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## Public Health Advisory

### Update on Magnetic Resonance Imaging (MRI) Contrast Agents Containing Gadolinium and Nephrogenic Fibrosing Dermopathy

The FDA has received additional information about a new disease, known as Nephrogenic Systemic Fibrosis or Nephrogenic Fibrosing Dermopathy (NSF/NFD), which may occur in patients with moderate to end-stage kidney disease after they have had a Magnetic Resonance Imaging (MRI) or Magnetic Resonance Angiography (MRA) scan with a gadolinium-based contrast agent. An MRI scan provides clear and detailed pictures of internal organs. An MRA test uses a gadolinium-based contrast agent to take detailed pictures of blood vessels. During some MRI scans and all MRA scans, a gadolinium-based contrast agent is injected into a patient's vein so blood vessels can be distinguished from other nearby tissues.

As of December 21, 2006, FDA has received reports of 90 patients with moderate to end-stage kidney disease who developed NSF/NFD after they had an MRI or MRA with a gadolinium-based contrast agent. Their NSF/NFD began from 2 days to 18 months after exposure to the contrast agent. Many, but not all of these patients, received a high dose of the contrast agent; some received only one dose. In light of these reports, FDA is notifying health care providers and patients of the following:

- **Patients with moderate to end-stage kidney disease** who receive an MRI or MRA with a gadolinium-based contrast agent may get NSF/NFD which is debilitating and may cause death.
- **Patients who believe they may have NSF/NFD should contact their doctor.** Patients who develop NSF/NFD have areas of tight, rigid skin and may have scarring of their body organs. The signs of NSF/NFD also include: burning, itching, swelling, hardening and tightening of the skin; red or dark patches on the skin; yellow spots on the whites of the eyes; stiffness in joints with trouble moving or straightening the arms, hands, legs, or feet; pain deep in the hip bones or ribs; and muscle weakness.
- **When a patient with moderate to end-stage kidney disease needs an imaging study, select imaging methods other than MRI or MRA with a gadolinium-based contrast agent** for the study whenever possible. If these patients must receive a gadolinium-based contrast agent, prompt dialysis following the MRI or MRA should be considered.
- **The FDA asks health care professionals and patients to report possible cases of**


**NSF/NFD** to the FDA through the MedWatch program by phone (1-800-FDA-1088) or by the Internet at <http://www.fda.gov/medwatch/index.html>.



Worldwide, about 215 patients with NSF/NFD have been reported. Of these reports, the medical histories of 75 of these patients were reviewed in detail, and all of the patients had received a gadolinium-based contrast agent for an MRI or MRA. Researchers have identified gadolinium in skin biopsies of patients with NSF/NFD.

Why NSF/NFD occurs in patients with moderate to end-stage kidney disease who receive gadolinium-based contrast agent is not yet known. The FDA is working with expert scientists to gather additional information about NSF/NFD.

Currently there are five FDA approved gadolinium-based contrast agents, Magnevist, MultiHance, Omniscan, OptiMARK, and ProHance. These contrast agents are FDA approved for use during an MRI scan, but not for use during an MRA scan. Although NSF/NFD has been reported for only 3 of the 5 gadolinium-based contrast agents, FDA believes that there is a potential for NSF/NFD to occur with the use of any of the approved gadolinium-based contrast agents.

You can find more details about NSF/NFD and gadolinium-based contrast agents in FDA's *[Information for Healthcare Professionals](#)*.

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FDA/Center for Drug Evaluation and Research



Information for Healthcare Professionals

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

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**FDA ALERT [6/2006, updated 12/2006]: Development of Serious, Sometimes Fatal Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy following exposure to Gadolinium-based Contrast Agents**

Since June 2006, FDA has been reviewing reports about patients who developed a new disease --Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD)-- after they received a gadolinium-based contrast agent during a magnetic resonance imaging scan (MRI) or magnetic resonance angiography (MRA). As of December 21, 2006, 90 individuals with NSF/NFD had been reported to FDA; all had moderate ( $GFR < 60$  mL/min/1.73m<sup>2</sup>) to end-stage renal disease ( $GFR < 15$  mL/min/1.73m<sup>2</sup>) prior to their MRI or MRA with a gadolinium-based contrast agent. Their clinical characteristics are described in more detail below. Physicians should carefully assess the need for gadolinium-based contrast agents in patients with moderate to end-stage renal disease when performing an MRI or MRA.

*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..*

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*To report any unexpected adverse or serious events associated with the use of this drug, please contact the FDA MedWatch program and complete a form on line at <http://www.fda.gov/medwatch/report/hcp.htm> or report by fax to 1-800-FDA-0178, by mail using the postage-paid address form provided on line, or by telephone to 1-800-FDA-1088.*

**Recommendations and Considerations for Health Care Professionals:**

- *For patients with moderate ( $GFR < 60$  mL/min/1.73m<sup>2</sup>) to end-stage renal disease ( $GFR < 15$  mL/min/1.73m<sup>2</sup>):* When recommending or performing an MRI or MRA, carefully weigh the benefits and risks associated with using a gadolinium-based contrast agent in light of recent reports of NSF/NFD observed following administration of these agents. Choose an alternative imaging method and/or contrast agent whenever possible.
- Although there are no published data to determine the utility of dialysis to prevent or treat NSF/NFD, consider prompt dialysis of patients with moderate to end-stage renal disease who undergo a MRI or MRA with a gadolinium-based contrast agent. Prompt dialysis of these patients will eliminate circulating gadolinium-based contrast agent. From the first to the



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*Questions? Call Drug Information, 1-888-INFO-FDA (automated) or 301-827-4570  
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## Information for Healthcare Professionals

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

third hemodialysis sessions, average gadolinium-based contrast clearance rates were 78%, 96%, and 99%, respectively.<sup>1</sup>

**Information for the patient:** Physicians who are requesting an MRI or MRA with a gadolinium-based contrast agent for a patient with moderate to end-stage kidney disease should discuss the following issues with their patient.

- Because the patient has moderate to end-stage kidney disease, they may develop NSF/NFD after receiving an MRI or MRA scan with a gadolinium-based contrast agent. NSF/NFD is a debilitating and potentially fatal disease.
- The signs and symptoms of NSF/NFD 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
- No studies have evaluated the role of dialysis on the chance of developing NSF/NFD in patients at risk. However, performing prompt dialysis to reduce the patient's gadolinium-based contrast agent body burden following an MRA or MRI may be appropriate.
- Patients at risk for NSF/NFD require close monitoring and clinical follow-up after having an MRI or MRA with a gadolinium-based contrast agent.

#### Background Information and Data

First identified in 1997, NSF/NFD has occurred in patients with moderate to end-stage renal disease. Patients with this condition develop fibrosis of the skin and connective tissues throughout the 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 make a definitive diagnosis. The disease is progressive and may be fatal. Its cause is unknown.



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Information for Healthcare Professionals

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

As of December 21, 2006 FDA has received reports to its Adverse Events Reporting System of 90 patients who developed NSF/NFD after they received a gadolinium-based contrast agent for an MRI or MRA; all had moderate to end-stage renal disease and many have been described in the scientific literature.<sup>2,3</sup> Their NSF/NFD began two days to 18 months after undergoing their contrast enhanced MRI or MRA. Many of these patients received a dose of gadolinium-based contrast agent exceeding that recommended in product labeling. Some patients developed NSF/NFD after receiving only one dose. Researchers have detected gadolinium deposits in skin biopsies from patients with NSF/NFD.<sup>4,5</sup>

Five gadolinium-based contrast agents (Magnevist, MultiHance, Omniscan, OptiMARK, and ProHance) are approved in the U.S. for magnetic resonance imaging (MRI). None are FDA-approved for MRA. The administered dose of gadolinium-based contrast with magnetic resonance angiography (MRA) is often higher (up to three times) than the approved dose for MRI. Though NSF/NFD has been reported following administration of three of the FDA approved gadolinium-based contrast agents (Magnevist, Omniscan, and OptiMARK), FDA believes that there is a potential for NSF/NFD to occur in patients at risk following administration of any of the approved gadolinium-based contrast agents.

Worldwide, about 215 cases of NSF/NFD have been reported to the International Center for NSF/NFD Registry. In 75 of the 215 cases reviewed in detail, all had received gadolinium-based contrast agents for MRA or MRI.

**References**

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

<sup>2</sup>Grobner T. Gadolinium-a specific trigger for the development of nephrogenic fibrosing dermatopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006; 21(4): 1104-1108 and erratum in 2006; 21(6): 1745.

<sup>3</sup>Maloo M et al. Nephrogenic systemic fibrosis among liver transplant recipients: a single institution experience and topic update. *Am J of Transplant* 2006; 6(9): 2212-2217.



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<sup>4</sup>High WA et al. Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. J Am Acad Dermatol 2006 In Press. <sup>5</sup>Boyd AS et al. Gadolinium deposition in nephrogenic fibrosing dermopathy. J Am Acad Dermatol 2006, In press.



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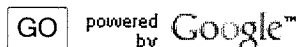
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## Questions and Answers on Gadolinium-Containing Contrast Agents

### 1. What information is new since the Questions and Answers from June 2006?

FDA's previous information was limited to 25 cases in patients that received Omniscan for Magnetic Resonance Angiography (MRA) at doses higher than approved and recommended for Magnetic Resonance Imaging (MRI).

FDA has received an additional 65 case reports of Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD) in patients who received Magnevist, Omniscan, and OptiMARK for MRI and MRA.

NSF/NFD has now been reported in patients who received the recommended doses of the contrast agents.

Researchers have found gadolinium deposits in the skin of patients who developed NSF/NFD.

### 2. What is gadolinium and what is its use in clinical medicine?

Gadolinium is a paramagnetic metal ion. Paramagnetic ions, such as gadolinium, tend to move into magnetic fields. This trait makes paramagnetic ions such as gadolinium useful for MRI and MRA.

Gadolinium-based contrast agents are manufactured by a chelating process, a procedure in which large organic molecules form a stable complex around the gadolinium. The chelate reduces the chances of toxicity that could result from exposure to free gadolinium. This stable complex is eliminated via the kidneys in patients with normal functioning kidneys.

Gadolinium-based contrast agents are approved by FDA for use with MRI as a contrast agent to provide an improved image of body organs and tissues.

Gadolinium-based contrast agents are also used for MRA, another imaging procedure used to evaluate blood vessels.

### 3. What is the difference between MRA and MRI?

MRA is a special type of MRI used to study blood vessels. MRA is utilized to aid in the detection of heart disorders, stroke, and vascular diseases.

**4. Can an MRI and MRA be performed without gadolinium-based contrast?**

Yes, MRI and MRA can be performed without contrast.

MRI with gadolinium-based contrast agents provides additional diagnostic information as compared to MRI without contrast.

The use of gadolinium-based contrast agents in MRA is not FDA approved. MRA with gadolinium-based contrast is thought by many radiologists to provide more detailed images of blood vessels than MRA without gadolinium-based contrast.

**5. Are there any FDA approved MRA contrast agents?**

No.

**6. Are there other approved MRI contrast agents that do not contain gadolinium?**

Yes. However, the two other approved MRI contrast agents, Feridex, I.V. (an iron-containing injectable solution) and Teslascan (a manganese-containing injectable solution) are FDA-approved only for the evaluation of lesions of the liver. Imaging contrast agents, such as iodinated contrast agents are used in Computed Tomography, plain X-ray and X-ray angiography. However, these iodinated contrast agents require X-ray imaging rather than MRI.

**7. What is the concern regarding gadolinium-based contrast agents?**

Patients with moderate (glomerular filtration rate less than 60 mL/min/1.73m<sup>2</sup>) to end-stage (glomerular filtration rate less than 15 mL/min/1.73m<sup>2</sup> or on dialysis) kidney disease who receive gadolinium-based contrast agents are at risk for developing a serious systemic fibrosing disease called Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD).

As of December 21, 2006, FDA has received 90 reports of NSF/NFD in patients who received gadolinium-based contrast agents for MRI and MRA. In addition, researchers have found gadolinium deposits in the skin of patients with NSF/NFD. The association between NSF/NFD was first reported in a May 29, 2006, press release from the Danish Medicines Agency (DMA) and the April 2006 report by Grobner et al in *Nephrology, Dialysis and Transplantation* (2006) Vol 21 (4):1104-1108 and following erratum (2006) 21(6): 1745.

**8. What is Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD)?**

NSF/NFD was first described in the medical literature in 2000. The first case of NSF/NFD was identified in 1997. The disease is observed in patients that have moderate to end-stage kidney disease. NSF/NFD causes fibrosis of the skin and connective tissues throughout the body. Patients develop skin thickening that may prevent bending and extending joints, resulting in decreased mobility of joints. NSF/NFD usually starts in the lower extremities. Fibrosis can also develop in the diaphragm, muscles in the thigh and lower abdomen, and lung vessels. The clinical course of NSF/NFD is progressive and may be fatal.

**9. What is the treatment for NSF/NFD?**

There is no known treatment for NSF/NFD.

Improved renal function (spontaneous or via renal transplantation) appears to slow or arrest NSF/NFD and may even result in a gradual reversal of NSF/NFD. Other treatments are being tested.

**10. How many gadolinium-based contrast agents has FDA approved? Was NSF/NFD seen with all of the U.S.-approved gadolinium-based contrast agents?**

There are five FDA approved gadolinium-based contrast agents (Magnevist, MultiHance, Omniscan, OptiMARK, and ProHance).

Of the 90 cases of NSF/NFD FDA has received, most have been associated with the administration of Omniscan. Other cases, however, have been associated with Magnevist and OptiMARK exposure. Although NSF/NFD has been reported for only 3 of the 5 gadolinium-based contrast agents, FDA believes that NSF/NFD may occur with the use of any of the approved gadolinium-based contrast agents.

**11. Do the gadolinium-based contrast agents cause NSF/NFD?**

Whether the gadolinium-based contrast agents are the only agents or conditions that may be associated with NSF/NFD in patients with renal disease is unknown. However, the 90 case reports FDA has received and the finding of gadolinium deposits in the skin of patients with NSF/NFD suggests that gadolinium-based contrast is a factor in the development of NSF/NFD in patients with moderate to end-stage kidney disease.

**12. What actions will FDA take regarding the new information about gadolinium-based contrast agent administration and the development of NSF/NFD in patients with moderate to severe kidney disease?**

FDA is continuing to evaluate the 90 case reports, is having ongoing discussions with NSF/NFD experts, is reviewing results of clinical trials with gadolinium-based contrast agents, and is working with the manufacturers to review all safety reports and adverse event reports. FDA will be initiating labeling changes for gadolinium-based contrast agents.

**13. What information was known about serious side effects prior to the approval of gadolinium-based contrast agents?**

The five U.S. approved gadolinium-based contrast agents were approved between 1988 and 2004. In the combined pre-marketing studies for these approved gadolinium-based contrast agents, over 3000 patients were studied.

The most common serious side effect from gadolinium-based contrast agents is an allergic reaction that is usually mild but is occasionally severe and even results in fatalities. Some patients develop skin conditions, such as rash, sweating, itching, hives, and facial swelling. Most of these conditions are allergic in nature.

Gadolinium-based contrast agents can be very irritating to the veins into which they are injected, causing irritation of blood vessels and skin and the formation of blood clots.

Very few patients with severely compromised kidney function or those on dialysis have been studied in clinical trials. The labels for gadolinium-based contrast agents caution that the risk of toxic reactions may be greater in patients with impaired kidney function because gadolinium is mostly excreted by the kidney.

#### **14. What should patients do with this new information?**

If you have moderate to end-stage kidney disease and a physician has requested an MRI or MRA study with a contrast agent, ask if there are other contrast agents that could be used or other diagnostic tests that could be done. If gadolinium-containing contrast agents are necessary, physicians and patients should carefully select the contrast agent based on the individual patient's medical care needs.

If you have moderate to end-stage kidney disease and you received a gadolinium-based contrast MRA, you should tell your doctor.

Call your doctor right away if any time after your gadolinium injection you get any of these conditions

- **Skin and eyes**
  - Swelling, hardening and tightening of your skin
  - Reddened or darkened patches on the skin
  - Burning or itching of your skin
  - Yellow raised spots on the whites of your eyes
- **Bones and muscles**
  - Stiffness in your joints; problems moving or straightening arms, hands, legs, or feet
  - Pain deep in your hip bones or ribs
  - Muscle weakness

#### **15. What should healthcare providers do in response to this new information?**

Physicians should consider the risks and benefits of using gadolinium-based contrast agents for MRI or MRA in patients with moderate to end-stage kidney disease. If such a patient receives gadolinium-based contrast agent, the physician should consider prompt dialysis. Physicians should also report all cases of NSF/NSD to the FDA's MedWatch at <http://www.fda.gov/medwatch/>.

#### **16. What additional actions are likely to follow?**

FDA will complete its ongoing analysis of these preliminary findings and then consider multiple options such as: modifying the product label or requiring additional studies. FDA may also consider other risk management options.

#### **17. Where can I find more information about gadolinium-based agents and about NSF/NFD?**