



GE Healthcare



## Important Drug Warning for Gadolinium-Based Contrast Agents

**Magnevist®** (gadopentetate dimeglumine) Injection

**MultiHance®** (gadobenate dimeglumine) injection, 529 mg/mL

**Omniscan™** (gadodiamide) Injection

**OptiMARK®** (gadoversetamide) Injection

**ProHance®** (Gadoteridol) Injection, 279.3 mg/mL

September 12, 2007

Dear Healthcare Professional,

The manufacturers of gadolinium-based contrast agents would like to inform you of important revisions to the prescribing information for the products listed in alphabetical order above. Gadolinium-based contrast agents are approved by the U.S. Food and Drug Administration (FDA) for use in magnetic resonance imaging (MRI).

Post-marketing reports show that the use of these agents increases the risk of the development of a serious medical condition called Nephrogenic Systemic Fibrosis (NSF), in patients with acute or chronic severe renal insufficiency (glomerular filtration rate  $<30\text{mL}/\text{min}/1.73\text{m}^2$ ) and patients with renal dysfunction due to the hepato-renal syndrome or in the perioperative liver transplantation period.

NSF leads to excessive formation of connective tissue in the skin and internal organs. NSF is progressive and may be debilitating or fatal. As of today, the FDA has received reports of over 250 cases of NSF after administration of gadolinium-based contrast agents.

As a result of these NSF cases, the package inserts of all gadolinium-based contrast agents have been revised to include the following Boxed Warning and update to the WARNINGS section.

## BOXED WARNING:

### **WARNING: NEPHROGENIC SYSTEMIC FIBROSIS**

Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with:

- acute or chronic severe renal insufficiency (glomerular filtration rate  $<30\text{mL}/\text{min}/1.73\text{m}^2$ ), or
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration (See WARNINGS).

## **WARNING:**

### **Nephrogenic Systemic Fibrosis (NSF)**

Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with acute or chronic severe renal insufficiency (glomerular filtration rate  $<30\text{mL}/\text{min}/1.73\text{m}^2$ ) and in patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced MRI. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a gadolinium-based contrast agent in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a gadolinium-based contrast agent and the degree of renal function impairment at the time of exposure.

Post-marketing reports have identified the development of NSF following single and multiple administrations of gadolinium-based contrast agents. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan™), followed by gadopentetate dimeglumine (Magnevist®), and gadoversetamide (OptiMARK®). NSF has also developed following sequential administrations of gadodiamide with gadobenate dimeglumine (MultiHance®) and gadoteridol (ProHance®.) The number of post-marketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific gadolinium-based contrast agent.

The extent of risk for NSF following exposure to any specific gadolinium-based contrast agent is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for

development of NSF was 4% (J Am Soc Nephrol 2006;17:2359). The risk, if any, for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent prior to any readministration. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

**Further Information**

The complete prescribing information for Magnevist®, MultiHance®, Omniscan™, OptiMARK® and ProHance®, as revised, is enclosed. The package inserts for the Magnevist®, MultiHance®, OptiMARK® and ProHance® pharmacy bulk packages have not been included in this mailing. These pharmacy bulk package inserts contain the same new safety information as the package inserts for these products. If you require further information regarding any of these products, information is available on the manufacturer’s website or by calling the manufacturer’s product information telephone number, as indicated below.

<b>Product</b>	<b>Sponsor</b>	<b>Phone</b>	<b>Web</b>
Magnevist	Bayer HealthCare Pharmaceuticals Inc.	1-888-842-2937 (option 4)	www.imaging.bayerhealthcare.com
MultiHance	Bracco Diagnostics Inc.	1-800-257-5181 (option 2)	www.bracco.com
Omniscan	GE Healthcare	1-800-654-0118 (option 2)	www.amershamhealth-us.com/omniscan
OptiMARK	Mallinckrodt Inc.	1-888-744-1414 (option 2)	www.imaging.mallinckrodt.com
ProHance	Bracco Diagnostics Inc.	1-800-257-5181 (option 2)	www.bracco.com

Additional information on NSF is available from the FDA website ([http://www.fda.gov/cder/drug/infopage/gcca/qa\\_200705.htm](http://www.fda.gov/cder/drug/infopage/gcca/qa_200705.htm)).

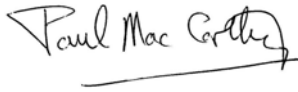
We are working with the FDA and other regulatory authorities worldwide to learn more about the occurrence of this disease after the administration of gadolinium-based contrast agents. We urge healthcare professionals to report adverse event information to the respective manufacturer of the product suspected of the adverse event, as indicated below:

<b>Product</b>	<b>Sponsor</b>	<b>Phone</b>
Magnevist	Bayer HealthCare Pharmaceuticals Inc.	1-888-842-2937 (option 1)
MultiHance	Bracco Diagnostics Inc.	1-800-257-5181 (option 1)
Omniscan	GE Healthcare	1-800-654-0118 (option 2)
OptiMARK	Mallinckrodt Inc.	1-888-744-1414 (option 2)
ProHance	Bracco Diagnostics Inc.	1-800-257-5181 (option 1)

Also, healthcare professionals may report adverse event information to the FDA's MedWatch program by phone (1-800-FDA-1088); on line (<https://www.accessdata.fda.gov/scripts/medwatch>); or by downloading Form 3500 at <http://www.fda.gov/medwatch/getforms.htm> and sending it to MedWatch by fax (1-800-FDA-0178) or by mail (5600 Fishers Lane, Rockville, MD 20852-9787).

Sincerely,

Bayer HealthCare Pharmaceuticals Inc.



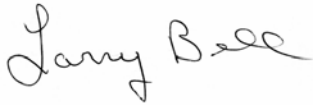
E. Paul MacCarthy, M.D.  
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