Advisory Committee Briefing Document
Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
Gadolinium Based Contrast Agents

NDAs 21-357/21-358

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

October 30, 2009

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

MultiHance®[a] (active ingredient: gadobenate dimeglumine) is a gadolinium-based contrast medium that belongs to the class of contrast media for magnetic resonance imaging (MRI), and, within this category, to the group of paramagnetic contrast media (ATC Class V08CA).

MultiHance was first approved in the United Kingdom on August 1, 1997 and is now approved in 44 countries for use in MRI of the central nervous system (CNS), MRI of the liver, and magnetic resonance angiography (MRA). In the United States, MultiHance was approved on November 24, 2004 for use in MRI of the CNS of adults and launched in February 2005.

MultiHance is a higher-relaxivity, gadolinium-based contrast agent (GBCA) that undergoes both renal and hepato-biliary excretion in humans. Its active ingredient is quite stable, as can be seen from the stability constants of MultiHance and other GBCAs in Table A.

Table A: Chemical structure and chelate stability of MultiHance and other gadolinium-based contrast agents (GBCAs) – from Idee et al.[1,2]

GBCA Brand Name (active ingredient)	Chemical Structure	Thermodynamic Stability Constant (logK, μ=0.1)	Conditional Stability Constant (logK', pH 7.4)
Omniscan™ (gadodiamide)[b]	Linear, Non-Ionic	16.9	14.9
OptiMARK™ (gadoversetamide)[c]	Linear, Non-Ionic	16.6	15.0
Magnevist® (gadopentetate dimeglumine)[d]	Linear, Ionic	22.1	17.7
MultiHance® (gadobenate dimeglumine)	Linear, Ionic	22.6	18.4
Eovist® (gadoxetic acid disodium salt)[e]	Linear, Di-Ionic	23.5	Not Available
ProHance® (gadoteridol)[f]	Macrocyclic, Non-Ionic	23.8	17.1
Gadovist® (gadobutrol)[g]	Macrocyclic, Non-Ionic	21.8	14.7
Dotarem® (gadoterate meglumine)[h]	Macrocyclic, Non-Ionic	25.8	18.8

[a] MultiHance® (gadobenate dimeglumine) is a registered trademark of Bracco Diagnostics Inc.

[b] Omniscan™ (gadodiamide) is a trademark of General Electric Healthcare

[c] OptiMARK™ (gadoversetamide) is a trademark of Covidien

[d] Magnevist® (gadopentetate dimeglumine) is a registered trademark of Bayer Healthcare

[e] Eovist® (gadoxetic acid disodium salt) is a registered trademark of Bayer Healthcare

[f] ProHance® (gadoteridol) is a registered trademark of Bracco Diagnostics Inc.

[g] Gadovist® (gadobutrol) is a registered trademark of Bayer Schering Pharma GmbH, Berlin, Germany. This product is not available in the United States.

[h] Dotarem® (gadoterate meglumine) is a registered trademark of Guerbet S.A., Villepinte, France. This product is not available in the United States.

Stability constants measure the propensity of GBCAs to release free gadolinium *in vivo*, where several cations (e.g., zinc, copper, iron or calcium) compete with gadolinium ion for the ligand and a number of anions (e.g., phosphate, carbonate, or hydroxyl) compete with the ligand for the gadolinium ion.[1]

The exchange of gadolinium ions with other metals, leading to dissociation of the gadolinium–ligand complex into free gadolinium ion and ligand is called "transmetallation". A validated *in vitro* stability test quantitatively evaluated the transmetallation potential of gadopentetate dimeglumine (Magnevist), its bisamide derivative gadodiamide (Omniscan), the higher-relaxivity gadobenate dimeglumine (MultiHance), and three macrocyclic GBCAs, gadoteridol (ProHance), gadobutrol (Gadovist, not available in the United States) and gadoterate meglumine (Dotarem, not available in the United States). The highest extent of transmetallation was seen for Omniscan and the lowest for the macrocyclic GBCAs. Among the three linear GBCAs, MultiHance was the most stable and underwent a slower and more limited transmetallation process than Magnevist, while the transmetallation process was much faster and more extensive for Omniscan than its parent complex Magnevist.[3]

As reported in the FDA-approved package insert[4], the relaxivity of MultiHance in human plasma, i.e., the measure of its signal enhancement efficacy on MR images, is twice as high as that of other agents approved in the United States for use in MRI of the CNS, e.g., Magnevist, ProHance, and Omniscan.[5,6,7] A higher relaxivity can translate into an improved contrast-to-noise ratio and lesion-to-brain ratio on the MR image at equivalent dose and may contribute to a better visualization of lesions without the need for higher doses.[8,9,10,11]

Humans exhibit biliary excretion of the active ingredient of MultiHance (approximately 2-4% of the injected dose).[12] In patients with renal impairment, the extent of biliary excretion goes up to 6-8% of the injected dose.[13]

MultiHance dosing in man occurs as a single administration. As of October 26, 2009, it is estimated that approximately 8 million patients, of whom approximately 3.2 million in the United States, have received at least one dose of MultiHance.[14]

2 Unconfounded and Confounded Cases of Nephrogenic Systemic Fibrosis (NSF)

NSF cases occurring after the sole administration of only one specific gadolinium-based contrast agent (GBCA) are defined as "unconfounded." If a case of NSF follows the administration of two or more agents, it is even more difficult to determine which agent, if any, is associated with the development of the disorder, and the case is reported as "confounded".[15] Cases may be spontaneously reported by health care professionals or also by patients. Of note, both in cases reported as "unconfounded" or as "confounded", it is not always possible to determine the specific identity of each GBCA or GBCAs potentially administered to a patient, because the brand name or the name of the active ingredient are not mentioned in the patient records.

3 Summary of NSF Cases From Spontaneous Reporting

As of October 26, 2009, Bracco has received no reports of unconfounded cases of NSF following the sole administration of MultiHance.

Overall, Bracco is aware of 14 confounded reportable cases for which it appears, based on available hospital records, that MultiHance was a GBCA identified, i.e., for 14 cases of what was reported as NSF followed the administration of MultiHance and other GBCAs (most commonly Omniscan [gadodiamide] and Magnevist [gadopentetate dimeglumine]).

4 Summary of NSF Reports From Literature

A literature search performed in PubMed for NSF cases related to all GBCAs, and specifically to MultiHance, using the terms "nephrogenic systemic fibrosis" and/or "nephrogenic dermopathy" plus "gadobenate dimeglumine", "MultiHance" up to October 21, 2009 yielded the following results.

A total of 129 articles reporting cases of NSF were identified. A bibliography that provides a list of the 129 articles reporting cases of NSF is included in Appendix 1. Overall, there were 29 reports of confounded cases and 593 of unconfounded cases. The distribution of unconfounded cases by GBCA was the following:

- Omniscan (gadodiamide): 347 cases;
- Magnevist (gadopentetate dimeglumine): 89 cases;
- OptiMARK (gadoversetamide): 5 cases;
- Gadovist (gadobutrol) (not available in the United States): 1 case;
- Unknown GBCA: 151 cases.

Reilly et al.[16] reported two unconfounded cases of NSF with MultiHance as extracted from the FDA Adverse Event Reporting System (AERS) database. Bracco is unable to confirm the existence of those two cases. Bracco has requested, but not yet received confirmation from FDA regarding these reports.

MultiHance was involved in 4 confounded cases. The distribution of confounded cases by GBCA was the following:

- Omniscan + Magnevist: 16 cases;
- Omniscan + Magnevist + Dotarem: 3 cases;
- Magnevist + MultiHance: 2 cases
- Omniscan + ProHance (gadoteridol): 3 cases
- Omniscan + MultiHance: 1 case;
- MultiHance + unknown GBCA: 1 case;

- Omniscan + Magnevist + OptiMARK: 1 case;
- Omniscan + Dotarem: 1 case;
- Omniscan + unknown GBCA: 1 case.

5 Clinical Studies of MultiHance in the Published Literature

A number of clinical studies have been published regarding changes in incidences of NSF in at-risk patients undergoing contrast-enhanced MRI following a switch to MultiHance from other GBCAs in respective clinical practices.

Altun et al[17] determined and compared the incidence of NSF following the switch from the use of Omniscan to MultiHance (in all adult patients, patients less than 1 year old, and pediatric patients at risk for NSF) and Magnevist (in pediatric patients older than 1 year and not at risk for NSF) and the adoption of restrictive policies in at-risk patients in tertiary care centers of two United States universities.

The restrictive policies adopted to minimize the risk of NSF are reported in Table B. A full standard dose (0.1 mmol/kg body weight) of MultiHance or Magnevist was used for all gadolinium-enhanced MR studies, including angiography, in patients without risk factors. In patients with risk factors for NSF, if use of a GBCA was unavoidable, the higher-relaxivity agent MultiHance was used, but only half the approved dose (0.05 mmol/kg) was administered. Half the dose of MultiHance was also used for patients with stage 1 and 2 chronic kidney disease (i.e., with estimated glomerular filtration rate, eGFR, above 60 mL/min/1.73 m^2), renal transplants, and patients with hypertension and diabetes mellitus, who had history of less than 10 years of disease, were less than 70 years old, or had no data regarding renal function.

Prior to the adoption of the restrictive policy:

- At one of the two centers (Center A), 49,010 patients underwent contrast-enhanced MRI in the study period, 925 of whom were at risk of NSF. Of those 925 at risk patients 35 developed NSF; 28 of those 35 patients had received only Omniscan, while the GBCA used could not be identified for the remaining 7 patients.
- At the second center (Center B), 16,230 patients underwent contrast-enhanced MRI, 312 of whom were at risk for NSF. Of those 312 at risk patients, 14 developed NSF; 9 of those 14 patients had received only Omniscan.
- The incidence of NSF in patients at risk receiving Omniscan at Center A was 3.03% (28/925 or 1:33).
- The incidence of NSF in patients undergoing dialysis and receiving Omniscan at Center B were was 2.88% (9/312 or 1:35).
- The total incidence of NSF in patients undergoing Omniscan-enhanced MRI at both centers was 0.057% (37/65,240 or 1:1763).

In the post-adoption period of the GBCA policy, with a 9-month follow-up period of each patient:

- At Center A, 10,477 patients underwent contrast-enhanced MRI, 147 of whom were at risk for NSF and received half-dose MultiHance. No cases of NSF were detected.
- At Center B, 14,690 patients underwent contrast-enhanced MRI, including 402 patients undergoing dialysis, who received half-dose MultiHance. No cases of NSF were detected.

The differences in the incidence of NSF between the pre-adoption and post-adoption period was statistically significant for both centers.

A group of physicians at the University of Wisconsin[18] published their observation of the incidence of NSF before and after they switched the used of GBCA from Omniscan to MultiHance in high risk patients presented with concurrent pro-inflammatory conditions including infection, arterial/venous thrombosis and major surgery. Data acquired from June 2005 to July 2006 revealed a 6.5% (6/91) incidence of NSF in hospitalized at risk patients all of whom received Omniscan for contrast-enhanced MRI or MRA. Data from November 2006 to October 2008 when MultiHance was used instead of Omniscan, there were no new cases of NSF (0/78) in the hospitalized at risk patients undergoing contrast-enhanced MRI or MRA. No cases of NSF were ever found also in 382 patients with eGFR < 30 mL/min/1.73m^2 who received MultiHance in the same active monitoring period. Overall, there have been no cases of NSF detected at the University of Wisconsin since switching to MultiHance.

Bryant et al[19] prospectively followed 168 consecutive patients for 3 months to determine the incidence of NSF in patients with stage 3 chronic kidney disease undergoing clinically indicated contrast-enhanced MRI with MultiHance. Twenty patients were lost to follow-up and no NSF was found in the remaining 148 patients.

All of the above institutions had previously reported NSF cases following the use of other GBCAs before they switched to MultiHance.[20,21,22,23] Hence, these studies sought to examine the incidence of NSF in patients receiving MultiHance. The results of the above published studies found no cases of NSF after switching to MultiHance and using of more restrictive policies for the use of GBCA in at risk patients.

Table B: Restrictive Policies to Minimize Risk of NSF (from Altun et al.[17]

GBCA use
Advantages and disadvantages were evaluated carefully for all patients. Non-GBCA imaging was performed whenever the patient's medical problem could be assessed safely and diagnostically with such techniques.
Patient eligibility
Serum creatinine and eGFR values were sought in clinical information system (CIS) for all patients; however, availability of these values was not required prior to gadolinium-enhanced MR imaging in patients without risk factors.
CIS and/or questionnaire were used to determine presence of acute or chronic renal disease and insufficiency with or without associated liver disease and liver transplantation, dialysis, renal surgery, renal tumors, renal transplantation, hypertension, and diabetes mellitus.
Serum creatinine and eGFR values were evaluated in detail, when necessary, in patients with diseases established in CIS and/or questionnaire in selected patients who underwent short-term follow-up or repeat gadolinium-enhanced MR.
GBCA half dose
Gadobenate dimeglumine half dose (0.05 mmol/kg) was administered to patients with risk factors for all MR studies, including angiography, if use was unavoidable.
Gadobenate dimeglumine half dose (0.05 mmol/kg) was administered to patients with stage 1 or 2 chronic kidney disease, renal transplants, and patients with hypertension and diabetes mellitus, who had history of less than 10 years of disease, were less than 70 years old, or had no data regarding renal function.
GBCA standard dose
Gadobenate dimeglumine and gadopentetate dimeglumine were used at standard doses (0.1 mmol/kg) for all gadolinium-enhanced MR studies, including angiography, in patients without risk factors.
Pregnancy
GBCA administration was avoided unless maternal survival was dependent on it.
Gadobenate dimeglumine half dose (0.05 mmol/kg) was employed whenever use was unavoidable.
Repeat gadolinium-enhanced MR
Not performed within 48 hours of initial study in patients without risk factors unless essential.
Performed after a less than 48-hour delay in low-risk patients if GBCA use was unavoidable.
Not performed in high-risk patients.
Patients with NSF
Gadobenate dimeglumine and gadopentetate dimeglumine were not administered
CIS: Clinical Information System

6 Prospective Sponsored Clinical Studies

Based on a request received from the United States Food and Drug Administration (FDA), Bracco is conducting a prospective, multicenter, multinational, large scale, clinical study (Study MH-136) to better understand the risk of NSF following the administration of MultiHance in patients with chronic kidney disease, i.e., in at-risk patients. This request was made by FDA to all of the Sponsors who hold approvals for gadolinium-containing contrast agents in the United States.

The study will enroll at least 1000 patients with eGFR <60 mL/min/1.73m^2, including 400 patients with GFR <30 mL/min/1.73m^2. The FDA specifically requested that the following be performed for each of the patients in the studies:

- The date and dose of the gadolinium-containing contrast agent administration is recorded;
- The patient glomerular filtration rate (GFR, or estimated GFR from serum creatinine) is recorded;
- A card (or similar contact mechanism) is provided to describe symptoms of NSF and contact information in the event NSF symptoms develop over the following 2 years;
- Telephone contacts and/or clinic visits are scheduled at 1, 3, 6, 12, 18, and 24 months after exposure to MultiHance.
- In case symptoms or signs of NSF develop, patients undergo physical examinations and deep skin biopsy, in order to confirm or exclude NSF.

In addition, even though not requested by the FDA, Bracco is conducting a control study (NSF-101) to evaluate the incidence of NSF in patients with stages 4 to 5 chronic kidney disease (estimated GFR <30 mL/min/1.73m^2) who have not had any exposure to gadolinium-based contrast agents within the previous 10 years.

6.1 NSF Study MH-136

Study MH-136 started on 27 September 2007 (date of initial protocol), with the first patient enrolled on 21 January 2008. As of 23 October 2009, 217 patients have been enrolled:

- 59 patients have been followed up for >1 year;
- 74 patients have been followed up for >6 months and <1 year;
- 41 patients have been followed up for >3 months and <6 months; and
- 43 cases have been followed up for <3 months.

Overall:

27 patients had GFR <30 mL/min/1.73m^2, and 190 had GFR between 30 and 59 mL/min/1.73m^2.

To date, no cases of NSF have been detected.

6.2 NSF Control Study (NSF-101)

In addition, the Sponsor is conducting a control study (NSF-101) to evaluating the incidence of nephrogenic systemic fibrosis in patients with Stages 4 to 5 chronic kidney disease (estimated GFR stably <30 mL/min/1.73m^2) who have not had exposure to gadolinium-based contrast agents within the past 10 years. This study will enroll at least 400 patients. Each eligible patient enrolled will be followed for 2 years. Ad hoc visits and controls will be performed every time signs/symptoms suggestive of NSF develop during the 2-year follow-up. The study started on 30 June 2008 (date of initial protocol), with the first patient enrolled on 21 October 2008. As of

23 October 2009, 301 patients have been enrolled, with 4 patients being discontinued for not meeting inclusion/exclusion criteria. Of the 297 patients remaining in the study:

- 66 patients have been followed up for >6 months and <1 year;
- 54 patients have been followed up for >3 months and <6 months; and
- 177 cases have been followed up for <3 months.

To date, no cases of NSF have been detected.

7 Conclusions

Clinical evidence has shown that centers that had reported NSF cases with other GBCAs and have begun using MultiHance have, to date, not experienced any occurrence of NSF since. Furthermore, Bracco has not received any reports of unconfounded cases of NSF following the sole administration of MultiHance and no cases of NSF have been detected in the prospective study MH-136 in at risk patients.

Despite the absence of unconfounded cases of NSF following the sole administration of MultiHance and the fact that the exact mechanism by which NSF develops remains unknown, Bracco does share FDA's concerns over patient safety, since patients with severe renal failure often show co-morbidities that require multiple medical exams, including the use of contrast-enhanced MRI. There is a need to continue to evaluate the risk-benefit of utilizing GBCA's, both individually and as a class, in patients with renal impairment in a comprehensive manner. Obviously, this evaluation should assess all of the risks for such patients and balance them with the benefit of acquiring potentially indispensable diagnostic information leading to the most successful patient management and treatment.

Given the current regulatory situation, based on the available clinical evidence, Bracco maintains the more restricted measures as to MultiHance, such as a specific contraindication for use in at risk patients, is not justified.

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Appendix 1: NSF Bibliography of Articles Reporting Cases of NSF

NSF Bibliography

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