351, 20808
MedDRA search terms (Version 21.1)	All preferred terms (PT)
* See Appendix A for a description of the FAERS database. † Approval date of Visipaque (iodixanol) single dose injection (NDA 20351)	

2.2 CAUSALITY ASSESSMENT

We assessed for a causal association with Visipaque (iodixanol) injection using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system as shown below in Table 2.

Table 2. Causality Classification and Criteria Based on the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) System[6]

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanation
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from March 22, 1996 to March 13, 2019 with Visipaque (iodixanol) injection.

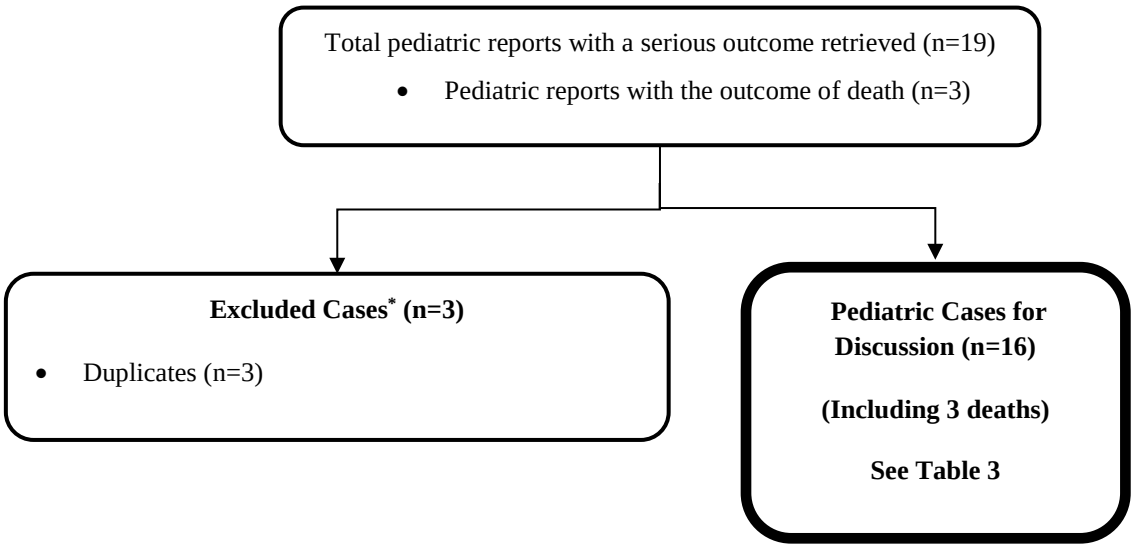
Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from March 22, 1996 to March 13, 2019 with Visipaque (Iodixanol) Injection			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	2186 (961)	1884 (663)	169 (61)
Pediatrics (0 - <17 years)	20 (1)	19‡ (0)	3‡ (0)

* 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. One additional report of pediatric death was identified among reports not reporting an age.

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 19 serious pediatric reports from March 22, 1996 to March 13, 2019. We reviewed all FAERS pediatric reports with a serious outcome. We excluded duplicate reports from the case series. We summarize the remaining cases in the sections below. Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with Visipaque (Iodixanol) Injection



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

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of the 16 pediatric cases.

Table 4 summarizes the 16 FAERS cases in pediatric patients with Visipaque (iodixanol) injection reporting a serious outcome received by FDA from March 22, 1996 to March 13, 2019.

Table 4. Characteristics of the FAERS Serious Pediatric Cases with Visipaque (Iodixanol) Injection Received by FDA from March 22, 1996 to March 13, 2019 (N=16)		
Age	0 - < 1 month	2
	1 month - <2 years	3
	2- < 6 years	2
	6- <12 years	2
	12- < 17 years	7
Sex	Male	12
	Female	2
	Unknown	2
Country	United States	0
	Foreign	16
Reported reason for use	CT imaging	8
	Loopogram	1
	Interventional chemosurgery	1
	Unknown	6
Visipaque concentration	270 mg/mL	3
	320 mg/mL	11
	Not reported	2
Serious outcome*	Death	3
	Life-threatening	2
	Hospitalization	6
	Other Serious	7

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

3.1.4 Summary of Fatal Pediatric Cases (N=3)

FAERS Case #7336274, France, Expedited, FDA Received Date March 11, 2010

A 15-day-old male born with a large cystic lymphangioma of the upper left extremity extending into the shoulder and chest was injected with 20 mL of Visipaque (320 mg/mL) into the cyst for opacification along with polidocanol and normal saline fluid mixture for flushing during lymphatic cyst lesion removal under general anesthesia. In addition, the patient received hydroxyethyl starch, albumin, and an unspecified electrolyte solution to maintain adequate arterial pressure during the procedure. Approximately 30 minutes after the procedure, the patient experienced respiratory arrest and was comatose requiring intubation. Chest X-ray revealed acute pulmonary edema. The patient rapidly decompensated and developed cardiogenic shock with severe dysfunction of both ventricles on echocardiography and required external cardio-respiratory support with extracorporeal membrane oxygenation (ECMO). The patient was treated with furosemide, dobutamine, and dopamine for cardiopulmonary support in addition to fomepizole and intralipid for reversal of polidocanol. His clinical condition was complicated by the development of disseminated intravascular coagulation (DIC), hyperlactatemia, and oligo-anuria. The ECMO circuit was clotted and cardiopulmonary support was terminated. The autopsy revealed pulmonary damage secondary to DIC and the presence of multivisceral

lymphangiectases. Based on the latter findings, the reporters postulated that the patient's lymphatic disease may have led to abnormal lymphatic permeability and resorption of drugs injected into the lesion.

Reviewer's comment: The autopsy reveals that death was multifactorial. The reporters conjecture that the anatomic lesion could have led to the potential abnormal resorption of multiple medications and this abnormal absorption might have led to pulmonary edema that evolved into multisystem organ dysfunction and death. Visipaque's role in the events that contributed to the fatal outcome is possible according to the WHO-UMC (Table 2); pulmonary edema and cardiovascular decompensation are respectively labeled in the Warnings and Precautions Section 5.4 and Adverse Reactions Section 6.1 of the Visipaque product label.[5] *Although the case lacks information about the patient's comorbidities and past medical history, we can infer his age and consequent vulnerability to more serious sequelae following medical complications is another potential factor to the fatal outcome.*

FAERS Case #7115476, China, Expedited, FDA Received Date September 4, 2009
An 8-month-old infant (unknown sex) received an unknown amount of Visipaque (320 mg/mL) for a cardiac CT. Route of administration was not reported. Four hours after Visipaque administration, the infant was found dead. Additional information was not provided.

FAERS Case #10479062, China, Expedited, FDA Received Date September 26, 2014
A 14-year-old male received 70 mL of Visipaque (320 mg/mL) intravenously for a contrast enhanced CT for an unknown indication. The patient experienced seizures ten seconds after Visipaque administration followed by hypopnea and pulselessness four minutes later. The patient was treated with epinephrine and dexamethasone and transferred to the intensive care unit where he died the following day. An autopsy was not performed, and no additional information was provided.

Reviewer's comment: Both cases lack clinical detail to assess for a causal relationship with Visipaque and adverse events leading to fatal outcomes according to the WHO-UMC criteria.

3.1.5 Summary of Non-Fatal Pediatric Serious Cases (N=13)

We identified 13 serious FAERS cases with Visipaque (iodixanol) injection in the pediatric population reporting a non-fatal serious outcome.

Cardiorespiratory Failures (n=2)
One case (#9271756) described a 5-month old male patient who developed cardiopulmonary arrest two minutes after intravenous administration of 11 mL Visipaque (270 mg/mL) for a CT angiography of the thoracic aorta. The patient had a history of Tetralogy of Fallot and was on concomitant unspecified antibiotic treatment. The patient was successfully resuscitated after five minutes of cardiopulmonary resuscitation. No additional information was provided. Another case (#13128003) described a 6-year-old male who experienced significant hypotension (with "blood pressure too low to measure"), shock, and transient oxygen desaturation after intra-arterial administration of 5 mL of Visipaque (320 mg/mL) for an interventional chemosurgery procedure

for retinoblastoma. The patient's symptoms resolved after 10 minutes with treatment of epinephrine. No additional information was provided.

Reviewer's comment: Both cases describe Visipaque use in pediatric patients for off-label reasons for use. Life-threatening or fatal cardiovascular reactions including hypotension, shock, and cardiac arrest are labeled within the Warnings and Precautions Section 5.4 of the Visipaque product label.[5] Both cases lack clinical detail to assess for a causal relationship. The cases do not contain additional detail to suggest increased severity of these labeled adverse events.

Cognitive and Neuromuscular Abnormalities (n=1)
One case (#11209655) described a 4-year-old male who experienced aphasia and "felt hot" immediately following intravenous administration of 19 mL Visipaque (270 mg/mL) for a CT of the facial bones. Approximately 30 minutes later, the patient also experienced hypertonia of lower limbs and hypotonia of the upper limbs that lasted approximately 30 minutes. Aphasia symptoms resolved after two hours. Evaluation with EEG was normal.

Reviewer's comment: The clinical findings of reversible aphasia with lower extremity hypertonia and upper extremity hypotonia are not congruent with known central or peripheral nervous system lesions or conditions. Visipaque administration is often associated with sensations of discomfort, warmth or pain and is labeled within the Adverse Reactions Section 6.1 of the Visipaque product label.[5] The patient's symptoms may represent transient contrast-induced encephalopathy, a condition that is labeled within the Adverse Reactions Section 6.2 of the product label and may include amnesia, hallucination, paralysis, paresis, transient speech disorder, aphasia, and dysarthria. Contrast-induced encephalopathy is currently labeled in the context of extravasation. In this case, the symptoms occurred without Visipaque extravasation but contrast-induced encephalopathy, including aphasia, has been reported with iodixanol use without extravasation in an adult.[7] However, in the absence of contextual clinical history, nonspecific symptoms in a young child may represent a broad range of potential diagnoses. Therefore, this case was assessed as possible according to the WHO-UMC criteria.

Extravasation (n=2)
Two cases described extravasation of Visipaque (320 mg/mL) in the anterior cubital region. One case (#7415848) described a 7-year-old male who had approximately 30 mL of Visipaque extravasated into the anterior cubital region resulting in induration, erythema, and edema on the affected arm; surgical intervention was not necessary, and the patient recovered with standard treatment without sequelae. Another case (#7458705) described an extravasation of approximately 40 mL of Visipaque into the anterior cubital region of a 16-year-old male that resolved with standard treatment without complications.

Reviewer's comment: Intravenous (IV) infiltration and drug extravasation, is a common complication of IV therapy in clinical practice.[8] Extravasation and injection site reactions are labeled within the Warnings and Precautions Section 5.6 of the Visipaque product label.[5] Both cases were assessed as probable according to the WHO-UMC criteria.

Hypersensitivity Reactions (n=7)
We identified seven cases reporting symptoms of hypersensitivity reactions. Descriptive characteristics of hypersensitivity reaction cases with Visipaque are available in Appendix C. Cutaneous reactions, including erythema, rash, and pruritis, were reported in six cases. Respiratory symptoms, including bronchospasm, cough, respiratory distress, and oxygen desaturation, were reported in two cases. Facial swelling was reported in one case. Most cases reported that the symptoms occurred within 24 hours of Visipaque administration. All cases reported treatment for hypersensitivity reactions with resultant symptom improvement or resolution. Three cases reported the presence of one or more concomitant medications; one (#8023470) of the three cases reported hypersensitivity adverse events occurred with remote Visipaque exposure (5 days prior) and closer temporal association to concomitant medications labeled for hypersensitivity (antiepileptic drugs and antibiotics). One case (#12185356) described the hypersensitivity reactions of facial swelling and respiratory distress, that occurred approximately 10 minutes after Visipaque administration, as an "intolerance" reaction, also reported that the patient had "at an earlier time reacted with weaker intolerance to unspecified contrast media." None of the cases provided information about dechallenge or rechallenge trials.

Reviewer's comment: Hypersensitivity reactions are labeled within Warnings and Precautions Section 5.2 of the Visipaque product label.[5] Visipaque can cause life-threatening or fatal hypersensitivity reactions including anaphylaxis. Manifestations include respiratory arrest, laryngospasm, bronchospasm, angioedema, and shock. Most severe reactions develop shortly after the start of the injection (within 3 minutes), but reactions can occur up to hours later. Causality was possible for six cases and unlikely in one case with remote Visipaque exposure and close temporal sequence of adverse events and concomitant medications. All cases lacked clinical information that could further enrich the causality assessment.

Cholestasis and Diarrhea (n=1)
One case (#13106126) described a 14-day-old male who experienced cholestasis, increased liver function tests, and dehydration a few hours after receiving a total of 50 mL of Visipaque (40 mL in ostomy and 10 mL in the rectum) for a loopogram. In addition, it was noted that there was a significant increase in the flow in the ostomy and diarrhea from the rectum days following Visipaque administration (specific time was not provided). It was noted that the patient "may" have Alagille syndrome or Vitamin B6 deficiency or both. No additional information was provided.

Reviewer's comment: Diarrhea is labeled for Visipaque (iodixanol) in the Clinical Trial Experience Section 6.1 of the product label;[5] it may also be secondary to cholestasis.[9] The report of Alagille syndrome in the patient is unclear. Alagille syndrome is a genetic disorder that can affect the biliary tree and result in liver dysfunction with clinical findings of hyperbilirubinemia and jaundice;[10] underlying Alagille syndrome may account for the cholestasis and abnormal liver function tests. Irrespective of confirmed presence or absence of Alagille diagnosis, the case lacks details about the clinical course and the patient history to determine the potential role of Visipaque in the development of the adverse events.

4 DISCUSSION

DPV reviewed all serious FAERS reports with Visipaque (iodixanol) injection in the pediatric population through <17 years of age during the period March 22, 1996 to March 13, 2019, and identified 16 foreign cases of serious adverse events, including 3 fatal cases. We assessed one of the fatal cases as having a possible causal association with Visipaque (iodixanol) injection based on a plausible temporal sequence and the adverse events (pulmonary edema and cardiovascular decompensation) leading to death are labeled risks of Visipaque (iodixanol). We assessed the remaining two cases as unassessable. The non-fatal cases described known labeled adverse events of cardiovascular events, extravasation, and hypersensitivity reactions. All cases had limited clinical information to assess causality. DPV did not identify any cases reporting intrathecal administration of Visipaque (iodixanol) injection.

5 CONCLUSION

There is no evidence from these data that there are new pediatric safety concerns with Visipaque (iodixanol) injection at this time.

6 RECOMMENDATION

DPV will continue monitoring for all adverse events associated with the use of Visipaque (iodixanol) injection use.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=16)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	9/2/2009	7103330	1	B0590198A	Expedited (15-Day)	15	Female	FRA	HO
2	9/4/2009	7115476	1	VISP-NO-0908S-0387	Expedited (15-Day)	0.67	Null	CHN	DE
3	3/11/2010	7336274	2	VISP-NO-1003S-0121	Expedited (15-Day)	0.04	Male	FRA	DE,LT
4	6/3/2010	7415848	1	VISP-NO-1005S-0253	Expedited (15-Day)	7	Male	FRA	OT
5	6/29/2010	7458705	1	VISP-NO-1006S-0309	Expedited (15-Day)	16	Male	FRA	OT
6	4/11/2011	7931539	2	VISP-NO-1103S-0114	Expedited (15-Day)	3	Male	RUS	HO
7	7/6/2011	8023470	1	FR-ROCHE-786339	Expedited (15-Day)	15	Male	FRA	OT
8	5/6/2013	9271756	1	CN-GE HEALTHCARE MEDICAL DIAGNOSTICS-VISP-NO-1304S-0597	Expedited (15-Day)	0.4	Male	CHN	HO,LT
9	9/19/2013	9536518	1	IT-GE HEALTHCARE MEDICAL DIAGNOSTICS-VISP-PR-1309S-0812	Expedited (15-Day)	15	Male	ITA	HO
10	1/30/2014	9855137	1	FR-GE HEALTHCARE MEDICAL DIAGNOSTICS-VISP-PR-1401S-0019	Expedited (15-Day)	16	Null	FRA	OT
11	9/26/2014	10479062	2	CN-GE HEALTHCARE MEDICAL DIAGNOSTICS-VISP-PR-1409S-0423	Expedited (15-Day)	14	Male	CHN	DE

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
12	6/22/2015	11209655	2	FR-GE HEALTHCARE MEDICAL DIAGNOSTICS-VISP-PR-1506S-0227	Expedited (15-Day)	4	Male	FRA	HO
13	3/16/2016	12185356	1	SE-GE HEALTHCARE MEDICAL DIAGNOSTICS-VISP-E2B_00000227	Expedited (15-Day)	13	Male	SWE	HO
14	1/11/2017	13106126	2	SE-GE HEALTHCARE MEDICAL DIAGNOSTICS-VISP-E2B_00000336	Expedited (15-Day)	0.03	Male	SWE	OT
15	1/18/2017	13128003 (13096793, 13097379, 13130444)†	2	CN-GE HEALTHCARE MEDICAL DIAGNOSTICS-VISP-PR-1701S-0006	Expedited (15-Day)	6	Male	CHN	OT
16	3/8/2019	16053805	1	MX-GE HEALTHCARE LIFE SCIENCES-2019CSU000820	Expedited (15-Day)	1	Female	MEX	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. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.

†Duplicate cases

Abbreviations: FRA=France, CHN=China, RUS=Russia, SWE=Sweden, MEX=Mexico, DE=Death, HO=Hospitalization, LT= Life-threatening, OT=Other medically significant

8.3 APPENDIX C. DESCRIPTION CHARACTERISTICS OF CASES OF HYPERSENSITIVITY REACTIONS WITH VISIPAQUE (IODIXANOL) INJECTION (N=7)

Descriptive Characteristics of Cases of Hypersensitivity Reactions with Visipaque (Iodixanol) Injection Use in FAERS, Received by FDA from March 22, 1996 to March 13, 2019 (n=7)		
Age	1 year	1
	3 years	1
	13 years	1
	15 years	3
	16 years	1
Sex	Male	4
	Female	2
	Unknown	1
Clinical findings*	Facial swelling	1
	Cutaneous manifestations	
	- Erythema	2
	- Pruritis	2
	- Rash, unspecified	3
	- Vesiculopapular rash	1
	Respiratory symptoms	
	- Bronchospasm	1
	- Cough	1
	- Oxygen desaturation	1
	- Respiratory distress	1
Time to symptom onset after Visipaque administration	4 minutes	1
	10 minutes	1
	6 hours	1
	Within 24 hours	1
	5 days	1
	Unknown	3
Concomitant medications†	Yes	3
	Not reported	4
Dechallenge or rechallenge trial	Not reported	7
WHO-UMC causality category§	Possible	6
	Unlikely	1

* A case can have one or more reactions

† Concomitant medications include medications that the patient was taking at the time of the event. All three cases that reported concomitant medications had inadequate information to assess for a temporal relationship between concomitant medication administration and hypersensitivity reactions

‡ A case can have one or more treatments

§ Cases of hypersensitivity events were assessed for a causal relationship with Visipaque using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system. See Table 2 for the causality classification and criteria based on the WHO-UMC system.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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