DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20-123/S-037 and 22-066/S-002

SUPPLEMENT APPROVAL

GE Healthcare
Attention: Paula Clark
Manager, Regulatory Affairs
101 Carnegie Center
Princeton, NJ 08540

Dear Ms. Clark:

Please refer to your Supplemental New Drug Application (sNDA) dated October 7, 2010, received October 8, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for OMNISCAN ™ (gadodiamide) Injection and OMNISCAN™ (gadodiamide) Pharmacy Bulk Package Injection.

We acknowledge receipt of your amendment dated December 8, 2010.

We also refer to our letter dated September 8, 2010, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for OMNISCAN ™ (gadodiamide) Injection and OMNISCAN™ (gadodiamide) Pharmacy Bulk Package Injection. This information pertains to the risk of nephrogenic systemic fibrosis (NSF) associated with the use of gadolinium-based contrast agents.

This supplemental new drug application provides for revisions to the labeling for OMNISCAN ™ (gadodiamide) Injection and OMNISCAN™ (gadodiamide) Pharmacy Bulk Package Injection. The agreed upon changes to the language included in our September 8, 2010 letter and the text emailed November 18, 2010 that was discussed during our November 19, 2010 teleconference are as follow (additions are noted by underline and deletion are noted by ~~strikethrough)~~.

1. Revise the BOXED WARNING within HIGHLIGHTS as follows (modify the font to maintain consistency with other text within the section):

WARNING: NOT FOR INTRATHECAL USE and NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

See full prescribing information for complete boxed warning

NOT FOR INTRATHECAL USE:

- **Inadvertent intrathecal use of OMNISCAN has caused convulsions, coma, sensory and motor neurologic deficits (~~5.4~~ 5.1).**

NSF:

- ~~**Gadolinium-based contrast agents (GBCAs) increase risk of NSF in patients with (5.2):**~~
  - ~~**acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m^2), or**~~
  - ~~**acute renal insufficiency of any severity due to hepato-renal syndrome or in perioperative liver transplantation period.**~~
- ~~**In these patients, avoid use of GBCAs unless diagnostic information is essential and not available with non-contrast enhanced MRI (5.2).**~~
- ~~**NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs (5.2).**~~

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.

- **Do not administer OMNISCAN to patients with:**
  - **chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or**
  - **acute kidney injury (4).**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.2).**

2. Revise the RECENT MAJOR CHANGES section within HIGHLIGHTS as follows (modify the font to maintain consistency with other text within the section):

~~Boxed Warning: Nephrogenic Systemic Fibrosis (NSF)~~	~~9/2007~~
~~Warnings and Precautions: Hypersensitivity Reactions (5.1)~~	~~9/2007~~
~~Warnings and Precautions: NSF (5.2)~~	~~9/2007~~
~~Warnings and Precautions: Acute Renal Failure (5.3)~~	~~9/2007~~
~~Warnings and Precautions: Not for Intrathecal Use (5.4)~~	~~9/2007~~

Boxed Warning	12/2010
Dosage and Administration (2.2, 2.3, 2.5)	12/2010
Contraindications (4)	12/2010
Warnings and Precautions (5.2)	12/2010
Geriatric Use (8.5)	12/2010
Patient Counseling Information (17)	12/2010

3. Revise the CONTRAINDICATIONS section within HIGHLIGHTS as follows (modify the font to maintain consistency with other text within the section):

~~None (4)~~
Patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2) or acute kidney injury (4).

4. Revise the WARNINGS AND PRECAUTIONS section within HIGHLIGHTS as follows (modify the font to maintain consistency with other text within the section):

- ~~*Anaphylactoid and other serious hypersensitivity reactions* including fatal reactions have occurred particularly in patients with history of allergy or drug reactions. Monitor patients closely for need of emergency cardiorespiratory support (5.1).~~
- *Nephrogenic Systemic Fibrosis (NSF)* has occurred in patients with impaired elimination of GBCAs ~~severe renal insufficiency~~. Higher than recommended dosing or repeat dosing appears to increase the risk (5.2).
- *Anaphylactoid and other serious hypersensitivity reactions* including fatal reactions have occurred particularly in patients with history of allergy or drug reactions. Monitor patients closely for need of emergency cardiorespiratory support (5.~~2~~3).
- *Acute renal failure* has occurred in patients with preexisting renal insufficiency. Use the lowest necessary dose of OMNISCAN and evaluate renal function in these patients (5.~~3~~4).

As noted below, modify the WARNINGS AND PRECAUTIONS section within the full prescribing information to reorder the presentation of the subsections; with "Not for Intrathecal Use" listed as the first risk (5.1), followed by "Nephrogenic Systemic Fibrosis (5.2)" and "Hypersensitivity Reactions (5.3)" etc.; similarly, modify the Table of Contents to match the new ordering of the subsections.

5. Within the full prescribing information, revise the BOXED WARNING as follows:

WARNING: NOT FOR INTRATHECAL USE and NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

NOT FOR INTRATHECAL USE:

Inadvertent intrathecal use of OMNISCAN has caused convulsions, coma, sensory and motor neurologic deficits [*see Warnings and Precautions (5.1) ~~(5.4)~~*].

NSF:

~~Gadolinium-based contrast agents increase the risk for NSF in patients with:~~

- **~~acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m^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 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~~

- **Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.**
- **Do not administer OMNISCAN to patients with:**
  - **chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or**
  - **acute kidney injury [*see Contraindications (4)*].**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **Do not exceed the recommended OMNISCAN dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration [*see Warnings and Precautions (5.2)*].**

6. Within the full prescribing information, revise the DOSAGE and ADMINISTRATION section as follows:

2.1 CNS (Central Nervous System)

Adults: The recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg) administered as a bolus intravenous injection. ~~An additional 0.4 mL/kg (0.2 mmol/kg) can be given within 20 minutes of the first dose [*see Dosage and Administration (2.3)*].~~

Pediatric Patients (2-16 years): The recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg) administered as a bolus intravenous injection [*see Dosage and Administration (2.3)*].

2.3 Dosage Chart

Remove the column under **ADULTS** for the 0.2 mmol/kg dosing

Other components of this section remain the same until (deletion of subsection 2.5):

~~**2.5 Repeat Dosing**~~

~~Sequential use during the same diagnostic session has been studied in adult CNS use only. If the physician determines repeat dosing is required in non-CNS imaging in adults or pediatric patients, renal function should be normal and the time interval between repeat doses should be at least 7 hours to allow for clearance of the drug from the body [*see Clinical Pharmacology (12.3)*].~~

7. Within the full prescribing information, revise the CONTRAINDICATIONS section as follows:

~~None~~

OMNISCAN is contraindicated in patients with:

- chronic, severe kidney disease (glomerular filtration rate, GFR < 30 mL/min/1.73m^2), or
- acute kidney injury.

8. Within the full prescribing information, revise the WARNINGS AND PRECAUTIONS section as follows:

5.2 Nephrogenic Systemic Fibrosis

~~[*see Boxed Warning*]~~

~~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 mL/min/1.73m^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.~~

~~Postmarketing 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®) or gadoteridol (ProHance®). The number of postmarketing 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 [s*ee Clinical Pharmacology (12.2) and Dosage and Administration (2*)].~~

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2) as well as patients with acute kidney injury. Do not administer OMNISCAN to these patients. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30 - 59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60 - 89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following OMNISCAN administration to GE Healthcare (1-XXX-XXX-XXXX) or FDA (1-800-1088 or www.fda.gov/medwatch).

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury 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 renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (e.g., age > 60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and the degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. When administering Omniscan, do not exceed the recommended dose and allow a sufficient period of time for elimination of the drug prior to any readministration [*see Boxed*

Warning, Contraindications (4), Clinical Pharmacology (12.2) and Dosage and Administration (2)].

9. Within the full prescribing information, revise the Geriatric Use (8.5) section as follows:

In clinical studies of OMNISCAN, 243 patients were between 65 and 80 years of age while 15 were over 80. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity in the elderly cannot be ruled out. In general, dose selection for an elderly patient should be cautious, ~~usually starting at the low end of the dosing range,~~ reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.
OMNISCAN is excreted by the kidney, and the risk of toxic reactions to OMNISCAN ~~may be~~ is greater in patients with impaired renal function [*see Warnings and Precautions (5.2) (5.4)*]. Because elderly patients are more likely to have decreased renal function, select dose carefully and ~~consider assessment of renal function~~ assess eGFR by laboratory testing before OMNISCAN use.

10. Within the full prescribing information, revise the PATIENT COUNSELING INFORMATION section as follows:

Patients receiving OMNISCAN should be instructed to inform their physician if they:

- are pregnant or breast feeding, or
- have a history of renal and/or liver disease, convulsions, asthma or allergic respiratory disorders, or recent administration of gadolinium-based contrast.

~~Gadolinium-based contrast agents increase the risk for NSF among patients with acute or chronic severe renal insufficiency or acute renal insufficiency due to the hepato-renal syndrome. This risk may increase with repetitive or higher than recommended doses of a gadolinium-based contrast agent. Instruct patients at increased risk for NSF to contact their physician if they develop 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 deep in the hip bones or ribs; or muscle weakness.~~

GBCAs increase the risk for NSF among patients with impaired elimination of the drugs. To counsel patients at risk for NSF:

- Describe the clinical manifestations of NSF
- Describe procedures to screen for the detection of renal impairment

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following OMNISCAN administration, such as 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.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call James Moore, Regulatory Project Manager, or Rene' Tyson, Safety Project Manager at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

Rafel Rieves, M.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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/s/

RAFEL D RIEVES
12/20/2010