Medical Imaging Drugs Advisory Committee Meeting

Gadolinium Retention after Gadolinium Based Contrast Magnetic Resonance Imaging in Patients with Normal Renal Function

Briefing Document
September 8, 2017

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this safety issue to the advisory committee in order to gain the committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 Briefing Document Introduction and Summary

FDA has convened this advisory committee to seek opinions and recommendations on regulatory approaches to the issue of gadolinium retention in the brain and other body organs following administration of Gadolinium Based Contrast Agents (GBCAs). The evidence indicating retention following the use of GBCAs has led to concerns that gadolinium retention may cause adverse reactions, if not immediately then at some later date. FDA will ask the committee to focus on scientific facts; observational data; nonclinical, clinical, and epidemiological study findings; post-marketing adverse event reports; and regulatory requirements in considering its responses to FDA questions. FDA's approach has been educational: alerting the public and clinicians to the retention phenomenon but not issuing any restrictions on use because toxic effects in humans have not been established.

We now seek advice from the committee on the strength of the scientific evidence that would support potential regulatory actions such as labeling changes in relation to gadolinium retention. We also seek suggestions on the design of further epidemiologic and other studies to investigate potential adverse events associated with gadolinium retention in humans.

In its deliberations, the committee should consider the issue of gadolinium retention in relation to all of the FDA-approved GBCAs, which are listed in the following table.

Tradename[1]	Active ingredient	Applicant	Indication	Chemical subclass	Approval year
Magnevist	gadopentetate dimeglumine, Gd-DTPA	Bayer	Neuro, Body	Linear	1988
Prohance	gadoteridol, Gd-HP-DO3A	Bracco	Neuro	Macrocyclic	1992
Omniscan	gadodiamide, Gd-DPTA-BMA	GE	Neuro, Body	Linear	1993
Optimark	gadoversetamide, Gd-DPTA-BMEA	Guerbet	Neuro, Liver	Linear	1999
Multihance	gadobenate dimeglumine, Gd-BOPTA	Bracco	Neuro, Vascular	Linear	2004
Eovist	gadoxetate disodium, Gd-EOB-DTPA	Bayer	Liver	Linear	2008
Ablavar (not marketed)	gadofosveset	Lantheus	Vascular	Linear	2008
Gadavist	gadobutrol	Bayer	Neuro, Vascular, Breast CA	Macrocyclic	2011
Dotarem	gadoterate meglumine	Guerbet	Neuro	Macrocyclic	2013

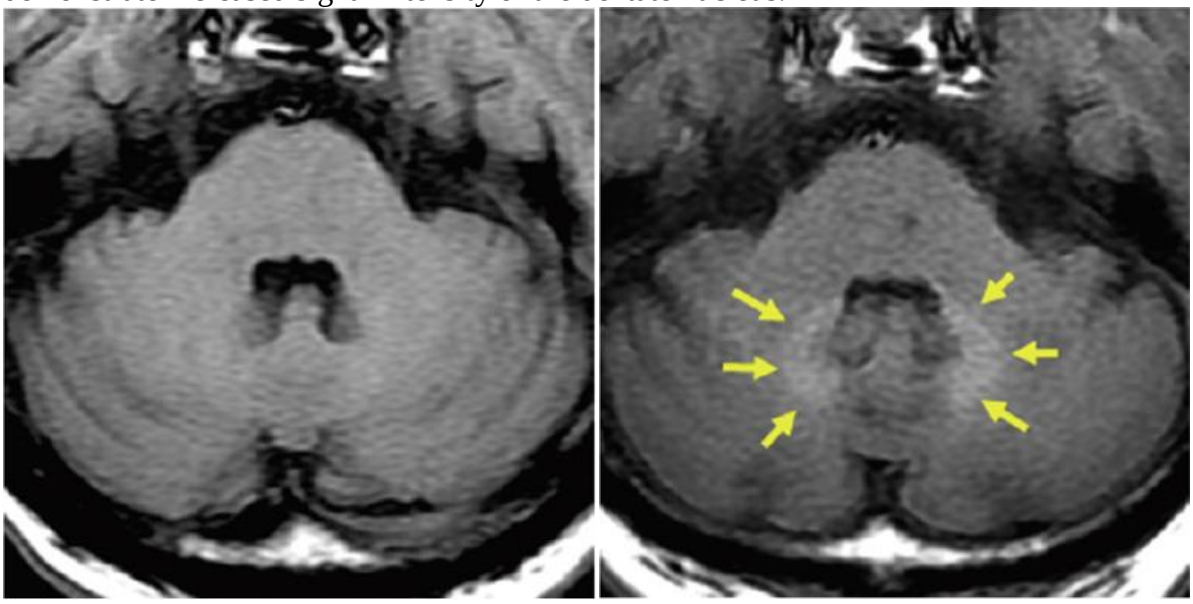
Gadolinium toxicity related to its retention was first suspected in patients with renal failure manifesting as a debilitating condition involving skin, joints and other organs, Nephrogenic Systemic Fibrosis (NSF). In 2009, FDA convened an advisory committee to provide recommendations for actions in response to then accumulating clinical and scientific data demonstrating that NSF developed following the administration of certain GBCAs to patients

[1] A note on nomenclature: FDA typically prefers not to use tradenames in public discussion of marketed drugs. In the case of GBCAs, however, there are reasons to make exception to this standard practice. First, multiple studies refer to distinct tradename- vs. active-ingredient-termed comparison arms (where the difference depends on the presence/amount of excess chelate in each formulation), meaning use of the ingredient terms might lead to confusion. Second, the use of multiple ingredient terms per drug is confusing.

with severe renal failure. The committee recommended contraindicating the GBCAs most commonly associated with NSF (Magnevist, Omniscan and Optimark) in patients with GFR < 30 mL/min/1.73m^2. Over the ensuing years, the labeling updates and changes in imaging practice led to a significant decrease of NSF cases. This approach of labeling (i.e., agent-specific warnings and restrictions limited to patients with severe renal failure most prone to NSF), education, and interaction with the practice community was the basis of our response to NSF.

More recently, data indicating gadolinium retention in patients with normal kidney function have begun to accumulate. As noted in other sections of this briefing document, publications by Kanda (**Figure 1**) and subsequently by other investigators alerted FDA to T1 signal intensity in various brain nuclei following non-contrast MRIs in patients who had previous GBCA contrast MRIs.

Figure 1: Gadolinium retention in a lung cancer patient. Axial unenhanced T1-weighted image of the first (left panel) and 9th (right panel) gadolinium-enhanced MRI exams. Arrows demonstrate increased signal intensity of the dentate nucleus.[2]



Brain retention was first identified following MRIs with linear GBCAs and later studies identified retention with macrocyclic GBCAs. Linear GBCAs consist of gadolinium linked to a larger open-chain molecule (a ligand). Macrocyclic GBCAs consist of gadolinium linked to a cyclic ligand. The linear GBCAs are chemically less stable in terms of their tendency to release gadolinium ions; the macrocyclic GBCAs tend to stay intact.

In response to these retention findings, the Office of Surveillance and Epidemiology (OSE) completed reviews of adverse events in conjunction with gadolinium retention reported to the FDA Adverse Event Reporting System (FAERS) database and in the medical literature. In addition, FDA sent information requests to the GBCA manufacturers asking for assessments of

[2] Kanda T, Nakai Y, Oba H, Toyoda K, Kitajima K, Furui S. Gadolinium deposition in the brain. Magnetic resonance imaging. 2016 Dec 31;34(10):1346-50

their pharmacovigilance data, acknowledging that long-term adverse effects would be difficult to discern in post-marketing reporting databases.

The most recent OSE review (see Pharmacovigilance Section in this briefing document) provides a cumulative assessment of spontaneous reports in FAERS and the published literature, and finds a heterogeneous group of adverse events reported in conjunction with gadolinium retention after GBCA exposure. While the adverse events lacked a consistent phenotype, some clustering around cutaneous, musculoskeletal, cognitive/neurological, and pain syndrome clinical categories was observed. The adverse events usually started within a short period following GBCA administration; followed a variable number of GBCA administrations, sometimes one; and occurred with most of the approved GBCAs. Overall, a causal association between these reported adverse events and gadolinium retention following GBCA exposure cannot be established based on currently available data in FAERS and the medical literature. Reports from the GBCA sponsors were similar. In addition, FDA has continued to receive reports from a consumer group self-reporting a variety of painful conditions following GBCA administration and measurable levels of urinary gadolinium over a prolonged period. The published epidemiology on potential risks associated with long-term retention of gadolinium in humans is sparse, with a single study suggesting no association between gadolinium exposure and subsequent risk of Parkinsonism over a relatively short duration of follow-up (see Epidemiology Section in this briefing document).

As evidence grew indicating brain retention following the use of GBCAs, FDA issued a Drug Safety Communication in July 2015 that acknowledged these reports, particularly that linear GBCAs lead to greater retention than macrocyclic GBCAs and stated that we were unable to identify any clinical conditions that were associated with gadolinium brain retention. FDA initiated a nonclinical rat study with the National Center for Toxicologic Research (NCTR) looking at potential behavioral and histopathological changes over a year period following the administration of all of the approved GBCAs. This study is ongoing.

Multiple preclinical and interval human autopsy studies have demonstrated that all GBCAs are retained for at least months in the brain, with linear GBCAs retained to a greater degree and likely for longer compared to macrocyclic GBCAs. Other nonclinical and clinical studies have shown that retention is higher in skin and bone and multiple other tissues compared to brain and that there is variability in retention among linear GBCAs.

GBCA retention has been a major symposium topic at recent national meetings of academic imaging organizations. At these meetings, no association between gadolinium brain retention and any untoward clinical effects was reported. Nevertheless, public and clinician concern continued to grow. The NIH issued guidelines listed below recommending that investigators consider use of macrocyclic GBCAs in clinical studies, particularly when a protocol called for repetitive GBCA MRI imaging. The following is quoted from that publication:[3]

[3] Malayeri, AA, et. al. National Institutes of Health Perspective on Reports of Gadolinium Deposition in the Brain, J. Am. Col Radio. (2016). 13 237-241

- GBCAs should be used only when clinically indicated or when specified in an institutional review board-approved protocol.

- When GBCAs are required, consider the use of a macrocyclic GBCA (i.e., Prohance, Dotarem and Gadavist).

- When GBCAs are required for patients with documented sensitivity (e.g., hives) to macrocyclic agents, it is appropriate to use linear agents.

- Site-specific MRI protocols should always consider FDA label indications and dosing schemes for administration of GBCAs.

- Encourage intra- and interdepartmental research programs to evaluate T1 shortening in the brain and other organs in patients who have received multiple doses of GBCAs

In 2016, at the request of the manufacturer of Optimark, a linear GBCA, labeling changes were made to the Pharmacokinetics Section of the Optimark label. The new subsection titled, "Deposition with Repeated Dosing," noted the increase in T1 signal, that gadolinium may present in other organs, and that retention may be greater with linear GBCAs than macrocyclic GBCAs. The subsection concluded by stating, "The clinical significance of gadolinium retention in the body and brain is… unknown."

In 2017, the EMA extensively reviewed and discussed at its committee meetings the greater and longer retention of linear GBCAs compared to the macrocyclic agents. Through their committee review process, EMA concluded that certain linear GBCAs be suspended from the European Market. They also could not identify any untoward effects and suspension was precautionary as stated in their July 21, 2017 press release (excerpted below – see Section 5 Appendix for the EMA public documents):[4]

> "There is currently no evidence that gadolinium deposition in the brain has caused any harm to patients; however EMA has recommended restrictions for some intravenous linear agents in order to prevent any risks that could potentially be associated with gadolinium brain deposition. Certain intravenous linear agents (Omniscan, Magnevist and Optimark) are to be suspended in EU. Other linear agents (Multihance and Eovist) can continue to be used for liver scans because they are taken up in the liver and meet an important diagnostic need."

FDA issued another Drug Safety Communication (DSC) on May 22, 2017, which reiterated our current finding of no known adverse effects related to GBCA brain retention. We noted that publications reported very rare fibrotic and pain conditions possibly associated with gadolinium retention in other body organs.[5] We continued to recommend that GBCAs be used only when

[4] http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/07/news_detail_002780.jsp&mid=WC0b01ac058004d5c1 accessed on July 31, 2017

[5] Semelka RC, et. al. Presumed Gadolinium Toxicity in Subjects With Normal Renal Function: A Report of 4 Cases.Invest Radiol. 2016 (10): 661-665

imaging data cannot be obtained by other modalities and that the lowest possible dose be administered.

Our current understanding involves the following:[6]

- Visible signal intensity increases in deep brain areas are more robustly associated with previous administration of linear compared to macrocyclic GBCAs (Jost 2016, Robert 2015, Zhang 2016, Kuno 2016);

- Gadolinium is present not only where increase signal intensity is seen in the brain, but also in other locations in the brain (Jost 2016).

- All of the GBCAs, regardless of structure or ionicity, are associated with some level of residual or accumulated gadolinium, with higher tissue gadolinium concentrations after administration of linear agents than after administration of macrocyclics (Robert 2016, Murata 2016); there is also variability in retention among linear GBCAs;

- Gadolinium concentrations in bone, liver, spleen, skin, and other organs are higher that gadolinium concentrations measured in brain (Lohrke 2017, Roberts 2016, Murata 2016);

- Gadolinium associated with macrocyclic agents may washout from the brain over time, whereas gadolinium from linear agents may not (Jost 2016, Frenzel 2017);

- No associated histopathology or morphologic findings have been reported in the brains of animal models after high dose GBCA administration (Smith 2016, Lorhke 2016);

- Histopathologic and morphologic skin findings are reported in an animal model after high doses of Omniscan and Optimark but not after high doses of other GBCAs (Lohrke 2017, Wible 2001);

- Sporadic case reports, most with unverified or unreported gadolinium retention, have been published raising the possibility of clinical symptoms related to GBCA administration (Bhawan 2013, Gathings 2014, Miller 2015, Barbieri 2016, Burke 2016, Semelka 2016a, Semelka 2016b, Ray 2016).

We note the following data gaps:

- Lack of a clear connection between the reported adverse events and extracranial retention;

- No clear toxic threshold for retention in the brain or other body organ has been identified;

[6] The provided references are listed among the References in Section 5 of the Briefing Document.

- Sparse (published) population-based data on risk associated with long-term retention of gadolinium, with a single study suggesting no association between gadolinium exposure and risk of parkinsonism

The limited evidence currently available leads FDA to believe that gadolinium brain retention may be a phenomenon without known clinical consequences. However, the human data are sparse and the long term effects are not known, and more research is necessary. Robust data are not available on gadolinium retention in other organs. It is prudent to warn patients and clinicians about gadolinium retention and the related differences among the GBCAs. It could be a factor when weighing the necessity of a GBCA MRI or choosing a specific agent.

We note that the clinical community has already been adjusting its GBCA prescribing practices. Using proprietary databases available to the FDA, an analysis of sales and patient utilization data for 2006 through 2016 indicate that GBCAs continue to be widely used in the US. During the time period examined, there was an increase in the utilization of macrocyclic GBCAs and a decrease in the utilization of linear GBCAs in the US. Data suggest a higher proportion of macrocyclic GBCA utilization vs linear GBCA utilization in the pediatric population compared to the adult population in 2016. Further analysis of utilization patterns are provided in the Drug Utilization Section of this briefing document.

In addition to the Pharmacovigilance, Epidemiology and Drug Utilization sections, this document contains the Medical Imaging section which further summarizes our thoughts on the available clinical and non-clinical data.

It is important to note that FDA's intention in convening the current Advisory Committee is to solicit advice limited in scope to safety issues surrounding post-GBCA gadolinium retention in patients with normal renal function. We do not plan on extending the discussion to overall risk-benefit considerations at this time. That would have to involve, for each drug, an assessment of demonstrated benefit in relation to all relevant safety issues and not just retention, which would be beyond the scope of this meeting.

In relation to gadolinium retention we provide to the Advisory Committee the following Draft Points for Consideration:

- Given the state of the scientific evidence of gadolinium retention in the skin, brain, and other tissues of patients with normal kidney function, what is the clinical significance, if any, of such retention?

- We are concerned about spontaneous reported adverse events following GBCA use and are unclear on their relation to gadolinium retention. What should be an approach to study it further?

- Can we identify patient populations (like the very young or the very old) in whom the risk of gadolinium retention and its clinical significance could be greater than in other populations?

- In addition to the steps we have already taken, should patients and health care providers be informed further and the risk of gadolinium retention further mitigated?

  For example, we are considering an addition of a warning to the GBCA labels which would communicate the finding of retention in the brain and other organs in patients with normal renal function, with inclusion of a statement that no known adverse effects causally associated with brain retention have been identified based on limited studies. We would indicate that certain linear agents are associated with greater retention than macrocyclic agents. Additional labeling information would be included on a drug-by-drug basis. The label would also acknowledge the occurrence of post-GBCA pain, skin reactions and other conditions where a causal association with GBCAs remains unconfirmed. Do you agree?

- Please discuss increased pharmacovigilance by the GBCA sponsors such as targeted follow-up which could lead to medical confirmation of events and documentation of gadolinium retention?

- Please comment on epidemiologic and mechanistic studies that sponsors should carry out to investigate the long term effects of gadolinium, including in specific populations:
  - Elderly;
  - Pediatric;
  - Patients with conditions requiring frequent monitoring such as breast cancer;
  - Patients with inflammatory conditions that might initiate an immunologic cascade with gadolinium.

Section 2
Pharmacovigilance

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

2 Pharmacovigilance Section

Date:	August 11, 2017
Reviewers:	Kathleen M. Phelan, RPh, Safety Evaluator Division of Pharmacovigilance II David Croteau, MD, FRCPC, Medical Officer Division of Pharmacovigilance I
Team Leaders:	Sara Camilli, PharmD, BCPS, Safety Evaluator Team Leader Allen Brinker, MD, MS, Medical Officer Team Leader Division of Pharmacovigilance II
Division Director:	S. Christopher Jones, PharmD, MPH, MS Division of Pharmacovigilance II
Product Names:	Gadolinium-Based Contrast Agents
Subject:	Gadolinium Retention and Associated Adverse Events
Application Type/Number:	Multiple (See Appendix A)
Applicant/Sponsor:	Multiple (See Appendix A)
OSE RCM #:	2017-1326
TSI #:	001427

2.1 Executive Summary

The primary purpose of this review is to characterize post-marketing reports of adverse events in conjunction with gadolinium retention after exposure to gadolinium-based contrast agents (GBCAs) in patients with normal renal function reported to the FDA Adverse Event Reporting System (FAERS) and in the medical literature. Nephrogenic systemic fibrosis (NSF) and acute hypersensitivity reactions are not discussed in this review, as those adverse reactions are well characterized in GBCA labels.

A heterogeneous group of adverse events has been reported in 139 patients (41 in FAERS and 98 in the medical literature) in conjunction with gadolinium retention after GBCA exposure. Many reported adverse events began after a single administration of GBCA, and were reported after exposure to linear GBCAs, macrocyclic GBCAs, and both. While adverse events identified in this review lacked a consistent phenotype, we observed some clustering around cutaneous, musculoskeletal, neurological/cognitive, and pain syndromes clinical categories. However, the clinical category "other" accounted for the highest number of adverse events, emphasizing the heterogeneity of the adverse events reported. While there is adequate evidence to demonstrate that gadolinium retention can occur, a causal association between these adverse events and gadolinium retention following GBCAs exposure cannot be established based on currently available data.

The self-reported nature of the information and the unverified evidence of gadolinium retention are the major limitations of the FAERS and the medical literature cases identified in this review. Other factors, such as nonspecific or delayed adverse events and the presence of websites and social media with interest in gadolinium retention, may have, potentially, led to under- or overestimation of the importance of the problem.

Despite the growing number of imaging publications on MRI signal abnormality presumed to represent gadolinium retention in the brain and post-mortem findings all characterizing gadolinium retention predominantly in cerebral and cerebellar deep grey nuclei, no robust cases with adverse events attributable to a pathologic process manifesting within those structures have been found.

While this review of FAERS and the medical literature cases did not confirm an apparent causal association between reported adverse events and gadolinium retention, reports in FAERS and the medical literature suggest a growing concern for untoward effects of GBCAs within both the lay public and the medical community.

2.2 Introduction

The primary purpose of this review is to characterize post-marketing reports of adverse events in conjunction with gadolinium retention after exposure to gadolinium-based contrast agents (GBCAs) in patients with normal renal function reported to the FDA Adverse Event Reporting System (FAERS) and in the medical literature. FAERS reports of gadolinium retention without adverse events and FAERS reports of persistent adverse events after exposure to GBCAs but without reported evidence of gadolinium retention are included for a broad review of gadolinium retention and potential adverse events. Nephrogenic systemic fibrosis (NSF) and acute

hypersensitivity reactions are not discussed in this review as those GBCA adverse reactions are well characterized in GBCA labels.

The Divisions of Pharmacovigilance (DPV) I and II initiated this review to support the upcoming advisory committee meeting on gadolinium retention.

2.2.1 Background

In 2015 and 2016, the Office of Pharmacovigilance and Epidemiology (OPE) completed three pharmacovigilance reviews of adverse events reported after exposure to GBCAs in patients with normal renal function at the request of the Division of Medical Imaging Products (DMIP).[1] The reviews focused on reports of gadolinium retention in the brain,[1] excretion in the urine,[2] or retention in any other body fluid or tissue.[3] The case reports in these reviews included patients who attributed symptoms to retained gadolinium and patients who were asymptomatic. All three reviews concluded that gadolinium can be retained in patients with normal renal function after they receive a GBCA, but that the clinical effects of gadolinium retention are uncertain.

The current review includes all relevant medical literature published since 1988 and retrieved by the searches described in section 2.3. The current review also describes gadolinium retention cases received by FDA in the year since those reviews (from June 1, 2016, to May 31, 2017), all gadolinium retention FAERS cases described in the three previous OPE reviews that meet the case definition in section 2.3.1.1, and all cases of adverse events after GBCA administration that are persisting at least 4 weeks after GBCA that were received by FDA in the year since those reviews.

On July 27, 2015, FDA issued a Drug Safety Communication (DSC) entitled, "FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for MRI." The DSC communicated, in part, "Recent publications in the medical literature have reported that deposits of GBCAs remain in the brains of some patients who undergo four or more contrast MRI scans, long after the last administration. It is unknown whether these gadolinium deposits are harmful or can lead to adverse health effects." The DSC update, issued on May 22, 2017, reiterated this understanding.

2.2.2 Regulatory History

DMIP opened Tracked Safety Issue (TSI) 001427 in June 2015 because of medical literature that demonstrated the retention of gadolinium in the brain after GBCA-enhanced MRIs in patients with normal renal function.

On July 27, 2015, and May 22, 2017, FDA issued DSCs on this topic stating that FDA was evaluating the risk of gadolinium retention after repeated use of GBCAs for MRI.

See Appendix A in section 2.8.1 for the GBCAs' approval dates, sponsors, indications, and structural class.

2.2.3 Product Labeling

Labeling for all approved GBCAs contains a boxed warning about NSF in patients with impaired renal function who receive GBCAs. Because of the greater risk of NSF with three of the linear GBCAs, as discussed at the December 8, 2009 joint meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committees, Magnevist (gadopentetate dimeglumine), Omniscan (gadodiamide), and Optimark (gadoversetamide) are contraindicated in patients with "chronic, severe kidney disease (glomerular filtration rate, GFR < 30 mL/min/1.73m^2), or acute kidney injury."

In August 2016, the sponsor added the following language to the *Pharmacokinetics* subsection of the Optimark (gadoversetamide) labeling. FDA concurred with this addition. Currently, Optimark is the only GBCA to mention gadolinium retention or deposition in labeling.

> *Deposition with Repeated Dosing*
>
> Increased signal intensity on non-contrast T1-weighted images within the brain, mainly the globus pallidus and the dentate nucleus, has been observed after multiple administrations of linear (ionic and nonionic) gadolinium-based contrast agents due to gadolinium deposition.
>
> Following repeated GBCA administration, gadolinium deposits may be present for months or years in bone, liver, skin, brain, and other organs. Deposition depends on multiple factors and may be greater following administration of gadoversetamide and other linear GBCAs than following administration of macrocyclic GBCAs. GBCAs have been associated with the development of NSF in patients with renal impairment [see Boxed Warning]. The clinical significance of gadolinium retention in the body and brain is otherwise unknown.

NSF is the only adverse event in any GBCA labeling that is currently attributed to gadolinium retention. GBCA labeling does not include any information about adverse events related to the retention of gadolinium in patients with normal renal function.

2.3 Methods and Materials

2.3.1 Case Definition

FAERS cases in this review are described in two categories: 1) cases that report evidence of gadolinium retention after GBCA use with or without adverse events, and 2) cases that report persistent adverse events after GBCA use but do not report evidence of gadolinium retention. Cases that report persistent adverse events but without evidence of gadolinium retention are included but described separately because these patients may be experiencing the same effects as those who were tested for gadolinium retention but may not be aware of possible retention or how to obtain testing.

2.3.1.1 FAERS cases that report gadolinium retention after GBCA administration with or without clinical adverse events

- Cases were included if they
  - reported exposure to a GBCA before either of the following:
    - laboratory tests, such as urine, blood, or hair analyses, found levels of gadolinium considered by the laboratory to be above normal levels for the test,[7] whether or not the level is reported OR
    - non-contrast MRI T1 hyperintense signal abnormality is observed
  - AND 4 weeks or longer after GBCA exposure
    - gadolinium level was reported to be above normal OR
    - any reported adverse events were persisting

- Cases were excluded if they
  - were MedDRA coded with PT *Nephrogenic systemic fibrosis* OR
  - reported that the patient had renal failure, renal insufficiency, eGFR < 30 mL/min/1.73m^2, or acute kidney injury at the time of GBCA administration OR
  - were published in the medical literature

Published FAERS cases are included in the Medical Literature sections of this review.

2.3.1.2 FAERS cases that report persistent adverse events but do not report evidence of gadolinium retention

- Cases were included if they
  - reported exposure to a GBCA before adverse events appear that are attributed by the reporter to gadolinium exposure AND
  - reported adverse events persisting 4 weeks or longer after GBCA exposure AND
  - were reported to FDA between June 1, 2016 and May 31, 2017

- Cases were excluded if they
  - were included in the case series of cases that report evidence of gadolinium retention OR
  - were MedDRA coded with the PT *Nephrogenic systemic fibrosis* OR
  - reported that the patient had renal failure, renal insufficiency, eGFR < 30 mL/min/1.73m^2, or acute kidney injury at the time of GBCA administration

No specific case definition was used for the medical literature review given the multiple purposes of the medical literature review as outlined in section 2.3.4.

2.3.2 FAERS Search Strategy

DPV searched the FAERS database with the strategy described in Table 1.

[7] For the purposes of this review, detection of gadolinium weeks or months following GBCA administration is considered abnormal as gadolinium is a trace element and not involved in any physiologic processes; the levels of gadolinium in the body considered normal in the absence of any GBCA exposure is, for practical purposes, zero.

Table 1. FAERS Search Strategy*	
Date of search	May 31, 2017
Time period of search	June 1, 2016† - May 31, 2017
Search type	FBIS quick query
MedDRA Search Terms	None selected
Product Terms	See Appendix C
* See Appendix B for a description of the FAERS database. † FDA received date June 1, 2016 was chosen to capture all reports received by FDA since the most recent OSE review of gadolinium retention.	

It was not feasible to review all FAERS reports received since the first GBCA was approved in 1988, so we reviewed all FAERS reports for a recent 1-year period and incorporated those FAERS cases from the three previous DPV reviews that fulfill the case definition in subsection 2.3.1.1.

2.3.3 Data Mining Search Strategy

DPV used Empirica Signal software with the strategy described in Table 2 to perform disproportionality analyses on FAERS data for the purpose of identifying patterns of associations or unexpected occurrences (i.e., potential signals). To find adverse events that are disproportionally reported for the GBCAs as a whole, all GBCA drug names as reported to FDA were consolidated into a single term. To reduce signal dilution when different terms could be used to code similar events, we assessed disproportionate reporting among the MedDRA High Level Terms (HLTs) in order to group similar medical concepts. For example, PT *Burning sensation* and PT *Skin burning sensation* may describe similar events and are both captured with the HLT *Paraesthesias and dysaesthesias*. FAERS reports coded with MedDRA PTs of the known GBCA adverse events nephrogenic systemic fibrosis and hypersensitivity reactions were removed from the database before this data mining run in order to see the data mining scores of signs and symptoms of these known events when the signs or symptoms are reported outside of an NSF or hypersensitivity case report. If a drug-event combination has a score (EB05) of ≥ 2, this score indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database. Data mining scores do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

Table 2. Data Mining Search Strategy*	
Data Refresh Date	April 27, 2017
Product Terms	GBCAs were grouped and treated as a single product in the data mining run. See Appendix D for specific terms in the GBCA group.
Empirica Signal Run Name	Special Projects: GBCA, HLT

Table 2. Data Mining Search Strategy*	
MedDRA Search Strategy (MedDRA 19.1)	All adverse events at the High Level Term (HLT) level of the MedDRA hierarchy Reports coded with PT *Nephrogenic Systemic Fibrosis*, PT *Anaphylactic reaction*, PT *Anaphylactic shock*, PT *Anaphylactic transfusion reaction*, PT *Anaphylactoid reaction*, PT *Anaphylactoid shock*, or PT *Hypersensitivity* were excluded before data mining analysis was run
Other Restriction	EB05 > 2
* See Appendix B for description of data mining of FAERS using Empirica Signal.	

2.3.4 Literature Search

DPV searched the medical literature from January 1, 1988, to July 12, 2017, with the strategies outlined in Tables 3, 4, and 5. All publications captured were reviewed for relevance. The primary purpose of the medical literature review was to document adverse events in conjunction with gadolinium retention after exposure to GBCAs in patients with normal renal function. For that purpose three strategies were used: 1) identify any reports including broad standard terms related to adverse events and toxicity after GBCA exposure; 2) identify any reports with specific adverse events following GBCA exposure which had already been reported in conjunction with gadolinium retention (e.g., pain syndromes) or were putative based on the topography of gadolinium retention reported in imaging and post-mortem studies (e.g., movement disorders with basal ganglia gadolinium retention);[4-6] and 3) determine whether gadolinium retention following GBCA exposure results in tissue integrity alteration including any histopathological changes. Even though captured using the search strategies above, NSF and acute hypersensitivity reactions are not discussed in this review as those GBCA adverse reactions are well characterized in the various GBCA labels. In order to identify adverse events clustering or consistent phenotypes, adverse events were grouped using a clinical categorization, i.e., based primarily on symptoms and signs as well as specific organ involvement whenever possible. MedDRA system organ classes were not used as reported adverse events from the medical literature were not MedDRA coded. In order to present the FAERS and medical literature findings as aggregate data, the same clinical categorization was used for unpublished adverse events found in FAERS even though they were MedDRA coded. While no case definition was used for the medical literature search, evidence of gadolinium retention included the following:

- Gadolinium presence in any body fluids or tissues
    - Documented: gadolinium measurement performed by publication authors OR extra-mural laboratory reports collected and verified by publication authors
    - Unverified: patient reports of abnormal gadolinium measurement but extramural laboratory reports not collected or verified by the publication authors
- Non-contrast MRI T1-weighted hyperintense signal abnormality presumed to represent gadolinium retention (i.e., inferred gadolinium retention)

Table 3. Medical Literature Search Strategy I	
Date of Search	July 12, 2017
Database	PubMed@FDA; Embase®
Search terms	(gadolinium OR “MR contrast media” OR “Magnetic resonance contrast media” OR "GADOPENTETATE" OR "GADOTERIDOL" OR "GADODIAMIDE" OR "GADOVERSETAMIDE" OR "GADOBENATE" OR "GADOXETATE" OR "GADOFOSVESET" OR "GADOBUTROL" OR "GADOTERATE" OR "Magnevist" OR "Prohance" OR "Omniscan" OR "Optimark" OR "Multihance" OR "Eovist" OR "Ablavar" OR "Gadavist" OR "Dotarem") AND ("adverse effect" OR "adverse effects" OR "adverse reaction" OR "adverse reactions" OR "adverse event" OR "adverse events" OR "adverse outcome" OR "adverse outcomes" OR complication* OR “drug effect” OR safe OR safety OR side effect* OR undesirable effect* OR “treatment emergency” OR “tolerability” OR toxicity OR ADRS) [ti]
Years included in search	1988*-present
Other criteria	Search fields limited to title
* The first GBCA was approved in the U.S. in 1988.	

Table 4. Medical Literature Search Strategy II	
Date of Search	July 12, 2017
Database	PubMed@FDA; Embase®
Search terms	((gadolinium OR “MR contrast media” OR “Magnetic resonance contrast media” OR "GADOPENTETATE" OR "GADOTERIDOL" OR "GADODIAMIDE" OR "GADOVERSETAMIDE" OR "GADOBENATE" OR "GADOXETATE" OR "GADOFOSVESET" OR "GADOBUTROL" OR "GADOTERATE" OR "Magnevist" OR "Prohance" OR "Omniscan" OR "Optimark" OR "Multihance" OR "Eovist" OR "Ablavar" OR "Gadavist" OR "Dotarem") OR (“T1 hyperintense” OR “high T1 signal” OR “increased T1 signal” OR “T1 hyperintensity”)) AND (“basal ganglia” OR “globus pallidus” OR “globus pallidi” OR “striatum” OR “caudate” OR “lentiform nucl*” OR “putamen” OR “thalam*” OR “dentate”))) AND (headache OR “bone pain” OR “joint pain” OR arthralgia OR “skin changes” OR erythema* OR plaques OR “vision changes” OR “hearing changes” OR “flu-like symptoms” OR nausea OR vomiting OR diarrhea OR dyspnea OR “difficulty breathing” OR “brain fog” OR “clouded mentation” OR encephalopathy OR “cognitive” OR “mood” OR “cerebellar” OR “ataxia” OR “movement disorder” OR “Parkinson*” OR “rigid*” OR “akinetic” OR “bradykinesia” OR “dystonia” OR “chorea” OR “tremor” OR “dyskinesia” OR “ballism*” OR “tic” OR “myoclonus” OR “akathisia”)
Years included in search	1988*-present
* The first GBCA was approved in the U.S. in 1988.	

Table 5. Medical Literature Search Strategy III	
Date of Search	July 12, 2017
Database	PubMed@FDA; Embase®
Search terms	(gadolinium OR "MR contrast media" OR "Magnetic resonance contrast media" OR "GADOPENTETATE" OR "GADOTERIDOL" OR "GADODIAMIDE" OR "GADOVERSETAMIDE" OR "GADOBENATE" OR "GADOXETATE" OR "GADOFOSVESET" OR "GADOBUTROL" OR "GADOTERATE" OR "Magnevist" OR "Prohance" OR "Omniscan" OR "Optimark" OR "Multihance" OR "Eovist" OR "Ablavar" OR "Gadavist" OR "Dotarem") AND (deposit* OR storage OR retention OR accumulat* OR precipit*) [ti]
Years included in search	1988*-present
Other criteria	Search fields limited to title
* The first GBCA was approved in the U.S. in 1988.	

2.4 Results

2.4.1 FAERS Case Selection

The purposes of the FAERS review were to 1) characterize all unpublished cases that reported evidence of gadolinium retention after GBCA administration received cumulatively through May 31, 2017, and 2) characterize unpublished reports of persistent adverse events after GBCA administration that did not report evidence of gadolinium retention and were received over a recent 1 year period (June 1, 2016 to May 31, 2017).

The FAERS search in Table 1, covering the time period June 1, 2016 to May 31, 2017, retrieved a total of 1,231 reports, 37 of which were coded with PT *Nephrogenic systemic fibrosis* and were removed. Additional FAERS cases from previous DPV reviews that met the case definition in section 2.3.1.1 were included in the cumulative case series, as described below.

After applying the case definitions outlined in section 2.3.1, removing medical literature cases for inclusion in the medical literature section, and accounting for duplicate reports,

- 41 cases were included in the cumulative case series of unpublished FAERS cases that reported evidence of gadolinium retention after GBCA administration, with or without clinical adverse events. This includes 9 cases identified from the search strategy in Table 1, plus 32 cases from the previous DPV reviews of this topic that met the case definition in section 2.3.1.1.
- 18 cases were included in the case series of unpublished FAERS cases received by FDA between June 1, 2016 and May 31, 2017 that report persistent adverse events but do not report evidence of gadolinium retention after GBCA administration. Cases that do not include testing for gadolinium retention but do report adverse events persisting for at least 4 weeks were not included in previous DPV reviews.

Table 6 (in section 2.4.2.1) summarizes both of these case series.

Table 7 (in section 2.4.2.1) lists the most frequently coded MedDRA preferred terms (PTs) in both case series grouped into broad clinical categories of reported adverse events based on the overall findings of this review.

Appendix E provides a line listing of all 59 cases.

2.4.2 FAERS Cases

2.4.2.1 Overview of FAERS cases reporting evidence of gadolinium retention after GBCA administration with or without clinical adverse events and FAERS cases reporting persistent adverse events but no evidence of gadolinium retention

Forty-one cases reported the presence of gadolinium in a body fluid or tissue. For the purposes of this review, detection of gadolinium weeks or months following GBCA administration is considered abnormal as gadolinium is a trace element and not involved in any physiologic processes; the levels of gadolinium in the body considered normal in the absence of any GBCA exposure is, for practical purposes, zero. However, the expected levels at various time points in individuals who have received a limited number of GBCA administrations needs further validation, as levels in some body tissues would be above zero for some unknown time after administration. Because different collection methodologies and body tissues/fluids were used, the gadolinium levels between cases are not comparable. Also, some FAERS cases do not report the type of collection methodology used, such as provoked or unprovoked urine levels, or the units of measurement. A provoked urine test is a collection methodology in which a timed specimen is collected after administration of a chelating agent. This procedure transiently increases elimination of gadolinium in urine to levels higher than would be present in an unprovoked test. These limitations make the actual values uninformative. Therefore, the values of the gadolinium test results are not presented here.

The number of GBCA administrations before symptom onset or gadolinium level testing is uncertain in almost all cases and is not included in the descriptive characteristics of the cases, but reported numbers range from 1 to 36 administrations.

Table 6. Descriptive Characteristics of Unpublished FAERS Cases of Gadolinium Retention After GBCA Administration, Received by FDA From 1969 to May 31, 2017, AND Descriptive Characteristics of Unpublished Cases of Persistent Adverse Events After GBCA Administration, Received by FDA From June 1, 2016 to May 31, 2017 (N=59)

	Cases that report evidence of gadolinium retention with or without clinical adverse events (N=41)	**Cases with persistent adverse events that do not report evidence of gadolinium retention (N=18)**
Reporter	Consumer – 27 Physician – 9 Other health professional – 4 Unknown – 1	Consumer – 17 Other health professional – 1

Table 6. Descriptive Characteristics of Unpublished FAERS Cases of Gadolinium Retention After GBCA Administration, Received by FDA From 1969 to May 31, 2017, AND Descriptive Characteristics of Unpublished Cases of Persistent Adverse Events After GBCA Administration, Received by FDA From June 1, 2016 to May 31, 2017 (N=59)			
	Cases that report evidence of gadolinium retention with or without clinical adverse events (N=41)		**Cases with persistent adverse events that do not report evidence of gadolinium retention (N=18)**
Report type	Direct – 22 Expedited – 18 Non-expedited – 1		Direct – 15 Expedited – 3
Year of initial report	2007 – 1 2010 – 1 2011 – 1 2012 – 3	2014 – 6 2015 – 15 2016 – 9 2017 – 5	2016 – 9 2017 – 9
Country of reporter	Australia – 2 France – 2 Germany – 2	Japan – 1 USA – 34	Spain – 1 Great Britain – 1 USA – 16
Serious outcomes[*]	None – 4 Death – 1 (brain cancer) Disability – 15 Hospitalization – 4 Required intervention – 4 Life threatening – 3 Other serious – 23		None – 1 Disability – 12 Hospitalization – 2 Life threatening – 3 Other serious – 7
Sex	Female – 34, Male – 6, Unknown – 1		Female – 16, Male – 2
Age in years	Range 7 to 81, mean 47, median 49.5 (N=37) Unknown – 4		Range 23 to 73, mean 50, median 53.5 (N=17) Unknown – 1
Renal function	Reported as normal – 19 eGFR 46 (no units) – 1[†] eGFR 76 mL/min/1.73 m^2 – 1 eGFR > 60 mL/min/1.73 m^2 – 2 Unknown – 18		Reported as normal – 2 Provided medical history without mention of renal function – 7 Unknown – 9

Table 6. Descriptive Characteristics of Unpublished FAERS Cases of Gadolinium Retention After GBCA Administration, Received by FDA From 1969 to May 31, 2017, AND Descriptive Characteristics of Unpublished Cases of Persistent Adverse Events After GBCA Administration, Received by FDA From June 1, 2016 to May 31, 2017 (N=59)		
	Cases that report evidence of gadolinium retention with or without clinical adverse events (N=41)	**Cases with persistent adverse events that do not report evidence of gadolinium retention (N=18)**
GBCAs used[‡]	Unknown – 8 *Macrocyclic* Gadavist (gadobutrol) – 9 Dotarem (gadoterate meglumine) – 3 Prohance (gadoteridol) – 1 *Linear* Magnevist (gadopentetate dimeglumine) –10 Multihance (gadobenate dimeglumine) – 10 Omniscan (gadodiamide) – 7 Optimark (gadoversetamide) – 1	Unknown – 7 *Macrocyclic* Gadavist (gadobutrol) – 4 *Linear* Magnevist (gadopentetate dimeglumine) – 4 Multihance (gadobenate dimeglumine) – 2 Optimark (gadoversetamide) –1
Tissue or body fluid tested for gadolinium[§]	Unspecified – 2 Urine – 29 Serum – 5 MRI of brain – 5 Hair – 5 Kidney and heart tissue – 1 CSF – 1	Urine – 1 (results not known at time of report, so not considered evidence of retention in this review)
Time to onset of adverse events	No adverse events reported – 7 Immediately – 3 ≤ 24 hours – 9 < 1 week – 6 1 to 2 weeks – 3 < 1 month – 3 Unknown – 10	Immediately – 2 ≤ 24 hours – 3 1 month – 1 “weeks” – 1 Unknown – 11

Table 6. Descriptive Characteristics of Unpublished FAERS Cases of Gadolinium Retention After GBCA Administration, Received by FDA From 1969 to May 31, 2017, AND Descriptive Characteristics of Unpublished Cases of Persistent Adverse Events After GBCA Administration, Received by FDA From June 1, 2016 to May 31, 2017 (N=59)

	Cases that report evidence of gadolinium retention with or without clinical adverse events (N=41)	**Cases with persistent adverse events that do not report evidence of gadolinium retention (N=18)**

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

† The patient reported that eGFR was normal prior to GBCA exposure and has been up and down over the 16 years since the first GBCA exposure with a nadir of 46 (no units) using the MDRD calculation method.

‡ One case may report use of more than one GBCA and may not report entire history of GBCA exposure. No case in which a macrocyclic GBCA was used said the macrocyclic was the only GBCA to which the patient was exposed.

§ One case may report more than one test for gadolinium retention or may report a test found gadolinium without specifying the tissue tested. Brain imaging is included as a surrogate of tissue measurement.

Table 7. Adverse Events (MedDRA Version 20.0 Preferred Terms) Reported in Three or More Unpublished FAERS Cases of Gadolinium Retention After GBCA Administration, Received by FDA From 1969 to May 31, 2017, or Persistent Adverse Events After GBCA Administration, Received by FDA From June 1, 2016 to May 31, 2017 (N=52)

	Cases that report evidence of gadolinium retention as well as adverse events (N=34)	**Cases that do not report evidence of gadolinium retention (N=18)**
Cutaneous	14 Patients *Rash* – 8 *Erythema* – 4 *Skin lesion* – 4 *Alopecia* – 3	4 Patients *Pruritus* or *Pruritus generalized* – 4
Musculo-skeletal	22 Patients *Arthralgia* - 11 *Muscular weakness* – 10 *Bone pain* – 7 *Muscle spasms* – 6 *Myalgia* – 6 *Muscle twitching* – 4 *Muscle tightness* – 3	6 Patients *Arthralgia* – 6

Table 7. Adverse Events (MedDRA Version 20.0 Preferred Terms) Reported in Three or More Unpublished FAERS Cases of Gadolinium Retention After GBCA Administration, Received by FDA From 1969 to May 31, 2017, or Persistent Adverse Events After GBCA Administration, Received by FDA From June 1, 2016 to May 31, 2017 (N=52)		
	Cases that report evidence of gadolinium retention as well as adverse events (N=34)	**Cases that do not report evidence of gadolinium retention (N=18)**
Pain	18 Patients *Pain – 10* *Burning sensation* or *Skin burning sensation* – 8 *Headache – 7* *Eye pain* – 4 *Pain in extremity* – 4	12 Patients *Headache* – 6 *Pain* – 6 *Burning sensation* or *Skin burning sensation* – 4 *Pain in extremity* – 4
Cognitive/ neuro-logical	21 Patients *Paraesthesia* – 12 *Tremor – 5* *Dizziness* – 4 *Cognitive disorder* – 4 *Disturbance in attention* – 4 *Hypoaesthesia* – 4 *Gait disturbance* – 3 *Memory impairment* – 3	7 Patients *Memory impairment* – 3 *Mental impairment* – 3 *Paraesthesia* – 3
Other adverse events	24 Patients *Fatigue* – 12 *Dyspnoea* – 5 *Nausea* – 5 *Asthenia* – 4 *Dysgeusia* – 4 *Insomnia* – 4 *Loss of personal independence in daily activities* – 4 *Blood pressure increased* – 3 *Chills* – 3 *Depression* – 3 *Fall* – 3 *Feeling abnormal* – 3 *Tinnitus* – 3 *Vision blurred* – 3	4 Patients *Malaise* – 4

2.4.2.2 Summaries of most-detailed FAERS cases that report evidence of gadolinium retention

FAERS Case # 13238462, Direct, 2017
This case was reported by the patient. A 49-year-old female received six IV injections of an unspecified GBCA between August 2003 and June 2008 to detect a tumor in her extremity and to monitor for recurrence after surgery. About 9 months after the last GBCA exposure, the patient had a lumbar puncture for an unspecified indication. Her cerebrospinal fluid was found to contain 2.5 ng/mL (reference <0.5 ng/mL) gadolinium. Since an unspecified time in 2003, the patient has had chronic fatigue, muscle pain, exercise intolerance, and trouble concentrating. In 2014, the patient underwent an enhanced MRI of her brain and internal auditory canal to investigate vertigo; results were not provided. The patient's medical history includes hypothyroidism, seasonal allergies, and arthritis in the spine; renal function is not mentioned.

FAERS Case #11805981, Direct, 2015
This case was reported by the patient. A 53-year-old female received six GBCA-enhanced MRIs over 9 months: 6 mL Gadavist (gadobutrol) (2), 7 mL Gadavist (gadobutrol) (2), 14 mL Multihance (gadobenate dimeglumine) (1), and 15 mL Magnevist (gadopentetate dimeglumine) (1) for newly diagnosed transverse myelitis. Additionally, she had received GBCAs three times over the preceding 9 years for an unspecified indication. Since about 2 months into the six more recent GBCA injections, the patient has had deep chronic bone pain, generalized muscle tightening, weakness, fatigue, and other, unspecified, symptoms. About 1 month before the last of the six more recent GBCA injections, a 24-hour urine gadolinium test found 17 mcg/specimen (Doctor's Data; reference < 0.6 mcg/specimen) and about 2 months after the final GBCA injection, a 24-hour urine gadolinium test found 6.9 mcg/specimen (Mayo Clinic; reference 0.0 – 0.4 mcg/specimen). The patient has normal renal function and no other medical conditions.

FAERS Case #11755699, Direct, 2015
This case was reported by the patient. A 52-year-old female received an unknown dose of Multihance (gadobenate dimeglumine) two times in a short time period, possibly 1 day, for MRA for tachycardia. The same day, she had red, pruritic patches on her skin. In the next 2 days, she developed disorientation, facial swelling, vomiting, diarrhea, a metallic taste in her mouth, headache, impaired vision, high blood pressure, stinging sensations, then numbness and tingling and red knees. She went to the ER, where x-rays found normal knee bones, and was given unspecified steroids. Over several months, she developed severe pain, difficulty swallowing, insomnia, weight loss, and inability to concentrate. In the subsequent 6 years, the patient has been diagnosed with hemolytic anemia and hyperparathyroidism. She experiences decreased intelligence, muscle weakness, fatigue, shortness of breath, joint stiffness, and skin thickening, with the skin around her knees "like hard rubber" and non-pinch-able. In addition, the patient reports body hair loss and gold-colored skin spots similar to freckles. Skin biopsy from an unspecified location showed fibrosis. The patient also reports sclerosis, but does not specify how this was diagnosed. Urine and hair testing found gadolinium. Mammograms and x-rays show abnormal calcification. Unspecified testing showed "abnormal" phosphorus. Previously, the patient was healthy and athletic. She reports normal kidney function. Reported medical conditions were tachycardia, low blood pressure, and allergies to antibiotics and mold.

2.4.2.3 Summaries of most-detailed FAERS cases that do not report evidence of gadolinium retention

FAERS Case # 12959507, Direct, 2016
This case was reported by the patient. A 53-year-old female reported receiving more than 10 IV administrations of GBCAs over 9 years for breast cancer screening. Beginning at an unspecified time and progressing over the years, the patient developed unspecified pain, migraine headaches, weakness, frequent urination, insomnia, and cognitive decline. She did not return for an MRI for 3 years, during which time the migraines abated. Immediately after having an MRI with gadolinium, the patient reports the migraines returned, and she had pain in her neck and back, pain in her right leg from hip to knee, a feeling of swollen joints, and feeling ill. The adverse events persisted at the time of the report, 3 months after the last GBCA administration, and she reported being disabled by pain. The patient's medical history includes breast cancer and chronic fatigue syndrome of unspecified duration; renal function is not mentioned.

FAERS Case #12618165, Direct, 2016
This case was reported by the patient. A 36-year-old female received IV Gadavist (gadobutrol) for a brain MRI. The patient had previously received an unspecified number of MRIs with GBCAs. On this occasion, extravasation occurred and additional Gadavist (gadobutrol) was administered in the same arm and in the other arm for a total of 59.8 mL. Beginning the same day, the patient developed pain in her side. Over an unspecified time, the patient developed tightness from the hand to the elbow of the arm where extravasation occurred and tightness in both legs. The patient reports progressive loss of mobility in the affected arm. The adverse events were persisting at the time of report, 2 months after Gadavist (gadobutrol) administration. The patient's medical history includes pituitary microadenoma, pernicious anemia, and multiple allergies; renal function is not mentioned.

2.4.3 Data Mining Results

The results of data mining are presented in Table 8. As noted in Appendix B in section 2.8.2, drug and event causality cannot be inferred from data mining scores. Data mining scores do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

The data are sorted by descending EB05, because the higher the EB05, the more disproportionately the term (e.g., HLT) is reported for that drug or class of drugs.

Table 8. Data Mining Results Using Empirica Signal for all MedDRA High Level Terms, Excluding Reports Coded as NSF or With Select Hypersensitivity Preferred Terms, Reported with GBCA Use and EB05 Scores > 2 Sorted by Descending EB05*†

	High Level Term	N	EB05
1	*Central nervous system histopathology procedures*‡	26	96.371
2	*Central nervous system imaging procedures*‡	72	14.901
3	*Urticarias*	3429	12.46
4	*Laryngeal spasm, oedema and obstruction*	389	9.693

Table 8. Data Mining Results Using Empirica Signal for all MedDRA High Level Terms, Excluding Reports Coded as NSF or With Select Hypersensitivity Preferred Terms, Reported with GBCA Use and EB05 Scores > 2 Sorted by Descending EB05*†

	High Level Term	N	EB05
5	*Skin histopathology procedures*‡	11	7.468
6	*Upper respiratory tract signs and symptoms*	1360	6.047
7	*Erythemas*	897	5.942
8	*Nasal congestion and inflammations*	220	5.916
9	*Nausea and vomiting symptoms*	5525	5.301
10	*Site specific vascular disorders NEC*	158	4.833
11	*Pharyngeal disorders (excl infections and neoplasms)*	159	4.481
12	*Lid, lash and lacrimal infections, irritations and inflammations*	102	4.168
13	*Phlebitis NEC*‡	91	4.128
14	*Oral soft tissue signs and symptoms*	142	3.962
15	*Ocular infections, inflammations and associated manifestations*	227	3.909
16	*Non-site specific vascular disorders NEC*‡	506	3.831
17	*Oral soft tissue swelling and oedema*	149	3.822
18	*Pruritus NEC*	1888	3.773
19	*Musculoskeletal and soft tissue histopathology procedures*‡	9	3.492
20	*Imaging procedures NEC*	52	3.456
21	*Breathing abnormalities*	2136	3.121
22	*Lacrimation disorders*	162	3.031
23	*Allergic conditions NEC*	635	3.025
24	*Coughing and associated symptoms*	726	3.014
25	*Non-site specific procedural complications*	354	2.998
26	*Oral soft tissue pain and paraesthesia*	112	2.524
27	*Ocular disorders NEC*‡	308	2.469
28	*Circulatory collapse and shock*	184	2.439
29	*Skin hyperplasias and hypertrophies*‡	20	2.409
30	*Apocrine and eccrine gland disorders*	496	2.408
31	*Angioedemas*	254	2.388
32	*Urinalysis NEC*‡	66	2.347
33	*Orbital structural change, deposit and degeneration*‡	7	2.249
34	*Peripheral vascular disorders NEC*‡	354	2.232
35	*Eye and eyelid infections*	125	2.214
36	*Tongue signs and symptoms*	171	2.182
37	*Blood gas and acid base analyses*	106	2.176
38	*Bronchospasm and obstruction*	375	2.133
39	*Vascular tests NEC (incl blood pressure)*	376	2.122

Table 8. Data Mining Results Using Empirica Signal for all MedDRA High Level Terms, Excluding Reports Coded as NSF or With Select Hypersensitivity Preferred Terms, Reported with GBCA Use and EB05 Scores > 2 Sorted by Descending EB05*†

	High Level Term	N	EB05

* A score (EB05) of ≥ 2 indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database.

† Reports coded with PT *Nephrogenic Systemic Fibrosis*, PT *Anaphylactic reaction*, PT *Anaphylactic shock*, PT *Anaphylactic transfusion reaction*, PT *Anaphylactoid reaction*, PT *Anaphylactoid shock*, or PT *Hypersensitivity* were excluded before data mining analysis was run.

‡ The cases in these HLTs were scanned for relevance to this review.

Several HLTs with EB05 > 2 are of interest for this review because they could include clinical manifestations of NSF (i.e., *Skin histopathology procedures, Musculoskeletal and soft tissue histopathology procedures, and Skin hyperplasias and hypertrophies*). Some HLTs include procedures that could provide evidence of gadolinium retention (i.e., *Central nervous system histopathology procedures, Central nervous system imaging procedures,* and *Urinalysis NEC).* Reports in these and some other HLTs that suggest possible systemic effects (i.e., *Ocular disorders NEC, Phlebitis NEC, Non-site specific vascular disorders NEC, Peripheral vascular disorders NEC, and Orbital structural change, deposit and degeneration*) were scanned for any cases relevant to this review of gadolinium retention after GBCA administration. HLTs that were not explored further are those that suggest hypersensitivity or self-limited adverse events (e.g., *Angioedemas* and *Nausea and vomiting symptoms).*

The case reports retrieved through data mining were very similar to those already retrieved from the FAERS and medical literature searches and do not add new information to this review except to note that, in the absence of reports coded with the PT *Nephrogenic systemic fibrosis*, NSF-like symptoms are still disproportionately reported to FDA.

2.4.4 Literature Search Results

The number of reviews on gadolinium retention after exposure to GBCAs has rapidly expanded over the past two years with many recent comprehensive reviews.[7-18] Most of those reviews reference case reports, case series, and observational studies reporting clinical, imaging, and histopathologic findings reported in conjunction with gadolinium retention after exposure to GBCAs and most include patients with normal renal function. Many publications reporting asymptomatic brain MRI T1-weighted hyperintense signal abnormality presumed to represent gadolinium retention were captured using the search strategies outlined in section 2.3 even though they do not fall under the primary purpose of this medical literature review. However, those publications were included in the results as they may give insight into the potential clinical manifestations of gadolinium retention based on neuroanatomic topography of gadolinium retention. The publications retrieved can be broadly divided into five main categories as outlined in Table 9 and are presented and discussed below accordingly.

Table 9. Summary of Publications on Gadolinium Retention Following Gadolinium-Based Contrast Agents Use in Patients With Normal Renal Function		
Publication Category	**Publication Types and Topics**	**Number of Publications**
Adverse events reported in conjunction with documented gadolinium retention	Case reports	1
	Case series	1
	Miscellaneous reports (encapsulating peritoneal fibrosis)	2
Adverse events reported in conjunction with unverified gadolinium retention	Case reports	1
	Surveys	2
	Retrospective observational studies	1
Acute and subacute adverse events reported with GBCA administration with or without residual clinical findings	Acute neurotoxicity case reports	12
	Systemic toxicity case reports	3
	Delayed adverse events prospective observational study	1
MRI signal abnormality presumed to represent gadolinium retention	Case reports	2
	Case series	1
	Prospective observational studies	2
	Retrospective observational studies	43
	Publications exclusively addressing linear CBCA Publications with at least a subset of patients exposed to macrocyclic GBCA	25 23
	Miscellaneous gadolinium retention case series	2
	Imaging tissue integrity retrospective observational studies	2
	Reviews	11
Tissue gadolinium measurements	Post-mortem brain retention Case reports Case series	7 1 6
	Tumor specimens retention case series	1
	Systemic retention Case series Retrospective observational Reviews	6 4 1 1
	Systemic retention risk factors Case reports Retrospective observational	4 1 3

2.4.4.1 Adverse events reported in conjunction with documented gadolinium retention

Adverse events reported in conjunction with documented supportive laboratory evidence of gadolinium retention (i.e., gadolinium measurement performed by publication authors or extra-mural laboratory reports collected and verified by publication authors) are limited to one small

case series of four patients and a single case report.[19,20] The case series entails four patients referred to the senior author due to his expertise in NSF. Those patients with reported normal renal function developed multiple and heterogeneous adverse events within hours to up to 4 weeks after GBCA exposure. While two of those patients were clinically assessed within a couple of months of exposure, two were not assessed until years after. Gadolinium retention was documented and quantified in all four cases using various body fluids and tissues.[19] The single case report describes a patient who underwent 61 brain MRIs over a period of 11 years for a supratentorial high-grade glioma who developed severe contractures in conjunction with documented evidence of cutaneous gadolinium retention along with histopathologic inflammatory changes. While a normal renal function is reported for this patient, at least one creatinine measurement appears high at 1.3 mg/dL. The contractures developed a few years after initial GBCA exposure, involved all four limbs and the neck, and were reportedly "of unknown etiology but possibly multifactorial in nature".[20] A summary of this case report and case series is presented in Appendix F. Those cases are also included in Appendix G which summarizes all publications addressing adverse events reported in conjunction with gadolinium retention, whether documented or unverified.

A case series examining gadolinium retention in patients with encapsulating peritoneal fibrosis identified gadolinium in the peritoneum of only one of the five patients and that patient happened to have the most severe course.[21] Another study published before the one above did not support any association with encapsulating peritoneal fibrosis and included two cases and two controls.[22] No reports of clinical manifestations associated with skin or bone gadolinium retention were found besides cases consistent with NSF.

2.4.4.2 Adverse events reported in conjunction with unverified gadolinium retention

A more heterogeneous group of adverse events reported in conjunction with unverified self-reported laboratory evidence of gadolinium retention in blood, urine, or other body fluids or tissues (i.e., patient self-reports of abnormal gadolinium measurement but extramural laboratory reports not collected or verified by the publication authors) was identified. The adverse events and other information relating to GBCA exposure were self-reported using two online anonymous electronic surveys posted to a private blog (www.gadoliniumtoxicity.com) discussing gadolinium toxicity, and a public Gadolinium Toxicity Facebook page.[4,5] Both surveys were designed and conducted by the same authors and solicited self-reported symptoms without a control group, creating an inherent selection bias acknowledged by the authors. A single case report with imaging suggestions but no tissue or body fluid evidence of gadolinium retention described neuropsychological impairment potentially resulting from gadolinium retention although radiation neurotoxicity was reported to have a confounding role.[23] A summary of the cases above is presented in Appendix G.

A small case series of two patients describing gadolinium-associated plaques with some histopathologic features similar to NSF has been reported but no gadolinium retention was assessed in those cases, and one case had abnormal renal function.[24] Similar cutaneous histopathologic findings, after but not before GBCA exposure, were also described in a single case report with serial squamous cell carcinoma specimens.[25] Those cases with gadolinium-associated plaques and the serial squamous cell carcinoma specimens are not included in Appendix G because there was no gadolinium retention (documented or unverified). Lastly, a

large retrospective observational study in several linked Canadian administrative databases did not reveal any increased relative risk of parkinsonism in patients exposed to GBCAs, although the majority of patients only had a single administration.[26] That study did not assess gadolinium retention. A more detailed appraisal of that study can be found in the Division of Epidemiology review.

The number of patients by clinical categories of reported adverse events based on the overall findings of this review (i.e., including FAERS cases with gadolinium retention and medical literature cases) are summarized in Figure 1. Cutaneous and musculoskeletal were the clinical categories with the most reported adverse events, although "other" accounted for the highest number. A substantial (23/98) proportion of patients reported adverse events after a single GBCA administration as outlined in Figure 2. The number of GBCA administrations was uncertain in the majority of FAERS cases and therefore only medical literature cases are included in Figure 2. The number of GBCA administrations or number of MRI studies with contrast is the most commonly reported dose-related parameter in the medical literature. Specific individual and cumulative doses of GBCAs were reported for only four patients (see Appendix F). None of those patients had evidence of doses above those recommended in prescribing information, although body weights were not specifically provided but could be inferred from GBCA volumes in some cases. While the majority of patients with reported adverse events in conjunction with gadolinium retention received linear, multiple unspecified, or unknown GBCAs, very few received exclusively macrocyclic GBCAs as outlined in Figure 3. Although the specific GBCA used in the most recent exposure is reported in the majority of cases, GBCA exposure history is uncertain in the majority of FAERS cases, and therefore, only medical literature cases are included in Figure 3. Quantitative gadolinium measurement in body fluid or tissue was available for only five patients using five different body fluids or tissues, some with different measurement units within the same tissue (e.g., urine, microgram/24-hour and microgram/gram), one patient with multiple serial urine measurements, and highly variable time after the last GBCA exposure extending from 28 days to up to 4 years (see Appendix F). Consequently, no dose-response relationship could be determined using cumulative GBCA dose and either gadolinium body fluid/tissue concentrations or adverse events due to the small number of patients having data available and the heterogeneity in body fluid/tissue gadolinium quantitative measurements as outlined above.

Figure 1. Number of Patients by Clinical Category of Reported Adverse Events Including FAERS and Medical Literature Cases

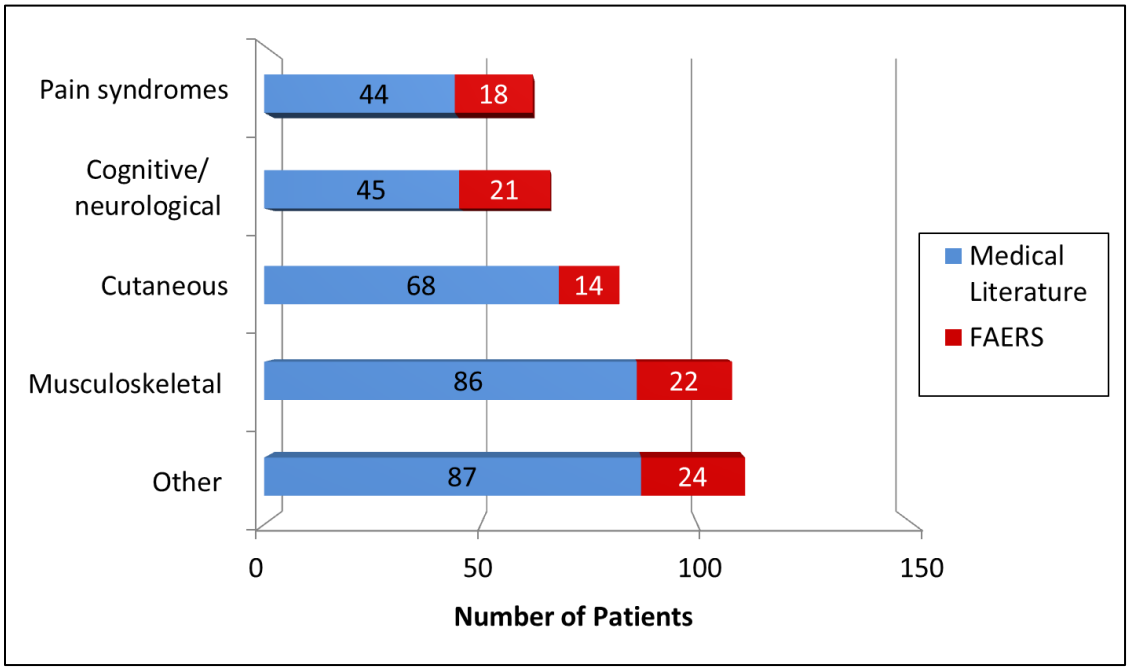


Figure 2. Number of GBCA Administrations Before Onset of Reported Adverse Events (Medical Literature Cases Only)

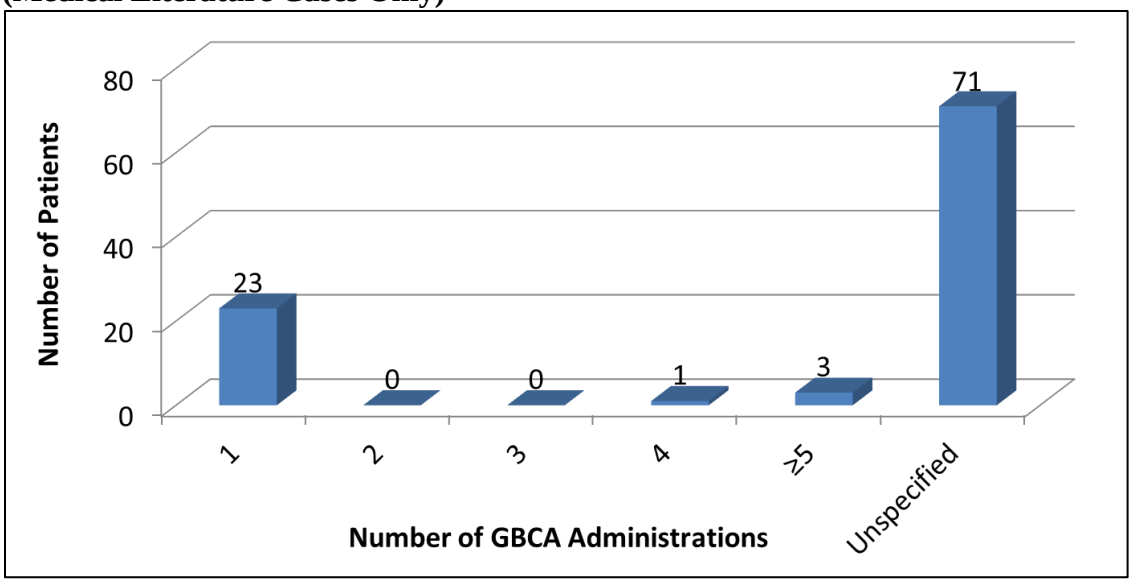
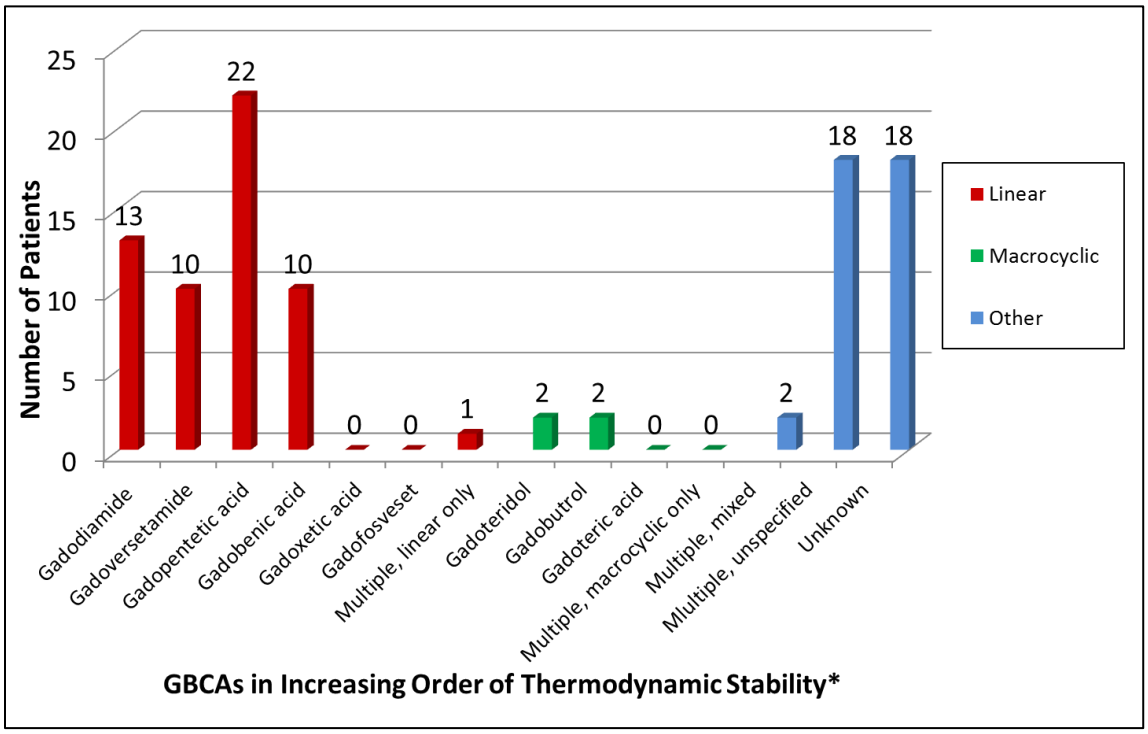


Figure 3. Number of Patients with Reported Adverse Events by GBCA Type in Increasing Order of Thermodynamic Stability* (Medical Literature Cases Only)



*GBCAs thermodynamic stability from Ramalho J, et al. Am J Neuroradiol. 2016;37(7):1192-1198.

2.4.4.3 Acute and subacute adverse events reported with GBCA administration with or without residual clinical findings

Three case reports of acute or subacute encephalopathy following intravenous GBCA were found.[27-29] While the focus of this literature review was on intravenous administration of GBCA, nine additional case reports of gadolinium encephalopathy, seizures, or other neurological adverse events after off-label use of intrathecal or intraventricular GBCA were identified following further medical literature search: six patients developed encephalopathy with or without seizures within hours of inadvertent high dose GBCA; one patient experienced non-convulsive status epilepticus after intraventricular GBCA administration; one patient with known iodine allergy developed painful lower extremity spasm after intrathecal gadoteridol for intrathecal pump integrity and position assessment; and one patient with known iodine allergy developed generalized motor seizures with encephalopathy 12 hours after a catheter dye study using gadodiamide performed for intrathecal pump malfunction.[30-38] Many of those patients had abnormal or unreported renal function. A few of those acute neurotoxicity cases had residual clinical findings, specifically cognitive impairment in one patient, bilateral optic atrophy in one, and cerebellar dysfunction in another, but no follow-up imaging was performed to document gadolinium retention or other central nervous system (CNS) alternative etiologies. One additional patient remained in a persistent vegetative state following an accidental intrathecal gadopentetic acid overdose administration. Those residual clinical findings do not appear confounded by pre-existing diseases or conditions including indications for imaging study. A summary of those case reports of neurotoxicity above is presented in Appendix H.

A prospective observational study of late (3 days) and very late (1 month) adverse events after contrast-enhanced and unenhanced MRI and CT was found.[39] While some adverse events were more frequently reported after MRI with GBCA compared to MRI without GBCA, including some late adverse events (3 days) with a higher frequency that was statistically significant, the authors acknowledged that the interpretation was limited by the confounding role of the pre-existing symptoms associated with the underlying indication for imaging. In addition, the study did not address symptoms occurring beyond 1 month after contrast agent administration. Single case reports of acute tubular necrosis, acute pancreatitis, and acute polyarthralgia have been reported.[40-42]

2.4.4.4 MRI signal abnormality presumed to represent gadolinium retention

The body of literature including case reports, case series, prospective, and retrospective observational (cross-sectional and longitudinal) studies addressing MRI T1-weighted hyperintense signal abnormality presumed to represent gadolinium retention in the brain, has been rapidly expanding since the first report in 2013.[43] While T1-weighted hyperintense signal abnormality may be caused by gadolinium retention, other paramagnetic molecules (e.g., manganese, calcium, copper oxide) may result in similar imaging features. Consequently, the term "presumed to represent" is used in this review even though post-mortem studies have supported the nature of those imaging features being gadolinium retention.

The original publications reporting MRI signal abnormality presumed to represent gadolinium retention in the brain are outlined in Appendix I. Those original publications include 2 single case reports, 1 case series of 3 patients, 2 prospective observational study, and 43 retrospective observational studies. Those publications encompass nearly 3500 patients, including several pediatric patients, and over 600 controls in total.[43-90] The majority of the results were reported as aggregate data and most publications reported T1-weighted hyperintense signal abnormality presumed to represent gadolinium retention in the brain while a minority did not report such imaging findings. Only a few studies encompassing 212 patients reported data at an individual level. Many reviews focused on gadolinium retention in the brain have also been published.[91-100]

Only one retrospective observational longitudinal study has specifically assessed clinical adverse events.[80] The study included 23 multiple sclerosis patients and reported low verbal fluency associated with hyperintense signal index in the dentate nucleus and globus pallidus as well as low episodic verbal memory (affecting both encoding and retention) associated with higher signal intensity index in the globus pallidus but not the dentate nucleus. Two other publications, one small case series and one retrospective observational study, attempted to assess adverse events reported in conjunction with gadolinium retention in the brain, but were inconclusive because of limitations including pre-existing symptoms before GBCA administration in many cases, an unclear temporal association, and the narrow window of assessment often targeting acute events.[46,48] A single case report with neuropsychological impairment associated with MRI signal abnormality presumed to represent gadolinium retention in the brain has been discussed earlier in this review under publications addressing adverse events reported in conjunction with gadolinium retention.[23]

The majority of the original publications above include patients with a history of multiple exposures to GBCAs, with most publications reporting five or more separate GBCA

administrations. The most common indications for imaging in those original publications were primary brain tumors, pituitary lesions, systemic malignancies, and multiple sclerosis. In general, the publications showed an increase in T1-weighted signal intensity proportional to the number of GBCA administrations. The brain regions most frequently involved were the cerebral and cerebellar deep grey nuclei. Because of that specific and consistent neuroanatomic topography presumed to represent gadolinium retention, adverse events encompassing motor (e.g., hypokinetic or hyperkinetic movement disorders, cerebellar syndrome) and cognitive functions as well as mood have been used in the search outlined in Table 4 (Medical Literature Search Strategy II). Gadolinium retention in the cerebral cortex has also been reported.[71] One publication reported short-term accumulation in the cerebrospinal compartment after systemic administration of either gadodiamide or gadoteridol in healthy subjects and in patients with intact blood-CNS barrier, while another publication showed long-term intraparenchymal brain retention after intrathecal administration of gadopentetic acid, suggesting additional sites of retention after different routes of administration.[101,102]

Gadolinium retention has been predominantly examined for and observed with linear GBCAs. However, 23 retrospective observational studies included at least a subset of patients who exclusively received macrocyclic GBCAs encompassing over 1600 patients and 253 controls.[45,47,57,60,61,63,64,66,67,72,73,75-79,81,82,85,86,88-90] A summary of those publications is presented in Appendix J where details about GBCA exposure, methodology used, and imaging interpretation are provided in addition to the information contained in Appendix I for those publications. While many of those studies with a subset of patients who exclusively received macrocyclic GBCAs did not show T1-weighted signal abnormality presumed to represent gadolinium retention in the brain, a growing number of publications and abstracts do, including three studies in patients with relapsing remitting multiple sclerosis, one in patients with glioblastoma multiforme, one in patients with melanoma, and one in pediatric patients with primary brain tumors, although some limitations have been raised regarding one publication by Stojanov and colleagues.[64,66,67,78,81,82,103] The retention of gadolinium associated with the use of macrocyclic GBCAs has also been addressed in one review.[104]

The tissue integrity of cerebral and cerebellar deep grey nuclei with T1-weighted hyperintense signal abnormality presumed to represent gadolinium retention is an important question pertaining to GBCA safety with which gadolinium retention occurs. Imaging evidence of tissue integrity was assessed in two recent publications with mixed results reported. The use of sodium MRI in multiple sclerosis patients with or without dentate nucleus T1-weighted hyperintense signal abnormality reported findings supporting tissue integrity despite signal abnormality presumed to represent gadolinium retention.[105] A functional imaging study using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in 15 subjects who underwent 3 to 6 MRIs with GBCAs and 15 controls revealed a statistically significant reduction of the maximum standard uptake value in the dentate nucleus and globus pallidus of patients compared to controls. Clinical adverse events were not addressed in those tissue integrity imaging studies.

2.4.4.5 Tissue gadolinium measurements

The overall findings of the few post-mortem studies published to date encompassing 42 patients and 38 controls is that gadolinium seems to be preferentially retained in cerebral and cerebellar

deep grey nuclei, but also hemispheric white matter and cerebellar cortex in adults and children, the majority of which had normal renal function, corroborating imaging study findings.[6,107-112] Post-mortem gadolinium retention in brain tissue has been reported for linear GBCAs, but also in seven patients who have exclusively received macrocyclic GBCAs.[109] Higher post-mortem concentrations have been generally reported in the dentate nucleus and globus pallidus compared to other brain regions. At an ultrastructural level, gadolinium retention has been localized to capillary endothelium and neural tissue (interstitium and nuclei) in three studies.[6,111,112] While three studies did not identify any gross histopathologic changes on light microscopy using hematoxylin-eosin stain,[6,109,112,113] one small case series in pediatric patients revealed histopathological changes using neurofilament immunohistochemistry in two out of three patients with findings consisting of mild to severe gliosis of the dentate nucleus with prominent axonal spheroids.[111]

One study found a positive correlation between gadolinium retention in neural tissue and T1-weighted signal intensity on MRI without contrast.[6] None of the cases in those post-mortem studies had any pre-mortem adverse events reported, although no studies explicitly stated whether pre-mortem adverse events were sought beyond clinical information such as immediate cause of death, imaging indication or major diagnosis, and laboratory results. A summary of those post-mortem studies is presented in Appendix K. Gadolinium retention was also observed in primary brain tumor specimens after GBCA administration, especially with less stable linear non-ionic GBCAs (gadodiamide) compared to more stable linear ionic GBCAs (gadobenic acid), with an interval between the first administration and the specimen collection ranging from 0 to 2556 days.[114]

Systemic retention in a number of tissues including skin, bone, and liver has been reported in patients with normal renal function and the retention in bone reportedly occurred at much higher level than in the brain.[109,113,115-119] Those publications did not describe symptoms attributable to retention in those tissues although they were not designed to collect such information. . Extracranial sites have been suggested as surrogates for brain tissue given the limitations inherent to MRI-based gadolinium measurement in brain tissue.[120] Zinc exposure and siderosis have been suggested as possible risk factors for systemic gadolinium retention.[118,121] In addition, brain irradiation and progressive forms of multiple sclerosis have been associated with T1-weighted hyperintense signal abnormality of the dentate nucleus, but the contribution of prior GBCA administration was not assessed in those studies as they predated the awareness of gadolinium retention.[122,123]

2.4.4.6 Unpublished Reports

A few data collection reports including symptoms and body fluid gadolinium measurements have been conducted by a support group of patients with self-reported gadolinium toxicity. Those reports have been generated by the Lighthouse Project and should be acknowledged even though they have not been published in peer-reviewed journals.[124,125]

2.5 Discussion

The primary purpose of this review was to identify adverse events in conjunction with gadolinium retention after exposure to GBCAs in patients with normal renal function reported to the FAERS database and in the medical literature. We considered cases that reported detectable

gadolinium in body fluids or tissues to be a supportive element of a potential causal association between the adverse events and gadolinium retention following GBCA exposure. However, the great majority of the cases identified had self-reported accounts of laboratory evidence of gadolinium retention and did not entail any collection or verification of laboratory reports by a clinician, greatly limiting the scientific value of both the FAERS and medical literature cases. In addition, validation of gadolinium ranges in various body fluids and tissues, including in patients undergoing a single or a small number of GBCA administrations, is needed to determine what represents clinically significant gadolinium retention following exposure to GBCAs. MRI T1-weighted hyperintense signal abnormality presumed to represent gadolinium retention was considered another supportive evidence of gadolinium retention.

A heterogeneous group of adverse events in conjunction with gadolinium retention has been reported in the medical literature and FAERS. For this review, DPV reviewed information on 139 patients with reported adverse events in conjunction with gadolinium retention, 98 from the medical literature and 41 from FAERS. While adverse events identified in this review lacked a consistent phenotype, we observed some clustering around cutaneous, musculoskeletal, neurological/cognitive, and pain syndromes clinical categories. However, the clinical category "other" accounted for the highest number of adverse events, emphasizing the heterogeneity of the adverse events reported. In addition, adverse events from multiple clinical categories were observed within many individual cases. While well-established NSF clinical manifestations (e.g., skin thickening or induration, contractures) would fall under the cutaneous and musculoskeletal categories, those specific clinical manifestations were uncommonly reported in this review and when they were reported, they were often associated with other adverse events in multiple clinical categories. In contrast to MRI T1-weighted hyperintense signal abnormality presumed to represent gadolinium retention in the brain, which typically becomes apparent after five or more GBCA administrations, a substantial number of patients in our review reported adverse events beginning after a single GBCA administration, not supporting a dose-response phenomenon. Further exploration of a possible dose-response phenomenon using cumulative doses of GBCA and either gadolinium body fluid/tissue concentrations or adverse events was not possible due to the very small number of patients with available data and other factors related to gadolinium body fluid/tissue measurement heterogeneity. While rare cases had some suggestions of positive dechallenge and rechallenge, they were difficult to ascertain due to the adverse event types (e.g., episodic disorders such as migraine) and the limited understanding of gadolinium retention kinetics. Although adverse events in the FAERS case series vary between individual cases, overall the two FAERS case series (i.e., with and without reported evidence of gadolinium retention) describe similar patient experiences. We note that the large proportion (more than 50%) of FAERS cases in both case series submitted directly to FDA follows an unusual pattern for gadolinium retention, as direct reports make up just over 5% of total reports in the FAERS database. This suggests that these reports could have been stimulated by FDA communications or other communications notifying the general public of this observation (e.g., websites and social media with interest in gadolinium retention) leading to more reports submitted.

Even though no gadolinium retention was suspected or known in publications addressing acute and subacute neurotoxicity with close temporal association with GBCA administration, these publications do provide some insight into potential gadolinium retention clinical manifestations

or sequelae, specifically the residual cognitive impairment and cerebellar dysfunction. However, the interpretation of those residual findings is limited by the lack of follow-up imaging to document gadolinium retention or alternative etiologies. Single case reports of acute tubular necrosis, acute pancreatitis, and acute polyarthralgia did not provide relevant insight into potential gadolinium retention clinical manifestations (e.g., neurotoxicity) or were transient and brief, less consistent with the expected persistence of potential clinical manifestations caused by gadolinium retention.

We conducted an exploratory disproportionality analysis of the FAERS data to look for patterns in adverse events reported to the FDA at the MedDRA HLT level. We looked for relevant HLTs that had an EB05 score greater than two and that could be associated with persistent adverse events, such as HLT *Skin histopathology procedures*. The case reports retrieved through data mining were very similar to those already retrieved from the FAERS and medical literature searches. Generally, patients reported onset of adverse events within hours to days after receiving a GBCA. Unspecified pain and burning sensations occurred early. Over time, patients noted skin changes and muscle or bone pain which eventually interfered with daily life. Cognitive difficulties were also reported. The consistent pattern of the reported experiences and the similarity between some of the adverse events in the FAERS cases and established NSF clinical manifestations (e.g., contractures) is noteworthy and may suggest some biological plausibility.[126] Lacking, however, are a medical evaluation of adverse events in cases where such events were attributed to retained gadolinium. In addition, in the FAERS cases with evidence of gadolinium retention, the laboratory test results appeared unverified in the cases in which it was measured in body fluids or tissue.

Many factors limiting the evaluation of adverse events reported in conjunction with gadolinium retention have been identified. The individual symptomatic areas often did not have corresponding tissue gadolinium measurement (e.g., cutaneous adverse events and gadolinium measurement limited to hair and urine, not including skin), although cutaneous gadolinium measurement has not been used as a diagnostic criterion for NSF but has later been shown to be elevated in lesional versus non-lesional skin in NSF.[126,127] The pre-existing clinical manifestations related to MRI study indication is a potentially confounding factor in cases reporting adverse events in conjunction with gadolinium retention as they may mask gadolinium retention potential clinical manifestations or be exacerbated by gadolinium retention. However, the imaging indications in one published case series of four patients could be individually matched with the adverse events reported in conjunction with gadolinium retention and did not appear linked.[19] The lack of details on investigation for and consideration of alternative etiologies (e.g., connective tissue diseases) is another important limitation. As noted above, the majority of individual and aggregate clinical observations in FAERS and the medical literature are self-reported, including adverse events and supportive laboratory evidence of gadolinium retention, greatly limiting their scientific value. Some factors may affect the recognition of clinical manifestations of gadolinium retention potentially leading to underestimation of the importance of the problem. Those factors include an insidious onset, a delayed onset, and non-specific and subjective symptomatology, which all may make adverse events difficult to recognize and to link to GBCA exposure by the patient and the clinician.

While not the primary scope of this review, many retrospective observational studies and a few published case series and case reports have examined MRI without contrast for the presence of T1-weighted hyperintense signal abnormality presumed to represent gadolinium retention in the brain following multiple GBCA administrations. Those publications are currently encompassing nearly 3500 patients, and although a majority of those patients are reported as having T1-weighted hyperintense signal abnormality presumed to represent gadolinium retention in the brain, the findings were reported as aggregate data in most publications and often without controls. Therefore, the cumulative number of patients from those original publications should not be used as a denominator for the purpose of determining the proportion of symptomatic or asymptomatic patients. Six publications or abstracts have reported MRI signal abnormality presumed to represent gadolinium retention associated with the exclusive use of macrocyclic GBCAs, while 17 other publications also addressing macrocyclic GBCAs did not report such signal abnormality. Consequently, this may suggest macrocyclic GBCAs may be retained as well, but perhaps to a lesser degree than linear GBCAs. It should be noted that tissue gadolinium quantification using T1-weighted signal intensity increase is limited in part due to the fact that predominantly chelated and macromolecule-bound gadolinium is detected by MRI while free and insoluble forms of gadolinium are not, leaving direct gadolinium tissue concentration measurement as the gold standard method for accurate quantification.[128] A number of inherent limitations related to MRI equipment, technique, and parameters to measure tissue gadolinium also exist.[120]

Most of the original publications and reviews on T1-weighted hyperintense signal abnormality presumed to represent gadolinium retention in the brain did not report any neurological manifestations associated with MRI signal abnormality presumed to represent gadolinium retention in the brain. However, the great majority of those studies were retrospective and observational and did not intend to specifically assess the presence or the absence of adverse events reported in conjunction with gadolinium retention in the brain. Therefore, it should not be assumed that all those patients were asymptomatic. Only one small retrospective observational study in multiple sclerosis patients addressed adverse events reported in conjunction with gadolinium retention in the brain and reported some correlation between MRI T1-weighted hyperintense signal abnormality presumed to represent gadolinium retention and a reduction in verbal fluency and episodic verbal memory. Tissue integrity was assessed using structural and functional imaging with mixed results reported, although the imaging modalities used were different.

A small number of publications encompassing 42 patients with post-mortem examinations including gadolinium quantification in brain tissue corroborate findings from imaging studies with predominant involvement of cerebral and cerebellar deep grey nuclei. However, only four publications conducted brain tissue histopathological analyses and did not report any gross abnormalities, with the exception of one publication reporting dentate nucleus gliosis and axonal spheroids in two patients. The causal role of gadolinium retention in those cases with histopathologic changes appears inconclusive due to the potential confounding role of external beam radiation therapy (radiation fields and technique not provided) and the relatively low specificity of the histopathologic findings which can be observed in a variety of pathologic conditions.[129] Despite the substantial number of imaging publications on MRI T1-weighted hyperintense signal abnormality presumed to represent gadolinium retention in the brain and

post-mortem publications all suggesting gadolinium deposition predominantly in cerebral and cerebellar deep grey nuclei, no robust cases of adverse events attributable to a pathologic process manifesting within those brain structures have been identified.

2.6 Conclusion

A heterogeneous group of adverse events reported in conjunction with gadolinium retention was identified in 139 patients. Many reported adverse events after a single GBCA administration, and adverse events have been reported with linear GBCAs, macrocyclic GBCAs, and both. While adverse events identified in this review lacked a consistent phenotype, we observed some clustering around cutaneous, musculoskeletal, neurological/cognitive, and pain syndromes. However, the clinical category "other" accounted for the highest number of adverse events, emphasizing the heterogeneity of the adverse events reported. The self-reported nature of the information and the unverified evidence of gadolinium retention are the major limitations of the medical literature and FAERS cases identified in this review. Many other factors may have a confounding role on the adverse events reported in conjunction with gadolinium retention or affect their recognition, potentially leading to over- or underestimation of the importance of the problem. Despite the substantial number of imaging publications on MRI T1-weighted hyperintense signal abnormality presumed to represent gadolinium retention in the brain and post-mortem findings all characterizing gadolinium deposition predominantly in cerebral and cerebellar deep grey nuclei, no robust cases with adverse events attributable to a pathologic process manifesting within those structures have been found. While this review of FAERS and medical literature cases did not confirm an apparent causal association between reported adverse events and gadolinium retention, they suggest a growing concern for untoward effects of GBCAs within both the lay public and the medical community.

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2.8 Appendices

2.8.1 Appendix A. Product Names, NDA Numbers, Dates of Approvals, Indications, and Applicants/Sponsors of GBCAs

NDA Number (approval date)	Product Name	Indications	Applicant/ Sponsor
Linear GBCAs			
NDA-021711 (12/22/2008)	Ablavar (gadofosveset trisodium)	IV use in MRA to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease	Lantheus Medical Imaging, Inc
NDA-022090 (7/3/2008)	Eovist Injection (gadoxetate disodium)	IV use in MRI of the liver to detect and characterize lesions in patients with known or suspected focal liver disease.	Bayer Healthcare Pharma-ceuticals Inc
NDA-019596 (6/2/1988) NDA-021037 (3/10/2000)	Magnevist (gadopentetate dimeglumine)	IV use in MRI in adults and children (2 years of age and older) to facilitate the visualization of lesions and abnormal vascularity in: • CNS: brain, spine, associated tissues • Extracranial/Extraspinal Tissues: head and neck • Body	Bayer Healthcare Pharma-ceuticals Inc
NDA-021357 NDA-021358 (all 11/23/2004)	MultiHhance (gadobenate dimeglumine)	IV use in •MRI in of the CNS in adults and children over 2 years of age to visualize lesions with abnormal blood-brain barrier or abnormal vascularity of the brain, spine, and associated tissues •MRA to evaluate adults with known or suspected renal or aorto-ilio-femoral occlusive vascular disease	Bracco Diagnostics Inc
NDA-020123 (1/8/1993) NDA-022066 (9/5/2007)	Omniscan (gadodiamide)	IV use in MRI to: • Visualize lesions with abnormal vascularity in the brain, spine, and associated tissues • Facilitate the visualization of lesions with abnormal vascularity within thoracic, abdominal, pelvic cavities, and retroperitoneal space	GE Healthcare

NDA Number (approval date)	Product Name	Indications	Applicant/ Sponsor
NDA-020937 NDA-020975 NDA-020976 (all 2/8/1999)	Optimark (gadoverset-amide)	IV use in MRI: • In patients with abnormal blood-brain barrier or abnormal vascularity of the brain, spine and associated tissues • To provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver in patients who are highly suspect for liver structural abnormalities on computed tomography	Mallinckrodt Inc
Macrocyclic GBCAs			
NDA-204781 (3/20/2013)	Dotarem (gadoterate meglumine)	IV use with MRI in brain (intracranial), spine and associated tissues in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity	Guerbet LLC
NDA-201277 3/14/2011)	Gadavist (gadobutrol)	IV use in MRI • To detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system in adult and pediatric patients (including term neonates) • To assess the presence and extent of malignant breast disease • To evaluate known or suspected supra-aortic or renal artery disease in adult and pediatric patients (including term neonates) .	Bayer Healthcare Pharma-ceuticals Inc
NDA-020131 (11/16/1992) NDA-021489 (10/9/2003)	Prohance (gadoteridol)	IV use in MRI to visualize • lesions with abnormal vascularity in the brain (intracranial lesions), spine, and associated tissues in adults and pediatric patients over 2 years of age. •lesions in the head and neck in adults	Bracco Diagnostics Inc

2.8.2 Appendix B. 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 post-marketing 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.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

2.8.3 Appendix C. Product List Used in FAERS FBIS Search

Product Names	
Ablavar	Multihance
Dotarem	Omniscan
Eovist	Optimark
Gadavist	Primovist
Magnevist	Prohance
Gadobenate dimeglumine	Gadolite
Gadobenic acid	Gadopentetate
Gadobutrol	Gadopentetate dimeglumine
Gadodiamide	Gadopentetate\meglumine
Gadofosveset	Gadopentetic acid
Gadofosveset trisodium	Gadoterate meglumine
Gadolinium	Gadoteridol
Gadolinium cation (3+)	Gadoversetamide
Gadolinium chloride hexahydrate	Gadoxetate disodium
Gadolinium oxide	Gadoxetic acid
Gadolinium zeolite	

Product Active Ingredients	
Gadobenate dimeglumine	Gadolinium oxide
Gadobenic acid	Gadopentetate dimeglumine
Gadobutrol	Gadopentetate\meglumine
Gadodiamide	Gadopentetic acid
Gadofosveset	Gadoterate meglumine
Gadofosveset trisodium	Gadoteridol
Gadolinium	Gadoversetamide
Gadolinium cation (3+)	Gadoxetate disodium
Gadopentetate	Gadoxetic acid
Gadoteric acid	Gadolinium zeolite
Gadolinium chloride hexahydrate	Motexafin gadolinium

2.8.4 Appendix D. Data Mining Custom Drug Term

GBCA (Custom Term) for Generic name (no hierarchy)	Generic name (no hierarchy) equals any of the following values: 'Ascorbic Acid And Biotin And Folic Acid And Gadolinium And Pantothenic Acid And Vitamin B1', 'Ascorbic Acid And Biotin And Gadolinium And Vitamin B1 And Vitamin B12 And Vitamin B2', 'Chloride And Gadolinium', 'Contrast Medium And Gadodiamide', 'Contrast Medium And Gadolinium', 'Contrast Medium And Gadolinium And Gadopentetic Acid', 'Contrast Medium And Gadoteric Acid', 'Diethylene Triamine Pentaacetate And Gadolinium', 'Diethylene Triamine Pentaacetate And Gadolinium And Gadopentetic Acid', 'Gadobenic Acid', 'Gadobenic Acid And Gadolinium', 'Gadobenic Acid And Meglumine', 'Gadobutrol', 'Gadobutrol And Gadolinium', 'Gadodiamide', 'Gadodiamide And Gadolinium', 'Gadofosveset', 'Gadolinium', 'Gadolinium And Gadopentetic Acid', 'Gadolinium And Gadoteridol', 'Gadolinium And Gadoversetamide', 'Gadopentetic Acid', 'Gadopentetic Acid And Meglumine', 'Gadoteric Acid', 'Gadoteridol', 'Gadoversetamide', 'Gadoxetic Acid'

2.8.5 Appendix E. FAERS Line Listing of Unpublished Cases of Gadolinium Retention After GBCA Administration Received by FDA Through May 31, 2017 AND FAERS Cases of Persistent Adverse Events After GBCA Administration Received By FDA From June 1, 2016 to May 31, 2017

FAERS Line Listing of Unpublished Cases of Gadolinium Retention After GBCA Administration, Received by FDA From 1969 to May 31, 2017									
Case	**Initial FDA Received Date**	**FAERS Case #**	**Version #**	**Manufacturer Control #**	**Case Type**	**Age (years)**	**Sex**	**Country**	**Serious Outcome(s)***
1	11/20/2007	6478759	1	n/a	DIRECT	59.93	FEMALE	USA	RI
2	10/28/2010	7667733	1	n/a	DIRECT	42	FEMALE	USA	DS
3	11/28/2011	8264279	1	n/a	DIRECT	51	FEMALE	USA	OT
4	01/18/2012	8342673	2	US-BAYER-2012-004992	15-DAY	8	MALE	USA	OT
5	02/29/2012	8432673	1	US-BRACCO-007314	15-DAY	58	FEMALE	USA	
6	11/26/2012	8923818	1	US-BAYER-2012-121502	15-DAY	51.329	FEMALE	USA	OT
7	01/29/2014	9853193	1	US-BRACCO-009081	15-DAY	57.629	FEMALE	USA	
8	02/18/2014	9912670	1	n/a	DIRECT	53	FEMALE	USA	OT
9	04/01/2014	10052474	1	n/a	DIRECT	47	FEMALE	USA	OT
10	08/21/2014	10400345	2	US-BRACCO-011191	PERIODIC	38	FEMALE	USA	
11	09/08/2014	10438613	4	JP-BAYER-2014-133921	15-DAY	42	FEMALE	JPN	OT
12	11/21/2014	10598295	1	US-BAYER-2014-168738	15-DAY		FEMALE	USA	OT
13	03/03/2015	10882732	7	US-BAYER-2015-028578	15-DAY	44	FEMALE	USA	DE
14	02/26/2015	10883145	1	n/a	DIRECT	50	UNK	USA	DS,HO,OT
15	04/28/2015	11074350	1	n/a	DIRECT	67	MALE	USA	LT
16	06/03/2015	11165382	1	n/a	DIRECT	33	FEMALE	USA	DS
17	06/16/2015	11199280	1	n/a	DIRECT	33	FEMALE	USA	DS,LT
18	06/19/2015	11202718	1	US-BAYER-2015-358854	15-DAY		FEMALE	USA	OT
19	06/29/2015	11231496	1	n/a	DIRECT	33	MALE	USA	
20	07/23/2015	11303115	3	AU-GE HEALTHCARE MEDICAL DIAGNOSTICS-OSCN-PR-1506S-0137	15-DAY		MALE	AUS	DS,OT

FAERS Line Listing of Unpublished Cases of Gadolinium Retention After GBCA Administration, Received by FDA From 1969 to May 31, 2017									
Case	**Initial FDA Received Date**	**FAERS Case #**	**Version #**	**Manufacturer Control #**	**Case Type**	**Age (years)**	**Sex**	**Country**	**Serious Outcome(s)***
21	08/14/2015	11381936	2	AU-GE HEALTHCARE MEDICAL DIAGNOSTICS-OSCN-PR-1508S-0165	15-DAY	63	FEMALE	AUS	HO,OT
22	08/17/2015	11394206	1	n/a	DIRECT	57	FEMALE	USA	LT,RI
23	09/15/2015	11508333	1	US-BAYER-2015-416987	15-DAY		FEMALE	USA	OT
24	10/26/2015	11664888	1	n/a	DIRECT	56	MALE	USA	DS,OT
25	11/18/2015	11755699	1	n/a	DIRECT	52	Female	USA	DS,OT
26	12/02/2015	11797605	1	n/a	DIRECT	29	FEMALE	USA	DS,OT
27	12/04/2015	11805981	1	n/a	DIRECT	52	FEMALE	USA	DS,HO,RI
28	03/04/2016	12147460	2	US-BAYER-2016-036479	15-DAY	30	MALE	USA	OT
29	05/09/2016	12347638	2	FR-BRACCO-002250	15-DAY	40	FEMALE	FRA	OT
30	06/07/2016	12442708	2	FR-GE HEALTHCARE MEDICAL DIAGNOSTICS-OSCN-PR-1606S-0089	15-DAY	77.796	FEMALE	FRA	OT
31	06/14/2016	12465327	1	US-GE HEALTHCARE MEDICAL DIAGNOSTICS-OSCN-PR-1606L-0093	15-DAY	7	FEMALE	USA	OT
32	06/16/2016	12474641	1	n/a	DIRECT	81	FEMALE	USA	RI
33	06/21/2016	12487557	1	n/a	DIRECT	59	FEMALE	USA	DS
34	09/16/2016	12750553	2	DE-BAYER-2016-176038	15-DAY	38	FEMALE	DEU	DS,OT
35	12/01/2016	12991790	2	US-BRACCO-014156	15-DAY	34	FEMALE	USA	OT
36	12/01/2016	12993782	1	n/a	DIRECT	59.78	FEMALE	USA	OT
37	02/15/2017	13238462	1	n/a	DIRECT	49	FEMALE	USA	DS
38	03/02/2017	13287007	1	DE-BAYER-2017-036383	15-DAY	60	FEMALE	DEU	HO,OT
39	05/03/2017	13510905	1	n/a	DIRECT	51.26	FEMALE	USA	DS
40	05/13/2017	13545408	1	n/a	DIRECT	45	FEMALE	USA	DS

FAERS Line Listing of Unpublished Cases of Gadolinium Retention After GBCA Administration, Received by FDA From 1969 to May 31, 2017

Case	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country	Serious Outcome(s)*
41	05/19/2017	13567025	1	n/a	DIRECT	36	FEMALE	USA	DS

*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. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.

Abbreviations (country): AUS=Australia, DEU=Germany, FRA=France, USA=United States
Abbreviations (serious outcomes): DE=Death, HO=Hospitalization, LT= Life-threatening, RI=Required intervention, DS= Disability, OT=Other medically significant

FAERS Line Listing of Unpublished Cases of Persistent Adverse Events After GBCA Administration, Received by FDA From June 1, 2016 to May 31, 2017

Case	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country	Serious Outcome(s)*
1	6/20/2016	12484930	1	n/a	Direct	59	FEMALE	USA	DS
2	6/27/2016	12503212	1	n/a	Direct	38	FEMALE	USA	DS
3	7/20/2016	12578014	1	n/a	Direct	65	FEMALE	USA	DS
4	8/2/2016	12618165	1	n/a	Direct	36	FEMALE	USA	DS,OT
5	8/26/2016	12691277	2	GB-BAYER-2016-153408	Expedited	54	MALE	GBR	OT
6	9/27/2016	12783443	1	n/a	Direct	62.89	FEMALE	USA	DS,OT
7	9/27/2016	12939612	1	n/a	Direct	37.74	FEMALE	USA	DS
8	11/15/2016	12959507	1	n/a	Direct	53	FEMALE	USA	DS
9	12/5/2016	13002785	1	n/a	Direct	24	MALE	USA	DS
10	2/7/2017	13192686	1	n/a	Direct	73	FEMALE	USA	DS
11	2/13/2017	13229508	1	n/a	Direct	54	FEMALE	USA	DS,HO,LT,OT
12	2/25/2017	13272648	1	n/a	Direct	60	FEMALE	USA	DS,HO,LT
13	2/28/2017	13280062	1	n/a	Direct	65	FEMALE	USA	OT
14	3/17/2017	13349526	1	n/a	Direct	48	FEMALE	USA	DS
15	4/1/2017	13395603	1	n/a	Direct	39	FEMALE	USA	LT
16	4/29/2017	13498866	1	n/a	Direct	59.3	FEMALE	USA	
17	5/3/2017	13508656	2	ES-BRACCO-001660	Expedited	23	FEMALE	ESP	OT
18	5/19/2017	13563214	1	US-GUERBET-US-20170083	Expedited		FEMALE	USA	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. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.
Abbreviations (country): ESP=Spain, GBR=Great Britain, USA=United States
Abbreviations: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, OT=Other medically significant

2.8.6 Appendix F. Summary of Individual Patients of Publications Reporting Adverse Events Reported in Conjunction With Documented Quantified Gadolinium Retention in Body Fluid or Tissue (Excluding Retention Only Indirectly Documented on Imaging)

Summary of Individual Patients of Publications Reporting Adverse Events Reported in Conjunction With Documented Quantified Gadolinium Retention In Body Fluid or Tissue (Excluding Retention Only Indirectly Documented on Imaging)					
Authors	**Semelka et al. 2016**				**Roberts et al. 2016**
Patient ID	**P2mo**	**P3mo**	**P7yr**	**P8yr**	-
Baseline characteristics					
Age range (at time of assessment)	29	43	58	55	30
Sex	F	F	F	F	M
Race/ethnicity	White	N/R	White	White	N/R
Renal function	Normal	Normal	Normal	Normal	Creatinine: 0.2-1.3 mg/dL [mean 0.5]
MRI indication					
	Suspected complex renal cyst	Rule out: multiple sclerosis (2), liver cancer (1), and breast cancer (1)	Tachyarrhythmia	Rule out multiple sclerosis (4); concussion (1); complex liver and renal cysts (1)	High-grade mixed glioma
GBCA exposure					
Number of administration before symptoms onset					
1	1	4	1	6	61
Exposure period (interval between first and last MRI)					
	2015	2015-2016 (2 months)	2009	1994-2007	2004-2015 (11 years)
GBCA* (in increasing order of thermodynamic stability) and cumulative dose					
gadodiamide				5x0.1 mmol/kg (78 mL cumulative)	Dose N/R
gadoversetamide		0.1 mmol/kg			
gadopentetic acid	0.1 mmol/kg (20 mL)				Dose N/R
gadobenic acid			0.1 mmol/kg (12 ml)	0.05 mmol/kg (8 mL)	Dose N/R
gadoxetic acid		0.025 mmol/kg			
gadofosveset					
gadoteridol					Dose N/R (likely highest cumulative

Summary of Individual Patients of Publications Reporting Adverse Events Reported in Conjunction With Documented Quantified Gadolinium Retention In Body Fluid or Tissue (Excluding Retention Only Indirectly Documented on Imaging)					
Authors	**Semelka et al. 2016**				**Roberts et al. 2016**
Patient ID	**P2mo**	**P3mo**	**P7yr**	**P8yr**	-
					dose)
gadobutrol		2x0.1 mmol/kg			
gadoteric acid					
Gadolinium retention including fluid/tissue used and concentrations (last GBCA exposure-testing interval)					
Institution performing measurement	Mayo Clinic	Mayo Clinic	Mayo Clinic	Authors' institutions	Authors' institutions
Urine	18 mcg/24h (31 days)	82, 15, 13, 7.6, 0.8, 3.3 mcg/24h (28, 48, 56, 69, 74, 103 days)	0.0655 mcg/g (4 years)		
Blood	0.7 ng/mL (33 days)				
Hair			0.0007 mcg/g (4 years)		
Skin					14.4 mcg/g (8 months)
Other				4.4 pg/g saphenous vein (1(8 years)	
Clinical Manifestations					
Last GBCA exposure-symptoms onset	Within 24 hours	Immediately after 4th MRI	Within 24 hours	2-3 weeks after last MRI	Continued serial MRI during symptoms development (8 years after first MRI)
Cutaneous manifestations	-	Diffuse nodular and linear subcutaneous abnormal firmness excluding face and hands; tightening of skin of face neck and distal limbs	Rash	Erythema and warmth of hands, feet and central torso	-
Musculoskeletal manifestations	Arthralgias	-	-	-	Severe contractures
Pain syndromes	Flu-like body aches; nociceptive paresthesia/dysesthesia	Nociceptive paresthesia/dysesthesia (painful tingling	Nociceptive paresthesia/dysesthesia (burning sensation)	Nociceptive paresthesia/dysesthesia (sharp knife pain) in	-

Summary of Individual Patients of Publications Reporting Adverse Events Reported in Conjunction With Documented Quantified Gadolinium Retention In Body Fluid or Tissue (Excluding Retention Only Indirectly Documented on Imaging)					
Authors	**Semelka et al. 2016**				**Roberts et al. 2016**
Patient ID	**P2mo**	**P3mo**	**P7yr**	**P8yr**	-
	(burning and sharp pins and needles) on central torso and limbs; headaches	sensation) on torso and limbs	involving central torso and all 4 limbs; headaches	distal limbs	
Cognitive/neurological	Non-nociceptive paresthesias; clouded mentation	Non-nociceptive paresthesias (crawling sensation); reduced temperature perception in hands and feet; memory impairment; muscle weakness	Clouded mentation; disorientation	-	-
Other clinical manifestations	-	Reduced ability to sense bladder fullness and void; expanding non-pitting edema from injection side to entire body; fatigue	Nausea; burning bladder; hypertensive spikes; metallic taste	Swelling of distal limbs	-
Physical examination (interval since last GBCA exposure)	No findings (2 months	Subcutaneous lesions; skin tightness; shiny appearance of skin over fingers (4 months)	Mild skin discoloration of hands; tightness sensation in webs between fingers; discolored legs and red rubbery texture of subcutaneous tissue around knees (7 years)	Thickening and erythema of skin of hands and feet (8 years)	Skin examination performed by dermatologist normal
Investigation other than gadolinium measurement	N/R	N/R	Skin biopsy (knee, 3 years after GBCA exposure); fibrosis and alopecia	N/R	Skin biopsy (right forearm and right shin, 8 months after last GBCA exposure): increased CD34 immunoreactivity in connective tissue septations of

Summary of Individual Patients of Publications Reporting Adverse Events Reported in Conjunction With Documented Quantified Gadolinium Retention In Body Fluid or Tissue (Excluding Retention Only Indirectly Documented on Imaging)					
Authors	**Semelka et al. 2016**				**Roberts et al. 2016**
Patient ID	**P2mo**	**P3mo**	**P7yr**	**P8yr**	-
					subcutaneous adipose tissue suggesting inflammation or injury
Treatment and response	N/R	Antihistamines, imatinib 100 mg/d for 2 weeks, prednisone 20mg; no effects on symptoms	N/R	N/R	N/R
Outcome	Progression over days with subsequent gradual diminution of symptoms but persistent clouded mentation, headaches, and arthralgias	Persistent symptoms	Persistence for 4 months with slight relief afterwards	Progressive diminution of symptoms but still persistent after 8 years	Unspecified (1)
*Only generic names included as publications may be from different countries F=female; GBCA=gadolinium-based contrast agents; M=male; MRI=magnetic resonance imaging; N/R=not reported					

2.8.7 Appendix G. Summary of Publications Addressing Adverse Events Reported in Conjunction With Gadolinium Retention Following Systemic GBCA Administration (Excluding Nephrogenic Systemic Fibrosis)

Summary of Publications Addressing Adverse Events Reported in Conjunction With Gadolinium Retention Following Systemic GBCA Administration (Excluding Nephrogenic Systemic Fibrosis)					
Authors	**Miller et al.**	**Semelka et al.**	**Burke et al.**	**Semelka et al.**	**Roberts et al.**
Year of publication	2015	2016	2016	2016	2016
Country of origin	US	US	US	US	US
Number of patients	1	4	50	42	1
Data sources	Chart review	Clinical assessment	Online survey with self-reported symptoms and gadolinium retention	Online survey with self-reported symptoms and gadolinium retention	Clinical assessment and chart review
Baseline characteristics					
Sex	M (1)	F (4)	N/R	M (14), F (27), unknown (1)	M (1)
Age range [mean]	21	29-58 [46]	N/R	28-69 [49.1]	30
Race/ethnicity	N/R	Caucasian (3); unspecified (1)	N/R	Caucasian (42); Hispanic (2)	N/R
Renal function	Normal	Normal (4)	N/R; personal or family history of renal disease (6)	Normal at the time of exposure (self-reported) (42)	Normal
MRI indication					
	Left orbit rhabdomyosarcoma	Complex renal cysts (1); complex liver cysts (1); rule out multiple sclerosis (2); tachycardia (1); concussion (1)	N/R	N/R	High-grade mixed glioma
GBCA exposure					
Number of administration before symptoms onset					
1		2		21	
2					
3					
4		1			
⩾5	1 [35 total]	1 [5 total]			1 [61 total]
Unspecified			50 (mean of 4.2; range 1-23 for entire	21 (single agent (7); multiple GBCA (14)	

Summary of Publications Addressing Adverse Events Reported in Conjunction With Gadolinium Retention Following Systemic GBCA Administration (Excluding Nephrogenic Systemic Fibrosis)					
Authors	**Miller et al.**	**Semelka et al.**	**Burke et al.**	**Semelka et al.**	**Roberts et al.**
			group)		
GBCA* (in increasing order of thermodynamic stability)					
gadodiamide			9	4	
gadoversetamide				4	
gadopentetic acid	1	1	11	9	
gadobenic acid		1	5	4	
gadoxetic acid					
gadofosveset			6		
gadoteridol				2	
gadobutrol			1	1	
gadoteric acid					
unknown			14	4	
multiple		2	4	14	1
Gadolinium retention					
Source of information	Indirectly documented	Documentation	Self-reported but not unverified	Self-reported but unverified	Documentation
Any		4	41	41	1
Urine		3	31	41	
Blood		1	5	8	
Hair		1	4	2	
Skin			3	2	1
Other	Globus pallidus; dentate nuclei; and posterior thalamus (by MRI)	Saphenous vein (1)	Thyroid (1); breast (1)	Thyroid (1); scalp (1)	Globus pallidus; dendate nuclei (by MRI)
GBCA administration –testing interval	Range, 2-15 years	>1 month after gadolinium administration	Information not collected	>30 days after gadolinium administration	8 months
Clinical Manifestations					
Latency last administration-symptoms	1 year	within 24 hours (3); within 2-3 weeks (1)	Immediately (33); within 6 weeks (16); 6 months (1)	Skin changes (2 weeks-2 months); metallic taste (within one day)	Continued serial MRI during symptoms development (8 years after first MRI)
Cutaneous/soft tissue		Distal limb skin	Skin changes (29)	Skin	

Summary of Publications Addressing Adverse Events Reported in Conjunction With Gadolinium Retention Following Systemic GBCA Administration (Excluding Nephrogenic Systemic Fibrosis)					
Authors	**Miller et al.**	**Semelka et al.**	**Burke et al.**	**Semelka et al.**	**Roberts et al.**
manifestations		thickening (3); rubbery subcutaneous tissue (3); rash (1); skin discoloration (2); erythema (1)		thickening/edema (22); skin discoloration (28)	
Musculoskeletal manifestations		Arthralgia (1)	Bone /joint pain (38)	Bone pain (33); joint stiffness (33); muscle spasms (30)	Contractures
Pain syndromes		Central torso pain (4); limb pain (4); headache (2)		Headache (28); central torso pain (15); glove & stocking pain (26)	
Cognitive/neurological	Cognitive impairment (executive functions, visual memory and reasoning, reading comprehension, math abilities) (1)	Clouded mentation (2); memory impairment (1); paresthesias (2);		Clouded mentation (29)	
Other clinical manifestations		Fatigue (1); labile hypertension (1); metallic taste (1); nausea (1); bladder symptoms (2)	Head & neck including headache, vision changes, and hearing changes (38); flu-like symptoms (15); digestive symptoms including nausea, vomiting, and diarrhea (23); chest symptoms/dyspnea (21); generalized whole body symptoms (30); other unspecified (37)	Buzzing sensation (24); fatigue (36); metallic taste (19)	

Summary of Publications Addressing Adverse Events Reported in Conjunction With Gadolinium Retention Following Systemic GBCA Administration (Excluding Nephrogenic Systemic Fibrosis)					
Authors	**Miller et al.**	**Semelka et al.**	**Burke et al.**	**Semelka et al.**	**Roberts et al.**
Outcome	Persistent symptoms (1)	Persistent symptoms (4)	N/R	Residual symptoms (42)	Unspecified (1)
*Only generic names included as publications may be from different countries F=female; GBCA=gadolinium-based contrast agents; M=male; MRI=magnetic resonance imaging; N/R=not reported; US=United States					

2.8.8 Appendix H. Case Reports of Neurotoxicity Reported With Systemic, Intrathecal, and Intraventricular GBCA Administration

H1. Case Reports of Neurotoxicity Reported with Systemic, Intrathecal, and Intraventricular GBCA Administration						
Author	**Erbay & Bhadelia**	**Maramattom et al.**	**Arlt et al.**	**Li et al.**	**Hui & Mullins**	**Kapoor et al.**
Year of publication	2001	2005	2007	2008	2009	2010
Country of origin	US	US	Germany	China	US	US
Baseline Characteristics						
Demographics (age and sex)	70 F	57 F	64 M	34 F	N/R	61 F
Renal function	Abnormal	Abnormal	Normal	Normal	N/R	N/R
GBCA* received and number of studies (in increasing order of thermodynamic stability)						
gadodiamide						1
gadoversetamide						
gadopentetic acid			1	1		
gadobenic acid						
gadoxetic acid						
gadofosveset						
gadoteridol	1 (MRA)					
gadobutrol						
gadoteric acid						
multiple linear only						
multiple macrocyclic only						
multiple mixed						
multiple unspecified						
unknown		4 (MRI ± MRA)			1 (MRI + MRA)	
Route	Intravenous	Intravenous	Intrathecal (intended for CT myelogram)	Intrathecal	Intravenous	Epidural
Dose	0.2 mmol/kg	60-80 mL	20 mL; followed by 20 mL of iotrolan	15 mL (0.5 mmol/mL)	N/R	Two 4 mL (1,148 mg)
MRI Indication	Renovascular disease	Left hemiparesis, gait difficulty	Cervical myelopathy	Myelography for rachial plexus injury	Syncope	Lumbar radiculopathy
Clinical manifestations						
Latency	Within one day	Over a few days	Within a few hours	Immediate	N/R	Over a few hours
Neurological symptoms and signs	Encephalopathy	Encephalopathy; left hemiparesis (pre-existing)	Encephalopathy; dysarthria; nausea and vomiting;	Headache; emesis; coma; seizures	Encephalopathy	Positional headache; encephalopathy;

H1. Case Reports of Neurotoxicity Reported with Systemic, Intrathecal, and Intraventricular GBCA Administration						
Author	**Erbay & Bhadelia**	**Maramattom et al.**	**Arlt et al.**	**Li et al.**	**Hui & Mullins**	**Kapoor et al.**
			blurred vision; nystagmus; limb ataxia			generalized motor seizures
Imaging	Subarachnoid and ventricular FLAIR and T1 hyperintensity	CSF becoming increasingly T1 hyperintense on successive MRIs	Subarachnoid space FLAIR hyperintensity	T1 hyperintense signal in CSF space and parenchyma and diffusion restriction (Day 6); disuse vasospasm on MRA (Day 6); residual parenchymal T1 hyperintense signal (8 months)	CSF compartment T1 hyperintensity	Subarachnoid and ventricular FLAIR and T1 hyperintensity
CSF abnormalities	Protein 60 mg/dL	9-13 cells/mL (44% lymphocytes; 56% monocytes)	Protein 139.3 mg/mL; elevated neuronal and glial markers (S-100, 14-3-3, tau, NSE)	Protein 264 mg/dL	N/R	Blood contaminated
Gadolinium measurement	CSF, imaging qualitative assessment only	Serum 28,591 ng/mL or 50 nmol/mL (Day 14)	CSF, 23,365 nmol/mL; 22.5 nmol/L (10 hours)	N/R	CSF 23,000 nmol/mL	N/R
Treatment	Dialysis	None	Dexamethasone 40 mg intravenous	Methylprednisolone 1000 mg/d for 7 days; CSF drainage through lumbar catheter	Serial hemodialysis	Epidural blood patch; fosphenytoin; endotracheal intubation
Outcome	Death from toxic megacolon	Severe apathy; retrograde amnesia; no follow-up imaging performed	Residual mild gait ataxia and concentration difficulty; no follow-up imaging performed	Recovered by Day 8	Complete resolution	Residual paroxysmal seizure-like symptoms
Reported alternative etiology	Systemic diseases	PRES; lacunar infarctions	None	None	None	None

H1. Case Reports of Neurotoxicity Reported with Systemic, Intrathecal, and Intraventricular GBCA Administration						
Author	**Erbay & Bhadelia**	**Maramattom et al.**	**Arlt et al.**	**Li et al.**	**Hui & Mullins**	**Kapoor et al.**
*Only generic names included as publications may be from different countries CSF=cerebrospinal fluid; CT=computed tomography; F=female; FLAIR=fluid attenuation inversion recovery; GBCA=gadolinium-based contrast agents; M=male; MRA=magnetic resonance imaging; MRI=magnetic resonance imaging; N/R=not reported; PRES=posterior leukoencephalopathy syndrome; US=United States						

H2. Case Reports of Neurotoxicity Reported with Systemic, Intrathecal, and Intraventricular GBCA Administration						
Author	**Park et al.**	**Jamal et al.**	**Samardzic et al.**	**Shah et al.**	**Singh et al.**	**Reeves et al.**
Year of publication	2010	2013	2015	2016	2016	2017
Country of origin	S. Korea	N/R	US	N/R	US	US
Baseline characteristics						
Demographics (age and sex)	42 M	59 M	67 F	68 F	59 M	60 F
Renal function	N/R	N/R	N/R	N/R	N/R	N/R
GBCA* received and number of studies (in increasing order of thermodynamic stability)						
gadodiamide			1	1		
gadoversetamide						
gadopentetic acid	1				1	
gadobenic acid						
gadoxetic acid						
gadofosveset						
gadoteridol						
gadobutrol						1
gadoteric acid						
multiple linear only						
multiple macrocyclic only						
multiple mixed						
multiple unspecified						
unknown		1				
Route	Intrathecal	Intra-ventricular	Epidural	Intrathecal	Intraventricular	Intrathecal
Dose	6 mL	10 mL	4 mL (287 mg/mL)	1 mL	10 mL	2 mL
MRI Indication	Spinal canal stenosis (accidental use of GBCA	Post-resection and embolization tentorial	Needle localization during fluoroscopic -guided injection	Catheter dye study for pump malfunction (iodine	Meningioma post-resection assessment;	Integrity and proper placement assessment of

H2. Case Reports of Neurotoxicity Reported with Systemic, Intrathecal, and Intraventricular GBCA Administration						
Author	**Park et al.**	**Jamal et al.**	**Samardzic et al.**	**Shah et al.**	**Singh et al.**	**Reeves et al.**
	instead of iodine contrast agent)	meningioma		allergy)	accidental connection of venous line to ventricular catheter	intrathecal catheter for pain management (iodine allergy)
Clinical manifestations						
Latency	6 hours	N/R	3 hours	12 hours	Within one hour, evolving over several hours	Less than 5 minutes
Symptoms and signs	Confusion and global aphasia; then stupor , rigidity, and seizures	Refractory non-motor status epilepticus (7 weeks)	Encephalopathy, nausea, dyspnea	Generalized motor seizures; encephalopathy	Nausea; hypertension; aphasia; right facial paresis; delirium; non-convulsive status epilepticus; coma	Painful lower extremity spasms
Imaging	high density throughout subarachnoid space (initial CT); normal CT on day 4	N/R	T1 hyperintense signal within the sulci, cisterns, membranous labyrinth, and orbits	Hyperdense CSF on CT	Hyperintense CSF; cerebral edema; right posterior cerebral artery ischemic stroke	N/R
CSF abnormalities	N/R	N/R	N/R	N/R	N/R	N/R
Gadolinium measurement	N/R	N/R	N/R	N/R	N/R	N/R
Treatment	Anticonvulsants	Multiple anticonvulsants; anesthetic agents	Dexamethasone 4 mg intravenous every 6 hours	N/R	Hyperventilation; dexamethasone; hypertonic saline; anticonvulsants; lumbar drain	Midazolam
Outcome	Residual bilateral optic atrophy	Following simple commands intermittently	"Discharged in good medical and neurological condition"	Discharged after 45 days	Persistent vegetative state at 2-year follow-up	Complete resolution with treatment
Reported alternative etiology	Subarachnoid hemorrhage (normal angiogram)	Tentorial meningioma	None	None	None	None

H2. Case Reports of Neurotoxicity Reported with Systemic, Intrathecal, and Intraventricular GBCA Administration

Author	Park et al.	Jamal et al.	Samardzic et al.	Shah et al.	Singh et al.	Reeves et al.

*Only generic names included as publications may be from different countries

CSF=cerebrospinal fluid; CT=computed tomography; F=female; FLAIR=fluid attenuation inversion recovery; GBCA=gadolinium-based contrast agents; M=male; MRA=magnetic resonance imaging; MRI=magnetic resonance imaging; N/R=not reported; PRES=posterior leukoencephalopathy syndrome; US=United States

2.8.9 Appendix I. Publications Addressing MRI Signal Abnormality Presumed to Represent Gadolinium Retention

Publications Addressing MRI Signal Abnormality Presumed to Represent Gadolinium Retention							
Author, year	**Publication type and country of origin**	**Number of subjects**	**Number of control**	**Brain imaging indications**	**GBCA* most commonly used**	**Gadolinium retention syndrome symptoms**	**Number of subjects assessed with gadolinium retention**
Adin et al., 2015	Retrospective observational (adult and pediatric); USA	184	53	Primary brain tumors treated with irradiation	Gadopentetic acid	N/A	103
Bae et al., 2017	Retrospective observational (adult); S. Korea	122	-	Lung cancer (91); breast cancer (20); other malignancies (11); 102/122 with brain metastases	Gadodiamide; gadopentetic acid; gadobutrol; gadoteric acid	N/A	linear GBCAs (6) (aggregate data only) but not macrocyclic GBCA (44)
Barbieri et al., 2016	Case series (adult); Switzerland	3	-	Encephalopathy (2); aphasia and somnolence (1)	Gadoteridol; gadodiamide	N/R besides alteration of consciousness, aphasia, confusion, and weakness which appear related to indication for MRI	3
Cao and Huang., 2016	Retrospective observational (adult); USA	50	-	Primary brain tumor (31); brain metastasis (6); demyelination (4); infection (8); CNS vasculitis (1) Irradiation in 30 (28 limited field; 2 whole brain)	Gadopentetic acid; gadobutrol	N/A	25/25 for gadopentic acid and 0/25 for gadobutrol (aggregate data only)
Cao and Zhang., 2016	Retrospective observational (adult); USA	50 (25 hemodialyzed)	26	Various neurological symptoms and conditions	Gadopentetic acid; gadodiamide; gadobenic acid	N/A	25 (hemodialyzed)/50 (aggregate data only)
Conte et al., 2017	Retrospective observational (adult); Italy	18	-	Stage II melanoma	Gadoxetic acid	N/A	0/18 (aggregate data only)
Errante et al., 2014	Retrospective observational (adult); Italy	75	-	MS (38) or brain metastases (37)	Gadodiamide	N/A	75/75 (aggregate data only)
Eisele et al., 2016	Retrospective observational (adult); Germany	41	-	Relapsing remitting MS (41)	Gadoteric acid	N/A	0/41 (aggregate data only)
Eisele et al., 2017	Retrospective	22	-	MS	Gadoteric acid	N/A	0/22 (aggregate data)

Publications Addressing MRI Signal Abnormality Presumed to Represent Gadolinium Retention							
Author, year	**Publication type and country of origin**	**Number of subjects**	**Number of control**	**Brain imaging indications**	**GBCA* most commonly used**	**Gadolinium retention syndrome symptoms**	**Number of subjects assessed with gadolinium retention**
	observational (adult); Germany						
Flood et al., 2017	Retrospective observational (pediatric); USA	46	57	Extracranial neoplasm (19); pituitary abnormality (10); transient parenchymal enhancement (5); orbit/optic nerve abnormality (3); mild volume loss (1); perimesencephalic lipoma (1); cavernous sinus cyst (1); clival mass (1); sinus disease (3); choroid plexus abnormality (1); temporalis abnormality (1)	Gadopentetic acid	N/A	46/46 (aggregate data only)
Forslin et al., 2017	Retrospective observational (adult); Sweden	23	23	Multiple sclerosis (23)	Gadodiamide; gadopentetic acid; gadoteric acid	N/A	23/23 (aggregate data only)
Hinoda et al., 2017	Retrospective observational (adult); Japan	48	48	High-grade glioma (18); low-grade glioma (15); meningioma (8); hemangiopericytoma (1); colloid cyst (1); dermoid (1); cavernous angioma (1); schwannoma (1); healthy volunteers (48)	Mixture of linear and macrocyclic	N/A	48/48 (aggregate data only)
Hu et al., 2016	Retrospective observational (pediatric); USA	21	21	Primary brain tumors (19); ataxia (1); nystagmus (1)	Gadopentetic acid	N/A	21/21 (aggregate data only)
Ichikawa et al., 2017	Retrospective observational (adult); Japan	99	33	Only reported for gadodiamide group: meningioma (11); astrocytic tumors (7); oligodendroglial tumors (3); metastatic tumors (3); acoustic neuroma	Gadoxetic acid; gadodiamide	N/A	0/99 (aggregate data only)

Publications Addressing MRI Signal Abnormality Presumed to Represent Gadolinium Retention							
Author, year	**Publication type and country of origin**	**Number of subjects**	**Number of control**	**Brain imaging indications**	**GBCA* most commonly used**	**Gadolinium retention syndrome symptoms**	**Number of subjects assessed with gadolinium retention**
				(2); other (7)			
Kahn et al., 2017	Prospective observational (adult); Germany	91	52	Control group only: headache (13); tumor staging (10); vessel anomaly (5); vertigo (3); epileptic focus (3); study purpose (3); paresthesia (2); dementia (2); bleeding (2); other (9)	Gadoxetic acid	N/A	91/91 (aggregate data only)
Kanda and Kawaguchi, 2013	Retrospective observational (adult); Japan	14	15	Lung cancer without metastases (29)	N/R	N/A	14
Kanda, Ishii et al., 2014	Retrospective observational (adult); Japan	381	16	Systemic malignancies and some with brain tumors (not accurately accounted for)	Gadopentetic acid; gadodiamide	N/A	381/381 (aggregate data only)
Kanda, Osawa et al., 2015	Retrospective observational (adult and pediatric); Japan	73	54	Brain metastasis (74); primary brain tumor (20); cerebritis (4); meningitis (4); demyelination (6); other (17)	Gadopentetic acid; gadoteridol	N/A	9/73
Khant et al., 2017	Case report (adult); Japan	1	-	Neurofibromatosis type 2-related tumors	Gadopentetic acid; gadoteric acid; gadoteridol	N/A	1
Kinner et al., 2017	Retrospective observational (adult and pediatric); unknown	162	-	N/R	N/R	N/A	162/162 (aggregate data only)
Kromrey et al., 2017	Retrospective observational (adult); Germany	271	116	Prospective population-based screening whole-body study	Gadobutrol	N/A	0/271 (aggregate data only)
Kuno et al., 2017	Retrospective observational (adult and pediatric); USA	9	26	Seizure (4); headache (2); meningioma (2); metastases screening (1)	Gadopentetic acid	N/A	9/9 (aggregate data only)
Langner et al., 2017	Retrospective observational (adult); Germany	217	-	Clinically isolated syndrome (MS) (217)	Gadobutrol	N/A	0/217 (aggregate data only)

Publications Addressing MRI Signal Abnormality Presumed to Represent Gadolinium Retention							
Author, year	**Publication type and country of origin**	**Number of subjects**	**Number of control**	**Brain imaging indications**	**GBCA* most commonly used**	**Gadolinium retention syndrome symptoms**	**Number of subjects assessed with gadolinium retention**
Marsecano et al., 2017	Retrospective observation (adult); unknown	158	-	MS (158)	Gadoteric acid; gadobutrol	N/A	158/158 (aggregate data only)
Moreno Negrete et al., 2017	Retrospective observational (adult); Spain	139	-	Melanoma (139)	Gadobutrol	N/A	41% (57/139)
Muller et al., 2017	Prospective observational (adult); Germany	17	-	GBM (17)	Gadobutrol	N/A	0/17 (aggregate data only)
Quattrocchi et al., 2015	Retrospective observational (adult); Italy	102	-	Meningioma (102)	Gadodiamide	N/A	102/102 (aggregate data only)
Radbruch et al., 2015a	Retrospective observational (adult); Germany	100	-	GBM (29); other glioma (58); non-glioma tumor (10); no tumor (3)	Gadopentetic acid; gadoteric acid	N/A	50/50 for gadopentic acid and 0/50 for gadoteric acid (aggregate data only)
Radbruch et al., 2015b	Retrospective observational (adult); Germany	30	-	Glioma WHO IV (7); glioma WHO III (6); glioma WHO II (8); lymphoma (4);other (5)	Gadobutrol	N/A	0/30 (aggregate data only)
Radbruch et al., 2016	Retrospective observational (adult); Germany	36	-	Glioma WHO I (1); glioma WHO II (6); glioma WHO III (20); glioma WHO IV (5); lymphoma (3); other (1)	Gadopentetic acid; gadobutrol; gadoteric acid	N/A	36/36 for gadopentetic acid, 0/36 for gadobutrol, 0/12 for gadoteric acid (aggregate data)
Radbruch et al., 2017a	Retrospective observational (adult); Germany	33	-	GBM (8); Glioma WHO I-III (23); choroid plexus papilloma (1); intramedullary melanocytic tumor (1)	Gadoteric acid; gadobutrol	N/A	0/33 (aggregate data only)
Radbruch et al., 2017b	Retrospective observational (pediatric); Germany	41	-	Glioma WHO I-III (23); craniopharyngioma (3); sarcoma (3); germinoma (2); other (10)	Gadoteric acid	N/A	0/41 (aggregate data only)

Publications Addressing MRI Signal Abnormality Presumed to Represent Gadolinium Retention							
Author, year	**Publication type and country of origin**	**Number of subjects**	**Number of control**	**Brain imaging indications**	**GBCA* most commonly used**	**Gadolinium retention syndrome symptoms**	**Number of subjects assessed with gadolinium retention**
Ramalho et al., 2015	Retrospective observational (adult); USA	69	-	Meningioma (20); pituitary lesions (19); stroke (13); PRES (1); aneurysm (1); acute hematoma (1); metastasis screening (3); CSF leak (1); trauma (1); miscellaneous tumors (11)	Gadodiamide; gadobenic acid	N/A	23/23 gadodiamide, 0/46 gadobenic acid (aggregate data only)
Roberts et al., 2016	Retrospective observational (pediatric); USA	16	-	Primary brain tumor (9); spinal cord tumor (1); MS (1);CSF leaks (1); brainstem encephalitis (1); extracranial tumor or vascular malformation (3);	Gadopentetic acid	N/A	16/16 (aggregate data only)
Roberts and Holden, 2016	Case report (adult); USA	1	-	Clival chordoma	Gadopentetic acid	N/R	1
Rossi-Espagnet et al., 2017	Retrospective observational (pediatric); Italy	50	59	Medulloblastoma (11); pilocytic astrocytoma posterior fossa (5); cranipharyngioma (4); pineal germinoma (4) ependymoma (4); grade III astrocytoma (3); acute lymphoblastic leukemia (2); ganglioglioma (2); GBM (2); primitive neuroectodermal tumor (2): other (11)	Gadoteric acid	N/A	50/50 (aggregate data only)
Schlemm et al., 2016	Retrospective observational (adult); Germany	97	-	MS (97)	Gadopentetic acid; gadobutrol	N/A	49/49 for gadopentetic acid and 0/48 for gadobutrol (aggregate data only)
Schneider et al., 2017	Retrospective observations (pediatric)	34	24	Non-neurologic indications	Gadobenic acid	N/A	0/34 (aggregate data only)

Publications Addressing MRI Signal Abnormality Presumed to Represent Gadolinium Retention							
Author, year	**Publication type and country of origin**	**Number of subjects**	**Number of control**	**Brain imaging indications**	**GBCA* most commonly used**	**Gadolinium retention syndrome symptoms**	**Number of subjects assessed with gadolinium retention**
Stojanov et al., 2016	Retrospective observational (adult); Serbia	58	-	Relapsing remitting MS (58)	Gadobutrol	N/A	58/58 (aggregate data only)
Tanaka et al., 2016	Retrospective observational (adult); Japan	27	-	MS (21); NMOSD (6)	Gadopentetic acid; gadodiamide	N/A	19/21 (aggregate data only)
Tedeschi et al., 2016	Retrospective observational (adult); Italy	74	-	Relapsing remitting MS (74)	Gadopentetic acid; gadobutrol; gadoteric acid	N/A	Correlation with number of administrations mainly with linear GBCAs (aggregate data only)
Tibussek et al., 2017	Retrospective observational (pediatric); Germany	24	24	Pilocytic astrocytoma (17), craniopharyngeoma (1), desmoplastic medulloblastoma (1), pleomorphic xanthoastrocytoma (1), dysembryoplastic neuroepithelial tumor (1), ganglioglioma (1), hypothalamic glioma (1), and low-grade glioma (1); headache (8), neurologic symptoms (5), behavioral changes (2), nutritional disorders (2), dizziness (1), seizure (2), tic disorder (1), relapsing emesis (1), trauma (1), and limited speaking ability (1).	Gadoteric acid (3); gadoteridol and gadoteric acid (24)	N/A	0/24 (
Towbin et al., 2017	Retrospective observational (pediatric); USA	53	-	N/R	Gadopentetic acid; gadoteric acid	N/A	27/53 (gadopentetic acid group) (aggregate data only)

Publications Addressing MRI Signal Abnormality Presumed to Represent Gadolinium Retention							
Author, year	**Publication type and country of origin**	**Number of subjects**	**Number of control**	**Brain imaging indications**	**GBCA* most commonly used**	**Gadolinium retention syndrome symptoms**	**Number of subjects assessed with gadolinium retention**
Vatnehol et al., 2016	Retrospective observational; Norway	27	-	GBM (27)	Gadobutrol	N/A	27/27 (aggregate data only)
Weberling et al., 2015	Retrospective observational (adult); Germany	50	-	Melanoma (47); glioma (2); ependymoma (1)	Gadobenic acid	N/A	50/50 (aggregate data only)
Wolansky et al., 2016	Retrospective observational (adult); USA	15		MS (15)	Gadopentetic acid	N/A	15/15 (aggregate data only)
Yoo et al., 2017	Retrospective observational (adult); S. Korea	189	-	GBM (5); other glioma (8); metastasis (119); ischemic lesion (5); demyelinating disease (1); others (51)	Gadobutrol	N/A	0/189 (aggregate data only)
Zhang et al., 2017	Retrospective observational (adult); USA	13	-	High-grade glioma (6); low-grade glioma (2); nonglioma primary brain tumor (5)	Gadodiamide; gadopentetatic acid; gadobenic acid	N/A	13/13 (aggregate data only)

*Only generic names included as publications may be from different countries

CNS=central nervous system; CSF=cerebrospinal fluid; GBCA=gadolinium-based contrast agents; GBM=glioblastoma multiforme; MRI=magnetic resonance imaging; MS=multiple sclerosis; NMOSD=neuromyelitis optica spectrum disorder; N/A=not assessed; N/R=not reported; PRES=posterior leukoencephalopathy syndrome; SLE=systemic lupus erythematous; WHO=World Health Organization

2.8.10 Appendix J. Subset of Publications of MRI Signal Abnormality Presumed to Represent Gadolinium Retention Addressing the Role of Macrocyclic GBCA

Subset of Publications of MRI Signal Abnormality Presumed to Represent Gadolinium Retention Addressing the Role of Macrocyclic GBCA							
Author, year	**Publication type and country of origin**	**Number of subjects and controls**	**Number of administration**	**Brain imaging indications**	**GBCA* (number of subjects unless indicated otherwise)**	**Methodology**	**Findings, limitations, and disclosures**
Bae et al., 2017	Retrospective observational (adult); S. Korea	122	Linear, 15-30; macrocyclic, 14-51; both, 12-65	Lung cancer (91); breast cancer (20); other malignancies (11); 102/122 with brain metastases	Gadodiamide only (2) Gadopentetic acid only (1) Both linear (3) Gadobutrol only (14) Gadoteric acid only (1) Both macrocyclic GBCA (29) Mixed (72)	DN:pons and GP:TH SI ratios relative change from between baseline and final MRI	Increased DN:pons ratio with linear GBCAs (aggregate data only) but not macrocyclic GBCA; small N for linear GBCAs
Cao and Huang., 2016	Retrospective observational (adult); USA	50	⩾0	Primary brain tumor (31); brain metastasis (6); demyelination (4); infection (8); CNS vasculitis (1) Irradiation in 30 (28 limited field; 2 whole brain)	Gadopentetic acid (25) Gadobutrol (25)	DN:pons and DN:CP SI ratios change from between baseline and final MRI	Increased DN:CP SI ratio with gadobutrol but not gadopentetic acid (aggregate data only); Bayer Pharmaceuticals engaged on statistics
Eisele et al., 2016	Retrospective observational (adult); Germany	41	⩾6	Relapsing remitting MS (41)	Gadoteric acid (41)	DN:pons and DN:cerebellum SI ratios change from between baseline and final MRI	No DN:pons or DN:cerebellum SI increase (aggregate data only); travel expenses and research financial support provided by Bayer to some authors
Eisele et al., 2017	Retrospective observational (adult); Germany	22	15-27 (mean 17)	MS	Gadoteric acid	DN:pons, DN:cerebellum SI ratios between baseline and last MRI	Absolute SI ratio differences did not statistically differ; no correlation with number ofcontrast-

Subset of Publications of MRI Signal Abnormality Presumed to Represent Gadolinium Retention Addressing the Role of Macrocyclic GBCA							
Author, year	**Publication type and country of origin**	**Number of subjects and controls**	**Number of administration**	**Brain imaging indications**	**GBCA* (number of subjects unless indicated otherwise)**	**Methodology**	**Findings, limitations, and disclosures**
							enhanced MRIs; travel expenses and research financial support provided by Bayer to some authors
Kanda, Osawa et al., 2015	Retrospective observational (adult and pediatric); Japan	73 + 54 controls	Gadopentetic acid, median 2, max 11; gadoteridol, median 2, max 15; both, median 2, max 5	Brain metastasis (74); primary brain tumor (20); cerebritis (4); meningitis (4); demyelination (6); other (17)	Gadopentetic acid only (23) Gadoteridol only (36) Both (14)	DN:cerebellum SI correlation with exposure	9/73 with increased DN:cerebellum SI (7 with linear only, 2 with both GBCA); DN:cerebellum SI correlation with number of administrations for linear GBCA but not macrocyclic; 31 subjects with grade 1 renal insufficiency; Grant from Bayer Healthcare
Kromrey et al., 2017	Retrospective observational (adult); Germany	271 + 116 controls	1	Prospective population-based screening whole-body study	Gadobutrol (271)	Relative (to CSF) SI of TH, GP, pons and DN, and DN:pons, GP:TH SI ratios compared between baseline and follow-up MRI	No SI changes over 5 years (aggregate data only); subjective visual evaluation, only one administration; some support by Bayer Healthcare
Langner et al., 2017	Retrospective observational (adult); Germany	217	⩾2	Clinically isolated syndrome (MS) (217)	Gadobutrol	Voxel-based GM-CSF and WM-CSF SI ratio compared to baseline and between groups based on	No SI ratio differences for each group and tissue class compared to baseline

Subset of Publications of MRI Signal Abnormality Presumed to Represent Gadolinium Retention Addressing the Role of Macrocyclic GBCA							
Author, year	**Publication type and country of origin**	**Number of subjects and controls**	**Number of administration**	**Brain imaging indications**	**GBCA* (number of subjects unless indicated otherwise)**	**Methodology**	**Findings, limitations, and disclosures**
						number of administrations	
Marsecano et al., 2017	Retrospective observation (adult); unknown	158	⩾2	MS (158)	Gadoteric acid (81) Gadobutrol (77)	DN:pons SI ratio between compared between baseline and last MRI	Increasing SI ratio with no statistically significant difference between the 2 groups
Moreno Negrete et al., 2017	Retrospective observation (adult); Spain	139	⩾4	Melanoma (139)	Gadobutrol (139)	DN and GP qualitative visual assessment; quantitative DN:pons and GP:TH SI ratios compared between baseline and last MRI	Hyperintense signal of DN and GP in 41%
Muller et al., 2017	Prospective observational (adult); Germany	17	5-14	GBM (17)	Gadobutrol	DN, GP, TH, Put, CN to frontal WM or pons T1 and T2 SI ratios between first and last MRI	Ratios of T1 SI and quantitative T1 and T2 remained unchanged for all target regions fron first to last time point and did not correlate with the number of gadobutrol administrations
Radbruch et al., 2015a	Retrospective observational (adult); Germany	100	⩾0 (mean 7)	GBM (29); other glioma (58); non-glioma tumor (10); no tumor (3)	Gadopentetic acid (50) Gadoteric acid (50)	DN:pons and GP:TH SI ratios compared between baseline and last MRI	SI increase in the SI ratios > 0 for gadopentetic acid but no different than 0 for gadoteric acid (aggregate data only); institutional and author grants from Guerbet; payments and

Subset of Publications of MRI Signal Abnormality Presumed to Represent Gadolinium Retention Addressing the Role of Macrocyclic GBCA							
Author, year	**Publication type and country of origin**	**Number of subjects and controls**	**Number of administration**	**Brain imaging indications**	**GBCA* (number of subjects unless indicated otherwise)**	**Methodology**	**Findings, limitations, and disclosures**
							personal fees from Guerbet for lectures and travels to some authors
Radbruch et al., 2015b	Retrospective observational (adult); Germany	30	⩾0 (mean 7)	Glioma WHO IV (7); glioma WHO III (6); glioma WHO II (8); lymphoma (4);other (5)	Gadobutrol (30)	DN:pons, DN:CSF, and GP:TH SI ratios compared between baseline and final MRI	DN:pons, DN:CSF, and GP:TH SI ratios no different than 0 (aggregate data only)
Radbruch et al., 2016	Retrospective observational (adult); Germany	36	⩾5 of gadopentetic and ⩾5 of gadobutrol	Glioma WHO I (1); glioma WHO II (6); glioma WHO III (20); glioma WHO IV (5); lymphoma (3); other (1)	Sequential gadopentetic acid (36); gadobutrol (36); gadoteric acid (12)	DN:pons SI ratios compared between baseline and final MRI for GBCA period	DN:pons SI ratios significantly >0 for gadopentetic acid but not for gadobutrol or gadoteric acid (aggregate data)
Radbruch et al., 2017a	Retrospective observational (adult); Germany	33	⩾20 (mean 23)	GBM (8); Glioma WHO I-III (23); choroid plexus papilloma (1); intramedullary melanocytic tumor (1)	Gadoteric acid and gadobutrol	DN:pons and DN: middle CP SI ratios compared between baseline and last MRI	SI ratios no different than 0 (aggregate data only); personal fees from Guerbet, Bayer and Bracco to some authors
Radbruch et al., 2017b	Retrospective observational (pediatric); Germany	41	⩾5 (mean 8.6)	Glioma WHO I-III (23); craniopharyngioma (3); sarcoma (3); germinoma (2); other (10)	Gadoteric acid (41)	DN:pons and DN: middle CP SI ratios compared between baseline and last MRI	SI ratios no different than 0 (aggregate data only); personal fees from Guerbet, Bayer and Bracco to some authors
Rossi-Espagnet et al., 2017	Retrospective observational (pediatric); Italy	50 + 59 controls	⩾6 (mean 10)	Medulloblastoma (11); pilocytic astrocytoma posterior fossa (5); cranipharyngioma (4); pineal germinoma (4)	Gadoteric acid (50)	DN:pons, GP:TH SI ratios change over time	DN:pons, GP:TH SI ratios increase correlating with number of administrations

Subset of Publications of MRI Signal Abnormality Presumed to Represent Gadolinium Retention Addressing the Role of Macrocyclic GBCA							
Author, year	**Publication type and country of origin**	**Number of subjects and controls**	**Number of administration**	**Brain imaging indications**	**GBCA* (number of subjects unless indicated otherwise)**	**Methodology**	**Findings, limitations, and disclosures**
				ependymoma (4); grade III astrocytoma (3); acute lymphoblastic leukemia (2); ganglioglioma (2); GBM (2); primitive neuroectodermal tumor (2): other (11)			
Schlemm et al., 2016	Retrospective observational (adult); Germany	97	Mean 2 (1-3)	MS (97)	Gadopentetic acid (49) Gadobutrol (48)	DN:pons SI ratios compared between baseline and last MRI	DN:pons SI ratio increase between first and last MRI and linear correlation with number of administrations for gadopentetic acid but not gadobutrol (aggregate data only); speaking, travel and personal fees from Bayer Healthcare to some authors
Stojanov et al., 2016	Retrospective observational (adult); Serbia	58	4.7 (4-6)	Relapsing remitting MS (58)	Gadobutrol (58)	DN:pons and GP:TH SI ratios compared between baseline and last MRI	DN:pons and GP:TH increase SI ratio between first and last MRI but correlation with number of administration only with DN:pons (aggregate data only)
Tedeschi et al., 2016	Retrospective observational	74 (35 with known	6	Relapsing remitting MS (74)	Gadopentetic acid (45 studies)	DN (normalized with brainstem) relaxation	nR1 correlation with number of

Subset of Publications of MRI Signal Abnormality Presumed to Represent Gadolinium Retention Addressing the Role of Macrocyclic GBCA							
Author, year	**Publication type and country of origin**	**Number of subjects and controls**	**Number of administration**	**Brain imaging indications**	**GBCA* (number of subjects unless indicated otherwise)**	**Methodology**	**Findings, limitations, and disclosures**
	(adult); Italy	GBCA type)			Gadobutrol (157 studies) Gadoteric acid (18 studies)	rate R1 (1/T1) (nR1)	administrations overall (p=0.00007) and with linear (p=0.003) and macrocyclic (p=0.039) GBCA (aggregate data only)
Tibussek et al., 2017	Retrospective observational (pediatric); Germany	24 + 24 controls	⩾9 (mean 14.2)	Pilocytic astrocytoma (17), craniopharyngeoma (1), desmoplastic medulloblastoma (1), pleomorphic xanthoastrocytoma (1), dysembryoplastic neuroepithelial tumor (1), ganglioglioma (1), hypothalamic glioma (1), and low-grade glioma (1); headache (8), neurologic symptoms (5), behavioral changes (2), nutritional disorders (2), dizziness (1), seizure (2), tic disorder (1), relapsing emesis (1), trauma (1), and limited speaking ability (1).	Gadoteric acid (3); gadoteridol and gadoteric acid (24)	DN, pons, GP, TH, and SN SI and DN:pons, GP:TH SI ratios compared between subjects and controls	No significant differences; no correlation between SI and GBCA administrations and total amount
Towbin et al., 2017	Retrospective observational (pediatric); USA	53	⩾5 (5-27)	N/R	Gadopentetic acid (27) Gadoteric acid (26)	Multiple structures SI ratios (see results)	GP:PT, GP:TH, GP:pulvinar, GP:frontal white matter, pons:4th ventricle, pons;globes, muscle:CSF SI

Subset of Publications of MRI Signal Abnormality Presumed to Represent Gadolinium Retention Addressing the Role of Macrocyclic GBCA							
Author, year	**Publication type and country of origin**	**Number of subjects and controls**	**Number of administration**	**Brain imaging indications**	**GBCA* (number of subjects unless indicated otherwise)**	**Methodology**	**Findings, limitations, and disclosures**
							ratios increase for gadopentetic group Only pons:globes, middle CP:globes, spinal cord:muscle with increased SI ratios for gadoteric acid group (aggregate data only)
Vatnehol et al., 2016	Retrospective observational; Norway	27	N/R	GBM (27)	Gadobutrol (27)	Normalized SI GP and DN	Significant change in normalized SI of both GP and DN (aggregate data only)
Yoo et al., 2017	Retrospective observational (adult); S. Korea	189	2-50 (mean 5.9)	GBM (5); other glioma (8); metastasis (119); ischemic lesion (5); demyelinating disease (1); others (51)	Gadobutrol	DN:pons, GP:TH SI ratios between baseline and last MRI	DN:pons, GP:TH SI ratios did not differe significantly from 0
*Only generic names included as publications may be from different countriesCN=caudate nucleus; CNS=central nervous system; CP=cerebellar peduncle; CSF=cerebrospinal fluid; DN=dentate nucleus; GBCA=gadolinium-based contrast agents; GBM=glioblastoma multiforme; GM=grey matter; GP=globus pallidus; MRI=magnetic resonance imaging; MS=multiple sclerosis; NMOSD=neuromyelitis optica spectrum disorder; N/A=not assessed; N/R=not reported; PRES=posterior leukoencephalopathy syndrome; Put=putamen; SI=signal intensity; SN=substantia nigra; SLE=systemic lupus erythematous; TH=thalamus; WHO=World Health Organization; WM=white matter							

2.8.11 Appendix K. Post-Mortem Publications Addressing Gadolinium Retention in Brain Tissue

Post-Mortem Publications Addressing Gadolinium Retention in Brain Tissue							
Authors	**Kanda et al.**	**McDonald et al.**	**Murata et al.**	**Stanescu et al.**	**Roberts et al.**	**McDonald et al.**	**McDonald et al.**
Year of publication	2015	2015	2016	2017	2017	2017	2017
Time period	2010-2013	2000-2014	2014-2015	N/R	N/R	2000-2015	2005-2014
Country of origin	Japan	US	Japan	US	US	US	US
Number of subjects	5	13	9	6	1	3	5
Baseline characteristics							
Subjects age range at time of death	N/R	22-72	26-80	8-11	17	8-13 (median 8)	47-73 (median 68)
Subjects MRI indications (or major diagnosis)	GBM; maxillary cancer; malignant lymphoma; brain infarction; pneumonia	Encephalitis; CNS metastases (4); GBM (5); subependymoma; pituitary adenoma; oligodendroglioma	SLE; liver cirrhosis; AML (2); DLBCL; gastric cancer; bladder cancer; hepatocellular carcinoma (2)	N/R	Epilepsy	Neuroblastoma (1); pontine glioma (2)	Carcinoid (1); cholangio-carcinoma (1); renal cell carcinoma (1); prostate cancer (1); hepatocellular carcinoma
Number of controls	5	10	9	0	1	3	10
Controls age range at time of death	N/R	56-92	19-79	-	4	5-7	60-88 (median 79)
Controls MRI indication (or major diagnosis)	Infectious endocarditis; primary unknown carcinoma; colon cancer; brain haemorrhage; brain infarction	TBI; dementia (2); lymphoma; TIA (2); seizure; hydrocephalus; lymphoma (2); intracranial hemorrhage	Interstitial pneumonia (2); AML; lung tumor; CAD (2); myocarditis; bladder cancer; heart disease	-	Epilepsy	N/R	TIA (2); dementia (2); lymphoma (2); TBI (1); seizure (1); hydrocephalus (1); ICH (1)
TIA	Normal	Normal	Normal	Normal	Normal	Normal	Normal except for 3 subjects with borderline function
Pre-mortem symptoms	N/A	N/A	N/A	Unclear whether assessed	N/A	N/A	N/A
GBCA* (in increasing order of thermodynamic stability)							
gadodiamide						3	5
gadoversetamide							

Post-Mortem Publications Addressing Gadolinium Retention in Brain Tissue							
Authors	**Kanda et al.**	**McDonald et al.**	**Murata et al.**	**Stanescu et al.**	**Roberts et al.**	**McDonald et al.**	**McDonald et al.**
gadopentetic acid	3						
gadobenic acid			1				
gadoxetic acid			1				
gadofosveset							
gadoteridol			5				
gadobutrol			2				
gadoteric acid							
unknown		13		6 ("linear and macrocyclic")			
multiple	2				1 (gadopentetic acid, unknown)		
Number of GBCA administration range	2-4	4-29	1-11	1-10	4	4-9	4-18
Last GBCA exposure-death range	15-1170 days	19-152 days (median 53 days)	5-392 days	N/R	84 days	N/R	1-1257 days (median 56 days)
Pathology and gadolinium measurements							
Neuroanatomic regions examined	DN; GPi; cerebellar white matter; frontal lobe cortex; frontal lobe white matter	DN; GP; TH	DN; GP; CN; PT; white matter; pons	DN; GP; PT; TH; white matter	Cerebellum	DN; GP; TH; pons	DN; GP; TH; pons
Other tissues examined	-	-	Bone; skin	-	-	-	-
Gadolinium presence	Present in all brain regions examined	Present in all brain regions examined	Present in all regions	Present in all patients	Present in multiple cerebellar regions	Present in all brain regions examined of all subjects	Present in all brain regions examined of all subjects
Gadolinium form detected (dissociated vs chelated)	N/A	N/A	Chelated to phosphate and original chelate in skin specimens only; N/A for brain or bone specimens	N/R	N/A	N/A	N/A
Gadolinium concentrations (SD)	Mean , 0.25 mcg/g (± 0.44); highest in DN and GPi mean,	0.1-58.8 mcg/g; highest in DN (mean 6.6)	Bone concentrations 23 times higher than	<0.004-0.1777 mcg/g; highest in GP; lowest for	DN 1.01 mcg/g; other cerebellar regions reported	DN, 0.8-3.0 mcg/g; pons 0.1-11 mcg/g; GP, 1.0-1.6 mcg/g;	DN, 2.2-8.9 mcg/g; pons 0.1-0.7 mcg/g;

Post-Mortem Publications Addressing Gadolinium Retention in Brain Tissue							
Authors	**Kanda et al.**	**McDonald et al.**	**Murata et al.**	**Stanescu et al.**	**Roberts et al.**	**McDonald et al.**	**McDonald et al.**
	0.44 (± 0.63)		brain	macrocyclic GBCA	as color-coded map	TH 0.2-0.9 mcg/g	GP, 2.1-19.4 mcg/g; TH 0.5-2.1 mcg/g
Histopathological findings	N/R	EM: deposition of gadolinium in capillary endothelium and neural interstitium LM; no gross histopathologic changes on LM H&E	LM H&E glial cells and neurons count in CN, GP, and PT showed no statistical differences between case and control	N/R	N/R	EM: gadolinium deposition in endothelium and scattered foci in neural interstitium; LM H&E and NF IHC: DN mildly to severely gliotic regions with prominent axonal spheroids (2/3 subjects)	EM: endothelial walls, neuronal tissue interstitium, neuron nuclei LM H&E: "no gross histologic difference" between subjects and controls
Correlation with pre-mortem T1-weighed MR image	N/A	Dose-dependent relationship	N/A	N/A	No T1-weighted MRI abnormality	N/A	N/A

*Only generic names included as publications may be from different countries
AML=acute myelogenous leukemia; CAD=coronary artery disease; CN=caudate nucleus; CNS=central nervous system; DLBCL=diffuse large B-cell lymphoma; DN=dentate nucleus; EM=electronic microscopy; GBCA = gadolinium-based contrast agent; GBM = glioblastoma multiforme; GP=globus pallidus; GPi=globus pallidus pars interna; H&E=hematoxylin and eosin; ICH=intracranial hemorrhage; IHC=immunohistochemistry; LM=light microscopy; MRI=magnetic resonance imaging; N/A=not assessed; N/R=not reported; NF=neurofilament; PT=putamen; SLE=systemic lupus erythematous; TBI=traumatic brain injury; TH=thalamus; TIA=transient ischemic attack

Section 3
Epidemiology

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

3 Epidemiology Section
Review of a Published Observational Study on Gadolinium-based Contrast Agents and Risk of Parkinsonism

Date:	August 11, 2017
Reviewer:	Hui-Lee Wong, Ph.D., M.Sc., Epidemiologist Division of Epidemiology I
Team Leader	Steven Bird, PharmD, Ph.D., Team Leader Division of Epidemiology I
Division Director	Simone P. Pinheiro, Sc.D. M.Sc. ALM, Acting Director Division of Epidemiology I
Drug Name(s):	gadolinium-based contrast agents (GBCA)
Subject	Review of "Welk B, et al., Association Between Gadolinium Contrast Exposure and the Risk of Parkinsonism. JAMA. 2016 Jul 5;316(1):96-8."
NDA (Drug Name):	020123 & 022066 (Omniscan); 019596 (Magnevist); 201277 (Gadavist); 022090 (Eovist); 020131 &021489 (ProHance); 021357 & 021358 (Multihance); 021711 (Ablavar); 020937, 020975 & 020976 (OptiMark); 204781 (Dotarem)
OSE RCM #:	2017-676

3.1 Executive Summary

To support a presentation by Division of Epidemiology-I (DEPI-I) /Office of Surveillance and Epidemiology (OSE) in a Medical Imaging Drugs Advisory Committee, DEPI I reviewed a publication of the association between gadolinium-based contrast agent (GBCA) exposure and the risk of parkinsonism in Canadian administrative databases.

Gadolinium deposits in the globus pallidus, a brain region which controls voluntary movement, and could potentially lead to neuronal damage manifesting as parkinsonism. Welk and colleagues conducted an observational study (retrospective cohort design) in linked administrative databases in Ontario, Canada to assess the association between GBCA exposure and the risk of parkinsonism.

This study identified a cohort of 246,557 patients in Canadian administrative databases that were enrolled between April 2003 and March 2013, had at least one contrast or non-contrast MRI scan (excluding scans of the brain or spine), were older than 66 years, and didn't have either parkinsonism or neurosurgery. Of the 246,557 patients, 40.5% received at least one dose of gadolinium and 1% received at least four doses of gadolinium. The authors found that the incidence of parkinsonism in patients who underwent at least one gadolinium-enhanced MRI scan was 3.17 cases per 1,000 person-years (95% confidence interval (CI): 2.99-3.36 per 1,000 person-years) and the incidence in patients whose MRI scans did not include gadolinium contrast was 2.71 cases per 1000 person-years (95% CI: 2.59-2.84 per 1,000 person-years) (Welk et al., 2016). Further, there was no observed evidence for higher risk of parkinsonism with an increased number of GBCA exposures. The crude incidence rate for individuals with one to three GBCA exposures was 3.17 cases per 1,000 person years, which was slightly higher than the incidence rate for those receiving 4 or more GBCA exposures (2.6 cases per 1,000 person-years).

While this study has a large sample size, dose-response analyses, and validated outcomes, the follow-up in the study, an approximate 4 year average, does not suffice for the potentially longer latent period anticipated in the development of parkinsonism. Future studies with longer follow-up and subgroup analyses of linear GBCAs and macrocyclic GBCAs would provide more information on GBCA and risk of parkinsonism. Additionally, future studies examining GBCA and other health outcomes, e.g., ataxia and other movement disorders, may provide greater understanding for the spectrum of possible adverse implications of gadolinium deposits in the brain.

3.2 Introduction

3.2.1 Background

Gadolinium-based contrast agents (GBCA) are used to enhance magnetic resonance imaging (MRI) to visualize abnormalities in body tissues and blood vessels. Deposits of GBCAs have been reported in patients undergoing gadolinium-enhanced MRI[1]. One area of the brain where gadolinium deposits is the globus pallidus, which controls voluntary movement. Damage to this area and death of brain cells that produce dopamine could cause symptoms of parkinsonism, a degenerative disorder of the central nervous system

characterized by tremor and impaired muscular coordination. Parkinsonism is neurologic syndrome characterized by the presence of at least three of the following: tremor, rigidity, gait disturbance, and bradykinesia.

3.2.2 Regulatory History

GBCA	NDA #1	NDA #2	NDA #3	1st Approved	Active Ingredient
Magnevist	019596	021037		6/2/1988	Gadopentetate dimeglumine
Prohance	020131	021489		11/16/1992	Gadoteridol
Omniscan	020123	022066		1/8/1993	Gadodiamide
Optimark	020937	020975	020976	12/8/1999	Gadoversetamide
Multihance	021357	021358		11/23/2004	Gadobenate dimeglumine
Eovist	022090			7/3/2008	Gadoxetate disodium
Ablavar	021711			12/22/2008	Gadofosveset trisodium
Gadavist	201277			3/14/2011	Gadobutrol
Dotarem	204781			3/20/2013	Gadoterate meglumine

(Source: Pharmacovigilance Review dated 2015/10/06)

Current product labelling does not include information on GBCA and the risk of parkinsonism.

3.2.3 Review Materials

The documents considered for this review:

- Welk B, et al., Association Between Gadolinium Contrast Exposure and the Risk of Parkinsonism. JAMA. 2016 Jul 5;316(1):96-8.
- Pharmacovigilance Review on the health literature for unusual findings on magnetic resonance imaging (MRI) that suggest gadolinium retention in the brain and the Division of Pharmacovigilance II (DPV-II) to review FDA Adverse Event Reporting System (FAERS) data. by Weissfeld JL (DEPI I) and Phelan KM (DPV) dated 06/10/2015
- OND/Division of Neurological Products (DNP) Consult to OND/DMIP on the symptoms seen as a result of deposition of a foreign substance, such as gadolinium or another heavy metal, in the dentate nucleus, dentate nucleus or throughout the brain, by Podskalny G (OND/DNP) dated 08/15/2016

3.3 Review Results

3.3.1 Study Design and Study Population

The study was a retrospective cohort design conducted in multiple linked administrative databases from Ontario, Canada. The study population consists of patients older than 66 years of age with universal health care and medication coverage. Using fee codes submitted by radiologists, all patients older than 66 years who underwent an initial MRI between April 2003 and March 2013 were identified. Patients whose initial MRI was of

the brain or spinal cord and those with prior parkinsonism or neurosurgery were excluded.

3.3.2 Study Objective

To assess the association between gadolinium exposure and parkinsonism among patients older than 66 who received at least one MRI.

3.3.3 Study Exposure

The study exposure is a gadolinium-exposed MRI. MRIs were identified using reimbursement fee codes X431 and X435 (neck); X441 and X445 (thorax); X451 and X455 (abdomen); X446 and X447 (breast); X461 and X465 (pelvis); and X471, X475, X488, and X489 (extremity). Administration of gadolinium during an MRI was identified using the OHIP code X487.

3.3.4 Study Outcome

The primary outcome, assessed from the initial MRI until death, emigration, or March 2015, was a new diagnosis of parkinsonism based on a validated definition (sensitivity, 81.7%; specificity, 99.7%; positive predictive value, 78.0%; negative predictive value, 99.8%; accuracy, 99.5%; and disease prevalence, 1.4%) using diagnosis codes from hospital admissions, physician visits, and medications for Parkinson disease[2]. The validation of the outcome was performed in healthcare administrative databases in the province of Ontario, Canada using primary care electronic medical records.

3.3.5 Statistical Analyses

For 105 covariates[3], the authors evaluated significant inequalities between patients who underwent only non–gadolinium-enhanced MRIs and those who underwent one or more gadolinium enhanced MRI. A subset of 38 covariates particularly relevant to parkinsonism (based on potential associations from the literature) or significantly different at baseline (standardized difference >10%) were included in a multivariable time-dependent Cox regression model. The hazard ratio (HR) is interpreted as the hazard of parkinsonism per additional gadolinium enhanced MRI exposure. Sensitivity analyses changing both the variables included for adjustment and the outcome definition were performed.

3.3.6 Study Results

Of the 246,557 patients (median age, 73 years [interquartile range, 69-78 years]; women, 54.9%) undergoing at least one MRI (not of the brain or spine) during the study period, 99,739 (40.5%) received at least one dose of gadolinium. The most common initial non–gadolinium-enhanced MRI was of an extremity (76.0%); the most common gadolinium-enhanced MRI was of the abdomen (39.2%). Among patients who underwent gadolinium-enhanced MRIs, 81.5% underwent a single MRI, and 2.5% underwent 4 or more gadolinium-enhanced MRIs. Table 1 tabulates the baseline characteristics for patients with and without gadolinium exposure. Table 2 from Welk 2016 below summarizes the hazard ratios of parkinsonism per additional gadolinium exposure.

Table 1. Selected Baseline Characteristics for Patients With vs Without Gadolinium Exposure[a]

	Exposure, No. (%)		
	Only Non-Gadolinium-Enhanced MRIs[b] (n = 146 818)	≥1 Gadolinium-Enhanced MRI[c] (n = 99 739)	Standardized Difference[d]
Demographics			
Age, median (IQR), y	72 (68-77)	73 (69-78)	12
Women	81 795 (55.7)	53 647 (53.8)	4
Rural residence	19 972 (13.6)	11 409 (11.4)	7
Socioeconomic status			
Lowest quintile	24 296 (16.5)	17 660 (17.7)	3
Highest quintile	34 646 (23.6)	22 696 (22.8)	2
Comorbidities in the past 5 y			
Dementia	8262 (5.6)	6272 (6.3)	3
Stroke	2644 (1.8)	3296 (3.3)	10
Cancer (bowel, breast, prostate, lung, rectal)	18 890 (12.9)	27 705 (27.8)	38
Melanoma	2076 (1.4)	1803 (1.8)	3
Seizure	403 (0.3)	419 (0.4)	2
Encephalitis, multiple system atrophy, progressive supranuclear palsy, primary lateral sclerosis	21 (<0.1)	9 (<0.1)	0
Comorbidity score, median (IQR)[e]	9 (6-11)	9 (7-12)	17
Medication use in the past 6 mo			
Atypical antipsychotics	2044 (1.4)	1515 (1.5)	1
Other antipsychotics	1135 (0.8)	2050 (2.1)	11
Antidepressants	13 041 (8.9)	8190 (8.2)	3
Cholinesterase inhibitors	1894 (1.3)	1358 (1.4)	1
SSRIs	11 375 (7.7)	7720 (7.7)	0
Anticholinergics	4262 (2.9)	2809 (2.8)	1
Healthcare utilization in the past year			
No. of prior neurology visits			
0	133 229 (90.7)	86 611 (86.8)	
≥1	13 589 (9.3)	13 128 (13.2)	6
No. of prior hospitalizations			
0	99 911 (68.1)	52 853 (53.0)	
≥1	46 907 (31.9)	46 886 (47.0)	14
Prior computed tomography of the head	16 903 (11.5)	18 391 (18.4)	19

Abbreviations: ADG, Aggregated Diagnostic Group; IQR, interquartile range; MRI, magnetic resonance imaging; OHIP, Ontario Health Insurance Plan; SSRIs, selective serotonin reuptake inhibitors.

[a] Patients were dichotomized into those with and without gadolinium exposure, and baselines were determined relative to the date of the initial MRI. A full list of measured covariates is included in the Supplement.

[b] MRI patients were identified using OHIP fee codes X431 and X435 (neck); X441 and X445 (thorax); X451 and X455 (abdomen); X446 and X447 (breast); X461 and X465 (pelvis); and X471, X475, X488, and X489 (extremity).

[c] Administration of gadolinium during an MRI was identified using the OHIP code X487, and patients could switch from those with no gadolinium exposure to those exposed to gadolinium at any time during follow-up. The total number of gadolinium-enhanced MRIs in this cohort was 129 120.

[d] Standardized differences were calculated using the group mean difference divided by the pooled SD, and they identify potential clinically significant differences (>10%) between large groups in population-based studies independent of the large sample size.

[e] Measured by the Johns Hopkins ADG system, which assigns a score to patients based on their health care utilization and the severity and chronicity of the medical problems for which they access health care services.

Table 2. New Diagnoses of Parkinsonism After MRIs (Not of the Brain or Spine) With or Without Gadolinium Exposure

Primary Analysis	Entire Cohort (N = 246 557)	Exposed to Only Non-Gadolinium-Enhanced MRIs (n = 146 818)	Exposed to Gadolinium-Enhanced MRIs		HR (95% CI)	P Value
			≥1 MRI (n = 99 739)	≥4 MRIs[a] (n = 2446)		
Total follow-up, person-years	991 937	625 185	366 752	6634		
Primary outcome, No. (%)	2861 (1.16)	1697 (1.16)	1164 (1.17)	17 (0.70)		
Rate (95% CI)[b]	2.88 (2.78-2.99)	2.71 (2.59-2.84)	3.17 (2.99-3.36)	2.56 (1.54-4.02)		
Unadjusted analysis[c]		Reference			1.08 (1.04-1.13)	<.001
Adjusted analysis[d]		Reference			1.04 (0.98-1.09)	.18
Sensitivity analysis						
Post hoc analysis 1[e]		Reference			0.99 (0.94-1.03)	.58
Post hoc analysis 2[f]		Reference			1.03 (0.98-1.09)	.29

Abbreviations: HR, hazard ratio; MRI, magnetic resonance imaging; SSRIs, selective serotonin reuptake inhibitors.

[a] Patients exposed to 4 or more MRIs with gadolinium are a subset of those who are exposed to 1 or more MRIs with gadolinium.

[b] Per 1000 person-years of observation.

[c] HR per additional gadolinium exposure.

[d] Adjusted analysis used the same statistical model and included 38 covariates selected from the 105 measured covariates that were either potential confounders or unbalanced at baseline (standardized difference, >10%). Specific covariates included demographics (age, sex, year of cohort entry, MRI study body part), comorbid conditions (dementia, stroke, solid organ cancer [bowel, lung, breast, prostate, rectal], melanoma, seizure, comorbidity score, congestive heart failure, coronary artery disease, hypertension, chronic liver disease, chronic kidney disease), medications (antipsychotics, atypical antipsychotics, antidepressants, cholinesterase inhibitors, SSRIs, anticholinergics, androgen deprivation therapy, antiplatelets, β-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, corticosteroids, total number of unique drug names), and health care utilization (number of hospitalizations, number of neurology visits, computed tomography of the head, echocardiogram, Holter monitor, carotid ultrasound).

[e] Post hoc analysis 1 had further adjustment for 12 additional covariates with standardized differences of 9% or 10%: atrial fibrillation or flutter, peripheral vascular disease, antineoplastic agents, narcotics, non–potassium-sparing diuretics, number of family physician visits, bone scan, cardiac catheterization, cardiac stress test, prior spine MRI, prior urine culture, prior chest x-ray.

[f] Post hoc analysis 2 was an adjusted analysis using an outcome definition independent of parkinsonism medications.[4]

Incident parkinsonism developed in 1.16% of unexposed patients and 1.17% of those exposed to gadolinium. In adjusted analysis there was no significantly increased hazard

of parkinsonism among patients per additional gadolinium enhanced MRI exposure. (HR, 1.04 [95%CI, 0.98-1.09], P = .18, Table 2; selected covariates in Table 1 and eTable 1, Supplement in Welk 2016). No significantly increased HR was found in either sensitivity analysis

3.3.7 Authors' Conclusions

The authors did not observe a significant association between gadolinium exposure and parkinsonism. They concluded that their study does not support the hypothesis that gadolinium deposits in the globus pallidus lead to neuronal damage manifesting as parkinsonism. They did state that their study does not cover other nonspecific symptoms (pain, cognitive changes) after gadolinium exposure.

3.4 Discussion

While this study has a large sample size, dose-response analyses and validated outcomes, the follow-up in the study of an approximate average of 4 years does not suffice for the potentially longer latent period anticipated in the development of parkinsonism. Notable limitations are discussed below.

Potentially insufficient follow-up

The authors did not report the median or mean follow-up time from MRI initiation to onset of parkinsonism. From Table 2, Welk 2016, we estimate the average follow-up time as approximately four years across all study participants [total follow-up / number of patients = 991,937 person-years / 246,557 patients = 4.02 years follow-up per patient]. The latency period of gadolinium toxicity potentially resulting in neuronal damage in the globus pallidus region remains unclear.

Manganese is another heavy metal that has been shown to deposit in the brain[4]. In human patients and animal models, neurons of the globus pallidus appear to be sensitive to manganese induced degeneration[4]. In a case report, a patient occupationally exposed to manganese from 1963 to 1982 complained of palpitation and hand tremor five years after first exposure (1968) but had more serious symptoms (1980 -1987) at least 13 years later[5]. The long latency in this case report provides some evidence that four years may not be a sufficiently long period of time to evaluate gadolinium induced parkinsonism. Future studies could be conducted in population sources with more than four years of follow-up.

Restricted generalizability

Welk 2016 study was restricted to older individuals and did not assess association between GBCA retention and the risk of parkinsonism among adults younger than 66 years old. Thus, it is unclear whether the results are applicable to younger populations.

Potential residual confounding cannot be ruled out

Welk 2016 did not report the mean number of MRIs in the gadolinium-exposed group and non-exposed groups, nor did it provide descriptive statistics for the contrast versus non-contrast groups in stratifications of the number of MRI exposures. Residual

confounding surrounding the reason why a contrast versus a non-contrast MRI was administered cannot be ruled out.

Lack of information regarding type of gadolinium contrast agent
Welk 2016 did not differentiate between linear and macrocyclic GBCA agents in gadolinium exposure. Evidence suggests that these agents result in differing levels of retention.

Lack of information regarding outcomes beyond parkinsonism
Welk 2016 examined only parkinsonism as a possible health outcome / adverse event for gadolinium retention in the brain. However, gadolinium is distributed in multiple sites throughout the brain (summarized in Pharmacovigilance Review by Weissfeld JL/DEPI I and Phelan KM/DPV). Lesions of the globus pallidus may produce parkinsonism and dystonia (OND/DNP consult by Podskalny G/DNP). Lesions of the dentate typically cause tremor, dysmetria of the limbs, ataxia and dysarthria (OND/DNP consult). Future assessments of these outcomes may be warranted.

3.5 Conclusion
While this study has a large sample size and validated outcomes, the estimated relatively short follow-up of approximately 4 years per patient does not suffice for the potentially longer latent period anticipated in the development of parkinsonism. Future studies with longer follow-up and subgroup analyses of linear GBCAs and macrocyclic GBCAs would provide more information on GBCA and risk of parkinsonism. Additionally, studies examining GBCA and other health outcomes, e.g., ataxia and other movement disorders, may facilitate greater understanding of the spectrum of possible adverse implications of gadolinium deposits in the brain.

3.5.1 References

1. References in FDA drug safety communication; https://www.fda.gov/Drugs/DrugSafety/ucm455386.htm, last accessed June 2017
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Section 4
Drug Utilization

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

4 Drug Utilization Section

Date:	July 24, 2017
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Drug Name(s):	Ablavar® (gadofosveset), Eovist® (gadoxetate), Dotarem® (gadoterate), Gadavist® (gadobutrol)®, Magnevist® (gadopentetate), MultiHance® (gadobenate), Optimark® (gadoversetamide), Omniscan® (gadodiamide), and Prohance® (gadoteridol)
Subject: Utilization	Gadolinium-Based Contrast Agents (GBCAs) Drug Review
Application Type/Number:	Multiple
OSE RCM #:	2017-676

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4.1 Executive Summary

In support of the MIDAC meeting on September 8, 2017, the Division of Epidemiology II (DEPI II) completed a drug utilization review describing the sales and use of gadolinium-based contrast agents (GBCAs) in the US adult and pediatric populations from 2006 through 2016. Proprietary drug utilization databases available to the Agency were used to conduct the analyses in this review.

The national estimate of GBCA sales from US manufacturers to non-retail channels[8] of distribution ranged from 7.5 million – 8.8 million packages sold annually for the review period. GBCAs were widely sold from 2006 through 2016 in the US. In 2006, an estimated 8.6 million packages of GBCAs were sold, primarily to hospitals and clinics. Linear GBCAs accounted for 95% (8.2 million packages) of total sales. However by 2016, sales of macrocyclic GBCAs accounted for 51% (4.5 million packages) and linear GBCAs accounted for 49% (4.3 million packages) of the estimated 8.8 million packages sold.

Sales of GBCAs from manufacturers to a number of pediatric specialty hospitals and clinics were also assessed from 2007 through 2016. During the examined time, sales from manufacturers to these facilities shifted from primarily linear GBCAs sales (97% of GBCA sales in 2007) to macrocyclic GBCAs sales (82% of GBCA sales in 2016). Of note, although a national estimate of all GBCA sales intended for pediatric utilization was not available for this review, the sales data captured represents trends of sales from manufacturers to a robust sample of 50 pediatric specialty hospitals and 5 pediatric specialty clinics.

Patient-level utilization data was also assessed for inpatient and outpatient (i.e. hospital affiliated clinics) utilization of GBCAs in US non-federal hospitals. Based on hospital discharge billing data, the national estimate of patients billed for an MRI/MRA procedure(s) and GBCAs ranged from 3.4 million – 4.5 million patients from 2006 through 2016, annually. A large proportion of patients billed for an MRI/MRA procedure(s) and GBCAs did not include information on the specific GBCA used. Despite the large number of patients billed for an unknown gadolinium agent, the increasing use of macrocyclic GBCAs since 2012 was consistent with the trends observed in US sales. Similar to adults, the increasing use of macrocyclic GBCAs since 2012 was also observed in pediatric patients; the majority of pediatric patients were billed for macrocyclic GBCAs compared to linear GBCAs in 2016. Finally, we examined the most frequent imaging performed of patients billed for an MRI/MRA procedure(s) and GBCA. In 2016, the most frequently performed MRI/MRA procedure(s) with a GBCA were for imaging of the head and non-extremities among adults; the most frequently performed MRI/MRA procedure was for imaging of the head among pediatric patients aged 0-17 years.

[8] Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings

4.2 Introduction

In support of the upcoming MIDAC meeting, the Division of Epidemiology II completed a drug utilization review describing the sales and use of GBCAs in the US adult and pediatric populations from 2006 through 2016.

4.3 Methods and Materials

4.3.1 Products Included[9]

Brand Drug Name	Generic Drug Name	Approval Date	Indication
ABLAVAR ***(discontinued)***	gadofosveset	December 2008	For use as a contrast agent in magnetic resonance angiography (MRA) to evaluate aortoiliac occlusive disease in adults with known or suspected peripheral vascular disease
DOTAREM	gadoterate	March 2013	For intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine, and associated tissues in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity
EOVIST	gadoxetate	July 2008	For use in MRI of the liver to detect and characterize lesions in patients with known or suspected focal liver disease
GADAVIST	gadobutrol	March 2011	For use with MRI: • to detect and visualize areas with disrupted BBB and/or abnormal vascularity of the central nervous system in adult and pediatric patients (including neonates); • to assess the presence and extent of malignant breast disease; • to evaluate known or suspected supra-aortic or renal artery disease in adult and pediatric patients (including neonates)
MAGNEVIST	gadopentetate	June 1988	For intravenous use in diagnostic MRI in adults and children (2 years of age or older) to facilitate the visualization of lesions and abnormal vascularity in: • central nervous system (brain, spine, and associated tissues • extracranial/extraspinal tissues (head and neck) • body
MULTIHANCE	gadobenate	November 2004	For intravenous use in: • MRI of the central nervous system in adults and children over 2 years of age to visualize lesions with abnormal BBB or abnormal vascularity of the brain, spine, and associated tissue

[9] Source: Drugs@ FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm; Accessed July 2017

Brand Drug Name	Generic Drug Name	Approval Date	Indication
			• MRA to evaluate adults with known or suspected renal or aorto-ilio-femoral occlusive vascular disease
OMNISCAN	gadodiamide	January 1993	For diagnostic MRI indicated for intravenous use to: • visualize lesions with abnormal vascularity in the brain, spine, and associated tissues • facilitate the visualization of lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities, and the retroperitoneal space
OPTIMARK	gadoversetamide	December 1999	For diagnostic MRI indicated for intravenous use: • in patients with abnormal BBB or abnormal vascularity of the brain, spine, and associated tissues • to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver in patients who are highly suspect for liver structural abnormalities on computed tomography
PROHANCE	gadoteridol	November 1992	For use in: • MRI of the central nervous system in adults and children over 2 years of age to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine, and associated tissue • MRI of the extracranial/extraspinal tissues to visualize lesions in the head and neck

4.3.2 Data Sources Used

Proprietary drug utilization databases available to the Agency were used to conduct the analyses in this review (*see Appendix B for a detailed description of the databases used*).

National Sales Distribution Data

QuintilesIMS Health, National Sales Perspectives™ (NSP) was used to determine the settings of care where GBCAs were sold from US manufacturers to the various channels of distribution in 2016. NSP was also used to determine the national estimate of packages sold for GBCAs from US manufacturers to non-retail channels of distribution, stratified by chemical structure (macrocyclic vs. linear) and product, from 2006 through 2016 annually.

Sales Distribution Data to Pediatric Specialty Hospitals and Clinics

The Symphony Health Solutions' PHAST NonRetail Monthly database was used to obtain the number of packages sold for GBCAs, stratified by chemical structure (macrocyclic vs. linear) and product, from US manufacturers and wholesalers to pediatric specialty hospitals and clinics, from 2007 through 2016 annually. Of note, the sales data obtained from this data source does not represent a national estimate of sales to pediatric

specialty hospitals and clinics in the U.S. The number of facilities represented in the data includes 50 pediatric specialty hospitals and 5 pediatric specialty clinics.

Non-Federal Hospital Patient-level Data

The QuintilesIMS, Hospital Visit Analyzer (HVA) database was used to obtain the national estimate of patients billed for an MRI/MRA procedure(s) and GBCA by patient age, stratified by chemical structure (macrocyclic vs. linear) and product, from US non-federal hospitals, from 2006 through 2016, annually. Data were obtained for inpatient and outpatient hospital visits. Outpatient hospital visits included MRI/MRA procedure(s) performed in clinics affiliated with US non-federal hospitals. Patient selection was based on the presence of billing for MRI or MRA procedure code(s), billing descriptions for GBCAs, or Healthcare Common Procedure Coding System (HCPCS) codes.

MRI and MRA procedure(s) were billed using Current Procedural Terminology (CPT) code(s) and HCPCS code(s), respectively (*see Appendix C for complete list of HCPCS and CPT codes*). Patients were included in the GBCA category if billing information included 1) HCPCS code A9579 (i.e. gadolinium-based magnetic resonance contrast agent, not otherwise specified), or 2) unspecified gadolinium product billing descriptions, or 3) MRI or MRA procedure code(s) with contrast, but no gadolinium HCPCS code or billing description. It is important to note that Magnevist, Omniscan, and Optimark do not have product specific HCPCS codes but are billed under HCPCS code A9579. Drug utilization trends for gadolinium products billed under HCPCS code A9579 were grouped in the unknown GBCA category.

The national estimate of patients billed for an MRI/MRA procedure(s) and GBCA, stratified by patient age, chemical structure, and procedure location were also included. Categories for procedure location included 1) head, 2) extremities, 3) non-extremity, and 4) unknown location. The non-extremity location included MRI/MRA procedure(s) of the neck, spine, breast, chest, heart, abdomen, and pelvis. The unknown location included patients with 1) billing descriptions for specified GBCAs or 2) HCPCS codes for specified gadolinium-based contrast agents, but without any MRI/MRA procedure code(s) to indicate the exam location.

4.4 Results

4.4.1 Settings of Care

In 2016, nearly 100% of vials, syringes, and bottles of GBCAs were distributed to non-retail settings (mainly non-federal hospitals)[10]. Accordingly, we focused our efforts only on the non-retail setting of care; patient-level data from outpatient retail pharmacies, mail-order/specialty pharmacies, and non-hospital affiliated clinics were not included.

[10] QuintilesIMS, National Sales Perspectives™ Database. 2016. Extracted June 2017. File NSP 2017-676 GBCAs by channel and calendar year 6-8-17.xlsx

4.4.2 National Estimates of Sales from US manufacturers to Non-Retail Settings

Figure 1 and Table 1 in the Appendix show the national estimate of packages sold for GBCAs from US manufacturers to non-retail channels of distribution from 2006 through 2016 annually. Total sales of GBCAs ranged from 7.5 million – 8.8 million packages sold annually. In 2006, sales of linear GBCAs accounted for 95% of total sales. However by 2016, sales of macrocyclic GBCAs accounted for 51% of sales and linear GBCAs accounted for 49% of sales.

Figure 1. National estimates of sales (in packages[1] sold) by macrocyclic vs. linear gadolinium-based contrast agents (GBCAs) from US manufacturers to non-retail channels of distribution, 2006 – 2016

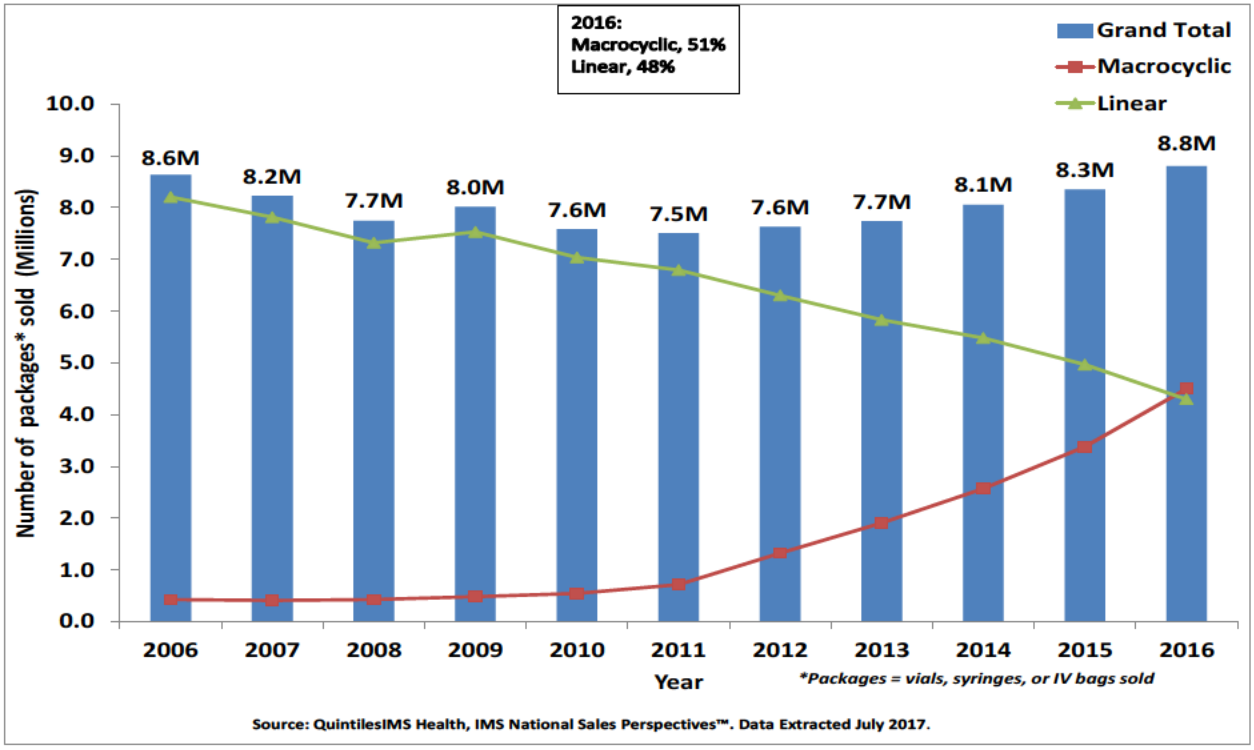


Figure 2 shows the national estimate of packages sold for macrocyclic GBCAs from US manufacturers to non-retail channels of distribution from 2006 through 2016 annually. Of the macrocyclic GBCAs, sales of Gadavist accounted for approximately 63% of macrocyclic product sales in 2016.

Figure 2. National estimates of sales (in packages[1] sold) of macrocyclic gadolinium-based contrast agents (GBCAs) from US manufacturers to non-retail channels of distribution, by product, from 2006 – 2016

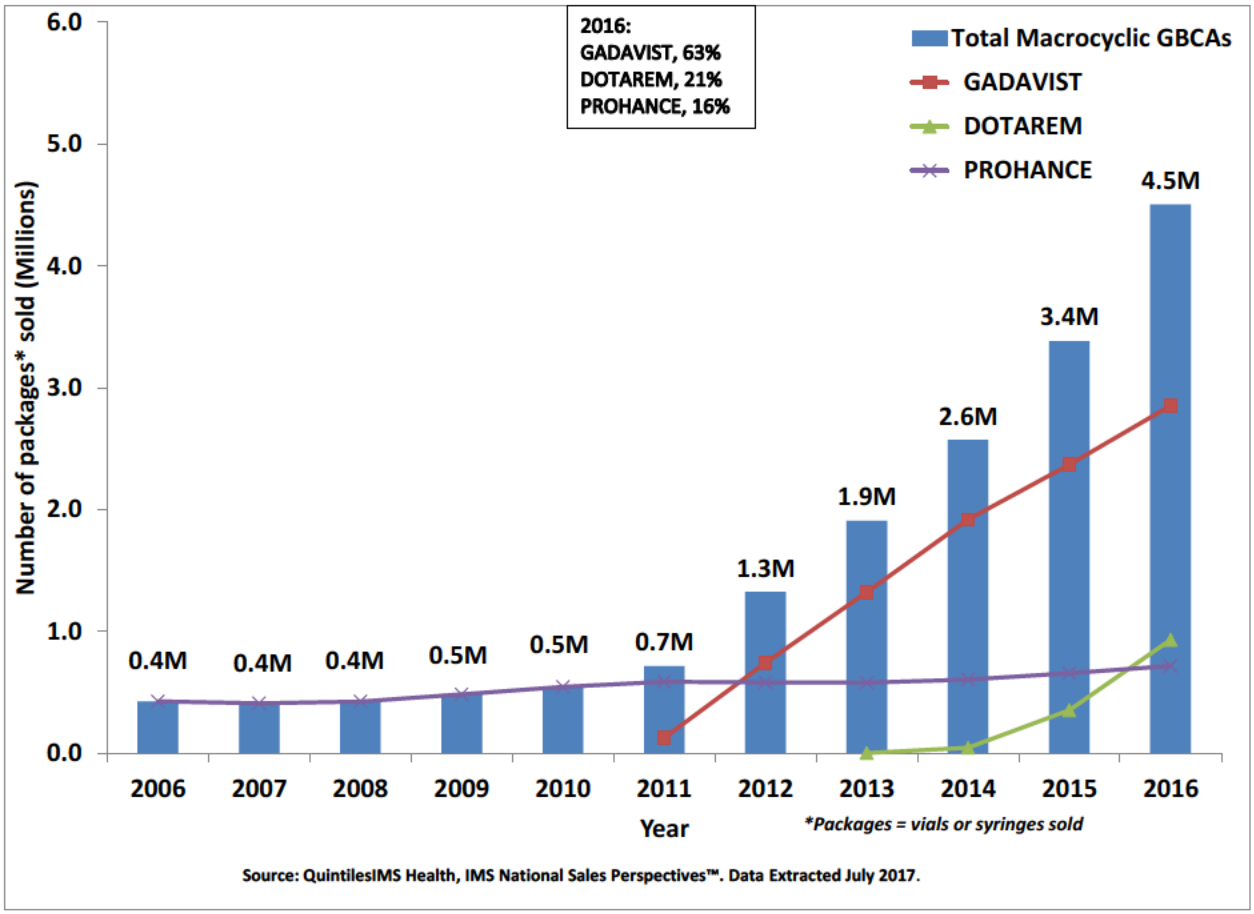
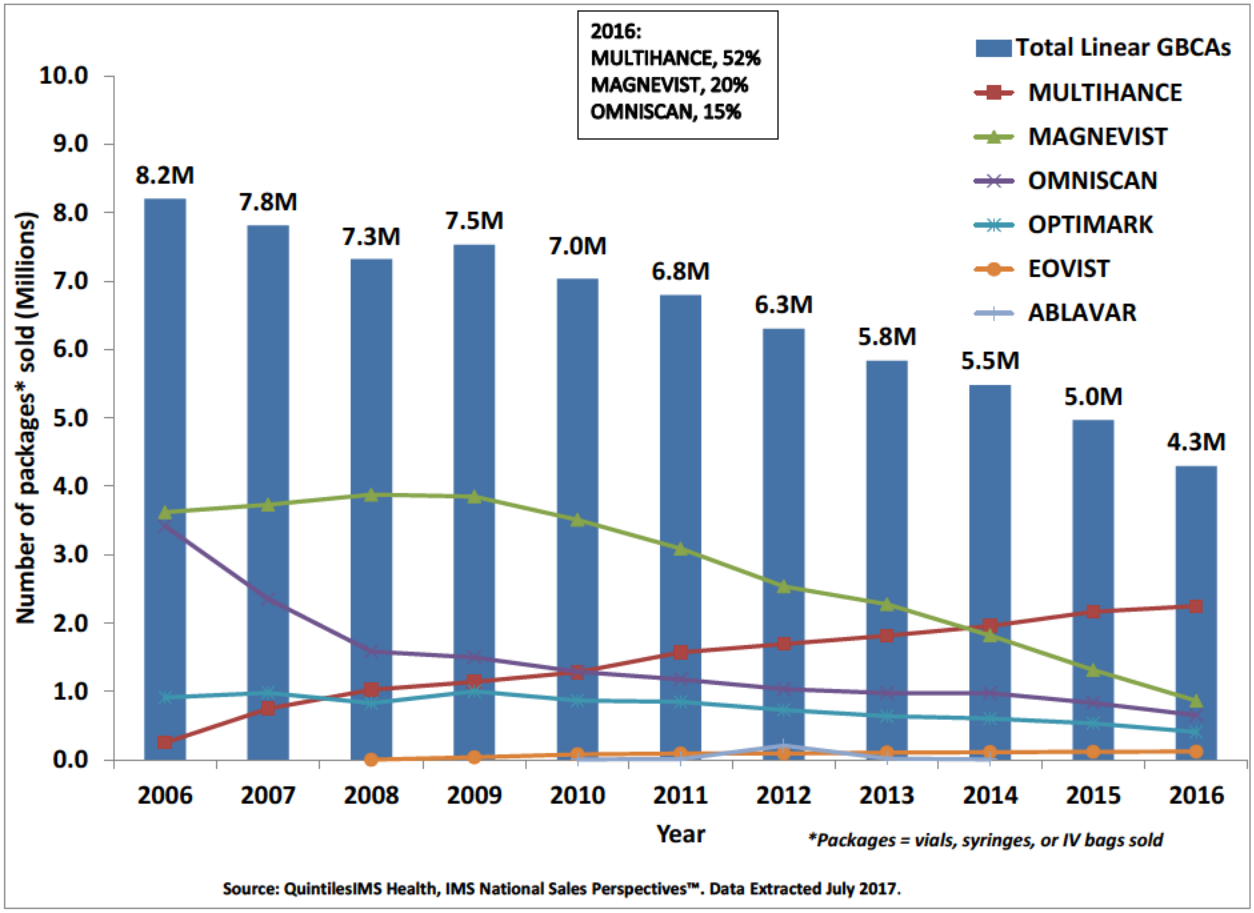


Figure 3 shows the national estimate of packages sold for linear GBCAs from US manufacturers to non-retail channels of distribution by product from 2006 through 2016. Prior to 2012, linear GBCAs accounted for more than 90% of total sales. However, total sales of linear GBCAs decreased steadily since 2006 for a 48% decrease in sales by 2016. In 2016, MultiHance accounted for 52% of sales for linear GBCAs followed by Magnevist (20%) and Omniscan (15%). Optimark and Eovist accounted for 10% and 3% of linear gadolinium sales in 2016, respectively. No sales were captured for Ablavar products since 2015.

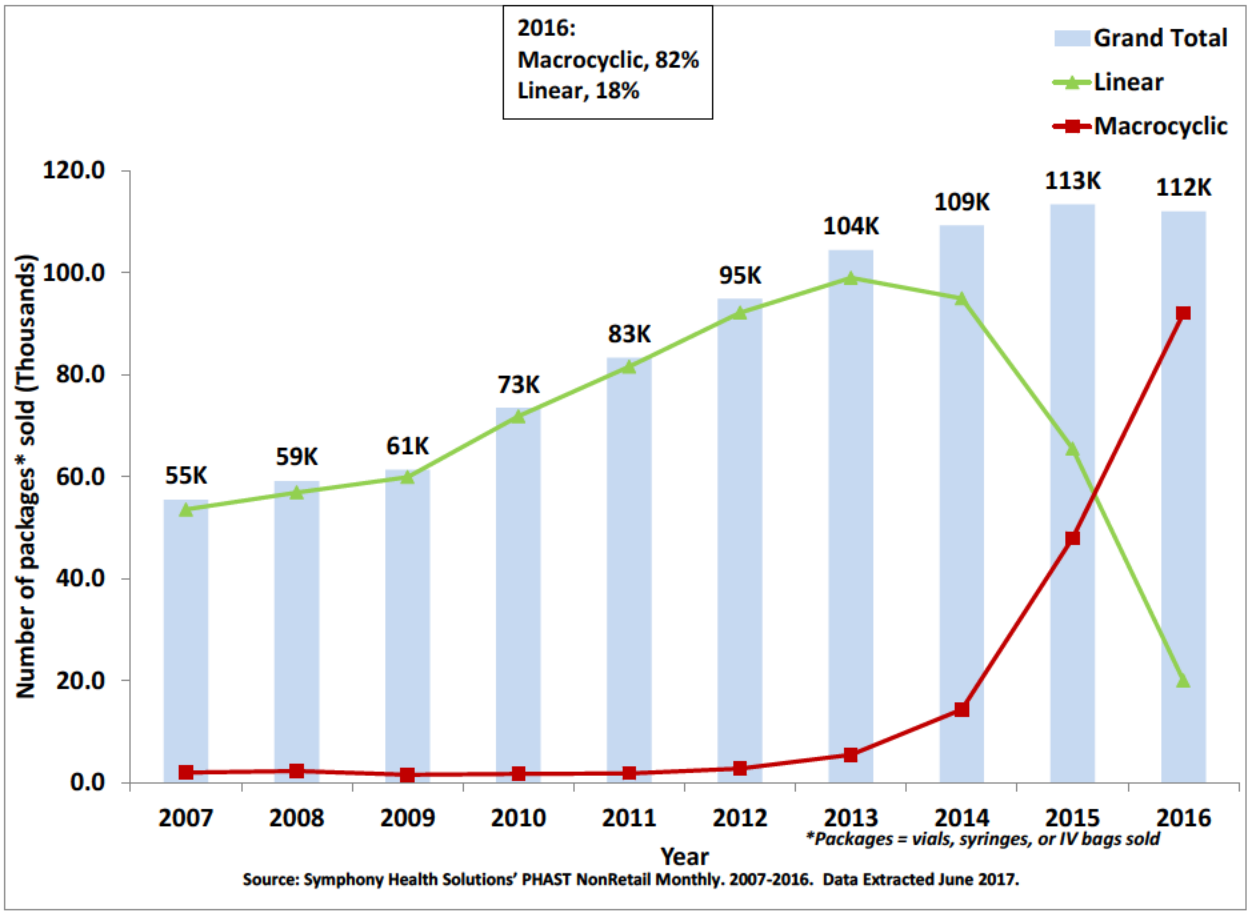
Figure 3. National estimates of sales (in packages[1] sold) for linear gadolinium-based contrast agents from US manufacturers to non-retail channels of distribution, 2006 – 2016



4.4.3 Sales from US manufacturers and wholesalers to pediatric hospitals and clinics

Figure 4 below and **Table 2** in the Appendix show sales (in packages sold) for GBCAs from US manufacturers and wholesalers to pediatric hospitals and clinics, from 2007 through 2016 annually. Sales of GBCAs ranged from 55,000 – 113,000 packages sold annually and increased 2-fold from 2007 to 2016. In 2007, sales of linear GBCAs accounted for 97% of total sales. However by 2016, trends reversed sharply and sales of macrocyclic GBCAs accounted for 82% of sales while linear GBCAs accounted for 18% of reported sales.

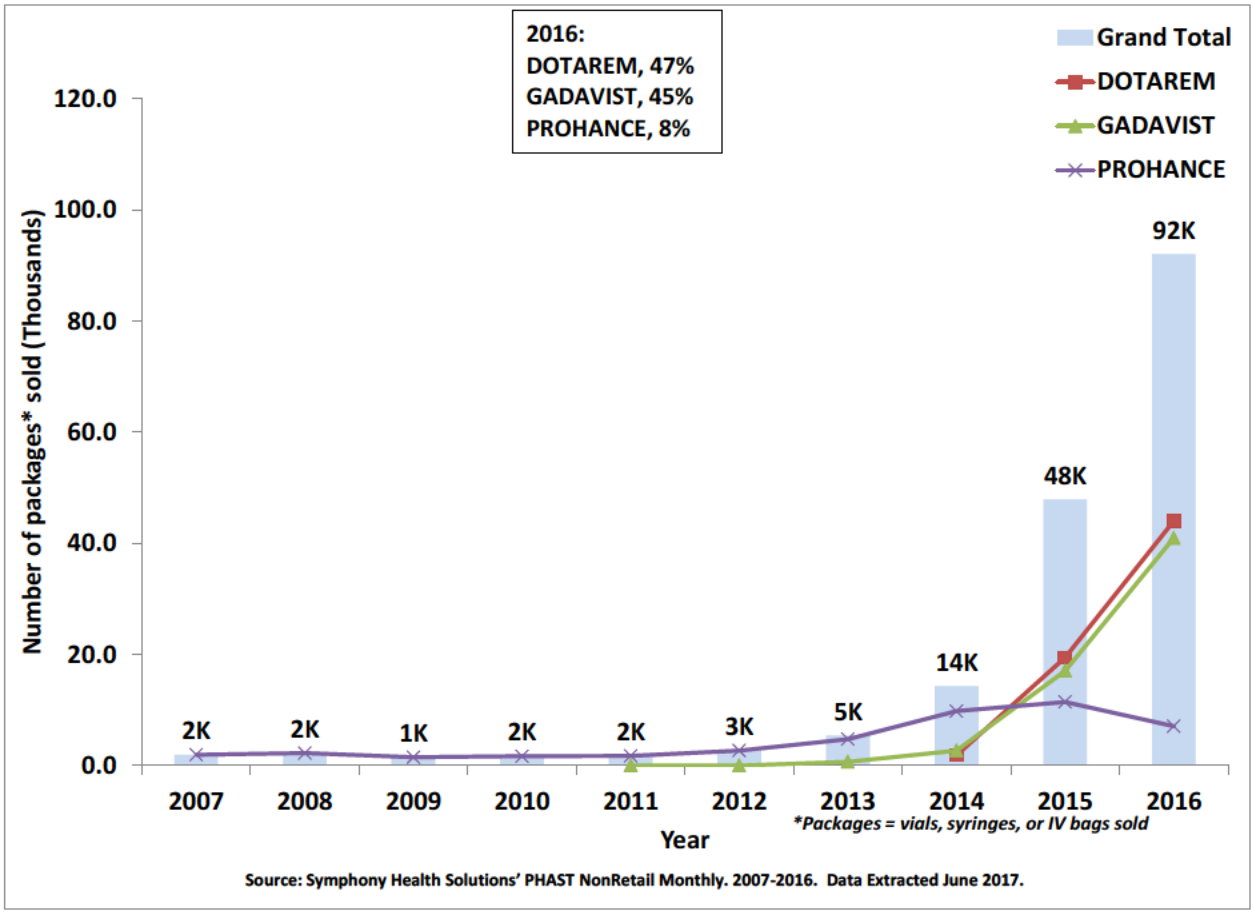
Figure 4. Sales (in packages[1] sold) by macrocyclic or linear gadolinium-based contrast agents from US manufacturers and wholesalers to pediatric hospitals and clinics*, 2007 – 2016



* Sales distribution data of the volume of GBCAs sold from manufacturers to 50 pediatric specialty hospitals and 5 pediatric specialty clinics were captured in this data source

Figure 5 shows the sales (in packages sold) for macrocyclic GBCAs from US manufacturers and wholesalers to pediatric hospitals and clinics from 2007 through 2016 annually. Beginning in 2014, a sharp increase in sales of macrocyclic gadolinium agents was observed. In 2016, Dotarem and Gadavist accounted for 47% and 45% of macrocyclic GBCAs sales, respectively.

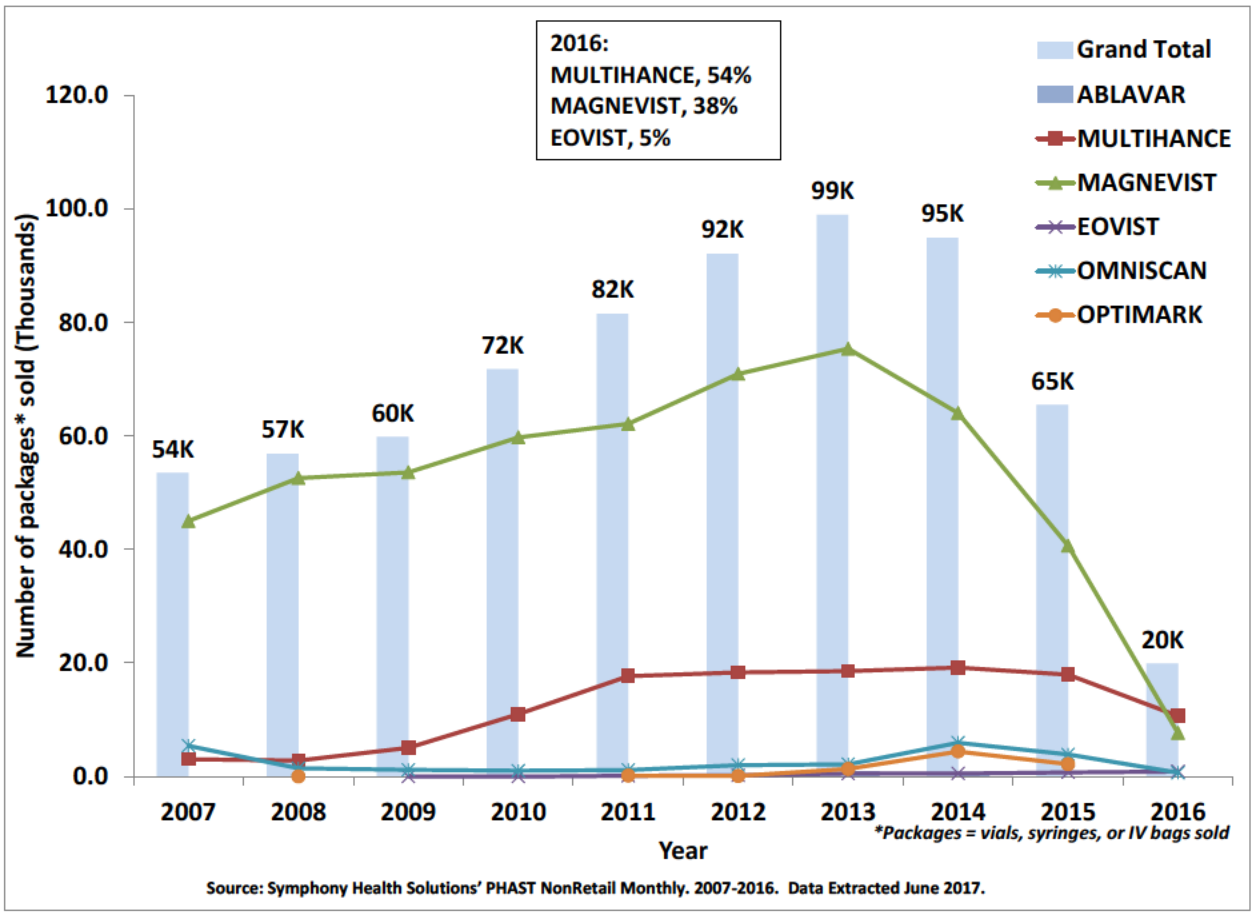
Figure 5. Sales (in packages[1] sold) for macrocyclic gadolinium-based contrast agents from US manufacturers and wholesalers to pediatric hospitals and clinics*, 2007 – 2016



* Sales distribution data of the volume of GBCAs sold from manufacturers to 50 pediatric specialty hospitals and 5 pediatric specialty clinics were captured in this data source

Figure 6 shows the sales (in packages sold) for linear GBCAs from US manufacturers and wholesalers to pediatric hospitals and clinics from 2007 through 2016 annually. Beginning in 2014, sales of linear GBCAs dropped sharply. In 2016, MultiHance accounted for 54% of sales, followed by Magnevist (38%) and Eovist (5%). Omniscan accounted for 3% of sales in 2016. No sales were captured for Optimark and Ablavar products in 2016.

Figure 6. Sales (in packages[1] sold) of linear gadolinium-based contrast agents from US manufacturers and wholesalers to pediatric hospitals and clinics*, 2007 – 2016



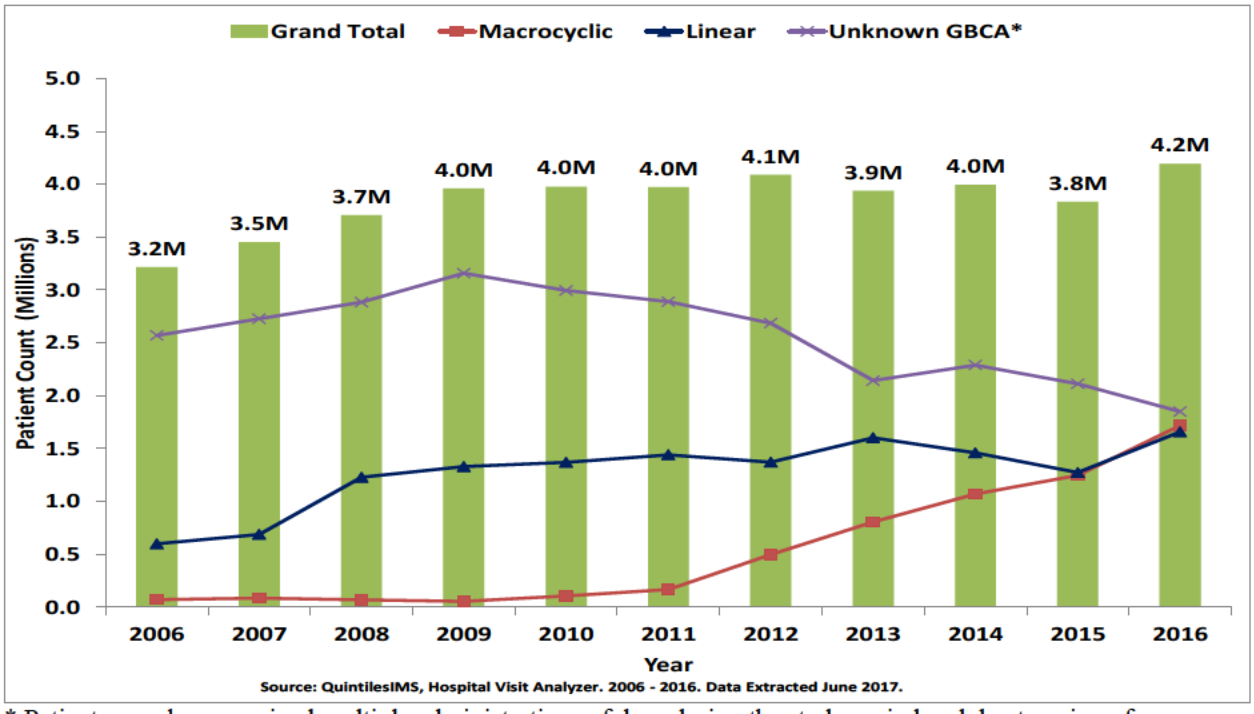
* Sales distribution data of the volume of GBCAs sold from manufacturers to 50 pediatric specialty hospitals and 5 pediatric specialty clinics were captured in this data source

4.4.4 Patient-level data in the US Non-Federal Hospital Setting

Table 3 in the Appendix shows the national estimate of patients billed for an MRI/MRA procedure(s) and GBCA, by patient age and product from US non-federal hospitals stratified from 2006 through 2016 annually. The number of patients billed for an MRI/MRA procedure(s) and a GBCA ranged from 3.4 million – 4.5 million patients annually for the review period. Drug utilization trends by gadolinium type and patient age (0-1, 2-17, and 18+ years) were provided in Figures 5-7 below.

Figure 7 shows the national estimate of adult patients (aged 18 years and older) billed for MRI/MRA procedure(s) and GBCA, stratified by chemical structure (macrocyclic vs. linear) from US non-federal hospitals from 2006 through 2016 annually. The number of patients billed for an MRI/MRA procedure(s) and GBCA ranged from 3.2 million – 4.2 million patients annually for the review period. Although the majority of patients did not include information on the type of gadolinium agent used, billing for macrocyclic GBCAs increased by 3-fold since 2012. In 2016, the number of patients billed for macrocyclic or linear GBCAs were nearly the same. Despite the large number of patients billed for an MRI/MRA procedure(s) with an unknown gadolinium agent, use of macrocyclic agents increased since 2012 and the similar number of patients billed for a specific macrocyclic or linear GBCAs in 2016 were consistent with the trend reported in US sales.

Figure 7. National estimates of patients (18+ years) billed for an MRI/MRA procedure(s) by macrocyclic or linear gadolinium-based contrast agent from US non-federal hospitals, 2006 – 2016

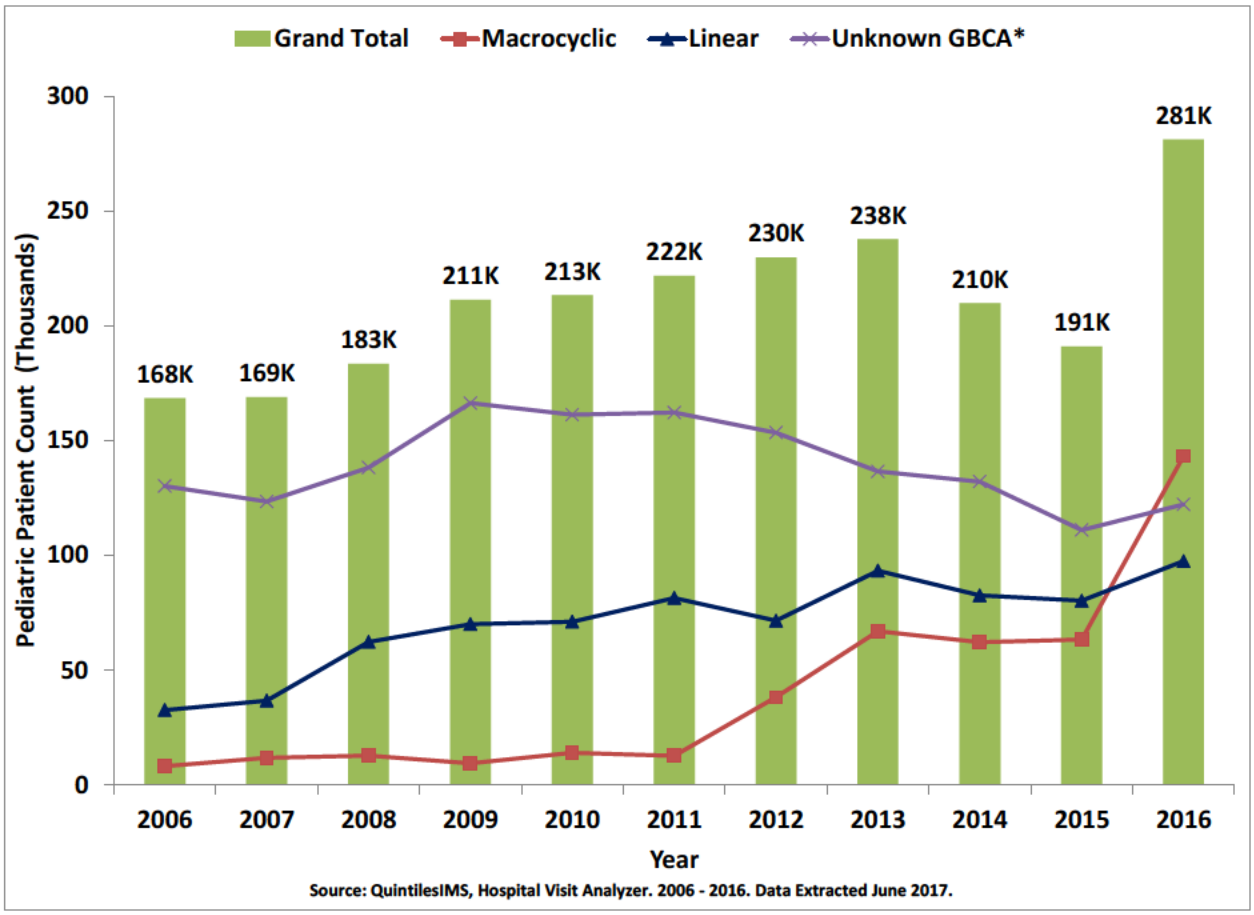


* Patients may have received multiple administrations of drug during the study period and due to aging of patients, patients may be counted more than once in the individual categories. For this reason, summing is

not advisable and will result in overestimates of patient counts. Unknown GBCAs represents 44-80% of patient utilization annually for the review period.

Figure 8 shows the national estimate of pediatric patients (aged 2-17 years) billed for an MRI/MRA procedure(s) and GBCA, stratified by chemical structure (macrocyclic vs. linear) from US non-federal hospitals from 2006 through 2016 annually. The number of pediatric patients age 2-17 years with a hospital billing for an MRI/MRA procedure(s) and GBCA ranged from 168,000 – 281,000 pediatric patients annually for the review period. The majority of pediatric patient did not include information on the GBCA used. However, billing for macrocyclic agents increased by nearly 4-fold since 2012, and the number of pediatric patients was slightly higher for macrocyclic GBCAs compared to linear GBCAs in 2016.

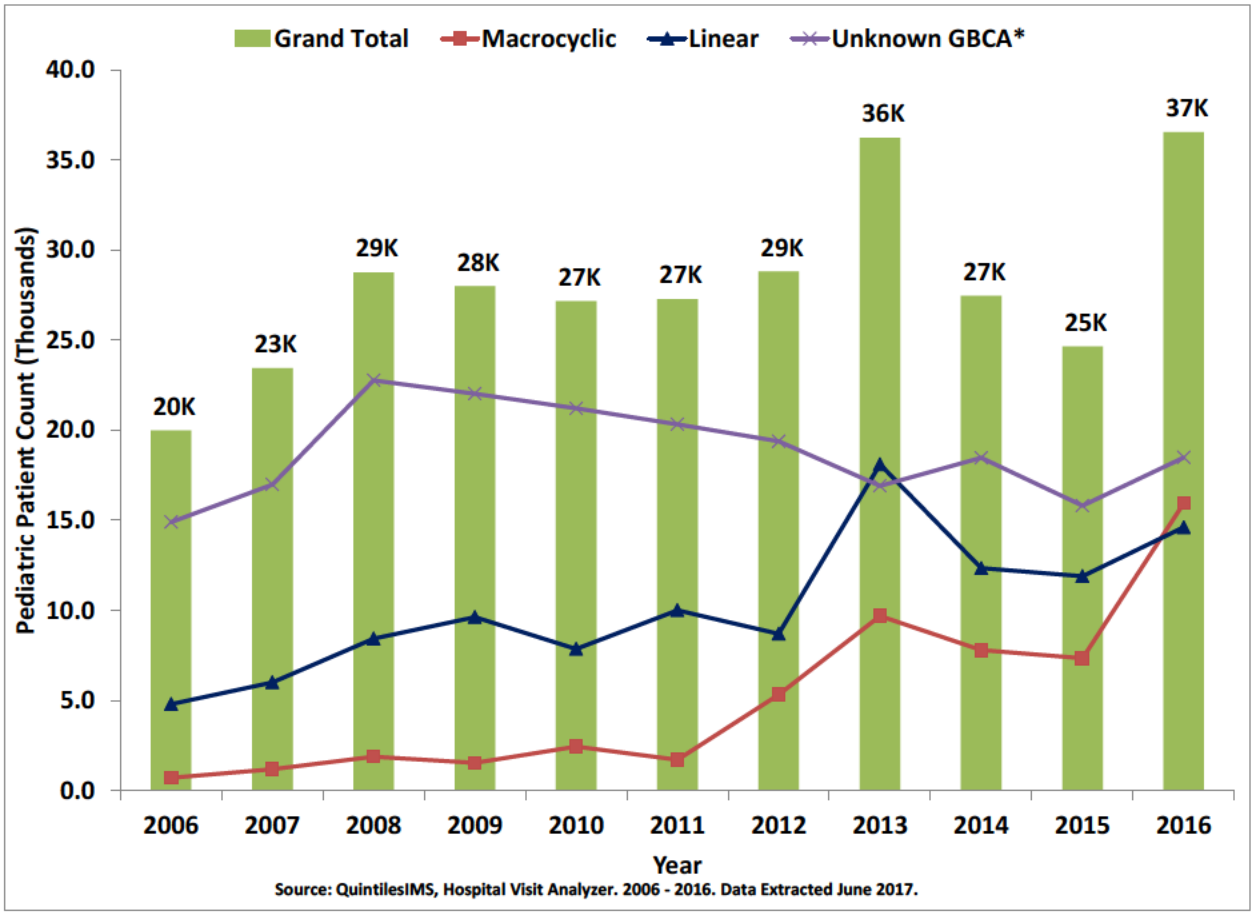
Figure 8. National estimates of pediatric patients (aged 2-17 years) billed for an MRI/MRA procedure(s) by macrocyclic or linear gadolinium-based contrast agent from US non-federal hospitals, 2006 – 2016



* Patients may have received multiple administrations of drug during the study period and due to aging of patients, patients may be counted more than once in the individual categories. For this reason, summing is not advisable and will result in overestimates of patient counts. Unknown GBCAs represents 43-77% of patient utilization annually for the review period.

Figure 9 shows the national estimate of pediatric patients (aged 0-1 year) billed for MRI/MRA procedure(s) and GBCA, stratified by chemical structure (macrocyclic vs. linear) from US non-federal hospitals from 2006 through 2016. The number of pediatric patient aged 0-1 year with a hospital billing for an MRI/MRA procedure(s) and GBCA ranged from 20,000 – 37,000 patients annually for the review period. The majority of pediatric patients did not include information on the specific GBCA used. However, billing for macrocyclic GBCAs increased approximately 3-fold since 2012.

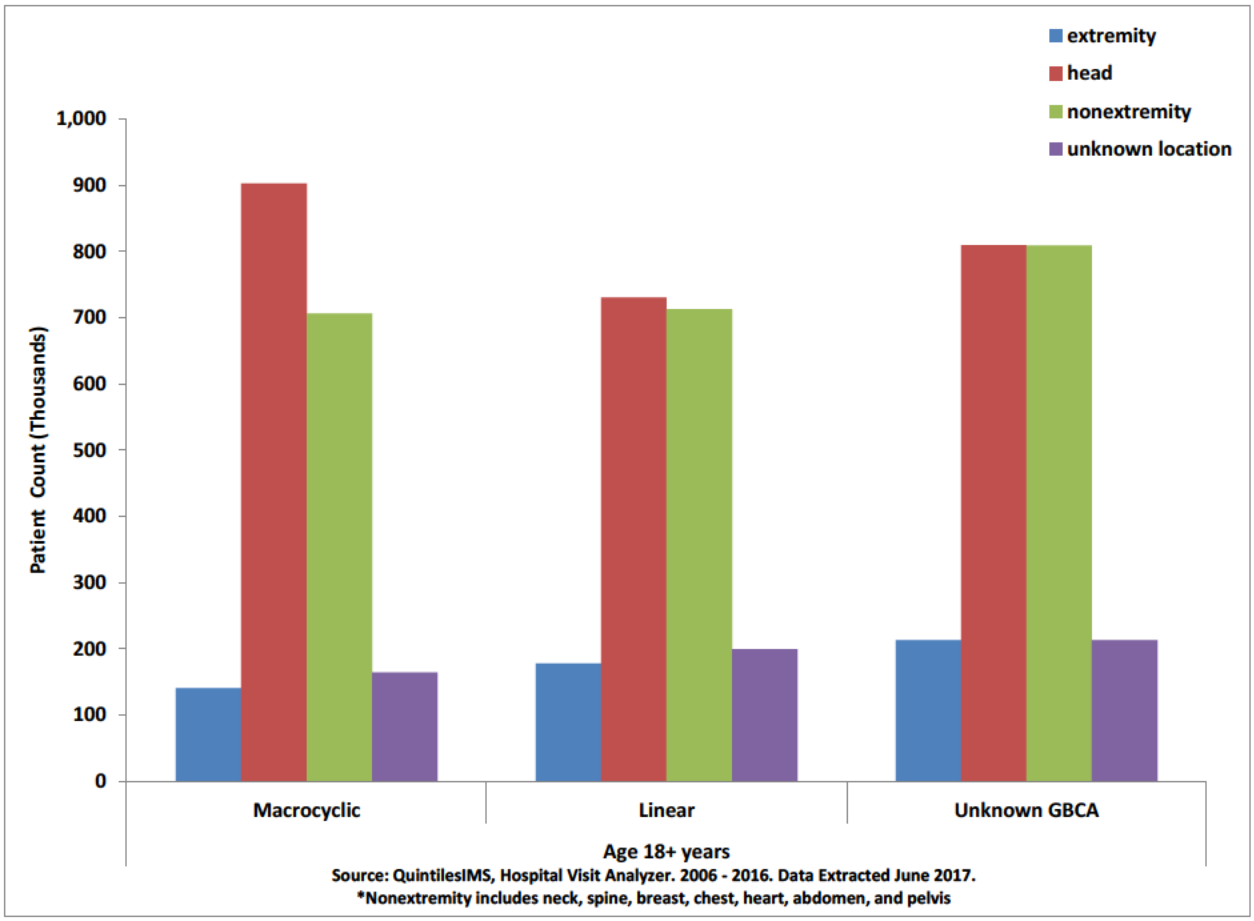
Figure 9. National estimates of pediatric patients (aged 0-1 year) billed for an MRI/MRA procedure(s) by macrocyclic or linear gadolinium-based contrast agent from US non-federal hospitals, 2006 – 2016



* Patients may have received multiple administrations of drug during the study period and due to aging of patients, patients may be counted more than once in the individual categories. For this reason, summing is not advisable and will result in overestimates of patient counts. Unknown GBCAs represents 47-79% of patient utilization annually for the review period.

Figure 10 shows the national estimate of adult patients (aged 18+ years) billed for an MRI/MRA procedure(s) and GBCA, stratified by chemical structure (macrocyclic vs. linear) and procedure location in the US non-federal hospital setting in 2016. The distribution was similar with MRI/MRA procedure(s) of the head and non-extremity locations accounting for the majority of patients regardless of GBCA type. A slightly higher proportion of patients were billed for an MRI/MRA procedure(s) of the head with macrocyclic GBCAs compared to linear GBCAs in 2016 (see Table 4 in the Appendix for the national estimate of patients billed for an MRI/MRA procedure(s) and GBCA, stratified by patient age, chemical structure, and procedure location, from US non-federal hospitals, from 2006 through 2016 annually).

Figure 10. National estimate of adult patients (aged 18+ years) billed for an MRI/MRA procedure(s) by macrocyclic vs. linear gadolinium-based contrast agent and procedure location from US non-federal hospitals, 2016

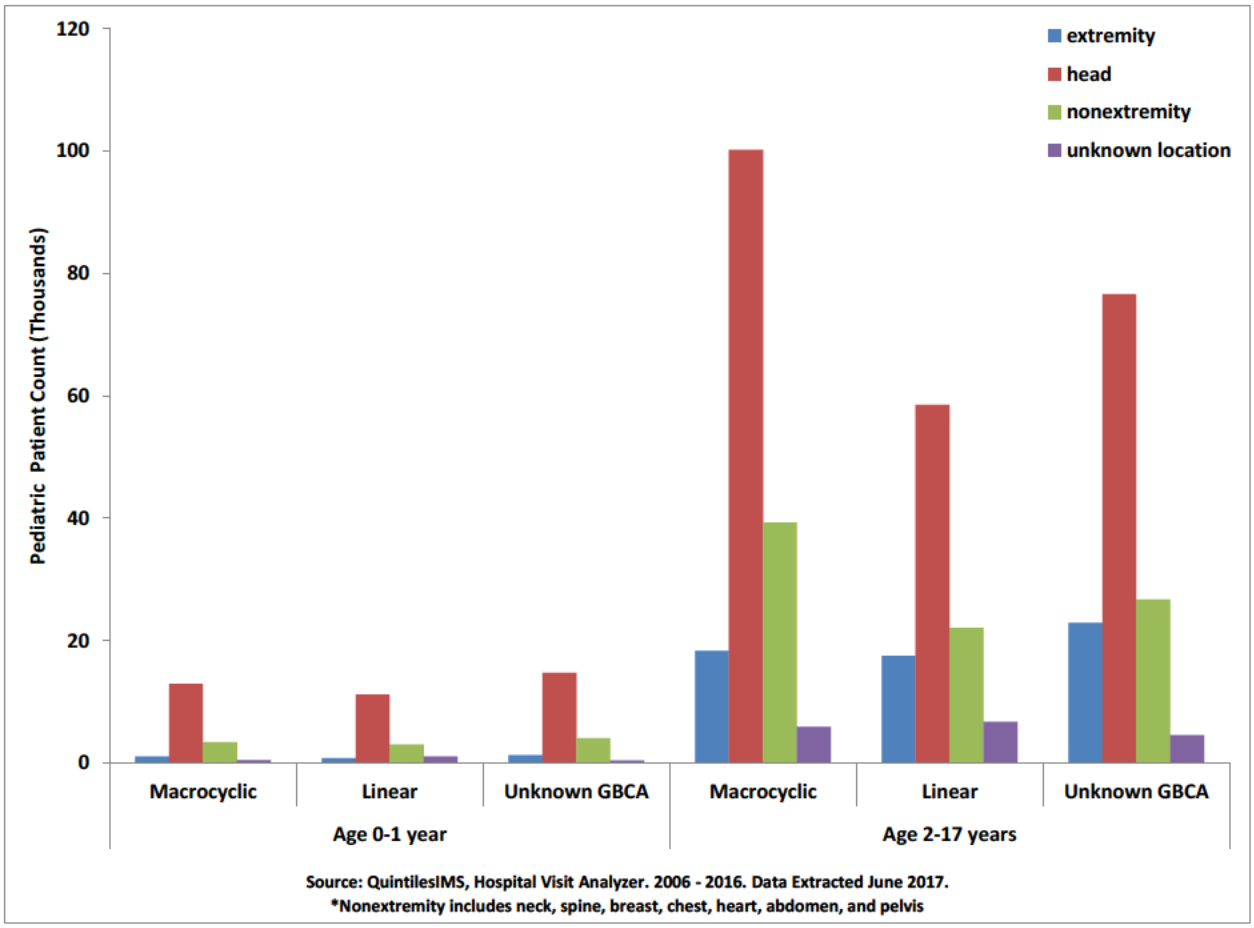


* Patients may have received multiple administrations of drug during the study period and due to aging of patients, patients may be counted more than once in the individual categories. For this reason, summing is not advisable and will result in overestimates of patient counts.

Figure 11 shows the national estimate of pediatric patients aged 0-1 year and 2-17 years billed for MRI/MRA procedure(s) and GBCA type, stratified by chemical structure (macrocyclic vs. linear) and procedure location in the US non-federal hospital setting in

2016. The distributions were similar in both pediatric age groups. MRI/MRA procedure(s) of the head accounted for the majority of procedures regardless of GBCA or age group. The majority of pediatric patients aged 2-17 years were billed for an MRI/MRA procedure(s) of the head with macrocyclic gadolinium agents compared to linear gadolinium agents in 2016.

Figure 11. National estimate of pediatric patients billed for an MRI/MRA procedure(s) by gadolinium-based contrast agent and exam location from US non-federal hospitals, 2016



* Patients may have received multiple administrations of drug during the study period and due to aging of patients, patients may be counted more than once in the individual categories. For this reason, summing is not advisable and will result in overestimates of patient counts.

4.5 Discussion

In support of the Medical Imaging Drugs Advisory Committee (MIDAC) meeting scheduled for September 8, 2017, this review examined drug utilization trends for GBCAs in the US from 2006 through 2016, annually. Our overall findings suggest that annual sales of linear GBCAs from US manufacturers to non-retail settings of care steadily decreased, while sales of macrocyclic GBCAs increased since 2012. The shift in sales from linear to macrocyclic agents demonstrated a change in the market since 2006

when linear agents accounted for 95% of total sales. In 2016, US sales of macrocyclic and linear GBCAs were almost evenly divided.

Our findings suggest that annual sales of linear GBCAs from US manufacturers and wholesalers to pediatric hospitals and clinics also decreased while sales of macrocyclic GBCAs increased since 2014. By 2016, macrocyclic GBCAs accounted for 82% of sales to the reported facilities.

Despite the high proportion of patients billed for an MRI/MRA procedure(s) with an unknown gadolinium agent, the increasing use of macrocyclic agents was observed among adult and pediatric patients in the US non-federal hospital setting since 2012. Since Magnevist, Omniscan, and Optimark do not have product specific HCPCS codes assigned, an assessment of drug utilization trends for linear GBCAs was more difficult. It is likely that these older linear GBCAs account for a substantial portion of patients billed for an MRI/MRA procedure(s) with an unknown GBCA. However, overall drug utilization trends for unknown GBCAs decreased among adults and pediatric patients aged 2-17 years since 2009. The same downward trend for unknown GBCAs was also observed in pediatric patients aged 0-1 year since 2008. Assuming the trend observed for patients billed for an MRI/MRA procedure(s) with an unknown GBCA reflects older linear GBCAs, the use of linear GBCAs decreased in US non-federal hospitals since 2009. This downward trend was similar to the trend observed in US sales to non-federal hospitals.

In 2016, the most frequently performed MRI/MRA procedure(s) with a GBCA for adult and pediatric patients were for imaging of the head and non-extremities among adults. Again, since the majority of patients billed for an MRI/MRA procedure(s) had an unknown GBCA, it is difficult to interpret our findings. However, it is likely that a substantial portion of these unknown GBCAs were older linear gadolinium agents.

Findings from this review should be interpreted in the context of the known limitations of the databases used. The sales data represent the amount of product being sold from US manufacturers and distribution centers into various drug dispensing/healthcare settings such as hospitals, clinics, etc. These data do not provide a direct estimate of patient use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

The sales distribution data obtained from the Symphony Health Solutions' PHAST NonRetail Monthly data shows the volume of GBCA sales from manufacturers to 50 pediatric specialty hospitals and 5 pediatric specialty clinics. Of note, these data trends do not represent national trends in sales for all pediatric utilization. A research letter published in the Journal of the American Medical Association Pediatrics reported that 1.5 million pediatric MRI examinations were performed for GBCAs in the US in 2015.[4] Therefore, the sales to pediatric hospitals and clinics in this review underestimate sales of gadolinium agents nationwide. Due to the sample size and the unreported pharmacy

information, there are limitations in the ability to identify national trends in the data. However, these data are representative of trends in GBCA sales intended for use by pediatric patients treated in these facilities; sales to acute care hospitals with pediatric departments were not represented in this data source but are included in the nationally estimated sales data.

The QuintilesIMS (QI) hospital sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals (such as children's hospitals and other standalone specialty hospitals), and does not necessarily represent all acute care hospitals in the US in all markets. However, trends in GBCA sales distribution data to children's specialty hospitals are provided in this analysis. Our patient-level findings can only be generalized to the non-federal hospital setting and do not necessarily represent other settings of care where GBCAs are used, including non-hospital affiliated clinics.

4.6 Conclusion

Based on sales and patient utilization data for 2006 through 2016, GBCAs were widely used in the US. During the review period, there was an increase in the utilization of macrocyclic GBCAs and a decrease in the utilization of linear GBCAs in the US. Data were suggestive of a higher proportion of macrocyclic GBCAs utilization vs linear GBCA utilization in the pediatric population compared to the adult population in 2016.

4.7 References

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4.8 Appendices

4.8.1 APPENDIX A: Drug Utilization Tables

Table 1. National estimates of sales (in packages[1] sold) for gadolinium-based contrast agents from US manufacturers to non-retail channels of distribution, 2006 - 2016

	2006		2007		2008		2009		2010		2011		2012		2013		2014		2015		2016	
	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*
Grand Total	8,630,971	*100.0%*	8,226,315	*100.0%*	7,745,277	*100.0%*	8,014,590	*100.0%*	7,582,391	*100.0%*	7,508,287	*100.0%*	7,627,138	*100.0%*	7,739,012	*100.0%*	8,051,264	*100.0%*	8,348,344	*100.0%*	8,797,762	*100.0%*
Macrocyclic gadolinium agents	**426,891**	***4.9%***	**412,040**	***5.0%***	**426,139**	***5.5%***	**484,715**	***6.0%***	**546,324**	***7.2%***	**715,285**	***9.5%***	**1,325,763**	***17.4%***	**1,907,661**	***24.6%***	**2,572,096**	***31.9%***	**3,382,147**	***40.5%***	**4,502,014**	***51.2%***
Gadavist (gadobutrol)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	127,899	*17.9%*	743,743	*56.1%*	1,322,927	*69.3%*	1,918,184	*74.6%*	2,368,672	*70.0%*	2,852,245	*63.4%*
Dotarem (gadoterate)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	3,695	*0.2%*	47,084	*1.8%*	354,941	*10.5%*	932,290	*20.7%*
ProHance (gadoteridol)	426,891	*100.0%*	412,040	*100.0%*	426,139	*100.0%*	484,715	*100.0%*	546,324	*100.0%*	587,386	*82.1%*	582,020	*43.9%*	581,039	*30.5%*	606,828	*23.6%*	658,534	*19.5%*	717,479	*15.9%*
Linear gadolinium agents	**8,204,080**	***95.1%***	**7,814,275**	***95.0%***	**7,319,138**	***94.5%***	**7,529,875**	***94.0%***	**7,036,067**	***92.8%***	**6,793,002**	***90.5%***	**6,301,375**	***82.6%***	**5,831,351**	***75.4%***	**5,479,168**	***68.1%***	**4,966,197**	***59.5%***	**4,295,748**	***48.8%***
MultiHance (gadobenate)	252,310	*3.1%*	749,005	*9.6%*	1,024,608	*14.0%*	1,139,559	*15.1%*	1,281,333	*18.2%*	1,571,835	*23.1%*	1,695,116	*26.9%*	1,814,943	*31.1%*	1,957,456	*35.7%*	2,164,698	*43.6%*	2,249,498	*52.4%*
Magnevist (gadopentetate)	3,620,527	*44.1%*	3,731,521	*47.8%*	3,878,201	*53.0%*	3,851,350	*51.1%*	3,510,872	*49.9%*	3,088,335	*45.5%*	2,537,048	*40.3%*	2,276,549	*39.0%*	1,819,714	*33.2%*	1,313,646	*26.5%*	863,932	*20.1%*
Omniscan (gadodiamide)	3,418,326	*41.7%*	2,351,745	*30.1%*	1,585,146	*21.7%*	1,499,396	*19.9%*	1,289,396	*18.3%*	1,177,082	*17.3%*	1,035,284	*16.4%*	975,914	*16.7%*	976,686	*17.8%*	834,111	*16.8%*	653,058	*15.2%*
Optimark (gadoversetamide)	912,917	*11.1%*	982,004	*12.6%*	828,355	*11.3%*	1,001,769	*13.3%*	867,332	*12.3%*	848,166	*12.5%*	730,046	*11.6%*	639,034	*11.0%*	604,504	*11.0%*	534,561	*10.8%*	408,142	*9.5%*
Eovist (gadoxetate)	0	*0.0%*	0	*0.0%*	2,828	*0.0%*	37,801	*0.5%*	81,746	*1.2%*	93,003	*1.4%*	95,171	*1.5%*	106,492	*1.8%*	112,954	*2.1%*	119,181	*2.4%*	121,118	*2.8%*
Ablavar (gadofosveset)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	5,388	*0.1%*	14,581	*0.2%*	208,710	*3.3%*	18,419	*0.3%*	7,854	*0.1%*	0	*0.0%*	0	*0.0%*

Source: QuintilesIMS Health, IMS National Sales Perspectives™*. 2006 - 2016. Extracted June 2017. File: NSP 2017-676 GBCAs by type and calendar year 7-19-17.xlsx*

[1]Packages refers to the number of vials, syringes, or bottles sold

Table 2. Sales (in packages[1] sold) for gadolinium-based contrast agents from US manufacturers and wholesalers to pediatric hospitals and clinics*, 2007 – 2016

	2007		2008		2009		2010		2011		2012		2013		2014		2015		2016	
	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*	Packages Sold	*Share*
Grand Total	**55,449**	***100.0%***	**59,098**	***100.0%***	**61,349**	***100.0%***	**73,464**	***100.0%***	**83,293**	***100.0%***	**94,820**	***100.0%***	**104,377**	***100.0%***	**109,241**	***100.0%***	**113,368**	***100.0%***	**111,990**	***100.0%***
Macrocyclic gadolinium agents	**1,920**	***3.5%***	**2,235**	***3.8%***	**1,470**	***2.4%***	**1,665**	***2.3%***	**1,750**	***2.1%***	**2,685**	***2.8%***	**5,400**	***5.2%***	**14,295**	***13.1%***	**47,905**	***42.3%***	**92,040**	***82.2%***
Dotarem (gadoterate)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	1,840	*12.9%*	19,435	*40.6%*	44,020	*47.8%*
Gadavist (gadobutrol)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	40	*2.3%*	0	*0.0%*	660	*12.2%*	2,675	*18.7%*	17,050	*35.6%*	40,960	*44.5%*
ProHance (gadoteridol)	1,920	*100.0%*	2,235	*100.0%*	1,470	*100.0%*	1,665	*100.0%*	1,710	*97.7%*	2,685	*100.0%*	4,740	*87.8%*	9,780	*68.4%*	11,420	*23.8%*	7,060	*7.7%*
Linear gadolinium agents	**53,529**	***96.5%***	**56,863**	***96.2%***	**59,879**	***97.6%***	**71,799**	***97.7%***	**81,543**	***97.9%***	**92,135**	***97.2%***	**98,977**	***94.8%***	**94,946**	***86.9%***	**65,463**	***57.7%***	**19,950**	***17.8%***
MultiHance (gadobenate)	3,070	*5.7%*	2,820	*5.0%*	5,075	*8.5%*	11,005	*15.3%*	17,705	*21.7%*	18,335	*19.9%*	18,600	*18.8%*	19,190	*20.2%*	17,955	*27.4%*	10,685	*53.6%*
Magnevist (gadopentetate)	45,029	*84.1%*	52,583	*92.5%*	53,594	*89.5%*	59,749	*83.2%*	62,138	*76.2%*	70,950	*77.0%*	75,382	*76.2%*	64,056	*67.5%*	40,683	*62.1%*	7,675	*38.5%*
Eovist (gadoxetate)	0	*0.0%*	0	*0.0%*	20	*<1.0%*	15	*<1.0%*	150	*0.2%*	220	*0.2%*	525	*0.5%*	540	*0.6%*	735	*1.1%*	900	*4.5%*
Omniscan (gadodiamide)	5,430	*10.1%*	1,450	*2.5%*	1,190	*2.0%*	1,030	*1.4%*	1,170	*1.4%*	2,030	*2.2%*	2,170	*2.2%*	5,970	*6.3%*	3,900	*6.0%*	690	*3.5%*
Optimark (gadoversetamide)	0	*0.0%*	10	*<1.0%*	0	*0.0%*	0	*0.0%*	170	*0.2%*	110	*0.1%*	1,350	*1.4%*	4,420	*4.7%*	2,190	*3.3%*	0	*0.0%*
Ablavar (gadofosveset)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	210	*0.3%*	490	*0.5%*	950	*1.0%*	770	*0.8%*	0	*0.0%*	0	*0.0%*

Source: Symphony Health Solutions' PHAST NonRetail Monthly. *2007-2016. Extracted July 2017. File:2017-676 PHASTNonRet GBCAs peds by year 2007-2016 6-26-17.xls*

[1]*Packages refers to the number of vials, syringes, or bottles sold*

* Sales distribution data of the volume of GBCAs sold from manufacturers to 50 pediatric specialty hospitals and 5 pediatric specialty clinics were captured in this data source

Table 3. National estimates of patients billed for an MRI/MRA procedure(s) and gadolinium-based contrast agent by patient age, stratified by chemical structure (macrocyclic vs. linear) and product, 2006 - 2016

	2006		2007		2008		2009		2010		2011		2012		2013		2014		2015		2016	
	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share	Patient Count	Share
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Grand total	**3,402,268**	***100.0%***	**3,643,279**	***100.0%***	**3,919,391**	***100.0%***	**4,197,458**	***100.0%***	**4,217,092**	***100.0%***	**4,220,289**	***100.0%***	**4,346,825**	***100.0%***	**4,207,937**	***100.0%***	**4,231,761**	***100.0%***	**4,047,642**	***100.0%***	**4,511,119**	***100.0%***
Age 0-17 years old	**188,373**	***5.5%***	**192,323**	***5.3%***	**212,083**	***5.4%***	**239,163**	***5.7%***	**240,382**	***5.7%***	**248,954**	***5.9%***	**258,547**	***5.9%***	**273,907**	***6.5%***	**237,336**	***5.6%***	**215,681**	***5.3%***	**317,637**	***7.0%***
Age 0-1 year old	**19,982**	***10.6%***	**23,449**	***12.2%***	**28,751**	***13.6%***	**27,983**	***11.7%***	**27,163**	***11.3%***	**27,279**	***11.0%***	**28,800**	***11.1%***	**36,235**	***13.2%***	**27,461**	***11.6%***	**24,643**	***11.4%***	**36,550**	***11.5%***
Macrocyclic gadolinium agents	**708**	***3.5%***	**1,181**	***5.0%***	**1,877**	***6.5%***	**1,527**	***5.5%***	**2,438**	***9.0%***	**1,699**	***6.2%***	**5,317**	***18.5%***	**9,685**	***26.7%***	**7,790**	***28.4%***	**7,345**	***29.8%***	**15,944**	***43.6%***
Dotarem (gadoterate)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	165	*2.1%*	282	*3.8%*	2,862	*18.0%*
Gadavist (gadobutrol)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	274	*16.1%*	3,168	*59.6%*	7,136	*73.7%*	6,439	*82.7%*	6,593	*89.8%*	12,403	*77.8%*
ProHance (gadoteridol)	708	*100.0%*	1,181	*100.0%*	1,877	*100.0%*	1,527	*100.0%*	2,438	*100.0%*	1,425	*83.9%*	2,149	*40.4%*	2,549	*26.3%*	1,194	*15.3%*	469	*6.4%*	740	*4.6%*
Linear gadolinium agents	**4,794**	***24.0%***	**6,001**	***25.6%***	**8,428**	***29.3%***	**9,624**	***34.4%***	**7,855**	***28.9%***	**10,006**	***36.7%***	**8,697**	***30.2%***	**18,108**	***50.0%***	**12,338**	***44.9%***	**11,897**	***48.3%***	**14,612**	***40.0%***
MultiHance (gadobenate)	106	*2.2%*	191	*3.2%*	1,466	*17.4%*	1,527	*15.9%*	1,794	*22.8%*	4,918	*49.1%*	4,728	*54.4%*	11,460	*63.3%*	5,692	*46.1%*	6,048	*50.8%*	9,519	*65.1%*
Ablavar (gadofosveset)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	22	*0.3%*	355	*2.0%*	87	*0.7%*	9	*0.1%*	161	*1.1%*
Magnevist (gadopentetate)	2,793	*58.3%*	5,080	*84.7%*	6,371	*75.6%*	7,416	*77.1%*	5,554	*70.7%*	4,374	*43.7%*	2,767	*31.8%*	4,663	*25.8%*	4,883	*39.6%*	3,797	*31.9%*	2,641	*18.1%*
Eovist (gadoxetate)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	19	*0.2%*	130	*0.7%*	95	*0.8%*	63	*0.5%*	154	*1.1%*
Omniscan (gadodiamide)	1,901	*39.6%*	759	*12.6%*	246	*2.9%*	446	*4.6%*	405	*5.2%*	390	*3.9%*	598	*6.9%*	1,163	*6.4%*	1,164	*9.4%*	1,471	*12.4%*	1,907	*13.1%*
Optimark (gadoversetamide)			6	*0.1%*	373	*4.4%*	296	*3.1%*	200	*2.6%*	349	*3.5%*	589	*6.8%*	422	*2.3%*	449	*3.6%*	534	*4.5%*	337	*2.3%*
Unknown gadolinium agents*	**14,898**	***74.6%***	**16,985**	***72.4%***	**22,768**	***79.2%***	**22,024**	***78.7%***	**21,210**	***78.1%***	**20,327**	***74.5%***	**19,383**	***67.3%***	**16,912**	***46.7%***	**18,464**	***67.2%***	**15,810**	***64.2%***	**18,482**	***50.6%***
Age 2 - 17 years old	**168,410**	***89.4%***	**168,903**	***87.8%***	**183,351**	***86.5%***	**211,228**	***88.3%***	**213,324**	***88.7%***	**221,762**	***89.1%***	**229,798**	***88.9%***	**237,815**	***86.8%***	**209,882**	***88.4%***	**191,039**	***88.6%***	**281,162**	***88.5%***
Macrocyclic gadolinium agents	**8,120**	***4.8%***	**11,760**	***7.0%***	**12,723**	***6.9%***	**9,382**	***4.4%***	**13,923**	***6.5%***	**12,619**	***5.7%***	**38,149**	***16.6%***	**66,897**	***28.1%***	**62,070**	***29.6%***	**63,303**	***33.1%***	**143,143**	***50.9%***
Dotarem (gadoterate)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	652	*1.1%*	1,612	*2.5%*	22,516	*15.7%*
Gadavist (gadobutrol)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	3,342	*26.5%*	22,856	*59.9%*	48,268	*72.2%*	52,015	*83.8%*	57,482	*90.8%*	117,339	*82.0%*
ProHance (gadoteridol)	8,120	*100.0%*	11,760	*100.0%*	12,723	*100.0%*	9,382	*100.0%*	13,923	*100.0%*	9,277	*73.5%*	15,293	*40.1%*	18,653	*27.9%*	9,475	*15.3%*	4,368	*6.9%*	4,558	*3.2%*
Linear gadolinium agents	**32,527**	***19.3%***	**36,677**	***21.7%***	**62,256**	***34.0%***	**69,982**	***33.1%***	**71,040**	***33.3%***	**81,407**	***36.7%***	**71,496**	***31.1%***	**93,282**	***39.2%***	**82,485**	***39.3%***	**80,196**	***42.0%***	**97,409**	***34.6%***
MultiHance (gadobenate)	1,132	*3.5%*	2,531	*6.9%*	10,877	*17.5%*	13,630	*19.5%*	17,863	*25.1%*	33,731	*41.4%*	35,702	*49.9%*	40,723	*43.7%*	39,190	*47.5%*	46,996	*58.6%*	64,341	*66.1%*
Ablavar (gadofosveset)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	37	*0.1%*	59	*0.1%*	453	*0.6%*	1,807	*1.9%*	1,072	*1.3%*	498	*0.6%*	1,550	*1.6%*
Magnevist (gadopentetate)	15,816	*48.6%*	25,304	*69.0%*	37,203	*59.8%*	40,749	*58.2%*	42,933	*60.4%*	36,836	*45.2%*	23,810	*33.3%*	36,377	*39.0%*	28,224	*34.2%*	19,150	*23.9%*	17,707	*18.2%*
Eovist (gadoxetate)	0	*0.0%*	0	*0.0%*	0	*0.0%*	59	*0.1%*	116	*0.2%*	135	*0.2%*	299	*0.4%*	501	*0.5%*	417	*0.5%*	448	*0.6%*	683	*0.7%*
Omniscan (gadodiamide)	15,486	*47.6%*	9,018	*24.6%*	11,187	*18.0%*	12,846	*18.4%*	9,366	*13.2%*	8,162	*10.0%*	8,596	*12.0%*	10,883	*11.7%*	10,341	*12.5%*	9,214	*11.5%*	11,598	*11.9%*
Optimark (gadoversetamide)	136	*0.4%*	325	*0.9%*	3,256	*5.2%*	3,205	*4.6%*	2,118	*3.0%*	3,301	*4.1%*	3,031	*4.2%*	3,468	*3.7%*	3,640	*4.4%*	4,388	*5.5%*	2,476	*2.5%*
Unknown gadolinium agents*	**130,153**	***77.3%***	**123,407**	***73.1%***	**138,189**	***75.4%***	**166,297**	***78.7%***	**161,202**	***75.6%***	**162,165**	***73.1%***	**153,412**	***66.8%***	**136,506**	***57.4%***	**132,044**	***62.9%***	**110,990**	***58.1%***	**122,158**	***43.4%***
Age 18+ years old	**3,213,940**	***94.5%***	**3,450,989**	***94.7%***	**3,707,362**	***94.6%***	**3,958,396**	***94.3%***	**3,976,812**	***94.3%***	**3,971,523**	***94.1%***	**4,088,380**	***94.1%***	**3,935,447**	***93.5%***	**3,994,433**	***94.4%***	**3,831,961**	***94.7%***	**4,193,588**	***93.0%***
Macrocyclic gadolinium agents	**72,074**	***2.2%***	**85,852**	***2.5%***	**69,974**	***1.9%***	**55,924**	***1.4%***	**106,836**	***2.7%***	**167,564**	***4.2%***	**498,204**	***12.2%***	**806,742**	***20.5%***	**1,070,389**	***26.8%***	**1,246,596**	***32.5%***	**1,717,719**	***41.0%***
Dotarem (gadoterate)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	1,113	*0.1%*	26,486	*2.1%*	180,507	*10.5%*
Gadavist (gadobutrol)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	49,546	*29.6%*	380,346	*76.3%*	726,355	*90.0%*	985,964	*92.1%*	1,133,396	*90.9%*	1,487,981	*86.6%*
ProHance (gadoteridol)	72,074	*100.0%*	85,852	*100.0%*	69,974	*100.0%*	55,924	*100.0%*	106,836	*100.0%*	118,042	*70.4%*	118,232	*23.7%*	80,681	*10.0%*	83,962	*7.8%*	88,730	*7.1%*	53,108	*3.1%*
Linear gadolinium agents	**600,037**	***18.7%***	**688,209**	***19.9%***	**1,229,056**	***33.2%***	**1,329,419**	***33.6%***	**1,369,503**	***34.4%***	**1,441,250**	***36.3%***	**1,371,425**	***33.5%***	**1,603,003**	***40.7%***	**1,459,580**	***36.5%***	**1,273,816**	***33.2%***	**1,657,576**	***39.5%***
MultiHance (gadobenate)	31,456	*5.2%*	101,118	*14.7%*	306,332	*24.9%*	342,246	*25.7%*	379,267	*27.7%*	437,306	*30.3%*	565,215	*41.2%*	716,667	*44.7%*	687,694	*47.1%*	745,379	*58.5%*	1,152,617	*69.5%*
Ablavar (gadofosveset)	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	707	*0.1%*	9,353	*0.6%*	13,201	*1.0%*	23,027	*1.4%*	29,828	*2.0%*	22,313	*1.8%*	12,147	*0.7%*
Magnevist (gadopentetate)	278,272	*46.4%*	371,085	*53.9%*	576,900	*46.9%*	652,891	*49.1%*	669,144	*48.9%*	630,032	*43.7%*	488,269	*35.6%*	637,708	*39.8%*	507,807	*34.8%*	270,000	*21.2%*	224,483	*13.5%*
Eovist (gadoxetate)	0	*0.0%*	0	*0.0%*	127	*0.0%*	6,206	*0.5%*	21,324	*1.6%*	34,416	*2.4%*	43,852	*3.2%*	46,010	*2.9%*	40,749	*2.8%*	39,348	*3.1%*	35,141	*2.1%*
Omniscan (gadodiamide)	276,956	*46.2%*	204,246	*29.7%*	284,363	*23.1%*	277,017	*20.8%*	262,042	*19.1%*	284,006	*19.7%*	255,185	*18.6%*	168,783	*10.5%*	175,613	*12.0%*	166,933	*13.1%*	202,288	*12.2%*
Optimark (gadoversetamide)	14,189	*2.4%*	19,391	*2.8%*	71,118	*5.8%*	67,202	*5.1%*	60,036	*4.4%*	67,099	*4.7%*	25,264	*1.8%*	30,565	*1.9%*	41,300	*2.8%*	48,445	*3.8%*	47,863	*2.9%*
Unknown gadolinium agents*	**2,569,476**	***79.9%***	**2,727,038**	***79.0%***	**2,884,250**	***77.8%***	**3,157,622**	***79.8%***	**2,994,801**	***75.3%***	**2,889,172**	***72.7%***	**2,686,318**	***65.7%***	**2,142,980**	***54.5%***	**2,289,306**	***57.3%***	**2,112,565**	***55.1%***	**1,850,074**	***44.1%***

Source: QuintilesIMS, Hospital Visit Analyzer. *2006 - 2016. Extracted June 2017. Source file: HVA 2017-676 GBCA by age, product, and image location 6-26-17.xlsx*

**Unspecified gadolinium agents includes (a) patients with codes for A9579 'gadolinium NOS' and (b) patients with MRIs/MRAs with contrast but no gadolinium HCPCS codes or freetext*

***Subtotals may not sum exactly, due to rounding. Patients may have received multiple administrations of drug during the study period and due to aging of patients during the study period, patients may be counted more than once across age groups. For this reason, summing is not advisable and will result in overestimates of patient counts.*

Table 4. National estimates of patients billed for an MRI/MRA procedure(s) and macrocyclic vs. linear gadolinium-based contrast agent, stratified by exam location, 2006 – 2016

	2006		2007		2008		2009		2010		2011		2012		2013		2014		2015		2016	
	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*
Grand total	**3,402,268**	***100.0%***	**3,643,279**	***100.0%***	**3,919,391**	***100.0%***	**4,197,458**	***100.0%***	**4,217,092**	***100.0%***	**4,220,289**	***100.0%***	**4,346,825**	***100.0%***	**4,207,937**	***100.0%***	**4,231,761**	***100.0%***	**4,047,642**	***100.0%***	**4,511,119**	***100.0%***
Age 0-17 years old	**188,373**	***5.5%***	**192,323**	***5.3%***	**212,083**	***5.4%***	**239,163**	***5.7%***	**240,382**	***5.7%***	**248,954**	***5.9%***	**258,547**	***5.9%***	**273,907**	***6.5%***	**237,336**	***5.6%***	**215,681**	***5.3%***	**317,637**	***7.0%***
Age 0-1 year old	**19,982**	***10.6%***	**23,449**	***12.2%***	**28,751**	***13.6%***	**27,983**	***11.7%***	**27,163**	***11.3%***	**27,279**	***11.0%***	**28,800**	***11.1%***	**36,235**	***13.2%***	**27,461**	***11.6%***	**24,643**	***11.4%***	**36,550**	***11.5%***
Macrocyclic gadolinium agents	**708**	***3.5%***	**1,181**	***5.0%***	**1,877**	***6.5%***	**1,527**	***5.5%***	**2,438**	***9.0%***	**1,699**	***6.2%***	**5,317**	***18.5%***	**9,685**	***26.7%***	**7,790**	***28.4%***	**7,345**	***29.8%***	**15,944**	***43.6%***
extremity	0	*0.0%*	32	*2.7%*	148	*7.9%*	66	*4.4%*	153	*6.3%*	118	*7.0%*	258	*4.8%*	399	*4.1%*	297	*3.8%*	284	*3.9%*	1,034	*6.5%*
head	277	*39.1%*	400	*33.9%*	1,261	*67.2%*	996	*65.2%*	1,631	*66.9%*	1,253	*73.7%*	3,690	*69.4%*	6,709	*69.3%*	6,389	*82.0%*	6,008	*81.8%*	12,907	*81.0%*
nonextremity†	40	*5.7%*	75	*6.3%*	321	*17.1%*	249	*16.3%*	476	*19.5%*	321	*18.9%*	1,011	*19.0%*	1,789	*18.5%*	1,410	*18.1%*	1,094	*14.9%*	3,430	*21.5%*
unknown location	391	*55.2%*	81	*6.9%*	337	*18.0%*	338	*22.1%*	408	*16.7%*	152	*9.0%*	1,579	*29.7%*	2,386	*24.6%*	236	*3.0%*	539	*7.3%*	447	*2.8%*
Linear gadolinium agents	**4,794**	***24.0%***	**6,001**	***25.6%***	**8,428**	***29.3%***	**9,624**	***34.4%***	**7,855**	***28.9%***	**10,006**	***36.7%***	**8,697**	***30.2%***	**18,108**	***50.0%***	**12,338**	***44.9%***	**11,897**	***48.3%***	**14,612**	***40.0%***
extremity	134	*2.8%*	180	*3.0%*	208	*2.5%*	288	*3.0%*	218	*2.8%*	627	*6.3%*	501	*5.8%*	487	*2.7%*	513	*4.2%*	419	*3.5%*	789	*5.4%*
head	2,562	*53.4%*	3,631	*60.5%*	4,675	*55.5%*	6,238	*64.8%*	5,111	*65.1%*	6,390	*63.9%*	5,746	*66.1%*	6,239	*34.5%*	6,465	*52.4%*	6,402	*53.8%*	11,206	*76.7%*
nonextremity	522	*10.9%*	792	*13.2%*	1,002	*11.9%*	1,477	*15.3%*	1,422	*18.1%*	1,830	*18.3%*	1,712	*19.7%*	1,808	*10.0%*	1,624	*13.2%*	1,322	*11.1%*	3,015	*20.6%*
unknown location	1,776	*37.1%*	1,684	*28.1%*	2,994	*35.5%*	2,067	*21.5%*	1,802	*22.9%*	2,385	*23.8%*	2,081	*23.9%*	10,368	*57.3%*	4,239	*34.4%*	4,257	*35.8%*	1,042	*7.1%*
Unknown gadolinium agents*	**14,898**	***74.6%***	**16,985**	***72.4%***	**22,768**	***79.2%***	**22,024**	***78.7%***	**21,210**	***78.1%***	**20,327**	***74.5%***	**19,383**	***67.3%***	**16,912**	***46.7%***	**18,464**	***67.2%***	**15,810**	***64.2%***	**18,482**	***50.6%***
extremity	505	*3.4%*	563	*3.3%*	1,207	*5.3%*	1,073	*4.9%*	1,016	*4.8%*	1,035	*5.1%*	868	*4.5%*	749	*4.4%*	805	*4.4%*	600	*3.8%*	1,253	*6.8%*
head	8,194	*55.0%*	7,208	*42.4%*	10,895	*47.8%*	15,709	*71.3%*	16,160	*76.2%*	14,677	*72.2%*	13,873	*71.6%*	10,939	*64.7%*	11,234	*60.8%*	9,632	*60.9%*	14,755	*79.8%*
nonextremity	2,158	*14.5%*	2,062	*12.1%*	4,197	*18.4%*	3,596	*16.3%*	3,436	*16.2%*	3,446	*17.0%*	3,699	*19.1%*	2,622	*15.5%*	2,829	*15.3%*	1,939	*12.3%*	4,022	*21.8%*
unknown location	4,732	*31.8%*	7,924	*46.7%*	7,575	*33.3%*	3,085	*14.0%*	2,550	*12.0%*	3,600	*17.7%*	3,132	*16.2%*	3,524	*20.8%*	4,469	*24.2%*	4,333	*27.4%*	411	*2.2%*
Age 2 - 17 years old	**168,410**	***89.4%***	**168,903**	***87.8%***	**183,351**	***86.5%***	**211,228**	***88.3%***	**213,324**	***88.7%***	**221,762**	***89.1%***	**229,798**	***88.9%***	**237,815**	***86.8%***	**209,882**	***88.4%***	**191,039**	***88.6%***	**281,162**	***88.5%***
Macrocyclic gadolinium agents	**8,120**	***4.8%***	**11,760**	***7.0%***	**12,723**	***6.9%***	**9,382**	***4.4%***	**13,923**	***6.5%***	**12,619**	***5.7%***	**38,149**	***16.6%***	**66,897**	***28.1%***	**62,070**	***29.6%***	**63,303**	***33.1%***	**143,143**	***50.9%***
extremity	465	*5.7%*	532	*4.5%*	918	*7.2%*	695	*7.4%*	1,519	*10.9%*	1,390	*11.0%*	3,840	*10.1%*	6,585	*9.8%*	6,835	*11.0%*	7,661	*12.1%*	18,326	*12.8%*
head	5,240	*64.5%*	6,155	*52.3%*	9,068	*71.3%*	6,628	*70.6%*	9,681	*69.5%*	8,347	*66.1%*	24,316	*63.7%*	42,373	*63.3%*	41,825	*67.4%*	41,022	*64.8%*	100,189	*70.0%*
nonextremity	1,025	*12.6%*	1,164	*9.9%*	2,176	*17.1%*	1,726	*18.4%*	2,616	*18.8%*	2,788	*22.1%*	7,814	*20.5%*	13,900	*20.8%*	14,608	*23.5%*	13,847	*21.9%*	39,310	*27.5%*
unknown location	2,096	*25.8%*	4,659	*39.6%*	2,333	*18.3%*	1,437	*15.3%*	1,688	*12.1%*	1,371	*10.9%*	9,279	*24.3%*	13,860	*20.7%*	3,641	*5.9%*	5,282	*8.3%*	5,899	*4.1%*
Linear gadolinium agents	**32,527**	***19.3%***	**36,677**	***21.7%***	**62,256**	***34.0%***	**69,982**	***33.1%***	**71,040**	***33.3%***	**81,407**	***36.7%***	**71,496**	***31.1%***	**93,282**	***39.2%***	**82,485**	***39.3%***	**80,196**	***42.0%***	**97,409**	***34.6%***
extremity	2,390	*7.3%*	3,042	*8.3%*	6,587	*10.6%*	7,431	*10.6%*	8,283	*11.7%*	10,783	*13.2%*	10,814	*15.1%*	14,017	*15.0%*	12,711	*15.4%*	11,041	*13.8%*	17,485	*18.0%*
head	19,993	*61.5%*	24,801	*67.6%*	37,818	*60.7%*	44,527	*63.6%*	42,077	*59.2%*	45,744	*56.2%*	41,659	*58.3%*	44,110	*47.3%*	38,290	*46.4%*	37,035	*46.2%*	58,509	*60.1%*
nonextremity	4,440	*13.7%*	5,883	*16.0%*	9,711	*15.6%*	11,856	*16.9%*	12,955	*18.2%*	15,815	*19.4%*	15,335	*21.4%*	17,050	*18.3%*	14,989	*18.2%*	12,167	*15.2%*	22,056	*22.6%*
unknown location	7,579	*23.3%*	5,488	*15.0%*	11,900	*19.1%*	10,825	*15.5%*	13,761	*19.4%*	19,022	*23.4%*	15,967	*22.3%*	26,692	*28.6%*	20,538	*24.9%*	23,730	*29.6%*	6,718	*6.9%*
Unknown gadolinium agents*	**130,153**	***77.3%***	**123,407**	***73.1%***	**138,189**	***75.4%***	**166,297**	***78.7%***	**161,202**	***75.6%***	**162,165**	***73.1%***	**153,412**	***66.8%***	**136,506**	***57.4%***	**132,044**	***62.9%***	**110,990**	***58.1%***	**122,158**	***43.4%***
extremity	14,701	*11.3%*	15,362	*12.4%*	17,472	*12.6%*	23,480	*14.1%*	22,754	*14.1%*	22,953	*14.2%*	21,809	*14.2%*	21,487	*15.7%*	21,256	*16.1%*	16,991	*15.3%*	22,897	*18.7%*
head	81,084	*62.3%*	69,572	*56.4%*	80,594	*58.3%*	110,502	*66.4%*	106,246	*65.9%*	103,576	*63.9%*	94,829	*61.8%*	74,045	*54.2%*	68,463	*51.8%*	54,740	*49.3%*	76,625	*62.7%*
nonextremity	19,883	*15.3%*	16,541	*13.4%*	19,915	*14.4%*	25,596	*15.4%*	28,462	*17.7%*	29,855	*18.4%*	29,871	*19.5%*	27,260	*20.0%*	25,664	*19.4%*	19,536	*17.6%*	26,692	*21.9%*
unknown location	21,461	*16.5%*	28,030	*22.7%*	27,317	*19.8%*	18,814	*11.3%*	17,954	*11.1%*	23,990	*14.8%*	22,538	*14.7%*	23,473	*17.2%*	24,114	*18.3%*	25,040	*22.6%*	4,546	*3.7%*
Age 18+ years old	**3,213,940**	***94.5%***	**3,450,989**	***94.7%***	**3,707,362**	***94.6%***	**3,958,396**	***94.3%***	**3,976,812**	***94.3%***	**3,971,523**	***94.1%***	**4,088,380**	***94.1%***	**3,935,447**	***93.5%***	**3,994,433**	***94.4%***	**3,831,961**	***94.7%***	**4,193,588**	***93.0%***
Macrocyclic gadolinium agents	**72,074**	***2.2%***	**85,852**	***2.5%***	**69,974**	***1.9%***	**55,924**	***1.4%***	**106,836**	***2.7%***	**167,564**	***4.2%***	**498,204**	***12.2%***	**806,742**	***20.5%***	**1,070,389**	***26.8%***	**1,246,596**	***32.5%***	**1,717,719**	***41.0%***
extremity	1,734	*2.4%*	2,775	*3.2%*	2,388	*3.4%*	3,226	*5.8%*	5,505	*5.2%*	6,886	*4.1%*	20,083	*4.0%*	43,081	*5.3%*	75,004	*7.0%*	98,333	*7.9%*	140,578	*8.2%*
head	26,593	*36.9%*	30,832	*35.9%*	25,880	*37.0%*	23,927	*42.8%*	46,916	*43.9%*	80,319	*47.9%*	230,044	*46.2%*	405,460	*50.3%*	556,156	*52.0%*	640,262	*51.4%*	902,548	*52.5%*
nonextremity	11,216	*15.6%*	13,308	*15.5%*	13,469	*19.2%*	13,272	*23.7%*	33,794	*31.6%*	50,295	*30.0%*	156,033	*31.3%*	287,251	*35.6%*	426,459	*39.8%*	473,616	*38.0%*	706,048	*41.1%*
unknown location	35,758	*49.6%*	43,308	*50.4%*	31,563	*45.1%*	18,262	*32.7%*	30,570	*28.6%*	50,413	*30.1%*	175,156	*35.2%*	199,324	*24.7%*	134,530	*12.6%*	176,221	*14.1%*	163,879	*9.5%*
Linear gadolinium agents	**600,037**	***18.7%***	**688,209**	***19.9%***	**1,229,056**	***33.2%***	**1,329,419**	***33.6%***	**1,369,503**	***34.4%***	**1,441,250**	***36.3%***	**1,371,425**	***33.5%***	**1,603,003**	***40.7%***	**1,459,580**	***36.5%***	**1,273,816**	***33.2%***	**1,657,576**	***39.5%***
extremity	30,001	*5.0%*	35,308	*5.1%*	67,111	*5.5%*	75,267	*5.7%*	72,874	*5.3%*	82,585	*5.7%*	86,324	*6.3%*	131,558	*8.2%*	132,148	*9.1%*	114,042	*9.0%*	177,569	*10.7%*
head	250,641	*41.8%*	311,316	*45.2%*	551,798	*44.9%*	613,412	*46.1%*	580,526	*42.4%*	590,594	*41.0%*	543,496	*39.6%*	685,753	*42.8%*	704,830	*48.3%*	572,902	*45.0%*	730,660	*44.1%*
nonextremity	168,950	*28.2%*	213,357	*31.0%*	377,568	*30.7%*	454,964	*34.2%*	481,775	*35.2%*	506,955	*35.2%*	513,167	*37.4%*	642,035	*40.1%*	673,606	*46.2%*	560,275	*44.0%*	712,723	*43.0%*
unknown location	193,563	*32.3%*	182,374	*26.5%*	331,614	*27.0%*	305,937	*23.0%*	367,378	*26.8%*	420,417	*29.2%*	417,175	*30.4%*	346,873	*21.6%*	107,240	*7.3%*	147,447	*11.6%*	198,915	*12.0%*
Unknown gadolinium agents*	**2,569,476**	***79.9%***	**2,727,038**	***79.0%***	**2,884,250**	***77.8%***	**3,157,622**	***79.8%***	**2,994,801**	***75.3%***	**2,889,172**	***72.7%***	**2,686,318**	***65.7%***	**2,142,980**	***54.5%***	**2,289,306**	***57.3%***	**2,112,565**	***55.1%***	**1,850,074**	***44.1%***
extremity	190,810	*7.4%*	208,700	*7.7%*	213,255	*7.4%*	244,461	*7.7%*	224,370	*7.5%*	213,610	*7.4%*	208,704	*7.8%*	204,267	*9.5%*	222,174	*9.7%*	203,405	*9.6%*	212,618	*11.5%*
head	1,259,104	*49.0%*	1,280,688	*47.0%*	1,370,526	*47.5%*	1,553,361	*49.2%*	1,430,679	*47.8%*	1,351,267	*46.8%*	1,218,813	*45.4%*	979,167	*45.7%*	1,109,272	*48.5%*	1,003,422	*47.5%*	809,581	*43.8%*
nonextremity	955,340	*37.2%*	1,042,098	*38.2%*	1,121,009	*38.9%*	1,233,153	*39.1%*	1,194,251	*39.9%*	1,147,268	*39.7%*	1,074,990	*40.0%*	836,637	*39.0%*	961,967	*42.0%*	900,219	*42.6%*	809,159	*43.7%*
unknown location	391,930	*15.3%*	442,030	*16.2%*	450,671	*15.6%*	446,999	*14.2%*	502,668	*16.8%*	580,933	*20.1%*	556,609	*20.7%*	364,933	*17.0%*	246,193	*10.8%*	246,753	*11.7%*	213,164	*11.5%*

Source: QuintilesIMS, Hospital Visit Analyzer. *2006 - 2016. Extracted June 2017. Source file: HVA 2017-676 GBCA by age, product, and image location 6-26-17.xlsx*

**Unspecified gadolinium agents includes (a) patients with codes for A9579 'gadolinium NOS' and (b) patients with MRIs/MRAs with contrast but no gadolinium HCPCS codes or freetext*

***Subtotals may not sum exactly, due to rounding. Patients may have received multiple administrations of drug during the study period and due to aging of patients during the study period, patients may be counted more than once across age groups. For this reason, summing is not advisable and will result in overestimates of patient counts. †Nonextremity includes neck, spine, cardiac, chest, abdomen, and pelvis*

4.8.2 APPENDIX B: Database Descriptions and Limitations

QuintilesIMS, National Sales Perspectives™: Retail and Non-Retail

The QuintilesIMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings

Symphony Health Solutions' PHAST™ NonRetail Monthly

The Symphony Health Solutions' PHAST NonRetail Monthly is a syndicated view of US pharmaceutical distribution sales to non-retail institutions (including hospitals, clinics, long term care, home health, and others) updated on a monthly basis. PHAST NonRetail measures the volume of sales activity in dollars (WAC, AWP) and units (extended units, pack units, volume units) from manufacturers and wholesalers into non-retail markets and classes of trade and over 100 sub-classes of trade. The database captures approximately 98% of the institutional market sales activities from major wholesalers. PHAST NonRetail monthly data is not projected.

QuintilesIMS, Hospital Visit Analyzer

The Hospital Visit Analyzer (HVA) provides hospital inpatient and outpatient encounter transactions and patient level data drawn from hospital operational files and other reference sources. Encounter information is available from 2002, is collected weekly and monthly and is available 25-30 days after the end of each monthly period. This robust data set includes >700 hospitals with hospital inpatient and outpatient encounter data linked to each appropriate patient as well as to select individual hospital departments by anonymized, consistent, longitudinal patient identifiers. These data include over 13 million patients and 60 million visits per year projected to approximately 37 million inpatient visits and 560 million outpatient (including Emergency Department) visits per year, representing acute care, short-term hospital inpatient sites, and their associated hospital emergency departments in order to measure and track the near term health care utilization of hospitalized patients. Each hospital patient encounter includes detailed drug, procedure, device, diagnosis, and applied charges data; location of initiation of each service within the hospital setting of care (e.g. Pediatric, Intensive Care Units) by day for each patient's entire stay; and patient demographics and admission/discharge characteristics. HVA is representative geographically and across payer types, such as commercial insurers, Medicare and Medicaid.

The QuintilesIMS (QI) hospital sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals (such as children's hospitals and other standalone specialty hospitals), and does not necessarily represent all acute care hospitals in the US in all markets. Caveats of the QI hospital data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of QI's hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown QI's patient level data to be representative and accurate across multiple therapeutic areas.

4.8.3 APPENDIX C: Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes

HCPCS code	Description
Gadolinium-based Contrast Agents	
A9575	Injection, gadoterate meglumine, 0.1 ml
A9576	Injection, gadoteridol, (prohance multipack), per ml
A9577	Injection, gadobenate dimeglumine (multihance), per ml
A9578	Injection, gadobenate dimeglumine (multihance multipack), per ml
A9579	Injection, gadolinium-based magnetic resonance contrast agent, not otherwise specified (nos), per ml
A9581	Injection, gadoxetate disodium, 1 ml
A9583	Injection, gadofosveset trisodium, 1 ml
A9585	Injection, gadobutrol, 0.1 ml
Not applicable	No HCPCS code available for gadopentetate, gadodiamide, or gadoversetamide
Magnetic Resonance Angiography	
C8900	Magnetic resonance angiography with contrast, abdomen
C8902	Magnetic resonance angiography without contrast followed by with contrast, abdomen
C8909	Magnetic resonance angiography with contrast, chest (excluding myocardium)
C8911	Magnetic resonance angiography without contrast followed by with contrast, chest (excluding myocardium)
C8912	Magnetic resonance angiography with contrast, lower extremity
C8914	Magnetic resonance angiography without contrast followed by with contrast, lower extremity
C8917	Magnetic Resonance Angiography Without Contrast Followed By With Contrast, Upper Extremity
C8918	Magnetic resonance angiography with contrast, pelvis
C8920	Magnetic resonance angiography without contrast followed by with contrast, pelvis
C8931	Magnetic resonance angiography with contrast, spinal canal and contents
C8933	Magnetic resonance angiography without contrast followed by with contrast, spinal canal and contents
C8934	Magnetic resonance angiography with contrast, upper extremity
C8936	Magnetic resonance angiography without contrast followed by with contrast, upper extremity

CPT code	Description
Magnetic Resonance Imaging	
70542	Magnetic resonance (eg, proton) imaging, orbit, face, and/or neck; with contrast material(s)
70543	Magnetic resonance (eg, proton) imaging, orbit, face, and/or neck; without contrast material(s), followed by contrast material(s) and further sequences
70545	Magnetic resonance angiography, head; with contrast material(s)
70546	Magnetic resonance angiography, head; without contrast material(s), followed by contrast material(s) and further sequences
70548	Magnetic resonance angiography, neck; with contrast material(s)
70549	Magnetic resonance angiography, neck; without contrast material(s), followed by contrast material(s) and further sequences
70552	Magnetic resonance (eg, proton) imaging, brain (including brain stem); with contrast material(s)
70553	Magnetic resonance (eg, proton) imaging, brain (including brain stem); without contrast material, followed by contrast material(s) and further sequences
70558	Magnetic resonance (eg, proton) imaging, brain (including brain stem and skull base), during open intracranial procedure (eg, to assess for residual tumor or residual vascular malformation); with contrast material(s)
70559	Magnetic resonance (eg, proton) imaging, brain (including brain stem and skull base), during open intracranial procedure (eg, to assess for residual tumor or residual vascular malformation); without contrast material(s), followed by contrast material(s) and further sequences
71551	Magnetic resonance (eg, proton) imaging, chest (eg, for evaluation of hilar and mediastinal lymphadenopathy); with contrast material(s)
71552	Magnetic resonance (eg, proton) imaging, chest (eg, for evaluation of hilar and mediastinal lymphadenopathy); without contrast material(s), followed by contrast material(s) and further sequences
71555	Magnetic resonance angiography, chest (excluding myocardium), with or without contrast material(s)
72142	Magnetic resonance (eg, proton) imaging, spinal canal and contents, cervical; with contrast material(s)
72147	Magnetic resonance (eg, proton) imaging, spinal canal and contents, thoracic; with contrast material(s)
72149	Magnetic resonance (eg, proton) imaging, spinal canal and contents, lumbar; with contrast material(s)
72156	Magnetic resonance (eg, proton) imaging, spinal canal and contents, without contrast material, followed by

	contrast material(s) and further sequences; cervical
72157	Magnetic resonance (eg, proton) imaging, spinal canal and contents, without contrast material, followed by contrast material(s) and further sequences; thoracic
72158	Magnetic resonance (eg, proton) imaging, spinal canal and contents, without contrast material, followed by contrast material(s) and further sequences; lumbar
72159	Magnetic resonance angiography, spinal canal and contents, with or without contrast material(s)
72196	Magnetic resonance (eg, proton) imaging, pelvis; with contrast material(s)
72197	Magnetic resonance (eg, proton) imaging, pelvis; without contrast material(s), followed by contrast material(s) and further sequences
72198	Magnetic resonance angiography, pelvis, with or without contrast material(s)
73219	Magnetic resonance (eg, proton) imaging, upper extremity, other than joint; with contrast material(s)
73220	Magnetic resonance (eg, proton) imaging, upper extremity, other than joint; without contrast material(s), followed by contrast material(s) and further sequences
73222	Magnetic resonance (eg, proton) imaging, any joint of upper extremity; with contrast material(s)
73223	Magnetic resonance (eg, proton) imaging, any joint of upper extremity; without contrast material(s), followed by contrast material(s) and further sequences
73225	Magnetic resonance angiography, upper extremity, with or without contrast material(s)
73719	Magnetic resonance (eg, proton) imaging, lower extremity other than joint; with contrast material(s)
73720	Magnetic resonance (eg, proton) imaging, lower extremity other than joint; without contrast material(s), followed by contrast material(s) and further sequences
73722	Magnetic resonance (eg, proton) imaging, any joint of lower extremity; with contrast material(s)
73723	Magnetic resonance (eg, proton) imaging, any joint of lower extremity; without contrast material(s), followed by contrast material(s) and further sequences
73725	Magnetic resonance angiography, lower extremity, with or without contrast material(s)
74182	Magnetic resonance (eg, proton) imaging, abdomen; with contrast material(s)
74183	Magnetic resonance (eg, proton) imaging, abdomen; without contrast material(s), followed by with contrast material(s) and further sequences
75553	Cardiac magnetic resonance imaging for morphology; with contrast material
75561	Cardiac magnetic resonance imaging for morphology and function without contrast material(s), followed by contrast material(s) and further sequences
75562	Cardiac magnetic resonance imaging for morphology and function without contrast material(s), followed by contrast material(s) and further sequences; with flow/velocity quantification
75563	Cardiac magnetic resonance imaging for morphology and function without contrast material(s), followed by contrast material(s) and further sequences; with stress imaging
75564	Cardiac magnetic resonance imaging for morphology and function without contrast material(s), followed by contrast material(s) and further sequences; with flow/velocity quantification and stress
77058	Magnetic resonance imaging, breast, without and/or with contrast material(s); unilateral
77059	Magnetic resonance imaging, breast, without and/or with contrast material(s); bilateral

Section 5
Medical Imaging

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation IV
Division of Medical Imaging Products

5 Medical Imaging Section
Review Comments

Date:	August 11, 2017
Reviewer:	Anthony Fotenos, MD, PhD
Team Leader:	Ira Krefting, MD Adebayo Laniyonu, PhD
Division Director:	Louis Marzella, MD, PhD Alex Gorovets, MD
Product Names:	Gadolinium-Based Contrast Agents
Subject:	Gadolinium Retention and Associated Adverse Events
Application Type/Number:	Multiple (See Appendix A of the Pharmacovigilance Section)
Applicant/Sponsor:	Multiple (See Appendix A of the Pharmacovigilance Section)
TSI #:	001427

5.1 Purpose of Medical Imaging Review Comments

The purpose of these medical imaging review comments is to summarize our understanding of the scientific data upon which we have relied to approach the issue of risk associated with gadolinium retention in patients with normal renal function. Although regulatory actions may differ among different regulatory agencies, we believe there is consensus about interpretation of available data. We have reviewed clinical and non-clinical data related to gadolinium retention in a variety of organs and tissues including the brain. The main elements of relevant human data review have been presented in sections 2 through 4 above. Here we emphasize the potentially important differences in retention among various tissues and possible differences among the GBCAs within a class.

5.2 Summary of European Medicines Agency Communications

We have followed the recent European deliberations on the topic of gadolinium retention in the brain with great interest and appreciation for their scientific vigor and depth and are aware of the recent actions by the European Medicines Agency (EMA). Specifically, on July 21, 2017, EMA publically announced its decision to restrict the use of some linear gadolinium agents and to suspend the marketing authorization of others (see **Table 1** and **Table 2** and link to additional information in **Appendix 6;** Table 1 summarizes FDA and EMA actions; Table 2 lists EMA recommendation for each of the currently marketed GBCAs**)**

It is important to point out that while our current and future regulatory actions, in relation to gadolinium retention, might differ from those of the EMA, our understanding is that such potential divergence does not reflect divergence in understanding of the available evidence and scientific data.

5.3 Summary of Scientific Consensus

Our current focus falls squarely on subacute/chronic toxicity, as opposed to acute toxicity, in patients with normal renal function. Unresolved questions include whether the risks of chronic pain and/or innate immune dys-homeostasis (particularly in skin), subtle neurological sequelae, reproductive toxicity, carcinogenesis, or other unanticipated adverse reactions are elevated as a consequence of gadolinium retention following GBCA administration. With respect to these questions, we believe that available scientific evidence obtained in the context of normal renal function, support many aspects of the consensus understanding outlined below. For a representative overview of some of the evidence underlying this understanding, we have summarized selected animal and human data on gadolinium retention by agent and tissue type across multiple studies in **Figure 1**. The figure is intended to support the bullet points below at-a-glance; however, readers interested in greater detail are referred to the granular discussion contained in the figure legend. For a more comprehensive review focused on clinical evidence, see the Pharmacovigilance Section.

- In controlled anatomical studies, skin and bone and most other sampled tissues retain gadolinium more than the brain (at least 10 to 100 times more; for example, **Figure 1D, E**).

- In controlled GBCA-comparison animal studies, linear GBCAs are generally retained more than macrocyclic GBCAs (roughly at least 5 to 15 times more in skin or bone, on

average, see **Figure 1A-E**). The degree of retention is complex, however, and depends on dose, dosing interval, the identity of GBCAs administered, timing of tissue sampling, and and identity of tissue sampled.

- The difference in retention between certain linear GBCAs appears to be more pronounced than the general difference in retention between linear and macrocyclic GBCAs, with the degree of difference being tissue dependent (for example, Omniscan-to-Multihance and Omniscan-to-Magnevist retention ratios, mostly in the skin, exceed Multihance-to-macrocyclic retention ratios; **Figure 1A, B, D**; also Robert 2016, McDonald 2017). We also note that in controlled GBCA-comparison studies, Omniscan is consistently the more retained GBCA. Multiple controlled GBCA-comparison studies in rats have also singled out Omniscan and to a lesser extent Optimark for inducing subacute/chronic gross and microscopic skin pathology (**Figure 1B, D**; also Cacheris 1990, Wible 2001, Runge 2005, Pietsch 2009b, Fretellier 2014; this is distinct from more subtle changes in immunological biomarkers, for example, in Do 2014). Whether this non-clinical observation has a clinical relevance in patients with normal renal function is unclear.

- Gadolinium that is retained more in the soluble than solid/radiocolloid state likely washes out over a period of months/years, meaning macrocyclic GBCAs (more than linear GBCAs) may approach background levels of gadolinium retention over this period, for example, in soft tissues such as skin and brain (Evans 1990; Pietsch 2009a, Birka 2015, Jost 2016, Lancelot 2016, Frenzel 2017). However, 100% washout of any GBCA, particularly from bone, is unlikely (see **Figure 1C, D**; also Darrah 2009, Birka 2015).

- Based on the limited safety evidence available to date, mostly dependent on investigations searching for incident subacute/chronic gross or unambiguous disease, no clinical consequences of gadolinium brain retention have been identified (see Pharmacovigilance and Epidemiology sections, McDonald 2017, Lohrke 2017).

Figure 1

Asterisk (*) indicates ≥ 1 animal with gross skin pathology

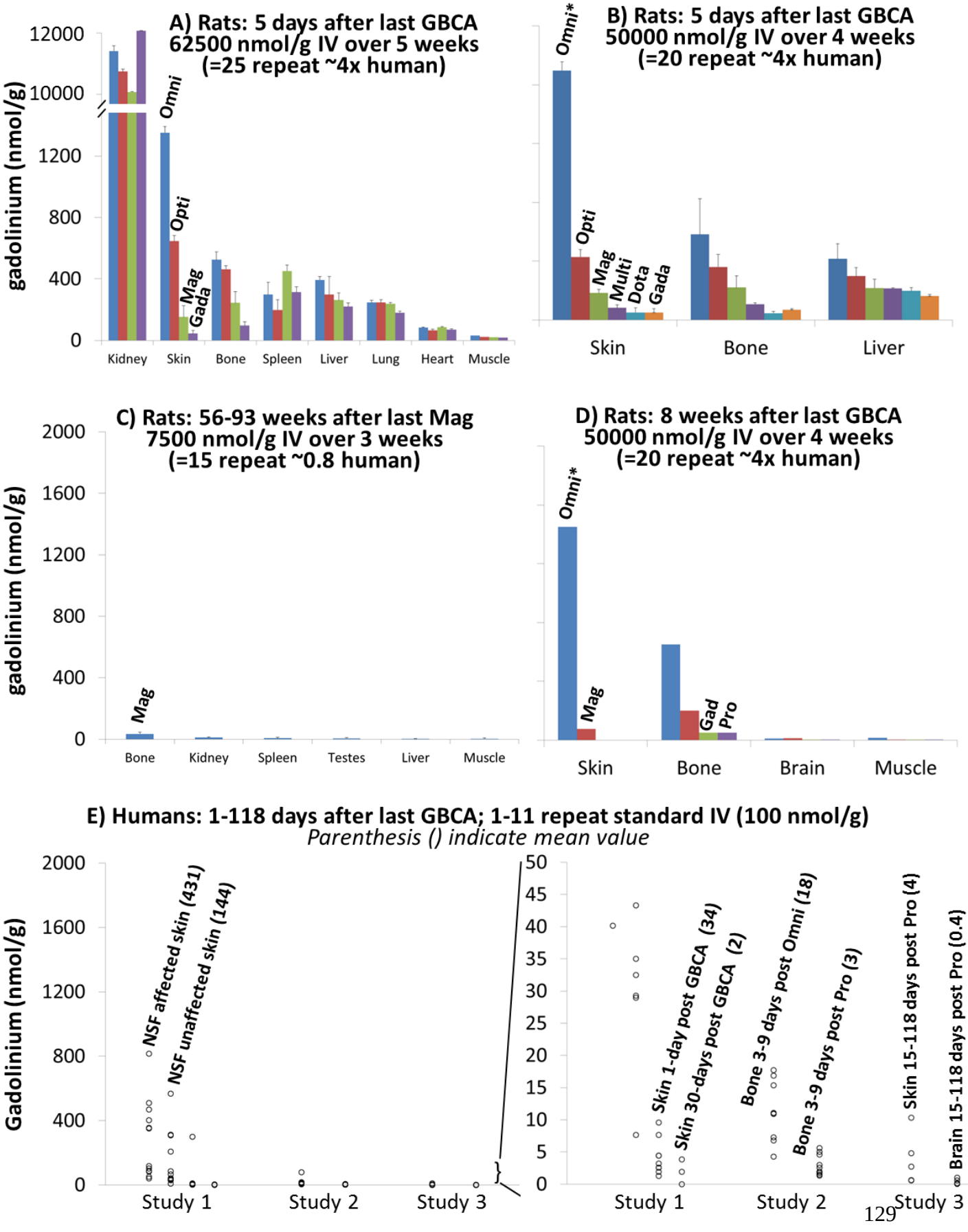

Fig 1. Summary of selected reports on total gadolinium retention quantified by spectrometry in the pharm/tox and clinical literature. The figures are drawn to facilitate visual comparison across studies, acknowledging that within-study comparisons are more reliable for precise quantitative evaluation given potential measurement calibration and methodological differences between studies. All studies occur in the context of normal renal function (except for Study 1-left in E). Bar height represents mean total gadolinium retention. Where shown, error bars represent ± standard deviation. Across the multiple studies depicted, the underlying spectrometry methods measure total gadolinium independent of species. Where reported in units of grams, a molecular weight of 158 was used to convert to moles.

Asterisks indicate reporting of grossly and microscopically observable skin pathology in one or more animals of the depicted group. Separate mechanistic investigation has demonstrated overlap between the subacute/chronic gadolinium-induced skin pathophysiology in these animals and gadolinium-induced NSF in humans [Pietsch 2009a, Todd 2016, Wagner 2016, Hamburg-Shields 2017], meaning animals with normal renal function can be used as a model to predict gadolinium-induced NSF.

A. Adapted from control group in zinc-depletion arm of Pietsch 2009c (Bayer KM06278/A40160; n=6/group).

B. Adapted from Sieber 2008 (Bayer KM06350/KM07031/A40180.1; n=6/group).

Comparing A and B, we note general consistency in the variation of gadolinium retention as a function of tissue type and GBCA (though B includes a more comprehensive survey of GBCAs).

C. Adapted from Steger-Hartmann 2010 (depicted values represent mean of estimates obtained from publication figure 2, based on sampling from one animal per time point obtained between 56 and 93 weeks post Magnevist administration).

Comparing A and C, we note the prominent difference between relative renal retention suggesting that gadolinium washes out from the kidney over a period of weeks/years following repeated GBCA administration.

D. Adapted from Lohrke 2017 (n=10/group; values estimated from publication figure 6, omitting error bars). Note that brain sampling was omitted from many earlier quantitative retention studies based on long-established patterns of relative distribution throughout the body (for example, Tweedle 1995).

E. Each dot represents one human subject. The same figure is shown zoomed out on the left for comparison to A-D and zoomed in on the right for internal evaluation.

Study 1 (total and last dose and identity of GBCA unspecified and combining separate studies labeled separately on the left and right from the same author). Left: Adapted from Christensen 2011 (publication table 2; in this prospective study of 13 patients with renal

failure and biopsy-confirmed NSF, mostly a single skin biopsy was obtained from an individually tailored area of affected skin and unaffected skin). Right: Christensen 2009 (values estimated from abstract figure 1; in this prospective study, 10 patients consented to skin biopsy 24 hours after GBCA administration; three followed-up for skin biopsy at 30 days; the outlier visible in the third-from-left group in the zoomed-out view was reported to have received "two consecutive contrast MRIs," suggesting longer spacing of repeated MRIs across multiple weeks or months may be protective; see also Pietsch 2011).

Acknowledging high inter-individual variability, Study 1 demonstrates that gadolinium skin retention in the tens to hundreds of nmol/g range can be associated with affected NSF skin lesions, is greater in magnitude than for NSF unaffected skin, and is much greater than for 9 of 10 normal-renal patients (< 10 nmol/g range), even 24 hours after GBCA administration.

Study 2. Adapted from White 2016 (a prospective, controlled study in which 19 patients were randomized to receive a single dose of Omniscan or Prohance 3-8 days prior to hip arthroplasty for bone measurements; depicted values represent first of reported repeated measurements from publication table 5). Study 2 demonstrates days-long bone retention for both agents, approximately 6-times more for Omniscan compared to Prohance.

Study 3. Adapted from Murata 2016 (brain values represent mean of all reported regional measurements in publication table 2 for the five patients reported to have received between 1 and 11 doses of Prohance 15 to 118 days prior to autopsy). This study demonstrates consistently lower brain retention between clinical and nonclinical investigations. Omni=Omniscan (gadodiamide); Opti=Optimark (gadoversetamide); Mag=Magnevist (gadopentetic acid); Multihance (gadobenic acid); Gad=Gadovist (gadobutrol); Dotarem (gadoteric acid); Pro=Prohance (gadoteridol).

5.4 Conclusion

Going forward, we favor an evidence-based approach focused on new safety communication and labeling, pharmacovigilance, and coordinated research oversight. We find:

- that gadolinium is retained more in most other sampled tissues compared to brain;
- that gadolinium is retained more and longer for certain GBCAs compared to others;
- that, for all or almost all of the millions of patients with normal renal function who have benefitted diagnostically from these drugs since 1988, the range of post-GBCA gadolinium retention probably falls below exposure thresholds that could induce grossly observable subacute/chronic adverse reactions.

We at the same time acknowledge:

- uncertainty around any retention threshold for potentially more subtle or rare reactions in any organ by which to make optimally informed decisions;

- need for better coordinated investigation of patients with unexplained post-GBCA pain and other symptoms to evaluate a causal link;

- need for better designed investigations in all patients with post-GBCA gadolinium retention, including epidemiologic and mechanistic studies based on more sensitive safety endpoints.

Of course, we remain open-minded and appreciative of the feedback from the September 8 advisory committee meeting.

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5.6 Appendix

Public documents related to July 21 recommendations on restrictions of linear gadolinium agents by the European Medicines Agency.

On July 21, 2017, EMA publically announced its decision to restrict the use of some linear gadolinium agents and to suspend the marketing authorization of others. The July 21, 2017 announcement states: "EMA's scientific review of gadolinium deposition in brain and other tissues is now concluded. The final recommendations will be sent to the European Commission, which will issue a final legally binding decision applicable in all EU Member States."

Table 1: Summary of recent EMA and FDA regulatory actions

Date	Action	Summary
7.27.2015	FDA DSC	FDA evaluating the risk of brain deposits with repeated use of GBCAs for MRI
3.10.2017	EMA PRAC Recommendation	PRAC recommends suspension for some linear agents, and use restrictions
5.22.2017	FDA DSC	FDA identifies no harmful effects to date with brain retention of GBCAs for MRI; review to continue
7.7.2017	EMA PRAC Final Recommendation	PRAC appeal reaffirms recommendation for suspension for some linear agents, and use restrictions
7.21.2017	EMA CHMP Opinion	CHMP confirms PRAC recommendations to restrict the use of some linear GBCAs and suspend the authorizations of others
9.8.2017	FDA AC meeting	***Pending***

DSC=Drug Safety Communication; PRAC=Pharmacovigilance Risk Assessment Committee; CHMP=Committee for Medicinal Products for Human Use

Table 2: Summary of EMA recommendations announced on July 21, 2017

Product	Type (formulation)	Recommendation
Artirem[1] / Dotarem (gadoteric acid)	macrocyclic (i.v.)	maintain
Artirem / Dotarem (gadoteric acid)	macrocyclic (intra-articular[2])	maintain
Gadovist[3] (gadobutrol)	macrocyclic (i.v.)	maintain
Magnevist (gadopentetic acid)	linear (intra-articular)	maintain
Magnevist (gadopentetic acid)	linear (i.v.)	suspend
Multihance (gadobenic acid)	linear (i.v.)	restrict use to liver scans
Omniscan (gadodiamide)	linear (i.v.)	suspend
Optimark (gadoversetamide)	linear (i.v.)	suspend
Primovist[4] (gadoxetic acid)	linear (i.v.)	maintain
Prohance (gadoteridol)	macrocyclic (i.v.)	maintain

[1]Gadoteric acid is marketed exclusively under the tradename Dotarem in the United States.
[2]Intra-articular formulations are not marketed as separate formulations in the United States.
[3]Gadobutrol is marketed under the tradename Gadavist (vs. Gadovist) in the United States.
[4]Gadoxetic acid is marketed under the tradename Eovist in the United States.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Gadolinium-containing_contrast_agents/human_referral_prac_000056.jsp, accessed August 2, 2017