Information for Healthcare Professionals

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

This information is not current. The FDA has issued new information about this safety issue, please see:
http://www.fda.gov/cder/drug/infopage/gcca/default.htm

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^2) to end-stage renal disease (GFR<15 mL/min/1.73m^2) 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..

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^2) to end-stage renal disease (GFR<15 mL/min/1.73m^2):* 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 third hemodialysis sessions, average gadolinium-based contrast clearance rates were 78%, 96%, and 99%, respectively.[1]

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

Information for Healthcare Professionals

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

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.

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.[2,3] 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.[4,5]

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

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

[2]Grobner T. Gadolinium-a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transplant 2006; 21(4): 1104-1108 and erratum in 2006; 21(6): 1745.

Report serious adverse events to FDA's MedWatch reporting system by completing a form on line at http://www.fda.gov/medwatch/report/hcp.htm, by faxing (1-800-FDA-0178), by mail using the postage-paid address form provided on line (HF-2, 5600 Fishers Lane, Rockville, MD 20853-9787), or by telephone (1-800-FDA-1088).

Questions? Call Drug Information, 1-888-INFO-FDA (automated) or 301-827-4570 Druginfo@cder.fda.gov

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[3]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.

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