DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20-131/S-024 and 21-489/S-002

SUPPLEMENT APPROVAL

Bracco Diagnostics, Inc.
Attention: Melanie Benson, M.S.,R.A.C.
Director, US Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Ms. Benson:

Please refer to your Supplemental New Drug Application (sNDA) dated October 8, 2010, received October 8, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for. ProHance® (gadoteridol) Injection and ProHance® Multipack™ (gadoteridol) Injection.

We acknowledge receipt of your amendment dated December 6, 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 ProHance® (gadoteridol) Injection and ProHance® Multipack™ (gadoteridol) 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 ProHance® (gadoteridol) Injection and ProHance® Multipack™ (gadoteridol) Injection. The agreed upon changes to the language included in our September 8, 2010 letter and the text emailed November 17, 2010 that was discussed during our November 18, 2010 teleconference are as follow (additions are noted by underline and deletion are noted by ~~strikethrough~~).

The final label further revises the last bullet in the boxed warning of the full prescribing information section and a sentence in the Nephrogenic Systemic Fibrosis section (5.1); both revisions address re-administration.

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

~~**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 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/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

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 systemic fibrosis affecting the skin, muscle and internal organs.

- **The risk for NSF appears highest among patients with:**
  - **chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or**
  - **acute kidney injury.**
- **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.**
- **For patients at highest risk for NSF, do not exceed the recommended ProHance dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration (See WARNINGS).**

2. Within the full prescribing information, revise the WARNINGS section as follows:

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 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.~~

~~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®) or 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 estimate 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**).~~

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. 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 ProHance administration to Bracco Diagnostics (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. For patients at highest risk for NSF, do not exceed the recommended ProHance dose and allow a sufficient period of time for elimination of the drug prior to re-administration. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown (See **CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION**).

3. Within the full prescribing information, revise the PRECAUTIONS section (subsection of "Information for patients:") as follows:

Patients scheduled to receive ProHance should be instructed to inform their physicians if the patient;

1. is pregnant or breast feeding
2. has anemia or diseases that affect the red blood cells
3. has a history of renal or hepatic disease, seizure, hemoglobinopathies, asthma or allergic respiratory diseases
4. has recently received a GBCA.

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 ProHance 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.

4. Within the full prescribing information, revise the DOSAGE AND ADMINISTRATION section as follows:

Central Nervous System
ADULTS: The recommended dose of ProHance (Gadoteridol) Injection is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min-60 mL/min) or bolus (> 60mL/min). ~~In patients suspected of having poorly enhancing lesions, in the presence of negative or equivocal scans, a second dose of 0.2 mmol/kg (0.4 mL/kg) may be given up to 30 minutes after the first dose.~~ In patients with normal renal function suspected of having poorly enhanced lesions, in the presence of negative or equivocal scans, a supplementary dose of 0.2 mmol/kg (0.4 ml/kg) may be given up to 30 minutes after the first dose.

Other portions of the DOSAGE AND ADMINISTRATION section are unchanged.

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAFEL D RIEVES
12/20/2010