FDA Drug Safety Communication: New warnings for using gadolinium-based contrast agents in patients with kidney dysfunction

12/2010 Update: The issues described below have been addressed in product labeling. Healthcare professionals and consumers can access the approval letters and latest prescribing information for these products:

- **Ablavar** (gadofosveset trisodium) (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&SearchTerm=ablavar&SearchType=BasicSearch)
- **Magnevist** (gadopentetate dimeglumine) (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&SearchTerm=Magnevist&SearchType=BasicSearch)
- **Multihance** (gadobenate dimeglumine) (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&SearchTerm=MultiHance&SearchType=BasicSearch)
- **Omniscan** (gadodiamide) (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&SearchTerm=Omniscan&SearchType=BasicSearch)
- **Optimark** (gadoversetamide) (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&SearchTerm=OptiMARK&SearchType=BasicSearch)
- **Prohance** (gadoteridol) (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&SearchTerm=ProHance&SearchType=BasicSearch)

Safety Announcement

Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary
Approved Gadolinium Based Contrast Agents

Safety Announcement

[09-09-2010] The U.S. Food and Drug Administration (FDA) is requiring changes in the drug label for gadolinium-based contrast agents (GBCAs) to minimize the risk of nephrogenic systemic fibrosis (NSF), a rare, but serious, condition associated with the use of GBCAs in certain patients with kidney dysfunction. GBCAs are intravenous drugs used in diagnostic imaging procedures to enhance the quality of magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA). (See **Approved Gadolinium-Based Contrast Agents** below).
These label changes are intended to help ensure these drugs are used appropriately, and that patients at risk for NSF who receive GBCAs are actively monitored for the development of NSF. Symptoms of NSF include scaling, hardening and tightening of the skin; red or dark patches on the skin; and stiffness. NSF can also cause fibrosis of internal organs which may lead to death. There is no effective treatment for NSF.

NSF has not been reported in patients with normal kidney function. Patients at greatest risk for developing NSF after receiving GBCAs are those with impaired elimination of the drug, including patients with acute kidney injury (AKI) or chronic, severe kidney disease (with a glomerular filtration rate or GFR < 30 mL/min/1.73m²). Higher than recommended doses or repeat doses of GBCAs also appear to increase the risk for NSF.

The revised labeling will enhance the safe use of GBCAs, by recommending that healthcare professionals:

- Not use three of the GBCA drugs--Magnevist, Omniscan, and Optimark-- in patients with AKI or with chronic, severe kidney disease. These three GBCA drugs are contraindicated in these patients.
- Screen patients prior to administration of a GBCA to identify those with AKI or chronic, severe, kidney disease. These patients appear to be at highest risk for NSF.
- Use the clinical history to screen patients for features of AKI or risk factors for chronically reduced kidney function.
  - Features of AKI consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury, or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess kidney function in the setting of AKI.
  - For patients at risk for chronically reduced kidney function (such as patients over age 60 years, patients with high blood pressure, or patients with diabetes), estimate the kidney function (GFR) through laboratory testing.
- Avoid use of GBCAs in patients suspected or known to have impaired drug elimination unless the need for the diagnostic information is essential and not available with non-contrasted MRI or other alternative imaging modalities.
- Monitor for signs and symptoms of NSF after a GBCA is administered to a patient suspected or known to have impaired elimination of the drug.
- Do not repeat administration of any GBCA during a single imaging session.

In 2006, FDA alerted the public about cases of NSF reported in patients who received GBCAs. In 2007, the agency required the addition of a boxed warning about the risk of NSF to the labeling of GBCA drugs.

Additional Information for Patients

- Understand that nephrogenic systemic fibrosis (NSF) is a rare, but serious side effect associated with the use of GBCAs among certain patients with kidney disease.
- NSF has not been reported in patients with normal kidney function.
- If you have kidney disease, discuss the necessity of a GBCA with your healthcare professional if a contrast MRI or MRA has been ordered.
- If you have kidney disease, contact your healthcare professional right away if you experience any of the following after receiving a GBCA: burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness.
- Report any side effects with these drugs to FDA’s MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Additional Information for Healthcare Professionals

- Record the specific GBCA and the dose administered to a patient.
- When administering a GBCA, do not exceed the recommended dose. Prior to any re-administration, allow
sufficient time for elimination of the GBCA from the body, e.g., multiple half-lives, as described in the Pharmacokinetics section of the labeling. GBCA elimination half-lives are prolonged in patients with renal impairment; for a GBCA that involves significant hepato-biliary elimination, liver dysfunction may also prolong elimination time.

- For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination from the body. The usefulness of hemodialysis in the prevention of NSF is unknown.

- Advise patients with kidney disease to contact a healthcare professional if any of the following symptoms occurs after receiving a GBCA: burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness.

- Report any adverse events with GBCAs to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

**Data Summary**

The decision to require these new recommendations in the drug labeling was based on FDA's review of the safety of GBCAs. Based on the Agency's review, it was determined that Magnevist, Omniscan, and Optimark are associated with a greater risk of developing NSF than other GBCAs in certain patients with kidney disease. As a result, use of these particular agents is contraindicated in patients with acute kidney injury or chronic, severe kidney disease. FDA has also determined that enhanced screening to identify patients at risk for NSF is necessary, and advises patients and healthcare professionals to report cases of NSF to FDA. Data suggest that NSF may follow the administration of any GBCA and the agency will continue to monitor post-marketing safety data to better characterize the risk of developing NSF following exposure to each GBCA. The safety of GBCAs was discussed at the December 8, 2009 Joint Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committee Meeting (http://wayback.archive-it.org/7993/20161023215403/http://www.fda.gov/AdvisoryCommittees/Committees-MeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm196216.htm) (the link contains the presentations given at the Advisory Committee meeting).

**Approved Gadolinium Based Contrast Agents**

- Ablavar (gadofosveset trisodium)
- Eovist (gadoxetate disodium)
- Magnevist (gadopentetate dimeglumine)
- Multihance (gadobenate dimeglumine)
- Omniscan (gadodiamide)
- Optimark (gadoversetamide injection)
- Prohance (gadoteridol)

**Related Information**

- Information on Gadolinium-Based Contrast Agents (/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142882.htm)
1-800-FDA-0178 Fax

**Report a Serious Problem**
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Mail to: MedWatch 5600 Fishers Lane
Rockville, MD 20857