Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Medical Imaging Drugs Advisory Committee
September 8, 2017 Meeting

Location: FDA White Oak Campus, 10903 New Hampshire Avenue, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland

Topic: The committee discussed the potential risk of gadolinium retention in the brain and other body organs in patients receiving gadolinium-based contrast agents for magnetic resonance clinical imaging procedures.

These summary minutes for the September 8, 2017, meeting of the Medical Imaging Drugs Advisory Committee of the Food and Drug Administration were approved on September 27, 2017.

I certify that I attended the September 8, 2017, meeting of the Medical Imaging Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	/s/
Jennifer Shepherd, RPh	Peter Herscovitch, MD, FACP, FRCPC, FSNMMI
Designated Federal Officer, MIDAC	Acting Chairperson, MIDAC

Summary Minutes
Medical Imaging Drugs Advisory Committee Meeting
September 8, 2017

The following is the final report of the Medical Imaging Drugs Advisory Committee meeting held on September 8, 2017. A verbatim transcript will be available in approximately four weeks, sent to the Division of Medical Imaging Products and posted on the FDA website at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/ucm553470.htm

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information Office.

The Medical Imaging Drugs Advisory Committee (MIDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on September 8, 2017 at the FDA White Oak Campus, 10903 New Hampshire Avenue, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA, Bayer Healthcare Pharmaceuticals, Inc., Bracco Diagnostics, Inc., GE Healthcare, and Guerbet LLC. The meeting was called to order by Peter Herscovitch, MD, FACP, FRCPC, FSNMMI (Acting Chairperson). The conflict of interest statement was read into the record by Jennifer Shepherd, RPh (Designated Federal Officer). There were approximately 230 people in attendance. There were sixteen (16) Open Public Hearing speakers.

Issue:
The committee discussed the potential risk of gadolinium retention in the brain and other body organs in patients receiving gadolinium-based contrast agents for magnetic resonance clinical imaging procedures.

Attendance:
MIDAC Members Present (Voting): Kimberly E. Applegate, MD, MS, FACR; Wesley E. Bolch, PhD *(via phone)*; Nicholas Dainiak, MD, FACP; Peter Herscovitch, MD, FACP, FRCPC, FSNMMI (Acting Chairperson); Paula M. Jacobs, PhD; Alicia Y. Toledano, ScD

MIDAC Members Not Present (Voting): David B. Hackney, MD; Andrew D. Hardie, MD; Raymond Y. Kwong, MD, MPH; Henry D. Royal, MD (Chairperson)

MIDAC Members Present (Non-Voting): Richard A. Frank, MD, PhD (Industry Representative)

Temporary Members (Voting): Jeffrey Brent, MD, PhD; Brenda Bryant (Patient Representative); Karen L. Furie, MD, MPH; Sean Hennessy, PharmD, PhD; Sonia Hernandez-Diaz, MD, MPH; Lawrence L. Latour, PhD; Evan Siegelman, MD; William K. Vaughan (Acting Consumer Representative); Michael H. Weisman, MD *(via phone)*

Guest Speaker: Brent Wagner, MD

FDA Participants (Non-Voting): Karen Bleich, MD; Anthony Fotenos, MD, PhD; S. Christopher Jones, PharmD, MS, MPH; Libero (Louis) Marzella, MD, PhD; Simone Pinheiro, ScD, MSc, ALM

Designated Federal Officer (Non-Voting): Jennifer Shepherd, RPh

Open Public Hearing Speakers: Matthew Davenport, MD (American College of Radiology); Sharon Williams and Hubbs Grimm (Lighthouse Project); Robert Lenkinski, PhD; Sammy Almashat, MD, MPH (Public Citizen's Health Research Group); Judy Gerrity; Elizabeth Morris, MD; Lori Combs; Scott Reeder, MD, PhD (International Society for Magnetic Resonance in Medicine); Emanuel Kanal, MD; Ann Wingren; John Prybylski, PharmD (University of North Carolina); David Enterline, MD; Sue Bunning (Medical Imaging & Technology Alliance); Curtis Ulleseit (Detox Research); Todd Walburg on behalf of Gena and Chuck Norris, Richard Semelka, MD

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Peter Herscovitch, MD, FACP, FRCPC, FSNMMI** Acting Chairperson, MIDAC
Conflict of Interest Statement	**Jennifer Shepherd, RPh** Designated Federal Officer, MIDAC
FDA Introductory Remarks Gadolinium Retention following Gadolinium Based Contrast Agents MRIs: Brain and Other Organs	**Ira Krefting, MD** Deputy Director for Safety Division of Medical Imaging Products (DMIP) Office of Drug Evaluation-IV (ODE-IV) Office of New Drugs (OND), CDER, FDA

FDA PRESENTATION

Regulatory Safety Actions & Risk Mitigation	**Michele Fedowitz, MD** Associate Director for Labeling DMIP, ODE IV, OND, CDER, FDA

GUEST SPEAKER PRESENTATION

The pathophysiology and retention of gadolinium	**Brent Wagner, MD** Associate Professor with Tenure Director, Clinical Nephrology Training Program University of Texas Health Science Center at San Antonio

INDUSTRY PRESENTATIONS	Bayer HealthCare Pharmaceuticals, Inc.
Presence of Gadolinium (Gd) in the brain and body	**Thomas Balzer, MD** Vice President, Medical & Clinical Affairs Radiology Radiology R&D Bayer HealthCare Pharmaceuticals, Inc.
INDUSTRY PRESENTATIONS	Bracco Diagnostics Inc.
Gadolinium Retention in Brain and Body Tissues: Safety Considerations	**Alberto Spinazzi, MD** Sr. Vice President, Global Medical and Regulatory Affairs Bracco Diagnostics Inc.
INDUSTRY PRESENTATIONS (CONT.)	GE Healthcare
Omniscan (gadodiamide) a gadolinium-based contrast agent (GBCA) for diagnostic magnetic resonance imaging (MRI)	
Introduction	**Mark Hibberd, MD, PhD** Global Head of Medical Services & Chief Medical Officer, Life Sciences GE Healthcare
Safety of Omniscan	**Robert McDonald, MD, PhD** Senior Associate Consultant Division of Neuroradiology Mayo Clinic, Rochester, Minnesota
Risk Mitigation and Conclusion	**Mark Hibberd, MD, PhD**
INDUSTRY PRESENTATIONS	Guerbet
An Overview on Gadolinum Retention after GBCA Use	**Pierre Desché, MD** VP of Development, Medical and Regulatory Affairs Guerbet Group
Clarifying Questions to Presenters	
BREAK	
FDA PRESENTATIONS	
Adverse Events with Gadolinium	**David Croteau, MD, FRCPC**

Retention after Gadolinium-Based Contrast Agent Exposure: FAERS and Medical Literature Review	Medical Officer, Division of Pharmacovigilance I Office of Pharmacovigilance and Epidemiology (OPE) Office of Surveillance and Epidemiology (OSE) CDER, FDA

FDA PRESENTATIONS (CONT.)

Epidemiologic Studies on the Safety of Gadolinium-Based Contrast Agents	**Steve Bird, PhD, PharmD** Team Lead, Division of Epidemiology I OPE, OSE, CDER, FDA
Gadolinium-Based Contrast Agents US Sales Data 2006-2016	**Patty Greene, PharmD** Drug Utilization Analyst Division of Epidemiology II OPE, OSE, CDER, FDA

FDA PRESENTATIONS (CONT.)

Gadolinium Retention: A Summary	**Karen Bleich, MD** Medical Officer DMIP, ODE IV, OND, CDER, FDA
Toward More Sensitive Endpoints in Evaluating the Safety of Post-GBCA Gadolinium Retention	**Anthony Fotenos, MD, PhD** Lead Medical Officer DMIP, ODE IV, OND, CDER, FDA

Clarifying Questions for Presenters

LUNCH

OPEN PUBLIC HEARING

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. In the evaluation of risk of gadolinium-based contrast agents (GBCAs) in 2009, FDA considered: the thermodynamic stability of the drugs; the in vitro kinetics of release of free gadolinium; histopathologic evidence of toxicity in juvenile and adult animals; clinical evidence of toxicity based on reports of systemic fibrosis; susceptible patient populations (i.e. those with moderate to severe renal insufficiency). GBCAs were risk-

stratified based on the totality of this evidence. Risk mitigation steps included warnings and contraindications in the prescribing information, public communications, increased pharmacovigilance and reporting for systemic fibrosis.

DISCUSSION: Given the new concerns raised by gadolinium retention in patients with normal renal function, please discuss how FDA should weigh this new finding in relation to the known risks.

In the absence of scientific criteria (e.g. toxicological or clinical thresholds) to inform risk assessment, which factors should FDA consider?

Include in your discussion the evidence of differential retention, establishment of empirically defined retention thresholds (e.g. retention with linear vs. macrocyclic agents), retention levels in specific organs (e.g. CNS, skin, bone), molecular forms of gadolinium (free vs. chelated vs. bound to biologic macromolecules).

Committee Discussion:
Many committee members stated that although gadolinium (Gd) does appear to persist in the brain and other tissues longer than originally thought, there is not enough evidence to assess the risks of gadolinium retention or to establish risk stratification across products. Several committee members commented on the need for more research to determine patient factors that may predispose patients to increased risk of Gd retention. Please see the transcript for details of the Committee discussion.

2. **DISCUSSION:** Based on FDA Adverse Event Reporting System (FAERS) and literature reports, is there evidence of a causal relationship between symptoms and signs in patients with normal renal function and gadolinium retention?

   Please consider in your discussion the shortcomings of FAERS and other uncontrolled data sources. Please discuss whether the potential risks of gadolinium retention might be greater in patient subgroups (e.g. pregnant women, pediatric patients, patients with inflammatory disorders in CNS and other organs, patients with chronic conditions requiring multiple exposures to GBCAs).

   Committee Discussion:
   The majority of the committee members stated that, based on FDA Adverse Event Reporting System (FAERS) and literature reports, there is insufficient evidence of a causal relationship between symptoms and signs in patients with normal renal function and gadolinium retention. Several committee members stated that even though there is not enough data available, special attention should be given to specific patient populations (e.g., pediatric patients, pregnant patients, etc.). Several committee members also agreed that the absence of evidence does not prove that there is no risk. Please see the transcript for details of the Committee discussion.

3. There are gaps in our understanding of gadolinium retention including toxicological thresholds, potential mechanism of toxicity, potential clinical and subclinical manifestation of toxicity in CNS and other organs.

   DISCUSSION: Please discuss the types of preclinical studies (e.g. comparative toxicokinetic studies of levels of gadolinium retention and functional and pathologic correlates in the CNS of juvenile and adult animals). Please discuss what clinical studies should be performed to better understand any potential safety risk associated with gadolinium retention; include in your discussion prospective studies such as registries, epidemiologic surveys, parallel arm studies of neurologic function, and retrospective studies using existing databases.

   Committee Discussion:
   While several different study design choices were suggested by the group, the consensus was that trials require more standardization and control, the current study outcomes/endpoints pose a challenge and need to be better defined, and that prospective population cohort studies would be beneficial. One member mentioned that randomized, controlled trials would not be feasible, and another committee member stated that denying patients gadolinium as a study control may put them at risk of impaired disease detection and would be unethical. Some members showed interest in animal studies, while others disagreed stating that efforts should be focused on patients with gadolinium exposure. The idea of registries was also introduced; however, other members stated that the necessary long-term patient participation would be difficult to achieve and the need for large number of patients may also pose challenges. Please see the transcript for details of the Committee discussion.

4. **VOTE:** Our plan for addressing the potential consequences of gadolinium retention is to revise the prescribing information for GBCAs as a class to include: a warning for retention for all GBCAs, with greater retention of all or some of the linear GBCAs compared to the macrocyclics in certain organs including the brain; recommended risk minimization steps for certain patient populations.

   Do you agree with this plan? Please summarize the reasons for your vote.

   YES 13 NO 1 ABSTAIN 1

   Committee Discussion:
   The majority of the committee members voted that they agreed with the FDA plan for addressing the potential consequences of gadolinium retention and revising the prescribing information for GBCAs as a class to include: a warning for retention for all GBCAs, with greater retention of all or some of the linear GBCAs compared to the macrocyclic GBCAs in certain organs including the brain; recommended risk minimization steps for specific patient populations. Several members who voted "Yes"

stated that while there is not enough data to establish risk, precautionary action is appropriate. The committee member who voted "No" commented that the risk minimization information should not be limited to providers, but should also be made available directly to patients. Two committee members who voted "Yes" commented that FDA should consider a regulatory action similar to the suspension of marketing authorization for certain GBCAs taken by a non-US public health agency. Please see the transcript for details of the Committee discussion.

5. **VOTE:** A number of clinical and preclinical studies are ongoing and we might request that manufacturers conduct additional studies that will inform our decisions about the need for further regulatory actions including withdrawal of approval and restriction of indicated populations.

   Do you agree with this plan? Please summarize the reasons for your vote.

   YES 15 NO 0 ABSTAIN 0

   Committee Discussion:
   The committee voted unanimously that they agreed with the plan that, to complement the clinical and preclinical studies ongoing, FDA might request that manufacturers conduct additional studies that will inform Agency decisions about the need for further regulatory actions including withdrawal of approval and restriction of indicated populations. Many committee members stated that more data are needed. Please see the transcript for details of the Committee discussion.

The meeting was adjourned at approximately 4:10 p.m.