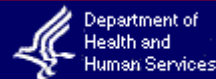


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Information for Healthcare Professionals

Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging (marketed as Magnevist, MultiHance, Omniscan, OptiMARK, ProHance)

FDA ALERT [6/2006, updated 12/2006 and 5/23/2007]: This updated Alert highlights FDA's request for addition of a boxed warning and new warnings about risk of nephrogenic systemic fibrosis (NSF) to the full prescribing information for all gadolinium-based contrast agents (GBCAs) (Magnevist, MultiHance, Omniscan, OptiMARK, ProHance). This new labeling highlights and describes the risk for NSF following exposure to a GBCA in patients with acute or chronic severe renal insufficiency (a glomerular filtration rate <30 mL/min/1.73m²) and patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the peri-operative liver transplantation period. In these patients, avoid the use of a GBCA unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging. NSF may result in fatal or debilitating systemic fibrosis. Requested changes to GBCA product labeling are summarized below.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

To report any serious adverse events associated with the use of this drug, please contact the FDA MedWatch program using the contact information at the bottom of this document.

FDA has requested manufacturers of all gadolinium-based contrast agents (GBCAs) to add a new Boxed Warning and new Warnings about Nephrogenic Systemic Fibrosis (NSF).

A new Boxed Warning and new Warnings section describe NSF, populations at risk for NSF, and advise on screening procedures, dosing and other considerations:

Boxed Warning:

- Exposure to GBCAs increases the risk for NSF in patients with:
 - acute or chronic severe renal insufficiency (glomerular filtration rate <30)

- mL/min/1.73m²), or
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.
- NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs.
- Avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI).
- Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.
- When administering a GBCA, do not exceed the dose recommended in product labeling. Allow sufficient time for elimination of the GBCA prior to any readministration.

Additional New Warnings:

- Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA.
- For patients receiving hemodialysis, healthcare professionals may consider prompt hemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if hemodialysis prevents NSF.
- Determine the renal function of patients by obtaining a medical history or conducting laboratory tests that measure renal function prior to using a GBCA.
- The risk, if any, for developing NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.
- Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was Omniscan, followed by Magnevist and OptiMARK. NSF has also developed following the sequential administration of Omniscan and MultiHance and Omniscan and ProHance. The distribution of the number of reports for the individual GBCAs may relate to multiple factors, including more limited use of some GBCAs, under-reporting of NSF, characteristics of the agent and a lack of patients' complete GBCA exposure history.

Recommendations and Considerations for Healthcare Professionals:

- Become familiar with the patient populations who are at known risk for NSF. To date, NSF has only been identified in patients with:
 - acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m²);
 - acute renal dysfunction due to the hepato-renal syndrome or in the perioperative liver transplantation period.

- Avoid using a GBCA in patients with known risks for developing NSF unless the diagnostic information is essential and can not be obtained with non-contrast enhanced MRI or other diagnostic procedures.
- Prior to administering a GBCA, evaluate patients for renal dysfunction by assessing their renal function, either by obtaining a medical history or conducting laboratory tests that measure renal function.
- When administering a GBCA, do not exceed the recommended GBCA dose in product labeling and allow a sufficient period of time for elimination of the agent from the body prior to any GBCA readministration. The elimination characteristics of each GBCA are described in the product label for each GBCA.
- For patients receiving hemodialysis, consider prompt hemodialysis after administration of a GBCA. Published data indicate that hemodialysis enhances GABA elimination. From the first to the third hemodialysis session, reported average GBCA clearance rates were 78%, 96%, and 99%, respectively.¹ Whether hemodialysis prevents NSF is unknown.
- Report possible cases of NSF to the FDA through the FDA's MedWatch program (see reporting information at the bottom of this page).

Information for the patient:

Physicians who are considering a GBCA for use in a patient who is at risk for NSF should discuss the following with the patient:

- The possibility of developing NSF, a debilitating and potentially fatal disease that involves the skin, muscle and internal organs.
- The signs and symptoms of NSF, which include:
 - *For the skin*—burning or itching, reddened or darkened patches; and/or skin swelling, hardening and/or tightening
 - *For the eyes*—yellow raised spots on the whites of the eyes
 - *For the bones, joints and muscles*—joint stiffness; limited range of motion in the arms, hands, legs, or feet; pain deep in the hip bone or ribs; and/or muscle weakness
- If the patient is receiving hemodialysis: Prompt hemodialysis immediately after administering a GBCA hastens its elimination. However, whether hemodialysis prevents or reduces the risk of NSF is unknown.
- After receiving a GBCA, those patients known to be at risk for NSF require clinical follow-up and long term monitoring for the disease.

Background Information and Data

First identified in 1997, NSF has been reported only in patients with acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m²) or patients with renal dysfunction

due to the hepato-renal syndrome or in the perioperative liver transplantation period. Patients with this condition develop fibrosis of the skin and connective tissues throughout their body. The skin thickening may inhibit flexion and extension of joints resulting in contractures. In addition, patients may develop widespread fibrosis of other organs. A skin biopsy is necessary to confirm the diagnosis. The condition may be debilitating or cause death. Its cause is unknown and there is no consistently successful treatment.

Five GBCAs (Magnevist, MultiHance, Omniscan, OptiMARK, and ProHance) are approved in the U.S. for magnetic resonance imaging (MRI). The GBCAs are sometimes used for MRA (magnetic resonance angiography) although none are FDA-approved for MRA. The administered dose of the contrast with magnetic resonance angiography (MRA) may be higher (up to three times) than the approved dose for MRI. NSF has been reported following administration of all five FDA approved gadolinium-based contrast agents (Magnevist, MultiHance, Omniscan, OptiMARK, and ProHance). However, some adverse event reports of NSF do not include complete information on patients' GBCA exposure history. Also, reports indicate that some patients received more than one GBCA prior to a NSF diagnosis. The lack of complete information of GBCA exposure, exposure to multiple GBCAs, along with similarities among all these contrast agents, make it impossible at present to definitively determine whether the extent of risks for developing NSF are the same for all the GBCAs.

In June 2006, FDA first notified healthcare professionals and the public about the risk of NSF following exposure to GBCAs after receiving reports of 25 patients with NSF from the Danish Health Authority. FDA issued additional information to healthcare professionals and the public in December 2006.

FDA review of spontaneously submitted post-marketing reports, sponsor-supplied information and the published literature identifies the following:

- FDA has received reports of patients who developed NSF after exposure to Magnevist, MultiHance, Omniscan, OptiMARK, and ProHance, unspecified GBCA, and multiple GBCAs (following multiple GBCA enhanced MRI scans).
- Among the reports that included renal status information, all patients had acute or chronic severe renal insufficiency, renal dysfunction due to the hepato-renal syndrome or renal dysfunction in the perioperative liver transplantation period. The vast majority of patients were receiving hemodialysis.
- To date, there has not been a report of NSF in a patient with normal renal function or mild to moderate renal insufficiency following GBCA exposure.
- The reported time between receiving a GBCA and subsequent diagnosis of NSF diagnosis is highly variable. Reported times range between days to many months.
- FDA has received reports of patients who died from complications related to NSF.

FDA has requested the manufacturers of the GBCAs to revise the product labels as soon as possible to include a new boxed warning and new Warnings section that describes the risk of NSF.

References

¹ Okada S et al. Safety of gadolinium contrast agent in hemodialysis patients. *Acta Radiol* 2001; 42(3): 399-341.

Report serious adverse events to
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<http://www.fda.gov/medwatch/report/hcp.htm>, by faxing (1-800-FDA-0178),
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Date created: May 23, 2007

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