DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

MEMORANDUM TO THE FILE

i. **NDA: 20-123, 22-066** **Product:** Omniscan
ii. **NDA**: **19-596, 21-037** **Product**: Magnevist
iii. **NDA: 20-976, 20-937,20-975** **Product**: OptiMARK
iv. **NDA**: **21-357, 21-358** **Product:** MultiHance
v. **NDA** : 20-131, 21-489 **Product:** ProHance

Topic: Gadolinium-Based Contrast Agents (GBCAs) and Nephrogenic Systemic Fibrosis (NSF) Date Completed: 5/15/07

Medical Reviewer: Melanie Blank, MD

I. OBJECTIVE

The purpose of this memorandum is to summarize the evidence for the causative role of gadolinium-based contrast agents in the development of NSF and to describe the risk modification steps culminating with the proposal to request revised class labeling from the drug manufacturers that includes a warning.

II. SUMMARY

a. GBCAs are gadolinium chelates (large organic molecules with a total of 8 bonds, 7 to Gd+++ (gadolinium) and 1 to H_2O). This structure makes the Gadolinium paramagnetic so that it can move with higher relaxivity in a strong magnetic field and therefore appear differently on an MRI (Magnetic Resonance Imaging) or MRA (Magnetic Resonance Angiography) scan than the surrounding tissue.

b. Unchelated gadolinium is a very toxic compound, particularly to the liver and to calcium channels

c. 5 gadolinium contrast agents are FDA approved for MRI. No GBCAs are FDA approved for MRA

d. GBCAs are administered IV and are indicated for CNS and body/liver MRI

i. Omniscan: CNS and total body
ii. Magnevist: CNS and total body
iii. OptiMARK: CNS and liver
iv. MultiHance: CNS
v. ProHance: CNS and head/neck

e. GBCAs are renally excreted and therefore severe renal insufficiency prolongs exposure

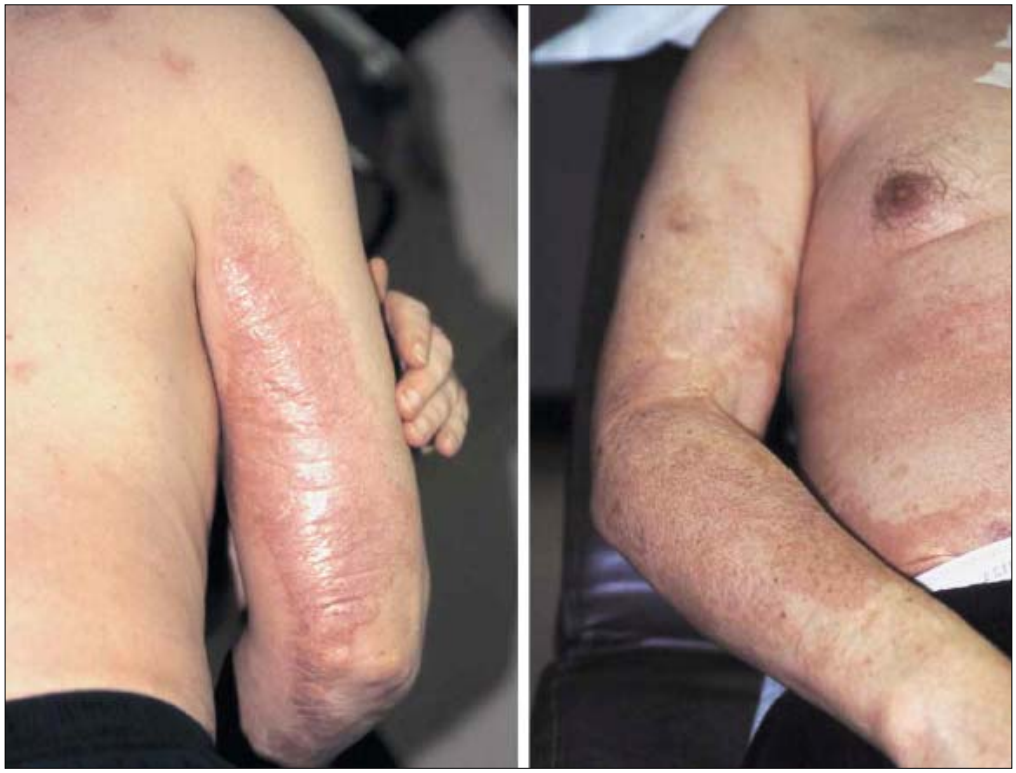
f. GBCAs are eliminated by hemodialysis but clearly not as efficiently as the normal kidney

g. Peritoneal dialysis is not as efficient as hemodialysis in clearing GBCAs.

h. NSF is a systemic condition that is only seen in patients with severe renal insufficiency (acute or chronic).
i. Since early 2006 a strong association between gadolinium contrast agents and NSF has become evident.
j. Unconfounded (only one agent administered to patient) cases of NSF have been reported in association with Omniscan, Magnevist and OptiMARK
k. Most cases of NSF are after high doses (as in MRA) or after repeated doses

III. Introduction to NSF
a. First described in 2000 among patients with renal failure.
b. Association with GBCA exposure not evident until 2006
c. NSF is a systemic fibrosing condition that is similar to scleroderma and scleromyxedema but spares the face and lacks the serological correlates
d. NSF is a disfiguring, disabling and potentially lethal condition

IV. NSF Association with GBCA
a. History of NSF and the recognition of association with GBCA exposure
1. 2000: Described as a skin condition similar to scleroderma: NFD
2. 2005: Systemic nature noted; renamed as NSF
3. 2006: GBCA implicated in 5/9 dialysis patients
4. 2006: Danish reports of 5% incidence among 400 renal failure patients undergoing MRI with Omnsican
5. 2007 CDC reports a cluster of cases at a Missouri hospital: GBCA only definitive correlate for development of NSF
6. Peer reviewed literature and AERS reports suggest higher or repeated GBCA doses used in NSF cases.
7. All of the cases of NSF in peer reviewed literature and AERS database have severe renal failure. Major operative theory at this point in time: renal failure prolongs GBCA exposure and therefore, toxicity
8. Acute renal dysfunction in the perisurgical liver transplantation and hepatorenal syndrome may confer a greater risk for development of NSF. Other potential risk factors include: acidosis, erythropoietin use, concomitant surgery or inflammation
9. Photographs of patient with NSF



(Editors' note: For privacy reasons, we have removed a photograph of one NSF patient from this report.)

b. Reports of unconfounded NSF in AERS database with market share data from Arlington Medical Resources

Trade Name	MFR	Appr	NSF cases Reported in AERS	~ Market share
Omniscan	GE	1993	74	30%
Magnevist	Berlex	1988	39	50%
Optimark	Mallinckrodt	1999	7	< 10%
ProHance	Bracco	1992	0	≤ 5%
MultiHance	Bracco	2004	0	< 5%

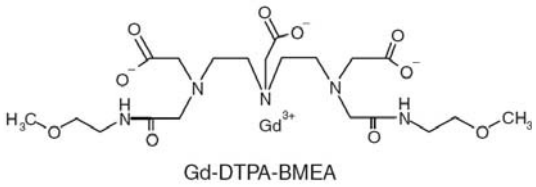
NSF cases for this table were analyzed in 2/07. More recent cases have not been included.

c. Peer Reviewed literature

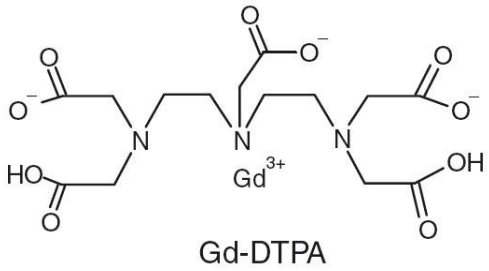
To date there have been approximately 60 cases of NSF associated with Omniscan in the peer reviewed literature and 2 cases of NSF associated with Magnevist. There have been no publications in which the other agents have been reported to be associated with NSF.

d. GBCA Molecular Structures

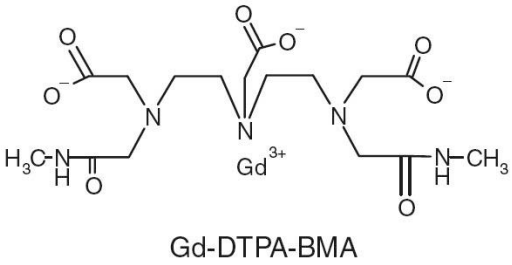
Notice how 4/5 of the agents are linear in their structure, whereas ProHance is cyclic and its chelate forms a trap like structure around the gadolinium ion



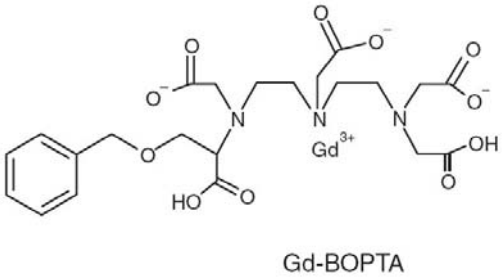
OptiMARK



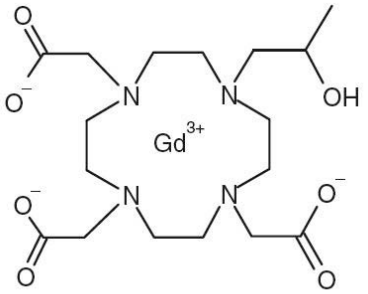
Magnevist



Omniscan



MultiHance



Gd HP-DO3A

ProHance

e. Other GBCA Molecular Features

The table below shows that there is a difference in the stability constants amongst the agents and a difference in the chelate excess. The agents with the lower stability constants have the larger amounts of chelate. The free chelate has a very high binding affinity for the Gd+++ so that if there is dechelation, there would theoretically be a better chance of another circulating chelate being available to bind it. Omniscan and OptiMARK have the lowest stability constants.

Trade Name	**NSF**	**Structure**	**Stability Constant (corrected for pH of 7.4)**	**Chelate excess**
Omniscan	Yes	Linear, non-ionic	$_{10}14.9$	12 mg/dL
Magnevist	Yes	Linear, ionic	$_{10}18.1$	0.4 mg/dL
Optimark	Yes	Linear, non-ionic	$_{10}15.0$	28.4 mg/dL
ProHance	Yes	Cyclic, non-ionic	$_{10}17.1$	0.23 mg/dL
MultiHance	Yes	Linear, ionic	$_{10}18.4$	0

V. Actions/ Guidelines taken to Date

a. <u>June, 2006 FDA PHA</u>

1. Use GBCA only when clearly needed in patients with advanced kidney failure (GFR < 15 mL/min)
2. Use lowest dose
3. Consider dialysis after GBCA administration

b. December, 2006 FDA PHA:

1. Patients with moderate to severe ESKD at risk
2. Avoid use of GBCA in these patients unless the agent "must" be used
3. Consider dialysis after GBCA administration
4. "FDA believes that there is a potential for NSF/NFD to occur with the use of any of the approved GBCA."

c. EMEA Action: 2007

1. Contraindicated Omniscan: "in patients with severe renal impairment (GFR < 30 mL/min/1.73 m^2) and those who have had or are undergoing liver transplantation."
2. Warnings for other GBCA: "There have been reports of NSF associated with use of some gadolinium-containing contrast agents in patients with severe renal impairment (GFR < 30 mL/min/1.73 m^2). As there is a possibility that NSF may occur with XXXX, it should only be used in these patients after careful consideration."

d. American College of Radiology: 2007

1. "Patients with any level of renal disease should not receive Omniscan."
2. "For all patients with stage 3, 4, or 5 kidney disease or those with acute kidney injury, it is recommended that one consider refraining from administering any GBMCAs unless a risk-benefit assessment for that particular patient indicates that the benefit of doing so clearly outweighs the risks."
3. For dialysis patients, dialyze immediately post-GBMCA administration

VI. Minutes from Drug Safety Oversight Board Meeting
See Appendix A

VII. Office of Surveillance and Epidemiology Consult
See Appendix B

VIII. REVIEWERS CONCLUSIONS AND RECOMMENDATION FOR FUTURE REGULATORY ACTION

1. My conclusion is that there is an undeniable and strong association between NSF and GBCAs. Although all GBCA exposure could potentially increase the risk of renal failure patients for NSF, to date, there have only been unconfounded cases of NSF in association with Omniscan, Magnevist and far fewer with OptiMARK. There is one case associated with MultiHance but this case was

confounded by a subsequent exposure to Omniscan. To date there have been no cases of NSF seen in association with ProHance.

The reason that I believe that Omniscan confers a greater risk for NSF is 3 fold:

a. Over twice as many cases have been seen with Omniscan than all the other agents combined. This difference is accentuated in the peer reviewed literature where there are only 2 cases of NSF reported in association with Magnevist and over 60 cases of NSF reported in association with Omniscan.
b. The U.S. patient exposure data for the different agents which was gotten from a reliable source (Arlington Medical Resources) estimates that Magnevist is responsible for 50% of the exposures to GBCAs, 3% for Omniscan followed by Prohance at approximately 10%. The others, MultiHance and OptiMARK account for approximately 5% of the patient exposure.
c. The different agents have different degrees of binding affinities between the gadolinium ion and the chelate. It is currently theorized that the pathophysiology of NSF may relate to the presence of free gadolinium ion in the tissues. Of all the agents, Omniscan has the greatest propensity for the occurrence of dechelation.

2. My recommendations are that there should be Class Labeling and a Boxed warning for all agents should be implemented that includes the following informational items:
    a. NSF, a disabling and potentially lethal condition, has been seen in association with most but not all of the 5 FDA approved agents, and most prominently with Omniscan.
    b. This prominence can not be explained by patient exposure data alone.
    c. The only epidemiological studies have been done with Omniscan and that the risk is approximately 4%, ie, in a high risk patient population exposed to Omniscan, the risk of developing NSF is 4%. The risk of developing NSF after exposures to the other GBCAs is not known.

d. Acute renal failure in the setting of hepatorenal syndrome and peri-liver transplant setting may increase risk for NSF
e. High dose, repeated dose over a short period of time and degree of renal insufficiency appear to be risk factors for the development of NSF.
f. At risk patients should be given the lowest dose possible if a GBCA agent needs to be administered. Giving repeated doses of GBCA within short time intervals needs to generally be avoided if possible.
g. Hemodialysis dramatically increases the rate of clearance of GBCAs in dialysis dependent patients. Therefore, hemodialysis within a 2 hour period of exposure should be highly considered.

3. All manufacturers of GBCAs should be asked to provide their exposure data to the FDA over the last year.

4. A voluntary patient registry should be implemented

Appendix A

Gadolinium Products: Considering and Refining Possible Options

Dr. Melanie Blank presented: an overview of the molecular/chemical structure of the five Gadolinium-based contrast agents (GBCA) that are currently marketed in the U.S. [see attached]; a brief history of the identification and documentation of Nephrogenic Systemic Fibrosis (NSF) as a unique disease associated with exposure to GBCA; and a possible explanation for the biologic plausibility, based on the molecular structure of the various GBCAs, for implicating exposure to some GBCAs as a cause of NSF and others not at this point.

All five GBCA products (which are from four different sponsors) are FDA-approved for use in CNS MRI. Three of these products are also approved for use in non-CNS "body" imaging. These three products have been directly implicated in the development of NSF. The three products that have been directly implicated as causing NSF have the largest market share of sales of GBCA products.

The five GBCA share many similar characteristics but differ in chemical structure, gadolinium-chelation, equilibrium constants and formulations. The EMEA has contraindicated only one GBCA for use in patients with severe renal impairment, which they defined as a glomerular filtration rate (GFR) of <30 mL/min/1.73m^2 and those who

have had or who are undergoing liver transplant. The other GBCA products sold outside the U.S. carry only Warnings about the risk for NSF.

DMIHP is considering class labeling for these products, pending discussions and finalization of OSE review findings. The reason presented as to why class labeling versus the approach being taken by the EMEA was that a consequence of having different labeling (contraindicate in the three GBCAs that appear to be associated with NSF) could be that the two products that are only approved for CNS MRI would be viewed as being safer and as a result effect off-label use of these products. In addition, if the three products linked to case reports of NSF have a contraindication, there will be no GBCA approved for body MRI in patients at risk for NSF.

A question was asked as to whether the denominator was known and if we could use sales data as a surrogate for the actual denominator. It was pointed out that in this particular case, the numerator was the greater issue because apparently the recent reports have been in batches from five or six institutions, and we recently received reports of 25 new cases all coming from a single institution. The utilization data we have is limited, but it estimated that roughly ten million contrast MRI procedures are performed per year. Also complicating the situation is the fact that those patients who developed NSF did so a while after their procedure as a result the reports were as a result of a retrospective look-back, thus leaving one with no "good" way of knowing which agent was actually used. In addition, GBCA purchase is done in bulk by MRI facilities, and there are no records that allow trace back of a patient to a specific GBCA product and lot.

Questions for the Board:

1. Do you agree with an approach similar to that of the EMEA, to have class labeling that includes Warnings for all five GBCA drugs but Contraindications for the three drugs indicated for body imaging?

    a. If not, please provide your best advice/recommendation regarding the class labeling.

    -Only Warnings for all
    -Contraindications and Warnings for all
    -Versions of differential labeling

2. Do you have suggestions regarding systematic processes for on-going safety monitoring, such as sponsor registries?

3. Please comment upon risk communication procedures (PHA/HCP sheet).

    a. Given that five products are involved and four sponsors, coordination of a single Dear Healthcare provider letter from all four sponsors may prove difficult or impossible. Do you regard FDA communication as sufficient without Dear Healthcare provider letters?

b. Besides an updated PHA/HCP, do you suggest any other public communication from FDA?

In response to the first question, the Board clarified that the approach used by the EMEA is not appropriate here because the US regulatory definition for a contraindication is different. The EMEA defines "contraindication" in relative terms. However, in the US, a product is contraindicated only when the risk always outweighs the benefit of use, and thus the product should never be used in the contraindicated situation. For the GABCs, there are circumstances (such as tumor identification) when administration of a GABCs to patients with severe renal failure may be necessary. The fact that NSF is likely to be grossly under reported was also recognized and to give any sort of benefit of doubt to any of the products would be giving a margin of comfort in the absence of information.

Following a discussion, the DSB recommended by consensus that the new labeling should include a Boxed Warning that would carry the same language for every product in the class. The Boxed Warning should briefly describe the illness (NSF), state the conditions for considering when to use/not use a GABC e.g., in patients with a GFR <30 mL/min. The Warnings could provide the specifics of the best overall estimate of NSF "attack rates" and provide guidance on dialysis post-procedure. The Boxed Warning would generally include the same language for each product in the class, with the exception of case descriptions. Those products that have been linked to case reports of NSF would state that (for example, "Patients have developed NSF after exposure to this drug") and products not linked would state that patients have developed NSF after exposure to other drugs in this class.

With regard to a systematic process for safety monitoring, the group discussed considering a multi-company exposure registry in order to identify a large number of exposed patients. The exposure registry could serve as a source of cases for a case control study, offering the advantage of defining GABC exposure prior to development of NSF. It was also mentioned that a registry of use could potentially provide enough information that the need for a case study could be eliminated. The question posed at the end of the discussion was regarding the issue of follow up of patients in a registry.

The last question discussed was regarding risk communications. There appeared to be agreement that there should be a new, more definitive recapitulation of the PHA and "sheet". Also discussed was the need for further discussion regarding increased risk with repeat use. The idea of having a conference call with stakeholders (including radiologists, nephrologists, general practitioners/family practice) and also working with them to disseminate our communications in effort to reach the largest audience was accepted by the group. It was further recommended that we update our information frequently and include the message that absence of cases does not imply there is no risk. There was uniform agreement to have a single "Dear Healthcare Provider" reviewed by us and sent by all four companies.

Appendix B
EXCERPT from the
MEMORANDUM by OSE's Allen Brinker, M.D. Susan Lu, R.Ph , and Kate Gelperin, M.D. dated May 10, 2007

SUBJECT: **Nephrogenic systemic fibrosis in association with gadolinium-based contrast agents**

RCM NUMBER: 2006-491

EXECUTIVE SUMMARY

Through February, 2007, FDA adjudicated 128 cases of nephrogenic systemic fibrosis or NSF following the administration of gadolinium-based contrast agents. Seventy-four (74) of these cases are linked to the gadolinium-based contrast agent Omniscan, 39 linked to the agent Magnevist, and 7 linked to the agent Optimark. Eight (8) cases stated only "gadolinium" and thus did not identify a specific agent. Six (6) cases specified receipt of multiple agents. These case counts include data from a primary case series (n=103) and a secondary analysis (n=25) of NSF reported in association with use of Magnevist that are consistent with the case criteria utilized in the primary analysis.

The mean age of cases within the primary case series was 50.3 years with male: female ratio of 1.8:1. Twenty (20) cases represented patients status-post renal transplant. An additional 15 cases represented patients status-post liver transplant. Of note, most cases within the primary case series were reported within a "batch" of two or more reports and reported more than one exposure to a gadolinium-based contrast agent. Absolute time to onset is thus difficult to infer from these data as it is unknown if the data within a selected case report describes time from the first exposure (if that is even known with certainty) or time since most recent exposure. With this substantial caveat, the *REPORTED* median time to onset is 23 days (mean = 56 days), with range from 1 day to 14 months. All

This memorandum is dedicated to the memory of Dr. Alice Chow who died before this review was completed.

adjudicated cases reported a clinical diagnosis of chronic or acute renal failure. Although the Agency is in possession of NSF reports describing patients with unspecified renal function, through April 2007 and after diligent follow-up on over 200 reports, there are no known documented cases of gadolinium contrast agent-associated NSF in patients with apparently normal or moderately impaired renal function.

As noted above, the majority of adjudicated cases of gadolinium contrast agent-associated NSF known to the Agency were reported within a "batch" of one or more reports in contrast to typical, isolated and apparently spontaneous reporting. Therefore, it is problematic to assume the relative case counts could be representative even with adjustment for exposure / utilization. To this end, the Agency does not have access to independent (Agency-based) exposure data. If adverse event reporting is a surrogate for exposure, then the apparent exposure to Magnevist, Prohance, and Omniscan would appear to be much greater than the exposure to Optimark and Multihance.

Although a causal association between gadolinium-based contrast agents and NSF has yet to be demonstrated through epidemiological studies, DDRE nonetheless recommends addition of a strong WARNING for NSF in product labeling for all 5 currently approved gadolinium-based contrast agents based on the clinical severity of gadolinium-based contrast agent associated NSF and the strength of the available data. This WARNING should note that gadolinium-based contrast agent-associated NSF has only been documented in the setting of documented renal failure or severe renal dysfunction. This case series includes 15 patients immediately status-post liver transplantation. Given the frequency of liver transplantation, this suggests this group of individuals may be at heightened risk for gadolinium-based contrast agent-associated NSF. Thus, it is also prudent to include perioperative liver transplantation as an apparent risk factor for gadolinium-based contrast agent-associated NSF.

The physico-chemical properties of Omniscan (n=74 cases) suggest that it may be associated with an increased risk for gadolinium-based contrast agent-associated NSF. However, the case series reported herein is unique to spontaneous reporting due to the

substantial number of reports submitted within batches from selected institutions. This suggests that reporting in this case has not been spontaneous and cases are not independent of each other. This limits the Agency's ability to infer differential risk for NSF between gadolinium-based contrast agents. This case series also contains NSF cases reported in association with Optimark (n=7), which has physico-chemical properties similar to Omniscan, and Magnevist (n=39 in total). This case series contains no NSF cases to date in association with the gadolinium-based contrast agent Prohance. One Omniscan-associated case also reported remote exposure to Multihance. No other cases in association with Multihance have been identified. Although we recommend a WARNING for NSF for all five gadolinium-based contrast agents, it may be prudent to consider stating differences in the presence or absence of NSF reports within approved labeling for all of these agents.

DDRE further recommends the Agency communicate to the public:1) that all cases of gadolinium-based contrast agent-associated NSF reported to date have occurred in patients with clinically significant (severe) renal failure; 2) there is no evidence that prophylactic dialysis decreases the risk for NSF following exposure to a gadolinium-based contrast agent regardless of renal function; and 3) patients immediately status-post liver transplantation may be at heightened risk for gadolinium-based contrast agent-associated NSF.