U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue

This is an update to the FDA Drug Safety Communication: FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI) issued on July 27, 2015.

Safety Announcement

[5-22-2017] A U.S. Food and Drug Administration (FDA) review to date has not identified adverse health effects from gadolinium retained in the brain after the use of gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI). All GBCAs may be associated with some gadolinium retention in the brain and other body tissues. However, because we identified no evidence to date that gadolinium retention in the brain from any of the GBCAs, including GBCAs associated with higher retention of gadolinium, is harmful, restricting GBCA use is not warranted at this time. We will continue to assess the safety of GBCAs and plan to have a public meeting to discuss this issue in the future.

Our recommendations for health care professionals and patients remain unchanged from July 2015 when we informed the public that we were investigating this potential risk with GBCAs. As is appropriate when considering the use of any medical imaging agent, **health care professionals** should limit GBCA use to circumstances in which additional information provided by the contrast agent is necessary, and assess the necessity of repetitive MRIs with GBCAs. **Patients, parents, and caregivers** should talk to their health care professionals if they have any questions or concerns about the use of GBCAs with MRIs. Retention of gadolinium affects only GBCAs, and does not apply to other types of scanning agents used for other imaging procedures, such as those that are iodine-based or radioisotopes.

GBCAs contain gadolinium, a type of heavy metal, that is linked to a carrier molecule. MRIs are a way to scan the body for problems such as cancer, infections, or bleeding. GBCAs are injected into a vein to enhance the quality of the MRI images of internal organs, blood vessels, and tissues, which helps health care professionals diagnose medical conditions. There are two types of GBCAs based on their chemical structures, *linear* GBCAs and *macrocyclic* GBCAs.

We evaluated scientific publications[1-17] and adverse event reports submitted to FDA. Some human and animal studies looked at GBCA use over periods longer than a year.

These publications and reports show that gadolinium is retained in organs such as the brain, bones, and skin. The publications show that *linear* GBCAs retain more gadolinium in the brain than *macrocyclic* GBCAs. However, our review did not identify adverse health effects related to this brain retention.

To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF) that occurs in a small subgroup of patients with pre-existing kidney failure. NSF is a painful skin disease characterized by thickening of the skin, which can involve the joints and cause significant limitation of motion within weeks to months. Recent publications report cases of reactions involving thickening and hardening of the skin and other tissues in patients with normal kidney function who received GBCAs and did not have NSF; some of these patients also had evidence of gadolinium retention.[3, 12, 16] We are continuing to evaluate such reports to determine if these fibrotic reactions are an adverse health effect of retained gadolinium.

The manufacturer of OptiMARK (gadoversetamide), a linear GBCA, updated its label with information about gadolinium retention in various body organs such as the brain, skin, and other organs. We are reviewing the labels of other GBCAs to determine if changes are needed.

A recent review by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) also identified no adverse health effects with gadolinium retention in the brain, but that Committee recommended suspending the marketing authorization of certain *linear* GBCAs because they cause a greater retention of gadolinium in the brain compared to *macrocyclic* GBCAs. The Committee's recommendation is currently undergoing an appeal, which will be further reviewed by the PRAC and subsequently by the EMA's Committee for Medicinal Products for Human Use.[18]

We are continuing to assess the safety of GBCAs. FDA's National Center for Toxicological Research (NCTR) is conducting a study on brain retention of GBCAs in rats. Other research is also being conducted about how gadolinium is retained in the body. We will update the public when new information becomes available and we plan to have a public meeting to discuss this issue in the future.

We urge patients and health care professionals to report side effects involving GBCAs or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

FDA-Approved GBCAs

Brand name	**Generic name**	**Structure**
Ablavar	gadofosveset trisodium	linear
Dotarem	gadoterate meglumine	macrocyclic
Eovist	gadoxetate disodium	linear
Gadavist	gadobutrol	macrocyclic
Magnevist	gadopentetate dimeglumine	linear

MultiHance	gadobenate dimeglumine	linear
Omniscan	gadodiamide	linear
OptiMARK	gadoversetamide	linear
ProHance	gadoteridol	macrocyclic

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Related Information

Information on Gadolinium-Based Contrast Agents

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