**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

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| **Date:** | November 25, 2019 |
| **Safety Evaluator:** | Danielle Molnar, PharmD, BCPS<br>Division of Pharmacovigilance II (DPV II) |
| **Medical Officer:** | Ivone Kim, MD, FAAP<br>DPV I |
| **Team Leader:** | Neha Gada, PharmD, BCPS<br>DPV II |
| **Deputy Division Director:** | Ida-Lina Diak, PharmD, MS<br>DPV II |
| **Product Name:** | DraxImage DTPA (technetium TC-99m pentetate kit) injection and inhalation |
| **Pediatric Labeling Approval Date:** | December 26, 2017 |
| **Application Type/Number:** | NDA 018511 |
| **Applicant/Sponsor:** | Jubilant DraxImage, Inc. |
| **OSE RCM #:** | 2019-1536 |

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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and for DraxImage diethylenetriaminepentaacetic acid (DTPA) (technetium TC-99m pentetate kit) in pediatric patients through age < 17 years of age. 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 unlabeled adverse events associated with DraxImage DTPA in pediatric patients.

The FDA approved DraxImage DTPA on December 29, 1989 and it is currently indicated for brain imaging; renal visualization, assessment of renal perfusion, and estimation of glomerular filtration rate; and lung ventilation imaging and evaluation of pulmonary embolism when paired with perfusion imaging. The approved pediatric labeling is for lung ventilation and evaluation of pulmonary embolism when paired with perfusion imaging and for renal visualization, assessment of renal perfusion, and estimation of glomerular filtration rate in pediatric patients through age < 17 years of age.

We reviewed all FAERS reports with DraxImage DTPA from December 26, 2016 through July 15, 2019 and there were none in pediatric patients. Therefore, there is no evidence from these data that there are pediatric safety concerns with DraxImage DTPA at this time. DPV recommends no regulatory action at this time and will continue to monitor all adverse events in the pediatric population associated with the use of DraxImage DTPA.

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for DraxImage diethylenetriaminepentaacetic acid (DTPA) (technetium TC-99m pentetate kit) 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 unlabeled adverse events associated with DraxImage DTPA in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

DraxImage DTPA is a kit for the preparation of Technetium Tc-99m pentetate injection, a radiodiagnostic agent, for intravenous or inhalation use. The active ingredient in DraxImage DTPA is DTPA, known by other names including pentetate and pentetic acid.[1] The non-radioactive DTPA in the DraxImage DTPA kit is combined with user-supplied radioactive technetium-99m to form the technetium Tc-99m pentetate product administered to the patient.

DraxImage DTPA (NDA 018511) was approved on December 29, 1989 for use in adult patients by injection. Use in the pediatric population was approved along with a new route of administration, inhalation, on December 26, 2017.

For adult and pediatric patients, DraxImage DTPA is approved for renal visualization, assessment of renal perfusion, and estimation of glomerular filtration; as well as for lung ventilation imaging and evaluation of pulmonary embolism when paired with perfusion imaging and administered by nebulizer. The third indication, brain imaging, is approved for the adult population only.

Use of DraxImage DTPA in pediatric patients through age < 17 years is supported by evidence from controlled studies in adults. Dosing and safety are based on clinical experience. The clinical review corresponding to the pediatric labeling evaluated available safety data including published literature and postmarketing safety data (from the sponsor and FAERS) and concluded that, although the data are limited, no new safety concern was identified.[1]

This DPV review was prompted by the pediatric labeling approved on December 26, 2017. DPV has not presented DraxImage DTPA before the Pediatric Advisory Committee (PAC) in the past.

## 1.2 RELEVANT LABELED SAFETY INFORMATION[2]

CONTRAINDICATIONS

Hypersensitivity to the active ingredient or to any component of the product [*see Warnings and Precautions (5.1)]*.

WARNINGS AND PRECAUTIONS

**Hypersensitivity Reactions**

Hypersensitivity reactions, including anaphylaxis, have been reported during post-approval diagnostic use of Technetium Tc 99m pentetate injection. Monitor all patients

for hypersensitivity reactions and have access to cardiopulmonary resuscitation equipment and personnel.

**Image Interpretation Risks in Lung Ventilation Studies**
In patients with obstructive pulmonary disease there may be deposition of particles in the proximal airways influencing image quality and interfering with diagnostic interpretation, therefore to ensure diagnostic quality, careful use of the nebulizer to assure optimal particle delivery is essential. If interfering particle deposition occurs, consider additional diagnostic options.

**Radiation Exposure Risk**
Technetium Tc 99m contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Ensure safe handling and preparation procedures to protect patients and health care workers from unintentional radiation exposure. Use the lowest dose of Technetium Tc 99m pentetate necessary for imaging. Encourage patients to drink fluids and void as frequently as possible after intravenous administration *[see Dosage and Administration (2.1, 2.3)]*.

Radiation risks associated with the use of Technetium Tc 99m pentetate are greater in pediatric patients than in adults due to greater radiosensitivity and longer life expectancy.

**Bronchospasm in Lung Ventilation Studies**
As with other inhaled medications, inhalation of Technetium Tc 99m pentetate solution may result in acute bronchoconstriction, especially in patients with heightened bronchoreactivity, such as patients with asthma or other lung or allergic disorders. Monitor all patients for bronchoconstriction.

ADVERSE REACTIONS

Most common adverse reactions reported with Technetium Tc 99m Pentetate injection include allergic reactions, rash, itching (6).

USE IN SPECIFIC POPULATIONS

**Lactation**

Risk Summary

There are limited data available in scientific literature on the presence of Technetium Tc 99m pentetate in human milk. There are no data available on the effects of Technetium Tc 99m pentetate on the breastfed infant or the effects on milk production. Based on the United States Nuclear Regulatory Commission guidelines for breast feeding interruption after exposure to radiopharmaceuticals, breastfeeding interruption is not recommended for Technetium 99m pentetate at levels less than 1000 MBq (30 mCi). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Technetium Tc 99m pentetate, any potential adverse effects on the breastfed child from Technetium Tc 99m pentetate or from the underlying maternal condition.

**Pediatric Use**
Technetium Tc 99m pentetate is indicated for lung ventilation and evaluation of pulmonary embolism when paired with perfusion imaging and for renal visualization, assessment of renal perfusion, and estimation of glomerular filtration rate in pediatric patients ages birth to less than 17 years of age. Pediatric use is supported by evidence from controlled studies in adults and dosing and safety are based on clinical experience. The radiation risk of Technetium Tc 99m pentetate is greater in pediatric patients than adults *[See Warnings and Precautions, (5.3)]*.

# 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 | July 16, 2019 |
| Time Period of Search | December 12, 2016† through July 15, 2019 |
| Search Type | Quick Query |
| Product Terms | Product Active Moiety: Technetium Tc-99m pentetate<br>Active Ingredient: Technetium Tc-99M pentetic acid<br>Product Active Ingredient: Technetium Tc-99M pentetate calcium trisodium<br>NDA #: 018511 |
| MedDRA Search Terms (Version 22.0) | All Preferred Terms (PTs) |
| * See Appendix A for a description of the FAERS database.<br>† One year prior to the approval date of pediatric labeling change. | |

# 3 RESULTS

## 3.1 FAERS

### *3.1.1 Total Number of FAERS Reports by Age*

Table 2 presents the number of adult and pediatric FAERS reports from December 12, 2016 through July 15, 2019 with DraxImage DTPA.

| **Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from December 12, 2016 through July 15, 2019 with DraxImage DTPA** | | | |
|---|---|---|---|
| | **All reports (U.S.)** | **Serious† (U.S.)** | **Death (U.S.)** |
| Adults (≥ 17 years) | 3 (2) | 1 (0) | 0 (0) |
| Pediatrics (0 - <17 years) | 0 (0) | **0 (0)** | 0 (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.

### *3.1.2 Selection of Serious Pediatric Cases in FAERS*

Our FAERS search retrieved zero serious pediatric cases from December 12, 2016 through July 15, 2019.

### *3.1.3 Summary of Fatal Pediatric Cases (N=0)*

We did not identify any fatal pediatric adverse event cases.

## 4 DISCUSSION

There were no reports for DraxImage DTPA in pediatric patients and, therefore, we did not identify any safety signals.

## 5 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns for DraxImage DTPA at this time.

## 6 RECOMMENDATION

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

## 7 REFERENCES


1. Hofling A, Clinical Review: DraxImage DTPA (NDA 018511 supplement 28), 2017, accessed August 8, 2019, https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present.
2. DraxImage DTPA (kit for the preparation of technetium Tc 99m pentetate injection), for intravenous and inhalation use [Prescribing Information], Kirkland, Quebec, Canada: Jubilant DraxImage Inc. Accessed July 17, 2019, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018511s028lbl.pdf.

# 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.

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DANIELLE M MOLNAR
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IVONE E KIM
11/25/2019 02:17:29 PM

NEHA GADA
11/25/2019 04:24:17 PM

IDA-LINA DIAK
11/25/2019 04:26:17 PM