
GE Healthcare Position Paper on NSF

April 2008

Eric S. Cantor, MD
Medical Director, Americas
GE Healthcare

Adrian Holden, MBBS
Medical Director, Europe & International
GE Healthcare

Derek Grant, PhD
Director, Discovery Biology
GE Healthcare

Please see Omniscan prescribing information located at the end of this document.

Table of Contents

Executive Summary	1
Review of Nephrogenic Systemic Fibrosis (NSF)	2
Reports of Contrast Media Involvement in NSF	3
Response of Health Authorities	4
Professional Societies' Guidance	5
Epidemiological Considerations	6
Stability of Gadolinium Contrast Agents <i>In Vivo</i>	7
Pharmacokinetic Studies	
Stability Data: Summary	
Animal Studies	
Conclusion	
References	11
Prescribing Information	13

Executive Summary

- Nephrogenic systemic fibrosis (NSF) is a rare, but serious, acquired systemic disease. To date, it only has been reported in patients with severely impaired renal function with a glomerular filtration rate (GFR) $< 30 \text{ mL/min/1.73m}^2$, who are on or approaching dialysis and those in acute renal failure. At present, there is no evidence that patients without renal impairment are at risk of developing this disease.
- Limited data are currently available on the causality of NSF; however, case reports and retrospective studies have demonstrated a strong association with the administration of gadolinium-based contrast agents [GBCAs] in renally-compromised patients, with the development of NSF.
- As of January 2008, GE Healthcare has logged, from multiple sources (MedWatch, healthcare professionals, literature, legal, etc.) approximately 340 reports of NSF after Omniscan™ (gadodiamide Injection) administration. This is usually associated with exposure to high doses. These cases have been reported to the FDA and global health authorities in accordance with regulatory guidelines.
- GE Healthcare actively seeks out and logs all cases that can provide patient identification information and claim to be NSF associated with Omniscan. Biopsy confirmation is not required and in the current database approximately 57% of the cases reported have had biopsy confirmation.
- The case reports of NSF from a number of countries indicate that almost all GBCA have been associated with the development of NSF.
- Health authorities have required label changes for all GBCA.
- Spontaneous reports early in an event's history do not necessarily imply a statistically significant difference in risk between agents.
- Predictions of in vivo stability and toxicity of gadolinium chelates based on an in vitro measure of stability such as thermodynamic stability may be inadequate, inconsistent, and potentially misleading.
- There are increasing numbers of cases in the literature describing NSF in patients with no history of gadolinium (Gd) exposure, supporting the view that NSF is a complex disease with a number of contributing factors, Gd may prove to be one, but not necessarily an essential factor.
- GE Healthcare is committed to ensuring the safety of patients, and to keeping our customers fully informed about using our products in the safest and most effective manner. The company recommends that all adverse events should be reported promptly to GE Healthcare or appropriate regulatory agencies.

Review of Nephrogenic Systemic Fibrosis (NSF)

Nephrogenic systemic fibrosis (NSF) is a rare, but serious, acquired systemic disease. To date, it only has been reported in patients with severely impaired renal function with glomerular filtration rate (GFR) <30 mL/min/1.73m², who are on or approaching dialysis and those in acute renal failure. There is no evidence that patients without renal impairment are at risk of developing this disease.¹ First described in the US in 2000,² identifying a case from 1997, NSF was initially thought to be confined to the skin and was named nephrogenic fibrosing dermopathy (NFD). In some patients, however, there is clinical involvement of other tissues (lung, skeletal muscle, heart diaphragm, esophagus, etc) and it is now commonly referred to as NSF. It can be a painful and debilitating condition that can contribute to a fatal outcome.

Risk factors associated with NSF include severe renal impairment, metabolic acidosis, hypercoagulability states, thrombotic events, high dose erythropoietin (EPO), recent vascular surgery, systemic inflammation, recent transplant failure, or sudden onset kidney disease with severe swelling of the extremities.⁵ Case studies indicate that NSF patients commonly have undergone a vascular surgical procedure or have experienced a thrombotic episode approximately two weeks before disease onset.⁶ There appears to be no predilection for any race/ethnic group, gender or age. NSF has been reported in children as young as 8 years old⁷ and in the elderly, but the majority of NSF reports are in middle-aged patients.⁵ There is no evidence that immature kidney function in neonates and infants in itself constitutes an increased risk of developing NSF. The reduced level of renal function is physiological in infants and neonates, and therefore normal for age, whereas the reduced renal function in adults in the setting of renal insufficiency is pathologic.

While the precise cause of NSF is still under investigation, exposure to a gadolinium-based contrast agents (GBCA) has been associated with NSF. Cases of NSF have been reported with all GBCA approved for use in the US, indicating that, to the extent there is an association, this may be a class-wide issue, and the FDA has consistently treated it as such.⁸ In Europe, the number of reported cases of NSF is lower than in the US and the European regulatory bodies have applied differential labeling to different GBCA. Currently the majority of available GBCA have been associated with NSF either as the sole agent administered or in confounded cases, i.e, associated with multiple gadolinium agents.

It is difficult to calculate a reliable estimate of an incidence rate or determine the relative safety of GBCA because many of the reported cases of NSF have occurred in clusters and have been based on spontaneous post-marketing reports. However, Deo et al have estimated an incidence rate of NSF in renally impaired patients (CKD Stage IV and V) exposed to gadolinium (Gd) to be 4.3 cases per 1,000 patient-years.⁹ The vast majority of renally-impaired patients who receive Gd have not developed NSF. Information from the American National Kidney Foundation estimates that 0.04% of the general population has Stage IV kidney disease. (GFR 15-30mL/min/1.73m²)

According to published literature, no definite causal link has been established for any GBCA to date, and other factors, in addition to GBCA, are likely to be involved in the pathogenesis of NSF.¹⁰ Nevertheless, the association between GBCA and NSF must be addressed in the interests of patient safety. Because of the uncertainty surrounding the cause(s) of NSF, and the possible causal role of GBCAs in the development of NSF in renally-compromised patients, it is reasonable to assume, until proven otherwise, that GBCA may pose a risk of NSF in patients with severe renal impairment. It also is important to distinguish between an association and actual causation, which is still unknown.

Reports of Contrast Media Involvement in NSF

In April 2006, GE Healthcare promptly reported to health authorities 25 NSF cases that had occurred during a 4-year period at two European hospitals. This was shortly after GE Healthcare became aware of these case reports and their alleged association to Omniscan. In response to these reports, and in close collaboration with GE Healthcare, the Danish Medicines Agency posted a healthcare advisory on its web site 29 May 2006, and the Food and Drug Administration (FDA) published a Public Health Advisory (PHA) on its web site on 8 June 2006 alerting the public to these reported cases of NSF¹¹.

During the same period of time, in June 2006, and in coordination with regulatory authorities, GE Healthcare distributed “Dear Healthcare Professional” (DHP) communications in several European and Asian countries and in the United States, informing healthcare providers about these reported cases of NSF associated with the use of Omniscan. In December 2006, GE Healthcare sent an updated DHP letter in the US reporting additional cases of NSF. As part of these communications, GE Healthcare actively solicited the reporting of any known or suspected cases of NSF associated with the use of Omniscan. Letters also were sent in many European countries in February 2007 in connection with a product license change for all gadolinium agents (see “Response of health authorities”).

To date, the database of NSF cases identified by GE Healthcare includes approximately 340 cases. These have been reported by GE Healthcare to regulatory authorities worldwide. Most cases originate from the US, and while only recently reported to GE Healthcare, have occurred over a period of several years (see Figures 1 and 2).

What is most notable from Figures 1 and 2 is the decrease in the number of cases diagnosed in 2007. This suggests a downward trend in the number of new NSF cases and also has been reported by at least one other GBCA manufacturer.

GE Healthcare is currently supporting efforts by the American College of Radiology (ACR) to develop a standard definition for NSF and we continue to seek additional information on the cases logged to make these data as accurate as possible. Until such time that a definition exists and all cases have been confirmed to a standard, careful consideration should be given when using information collected from a spontaneous reporting system.

Figure 1. Number of NSF cases by year of diagnosis

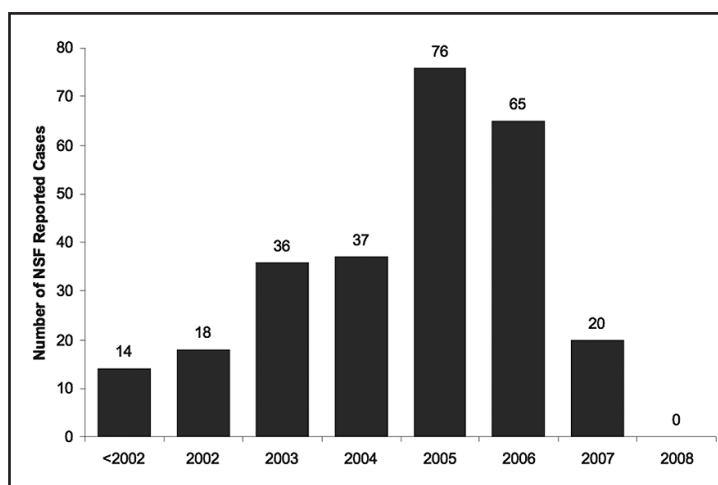
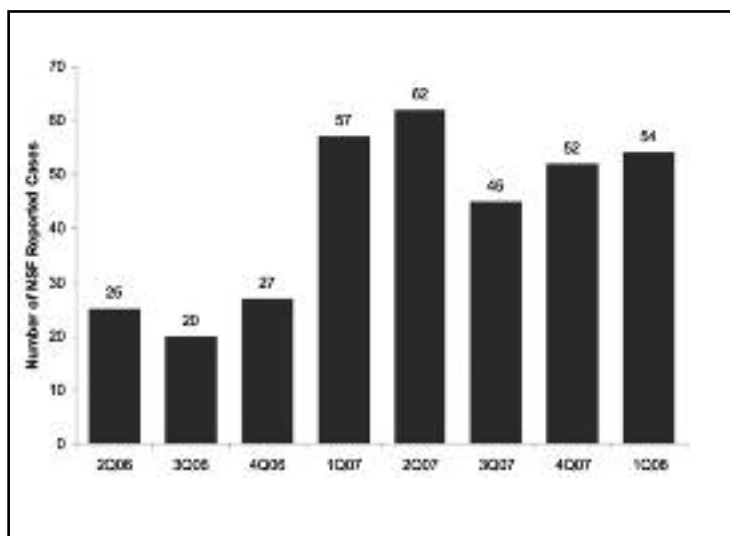


Figure 2. Number of NSF cases by date reported

There are 36 cases where no diagnosis dates have been reported.*



*There have been no new reports of diagnosed NSF in Q407 or Q108.

Response of Health Authorities

Regulatory agencies have taken an incremental approach, based on a review of the available scientific information, in dealing with the association between GBCA and NSF.

The FDA issued Public Health Advisories (PHAs) applicable to all GBCA in June and December 2006.¹¹

In May 2007, the FDA requested class label changes for the entire class of GBCA that included a new boxed warning¹²:

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

- Acute or chronic severe renal insufficiency (glomerular filtration rate < 30mL/min/1.73m²), 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 re-administration.”

In addition to requesting label changes, the FDA revised information from the December PHA by specifying the patient groups thought to be at risk: the available data show NSF risk in patients with severe renal insufficiency, whether acute or chronic, but not moderate renal insufficiency.

European regulators recommend caution with the use of all GBCA in certain groups of patients, but at this time they have not recommended the same label change for all products. In early 2007, in cooperation with the European Community Pharmacovigilance Working Party (PhVWP), GE Healthcare modified prescribing information to include a contraindication for Omniscan in patients with severe

renal insufficiency and in liver transplant patients. The new label also states that Omniscan should be used in neonates and infants under one year of age only after careful consideration and with caution in patients with moderate renal insufficiency. The PhVWP also recommended a warning for all other GBCA in patients with severe renal impairment. In June 2007, the PhVWP requested changes to the prescribing information for Magnevist [gadopentetic acid] comparable to those already affected for Omniscan. In keeping with the incremental, step wise approach, a question and answer document from the UK Commission on Human Medicines includes a statement that “This issue will be monitored closely as evidence accumulates, and new advice will be issued when necessary”.

Professional Societies’ Guidance

The American College of Radiology (ACR) and the European Society of Urogenital Radiology (ESUR) has produced documents to aid healthcare professionals in managing the risk of NSF associated with GBCA. Because each document is produced at a point in time and in a period in which clinical information is dynamic, there are aspects to each report that may require re-evaluation.

In March 2007, the ACR’s Blue Ribbon Panel on MR Safety released online (at ajronline.org) the “ACR Guidance Document for Safe MR Practices: 2007”.¹³ At the time this was published in AJR (June 2007), it was accompanied by an editorial from Dr van Moore,¹⁴ Chairman of the Board of Chancellors of the ACR. It laid out the levels of review necessary for the recommendations of this report to become ACR policy, and made clear that, at present, the report represents the opinion of the Blue Ribbon Panel and not official ACR policy. It is important to point out that at the time this guidance was published, 21 cases of NSF associated with Magnevist™ [gadopentetic acid] had been reported by Bayer Schering while Bracco had not reported any cases of NSF associated with their agents.

As of October 2007, there were 125 FDA reported cases for Magnevist™ and possibly 10 cases of NSF where Multihance™ [gadobenic acid] was one of the agents administered to the patient.¹⁵ This more deliberate approach to guidelines is warranted in a period of rapidly changing information. As noted above, the recommendations of the FDA have changed between December 2006 and May 2007 with respect to patients thought to be at risk of NSF. While the Blue Ribbon Panel document on Safe MR Practices (accepted for publication in December 2006) recommends against use of Omniscan in patients “with any level of renal disease”, in May 2007 the FDA clarified earlier reports and stated that it had not received any NSF reports for patients with moderate renal insufficiency.¹² We think it likely that the Blue Ribbon panel’s guidance will be reconsidered and amended as new information comes to light.

The academic members of the ESUR issued the “ESUR Guideline: Gadolinium based contrast media and Nephrogenic Systemic Fibrosis” in July 2007.¹⁶ A key feature of this guideline is to discriminate between GBCA, suggesting different levels of caution be taken between products (specifically, whether to measure serum creatinine before administration of the contrast agent). The conclusion that there are different risk levels is based on numbers of reported adverse events reported to date. As noted previously, the European regulatory agencies are making decisions in an incremental fashion. Initially, these bodies did not require a contraindication for Magnevist in severe renal impairment, but then did so in June 2007, after a substantial number of NSF cases were reported. This raises the question of whether patient safety is best served by trying to discriminate between agents based on incomplete and changing information. Some of the fundamental challenges in dealing with adverse event reporting are detailed in the next section.

Epidemiological Considerations

Relatively recent spontaneous case reports have formed the basis for hypotheses regarding the relationship of NSF to GBCA. Important considerations common to epidemiological science should be borne in mind before drawing conclusions from those data. The challenges involved in using spontaneous reporting of adverse events to gauge the risk posed by different products was emphasized by the FDA in their May 2007 Information for Healthcare Professionals:

“The lack of complete information of GBCA (gadolinium-based contrast agent) exposure, exposure to multiple GBCAs, along with similarities among all these contrast agents, make it impossible at present to definitively determine whether the extent of risks for developing NSF is shared by all GBCAs or vary for some of them.”¹²

Many cases of NSF have occurred in clusters and the numbers of reported Gd-associated cases have changed significantly over the months since reporting began, making it difficult to calculate a reliable estimate of an incidence rate or to make determinations regarding the relative safety of GBCA. Careful studies to estimate an incidence rate of NSF in renally-impaired patients exposed to GBCA⁹ suggest that the vast majority of renally-impaired patients who receive GBCA have not developed NSF, making it a difficult phenomenon to study through spontaneous reporting. Other factors that may affect the number of reported cases include:

- ***Differences in case definition and handling by manufacturers.*** To date, there has not been harmonization of case definition and reporting standards for NSF across all contrast agent manufacturers. For example, GE Healthcare has always taken a broad view of what constitutes NSF and a reportable adverse event, and has not and does not require biopsy confirmation or an exclusive link to Omniscan administration before reporting a case to regulatory authorities. The clinical and histopathologic criteria used by providers vary significantly across the globe.

GE Healthcare was the first manufacturer to distribute “Dear Healthcare Professional” communications on this issue. As part of these communications, GE Healthcare actively solicited the reporting of any known or suspected cases of NSF associated with the use of Omniscan. Thus, it is possible that the early number of reports for Omniscan may be attributable, at least in part, to the fact that GE Healthcare has proactively communicated on this issue and encouraged healthcare professionals to report NSF cases (see Figure 1 on page 3).

- ***Possible bias in reporting frequency.*** Reports to date have shown that cases of NSF occur in clusters from relatively few healthcare institutions and thus do not appear to be independent events. The increased number of early reports of NSF cases associated with Omniscan may, in part, have been due to reporting bias caused by increased physician awareness of the concern around Omniscan. It is well established that spontaneous reporting data do not provide a robust basis for assessments of relative safety since they are susceptible to inaccuracies, recall, and reporting bias. It is possible this imbalance in awareness and use of products is responsible for under-reporting of cases associated with other GBCA.
- ***Patient populations exposed to different GBCA.*** Determining the relative risk for different products would require knowing the number of administrations made to the population at risk. While numbers are easily obtainable for total doses of a product provided to medical professionals, it is not presently possible to determine the doses delivered to individual patients who are severely renally compromised. The number of doses administered to the at-risk population would not be a simple function of market share when products are predominantly used in different clinical settings (e.g., tertiary medical centers versus imaging centers), and when products have different approved indications and/or contraindications (e.g. pre-existing contraindications for use in renally-compromised patients that were present for some products in European countries prior to NSF becoming an issue). It also is

important to consider which products have been and are available in those countries from which the majority of cases have arisen. The majority of NSF cases have been reported in the USA. GBCA that are not licensed or used in the USA, such as Dotarem™ [gadoteric acid], Vasovist™ [gadofosveset], and Gadovist™ [gadobutrol], might be expected to have less associated cases under these circumstances.

- **Labeling differences between contrast agents.** It should also be noted that Dotarem has historically been contraindicated for use in patients with renal impairment in Germany and the Netherlands while Omniscan is indicated for use at a higher dose level than many other agents. Specific labeling varies by region and needs to be considered.

The uneven distribution of other factors that may contribute to the development of NSF might influence the clustering phenomenon and confound the spontaneous reporting data. Also, the appearance of NSF several years after the introduction of GBCA means that estimates of risk for a particular agent based on a simple metric of “doses delivered” would not be an accurate assessment of risk.

Stability of Gadolinium Contrast Agents *In Vivo*

Theoretical Considerations

Grobner¹⁷ and Broome et al,¹⁸ among others, have suggested that one mechanism by which a gadolinium-based contrast agent (GBCA) might trigger NSF is through release of free gadolinium ions, possibly through transmetalation (a reaction in which an endogenous metal such as zinc is exchanged for the gadolinium in the chelate). Broome et al stated that, if the free gadolinium postulate was true, then gadolinium chelates with lower stability constants would be more likely to release gadolinium and this might trigger NSF. Broome referred to gadodiamide as one agent with a lower stability constant compared to other agents. The relevance of this measurement is unclear. Several other publications have addressed the stability of GBCA and of Omniscan in particular.^{19,20}

The role of stability constants (including the important factor of selectivity of the ligand for gadolinium over other endogenous metal ions) in the aetiology of NSF is still under scientific investigation. Much of the research conducted to date is in animals or in vitro, and the relevance of such studies to humans must be judged very carefully. Furthermore, the human studies must be viewed in light of the entire body of knowledge on GBCA for proper interpretation. Although GBCA are associated with the development of NSF, it is not at all clear that free Gd release is the causative mechanism of the association.

- The intrinsic thermodynamic stability constant (K_{therm}), reflecting the affinity of a metal for a ligand is dependent on the conditions under which it is measured, and is greatly influenced by pH. Differences in thermodynamic stability constants between gadolinium chelates do not correlate with acute toxicity or reported numbers of cases of NSF.
- The selectivity constant (K_{sel}), indicates the selectivity of the ligand for the bound metal over other endogenous ions, particularly zinc. Omniscan has a high K_{sel} value. K_{sel} correlates better with acute toxicity (LD_{50}) than does K_{therm} , and though related to stability, does not correlate to the numbers of NSF cases reported to date.
- The kinetics, or the rate of transmetalation reactions, if they are substantially slower than their clearance rates, can result in significantly lower toxicity than predicted by the thermodynamic stability constant, solubility, and selectivity.

The most often quoted measure of stability is the intrinsic thermodynamic stability constant (K_{therm}), which is expressed in logarithmic terms. This number is measured in vitro under extreme conditions that would be incompatible with life.

As shown in the recent article by Ersoy²¹, stability constants become increasingly similar as the constant reflects a more physiological environment. The table below shows the conditional stability constants, which reflect the calculated stability at a pH of 7.4.

Table 1: Thermal stability constants of GBCA in vitro

	Dotarem®	ProHance®	MultiHance®	Magnevist®	OMNISCAN™	OptiMARK®
Stability log K_{therm}	25.4	22.8	22.6	22.1	16.8	16.6

In terms of the conditional stability constant, Magnevist, a linear GBCA, is currently associated with 125 FDA reported cases of NSF, but it is more stable than ProHance, a macrocyclic GBCA, which is currently associated with one case of NSF unconfounded with any other GBCA.

Table 2: Thermal stability constants of GBCA at pH 7.4 reflective of a more physiological environment

	Dotarem®	ProHance®	MultiHance®	Magnevist®	OMNISCAN™	OptiMARK®
Stability log K_{cond}	19.0	17.1	18.4	17.7	14.9	15.0

Of note is that the drop in stability from thermodynamic to conditional constants is much greater for the macrocyclics, than for Omniscan. The stability of Dotarem and ProHance™ [gadoteridol], for example, decreases approximately 1,000,000 times compared to 100 times for Omniscan. It is unknown whether this trend continues further with increasingly physiological conditions, for example, where other cations are present, such as sodium, calcium, potassium, zinc, etc.

Some authors also raise the question of different kinetic stability and point out that the macrocyclic agents have higher kinetic stability than the linear agents. However, as with thermodynamic stability, this is an in vitro measurement performed at non-physiological pH. As such it is unclear what relevance this has to the clinical situation especially when one considers that there is no good evidence linking the stability of GBCA to NSF. The claims of greater safety of macrocyclic agents due to higher stability are further brought into question as there is a non-confounded NSF case associated with ProHance, a macrocyclic GBCA. This raises questions about the potentially simplistic message that macrocyclics are safe with respect to NSF.

As no comparative in vivo constants are available, it is impossible to know how the stability of the products would compare in a truly physiological setting. What is clear is the difference in numbers of reported cases cannot be solely explained through the stability constants that are commonly referenced in the literature. This is supported by a recent article by Dr. Mark Perazella from Yale University School of Medicine, and Dr. Robert Reilly from the Department of Medicine, University of Texas Southwestern, where they question if the stability of chelated agents can be used to explain relative toxicity.²² Regardless of this, GE Healthcare continues to invest heavily into research to fully understand the stability of agents in vivo and determine if there is any relevance to NSF.

Clearly more needs to be considered in evaluating in vivo stability of contrast agents. Cacheris et al²³ attempted to clarify the situation using “biospeciation” calculations, which take into account the relative stabilities of possible complexes. They defined the selectivity constant (K_{sel}), which is a hybrid constant applicable at pH 7.4 that takes into account the various possible ion exchange reactions in the body. K_{sel} indicates the selectivity of the ligand for gadolinium over endogenous ions (hydrogen, zinc, copper, calcium.) Iron was not included in their calculations because it is so tightly bound to ferritin as to be unavailable for reaction.

Pharmacokinetic Studies

Several studies have investigated the pharmacokinetics of Omniscan *in vivo*. These indicate the kinetics of tissue uptake and release of GdDTPA-BMA are different compared to free gadolinium, and show that GdDTPA-BMA is stable in plasma and is excreted unchanged in the urine.²⁵

If Omniscan was prone to dechelation *in vivo*, then it would be expected that this would lead to detection of metabolites, and for the distribution and retention kinetics to resemble that of the free Gd metal. However, several studies have shown that there is no detectable metabolism of the injected chelates, even in patients with prolonged retention due to renal impairment.^{28,29} Similarly, in experimental animals the biotransformation of ¹⁴C-gadodiamide was studied after i.v. injection in rats of 0.3 mmol/kg of a radiolabeled formulation of gadodiamide injection. Biotransformation in blood was negligible, and gadodiamide was excreted unchanged in the urine.²⁷ In further studies in rodents, the distribution of gadodiamide was shown to be quantitatively and qualitatively different to that of the free Gd metal.^{25,30} These findings were supported by autoradiography data, which showed that the tissue distribution of ¹⁵³Gd-labeled gadodiamide was similar to that of ¹⁴C-labeled gadodiamide, demonstrating that both metal and ligand behaved in exactly the same way.³¹ Supporting evidence comes from a study showing that the serum concentration of total gadolinium, analyzed by inductive coupled plasma-atomic emission spectroscopy (ICP-AES), was identical to the serum concentration of the gadodiamide complex analyzed by HPLC, indicating that all gadolinium was in the form of the gadodiamide complex.³¹

The serum and peritoneal dialysate samples from end-stage renal disease patients were analyzed for the concentrations of gadolinium and GdDTPA-BMA by ICP-AES and HPLC, respectively.²⁹ Samples obtained 2, 4 and 7 days after dosing were compared with similar samples obtained shortly after dosing. There were no differences in the results using the two different methods of chemical analysis at the 1 hr, 2, 4 or 7 days post-dosing time-points. These data showed that there was no measurable transmetalation of GdDTPA-BMA during the 7-day post-treatment period, or degradation of the ligand. In addition, a separate study showed that urine from renally-impaired patients treated with Omniscan also showed no evidence of biotransformation.³²

Stability Data: Summary

The different measures of stability indicate that *in vitro* measurement in simple solutions is, of itself, insufficient to predict *in vivo* behavior or toxicity. The *in vivo* stability of the Gd chelates may involve the interplay between a number of different variables including pH, other metal ions, endogenous ligands that can bind Gd and precipitating anions, as well as the elimination time in relation to the stability kinetics. All of these different factors may play a role in determining the stability of the Gd chelate, the release of Gd, and toxicity. Predictions of *in vivo* stability and toxicity of Gd chelates based on a single *in vitro* measure of stability such as thermodynamic stability are therefore inadequate.

If Omniscan were prone to dechelation *in vivo*, then it would be expected this would lead to detection of metabolites, and for the distribution and retention kinetics to resemble that of the free Gd metal. However, several studies have shown that there is no detectable metabolism of the injected chelates, even in patients with prolonged retention due to renal impairment, and the distribution of gadodiamide is quantitatively and qualitatively different to that of the free Gd metal.

Irrespective of these theoretical concerns over the stability of the different contrast agents and the possible role of Gd, the case reports of NSF from a number of countries show that most GBCA are associated with the development of NSF, indicating that, to the extent NSF is associated with the class of GBCA, it is a class-wide effect.

Animal Studies

Currently there is no animal model of human NSF. Although a recent publication by Sieber et al claims to have developed such a model, rats in that study had normal renal function and the key feature of dermal fibrosis was not present in those rats with reported skin changes.³⁸ The paper described skin lesions in rats treated for 20 days with either Omniscan or gadodiamide and no lesions in rats treated with Magnevist (which is known to be associated with reported cases of NSF).³⁸ The lesions, both grossly and histomorphologically, were very similar to those reported 15 years ago in a repeat dose study by Harpur et al.³⁹ Sieber et al reported only minimal to slight dermal fibrosis and increased infiltration of different cells, partly positive for CD34 cells, which is somewhat different to the significant fibrosis and other histomorphological changes seen in human NSF.⁴⁰

Edward et al demonstrated that fibrocytes cultured from NSF patients produced more collagen and hyaluronan than would normally be expected. When NSF sera was added to an *in vitro* culture of normal fibrocytes without gadolinium, these fibrocytes began to produce increased collagen and hyaluronan as well. Although the addition of gadodiamide to fibrocyte culture increased proliferation of fibrocytes, it is worthy of note that exposure to GdCl₃ did not produce fibrocyte stimulation. This calls into question the theory of free Gd causation of NSF seen in the Sieber study.

There is a possibility that the rat has a predilection for developing these particular skin lesions after exposure to very high doses of Omniscan. Daily intravenous injections for 28 days with 1.25 mmol/kg/day Omniscan to nonhuman primates, a cumulative dose of 35 mmol/kg or 350 times the standard clinical dose, only produced renal proximal tubule vacuolation and reduced blood levels of zinc and inorganic phosphorus; no gross or microscopic skin lesions were seen.³⁹ The pruritus, excessive scratching and, as a consequence, superficial abrasions of the skin may explain these lesions. In summary, as dermal fibrosis is a cardinal feature of human NSF, the lack of clear evidence of it in the Sieber study, no histomorphological changes in the rats given Magnevist coupled together with the primate results from Harpur, suggest that the rat does not represent a good model of NSF.

Conclusion

- Nephrogenic systemic fibrosis (NSF) is a rare, but serious, acquired systemic disease. To date, it only has been reported in patients with renal insufficiency, particularly those with severely impaired renal function with a glomerular filtration rate (GFR) < 30 mL/min/1.73m², who are on or approaching dialysis and those in acute renal failure. At present, there is no evidence that patients without renal impairment are at risk of developing this disease.
- Limited data are currently available on the causality of NSF; however, case reports have associated the administration of GBCA in renally compromised patients with the development of NSF.
- The case reports of NSF from a number of countries indicate that almost all GBCA have been associated with the development of NSF.
- Numbers of spontaneous reports early in an event's history do not necessarily imply a statistically significant difference in risk between agents.
- Predictions of *in vivo* stability and toxicity of gadolinium chelates based on an *in vitro* measure of stability such as thermodynamic stability may be inadequate, inconsistent, and potentially misleading.
- There are increasing numbers of cases in the literature describing NSF in patients with no history of gadolinium (Gd) exposure, supporting the view that NSF is a complex disease with a number of contributing factors of which Gd may be one, but not necessarily an essential factor.

- GE Healthcare is committed to ensuring the safety of patients, and to keeping our customers fully informed about using our products in the safest and most effective manner. The company recommends that all adverse events should be reported promptly to GE Healthcare or to appropriate regulatory agencies.
- GE Healthcare is proactively working with researchers and clinical experts across therapeutic areas to better understand the mechanisms of this disease, delineate risk, and ensure the safety of our products.

Omniscan™ (gadodiamide) Injection is a trademark of GE Healthcare.

Magnevist® (gadopentetate dimeglumine) injection is a registered trademark of Berlex Laboratories Inc.

ProHance® (gadoteridol injection) and MultiHance® (gadobenate dimeglumine injection) are registered trademarks of Bracco Diagnostics Inc.

References

1. Thomsen HS. Nephrogenic systemic fibrosis: a serious late adverse reaction to gadodiamide. *Eur Radiol.* 2006; 16:2619-2621.
2. Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet.* 2000;356:1000-1001.
3. Ting WW, Stone MS, Madison KC, Kurtz K. Nephrogenic fibrosing dermatopathy with systemic involvement. *Arch Dermatol.* 2003;139:903-906.
4. Cowper SE, Bucala R, LeBoit PE. Nephrogenic fibrosing dermatopathy/nephrogenic systemic fibrosis – setting the record straight. *Semin Arthritis Rheum.* 2006;35:208-210.
5. Cowper SE. The International Center for Nephrogenic Fibrosing Dermatopathy Research (ICNFDR). Official site of the Nephrogenic Fibrosing Dermatopathy (NFD/NSF) Registry, 1-6. Accessed March 27, 2007.
6. DeHoratius DM, Cowper SE. Nephrogenic systemic fibrosis: an emerging threat among renal patients. *Semin Dial.* 2006;19:191-194.
7. Jain SM, Wesson S, Hassanein A, Canova E, Hoy M, Fennell RS et al. Nephrogenic fibrosing dermatopathy in pediatric patients. *Pediatr Nephrol.* 2004;19:467-470.
8. FDA. Development of Serious and Sometimes Fatal Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermatopathy. *Journal of Radiology Nursing.* 2007;26:29-30.
9. Deo A, Fogel M, Cowper SE. Nephrogenic Systemic Fibrosis: A Population Study Examining the Relationship of Disease Development to Gadolinium Exposure. *Clin J Am Soc Nephrol.* 2007;2:264-267.
10. Kuo PH, Kanal E, Abu-Alfa AK, Cowper SE. Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. *Radiology.* 2007;242:647-649.
11. FDA. Public Health Advisory. Update on Magnetic Resonance Imaging (MRI) Contrast Agents Containing Gadolinium and Nephrogenic Fibrosing Dermatopathy. FDA. Accessed May 23, 2007.
12. FDA. Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging (marketed as Magnevist, MultiHance, Omniscan, OptiMARK, and ProHance). Accessed May 23, 2007.
13. Kanal E, Barkovich AJ, Bell C, Borgstede JP, Bradley WG, Jr., Froelich JW, et al. ACR Guidance Document for Safe MR Practices: 2007. *Am J Roentgenol.* 2007;188:1447-1474.
14. Van Moore A. Commentary on “ACR guidance document for safe MR practices: 2007”. *Am J Roentgenol.* 2007;188:1446.
15. Penfield JG, Reilly RE. Nephrogenic Systemic Fibrosis Risk: Is There a Difference between Gadolinium-Based Contrast Agents? *Semin Dial.* 2008;21:129-134.
16. Academic members of the ESUR Contrast Media Safety Committee. ESUR guideline*: Gadolinium based contrast media and Nephrogenic Systemic Fibrosis. Accessed July 17, 2007.
17. Grobner T. Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermatopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant.* 2006;21:1104-1108.
18. Broome DR, Girguis MS, Baron PW, Cottrell AC, Kjellin I, Kirk GA. Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *Am J Roentgenol.* 2007;188:586-592.
19. Idée JM, Port M, Raynal I, Schaefer M, Le Greneur S, Corot C. Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: a review. *Fundam Clin Pharmacol.* 2006;20:563-576.

20. Khurana A, Runge VM, Narayanan M, Greene JF, Jr., Nickel AE. Nephrogenic systemic fibrosis: a review of 6 cases temporally related to gadodiamide injection (Omniscan). *Invest Radiol.* 2007;42:139-145.
21. Ersoy H, Rybicki FJ. Biochemical safety profiles of gadolinium-based extracellular contrast agents and nephrogenic systemic fibrosis. *J Magn Reson Imaging.* 2007;26:1190-1197.
22. Perazella MA, Reilly RF. Nephrogenic Systemic Fibrosis: Recommendations for Gadolinium-Based Contrast Use in Patients with Kidney Disease. *Semin Dial.* 2008;21:171-173.
23. Cacheris WP, Quay SC, Rocklage SM. The relationship between thermodynamics and the toxicity of gadolinium complexes. *Magn Reson Imaging.* 1990;8:467-481.
24. Murphy KP, Szopinski KT, Cohan RH, Mermillod B, Ellis JH. Occurrence of adverse reactions to gadolinium-based contrast material and management of patients at increased risk: a survey of the American Society of Neuroradiology Fellowship Directors. *Acad Radiol.* 1999;6:656-664.
25. Hals PA, Høgset A. Disposition of gadolinium after high and low doses of gadolinium chloride to mice: Organ distribution, elimination, and subcellular localization in liver cells. *Magn Reson Med.* 1990;1199.
26. Van Wagoner M, O'Toole M, Worah D, Leese PT, Quay SC. A phase I clinical trial with gadodiamide injection, a nonionic magnetic resonance imaging enhancement agent. *Invest Radiol.* 1991;26:980-986.
27. Normann PT, Hals PA. In vivo stability and excretion of gadodiamide (GdDTPA-BMA), a hydrophilic gadolinium complex used as a contrast enhancing agent for magnetic resonance imaging. *Eur J Drug Metab Pharmacokinet.* 1995;20:307-313.
28. Joffe P, Thomsen HS, Meusel M. Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. *Acad Radiol.* 1998; 5:491-502.
29. Normann PT, Joffe P, Martinsen I, Thomsen HS. Quantification of gadodiamide as Gd in serum, peritoneal dialysate and faeces by inductively coupled plasma atomic emission spectroscopy and comparative analysis by high-performance liquid chromatography. *J Pharm Biomed Anal.* 2000;22:939-947.
30. Hustvedt SO, Normann PT. Biodistribution and elimination of gadolinium chelates and GdCl₃ in rats. *Soc Magn Reson.* 1999.
31. Normann PT, Hustvedt SO, Storflor H, Hals PA. Preclinical safety and pharmacokinetic profile of gadodiamide injection. *Clin MRI.* 1995;5:95-101.
32. Reinton V, Berg KJ, Svaland M, Andrew E, Normann PT, Rootwelt K. Pharmacokinetics of gadodiamide injection in patients with moderately impaired renal function. *Acad Radiol.* 1994;1(Suppl 1):S56-S61.
33. Gibby WA, Gibby KA, Gibby WA. Comparison of Gd DTPA-BMA (Omniscan) versus Gd HP-DO₃A (ProHance) retention in human bone tissue by inductively coupled plasma atomic emission spectroscopy. *Invest Radiol.* 2004;39:138-142.
34. White GW, Gibby WA, Tweedle MF. Comparison of Gd(DTPA-BMA) (Omniscan) versus Gd(HP-DO₃A) (ProHance) relative to gadolinium retention in human bone tissue by inductively coupled plasma mass spectroscopy. *Invest Radiol.* 2006;41:272-278.
35. Tweedle MF, Wedeking P, Kumar K. Biodistribution of radiolabeled, formulated gadopentetate, gadoteridol, gadoterate, and gadodiamide in mice and rats. *Invest Radiol.* 1995;30:372-380.
36. Boyd AS, Zic JA, Abraham JL. Gadolinium deposition in nephrogenic fibrosing dermopathy. *J Am Acad Dermatol.* 2007;56:27-30.
37. High WA, Ayers RA, Chandler J, Zito G, Cowper SE. Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. *J Am Acad Dermatol.* 2007;56:710-712.
38. Sieber MA, Pietsch H, Walter J, Haider W, Frenzel T, Weinmann HJ. A preclinical study to investigate the development of nephrogenic systemic fibrosis: a possible role for gadolinium-based contrast media. *Invest Radiol.* 2008;43:65-75.
39. Harpur ES, Worah D, Hals PA, Holtz E, Furuhashi K, Nomura H. Preclinical safety assessment and pharmacokinetics of gadodiamide injection, a new magnetic resonance imaging contrast agent. *Invest Radiol.* 1993;28:S28-S43.
40. Cowper SE. Nephrogenic systemic fibrosis: a review and exploration of the role of gadolinium. *Adv Dermatol.* 2007;23:131-154.

GE Healthcare



ONC-2S-OSLO

OMNISCAN™
(gadodiamide) Injection

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use OMNISCAN safely and effectively. See full prescribing information for OMNISCAN.

OMNISCAN™ (gadodiamide) Injection for Intravenous Use

Initial U.S. Approval: 1993

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).

NSF

- Gadolinium-based contrast agents (GBCAs) increase risk of NSF in patients with:
 - acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m²), 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.

NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs (5.2).

RECENT MAJOR CHANGES

- Boxed Warning: Nephrogenic Systemic Fibrosis (NSF) 9/2007
- Warnings and Precautions: hypersensitivity reactions, NSF, acute renal failure, inadvertent intrathecal use (5.1, 5.2, 5.3, 5.4) 9/2007

INDICATIONS AND USAGE

OMNISCAN is a gadolinium-based contrast agent for diagnostic magnetic resonance imaging (MRI) indicated for intravenous use to:

- Visualize lesions with abnormal vascularity in the brain, spine, and associated tissues (1.1)
- Facilitate the visualization of lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities, and the retroperitoneal space (1.2)

DOSAGE AND ADMINISTRATION

- CNS – Adults and Pediatrics; 2-16 years of age: 0.2 mL/kg (0.1 mmol/kg) (2.1, 2.4)
- Body – Adults and Pediatrics; 2-16 years of age:
 - Kidney: 0.1 mL/kg (0.05 mmol/kg)
 - Intrathoracic, intra-abdominal, and pelvic cavities: 0.2 mL/kg (0.1 mmol/kg) (2.2, 2.4)

DOSAGE FORMS AND STRENGTHS

Sterile aqueous solution for intravenous injection; 287 mg/mL (3)

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- 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 severe renal insufficiency. Higher than recommended dosing or repeat dosing appears to increase the risk (5.2).
- 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).

ADVERSE REACTIONS

- The most frequent adverse reactions (≤ 3%) observed during OMNISCAN adult clinical studies were nausea, headache, and dizziness (6.1)
- Serious or life-threatening reactions include: cardiac failure, arrhythmia and myocardial infarction (6.1, 6.3)

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

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

- 1 INDICATIONS AND USAGE**
 - 1.1 CNS (Central Nervous System)
 - 1.2 Body (Intrathoracic [noncardiac], Intra-abdominal, Pelvic and Retroperitoneal Regions)
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 CNS (Central Nervous System)
 - 2.2 Body (Intrathoracic [noncardiac], Intra-abdominal, Pelvic and Retroperitoneal Regions)
 - 2.3 Dosage Chart
 - 2.4 Dosing Guidelines
 - 2.5 Repeat Dosing
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Hypersensitivity Reactions
 - 5.2 Nephrogenic Systemic Fibrosis
 - 5.3 Acute Renal Failure
 - 5.4 Not for Intrathecal Use
 - 5.5 Impaired Visualization of Lesions Detectable with Non-contrast MRI
 - 5.6 Laboratory Test Findings
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Studies Experience (Adults)
 - 6.2 Clinical Studies Experience (Pediatrics)
 - 6.3 Postmarketing Experience
- 7 DRUG INTERACTIONS**
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
 - 8.6 Renal/Hepatic Impairment
- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES**
 - 14.1 CNS (Central Nervous System)
 - 14.2 Body (Intrathoracic [noncardiac], Intra-abdominal, Pelvic and Retroperitoneal Regions)
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 (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/1.73m²), 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 [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

1.1 CNS (Central Nervous System)

OMNISCAN is a gadolinium-based contrast agent indicated for intravenous use in MRI to visualize lesions with abnormal vascularity (or those thought to cause abnormalities in the blood-brain barrier) in the brain (intracranial lesions), spine, and associated tissues [see *Clinical Studies* (14.1)].

1.2 Body (Intrathoracic [noncardiac], Intra-abdominal, Pelvic and Retroperitoneal Regions)

OMNISCAN is a gadolinium-based contrast agent indicated for intravenous use to facilitate the visualization of lesions with abnormal vascularity within the thoracic (noncardiac), abdominal, pelvic cavities, and the retroperitoneal space [see *Clinical Studies* (14.2)].

2 DOSAGE AND ADMINISTRATION

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)].

2.2 Body (Intrathoracic [noncardiac], Intra-abdominal, Pelvic and Retroperitoneal Regions)

Adult and Pediatric Patients (2-16 years of age): For imaging the kidney, the recommended dose of OMNISCAN is 0.1 mL/kg (0.05 mmol/kg). For imaging the intrathoracic (noncardiac), intra-abdominal, and pelvic cavities, the recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg) [see *Dosage and Administration* (2.3)].

2.3 Dosage Chart

BODY WEIGHT		PEDIATRIC		ADULTS		
		0.05 (mmol/kg)	0.1 (mmol/kg)	0.05 (mmol/kg)	0.1 (mmol/kg)	0.2 (mmol/kg)
kg	lb	VOLUME (mL)		VOLUME (mL)		
12	26	1.2	2.4	-	-	-
14	31	1.4	2.8	-	-	-
16	35	1.6	3.2	-	-	-
18	40	1.8	3.6	-	-	-
20	44	2	4	-	-	-
22	48	2.2	4.4	-	-	-
24	53	2.4	4.8	-	-	-
26	57	2.6	5.2	-	-	-
28	62	2.8	5.6	-	-	-
30	66	3	6	-	-	-
40	88	4	8	4	8	16
50	110	5	10	5	10	20
60	132	6	12	6	12	24
70	154	7	14	7	14	28
80	176	8	16	8	16	32
90	198	-	-	9	18	36
100	220	-	-	10	20	40
110	242	-	-	11	22	44
120	264	-	-	12	24	48
130*	286	-	-	13	26	52

*The heaviest patient in clinical studies weighed 136 kg.

2.4 Dosing Guidelines

Inspect OMNISCAN visually for particulate matter and discoloration before administration, whenever solution and container permit.

Do not use the solution if it is discolored or particulate matter is present.

Draw OMNISCAN into the syringe and use immediately. Discard any unused portion of OMNISCAN injection.

To ensure complete delivery of the desired volume of contrast medium, follow the injection of OMNISCAN with a 5 mL flush of 0.9% sodium chloride, as provided in the Prefill Plus needle-free system. Complete the imaging procedure within 1 hour of administration of OMNISCAN.

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)].

3 DOSAGE FORMS AND STRENGTHS

Sterile aqueous solution for intravenous injection; 287 mg/mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Anaphylactoid and anaphylactic reactions, with cardiovascular, respiratory and cutaneous manifestations, resulting in death have occurred. If such a reaction occurs, stop OMNISCAN Injection and immediately begin appropriate therapy. Observe patients closely, particularly those with a history of drug reactions, asthma, allergy or other hypersensitivity disorders, during and up to several hours after OMNISCAN Injection.

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/1.73m²) 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 the 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 [see *Clinical Pharmacology* (12.2) and *Dosage and Administration* (2)].

5.3 Acute Renal Failure

In patients with renal insufficiency, acute renal failure requiring dialysis or worsening renal function have occurred, mostly within 48 hours of OMNISCAN Injection. The risk of renal failure may increase with increasing dose of gadolinium contrast. Use the lowest necessary dose of contrast and evaluate renal function in patients with renal insufficiency. Acute renal failure was observed in < 1% of patients in OMNISCAN clinical studies [see *Adverse Reactions* (6)].

OMNISCAN is cleared by glomerular filtration. Hemodialysis also enhances OMNISCAN clearance [see *Use in Specific Populations* (8.5, 8.6)].

5.4 Not for Intrathecal Use

Inadvertent intrathecal use of OMNISCAN has occurred and caused convulsions, coma, sensory and motor neurologic deficits.

5.5 Impaired Visualization of Lesions Detectable with Non-contrast MRI

Paramagnetic contrast agents such as OMNISCAN might impair the visualization of lesions which are seen on the non-contrast MRI. This may be due to effects of the paramagnetic contrast agent, or imaging parameters. Exercise caution when OMNISCAN MRI scans are interpreted in the absence of a companion non-contrast MRI.

5.6 Laboratory Test Findings

Asymptomatic, transitory changes in serum iron have been observed. The clinical significance is unknown.

OMNISCAN interferes with serum calcium measurements with some colorimetric (complexometric) methods commonly used in hospitals, resulting in serum calcium concentrations lower than the true values. In patients with normal renal function, this effect lasts for 12-24 hours. In patients with decreased renal function, the interference with calcium measurements is

expected to last during the prolonged elimination of OMNISCAN. After patients receive OMNISCAN, careful attention should be used in selecting the type of method used to measure calcium.

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Clinical Studies Experience (Adults)

In clinical studies 1160 patients were exposed to OMNISCAN. The most frequent adverse reactions were nausea, headache, and dizziness that occurred in 3% or less of the patients.

The following adverse reactions occurred in 1% or less of patients:

Application Site Disorders: Injection site reaction.

Autonomic Nervous System Disorders: Vasodilation.

Body as a Whole-General Disorders: Anaphylactoid reactions (characterized by cardiovascular, respiratory, and cutaneous symptoms), fever, hot flushes, rigors, fatigue, malaise, pain, syncope.

Cardiovascular Disorders: Cardiac failure, rare arrhythmia and myocardial infarction resulting in death in patients with ischemic heart disease, flushing, chest pain, deep thrombophlebitis.

Central and Peripheral Nervous System Disorders: Convulsions including grand mal, ataxia, abnormal coordination, paresthesia, tremor, aggravated multiple sclerosis (characterized by sensory and motor disturbances), aggravated migraine.

Gastrointestinal System Disorders: Abdominal pain, diarrhea, eructation, dry mouth/vomiting, melena.

Hearing and Vestibular Disorders: Tinnitus.

Liver and Biliary System Disorders: Abnormal hepatic function.

Musculoskeletal System Disorders: Arthralgia, myalgia.

Respiratory System Disorders: Rhinitis, dyspnea.

Skin and Appendage Disorders: Pruritus, rash, erythematous rash, sweating increased, urticaria.

Special Senses, Other Disorders: Taste loss, taste perversion.

Urinary System Disorders: Acute reversible renal failure.

Vision Disorders: Abnormal vision.

6.2 Clinical Studies Experience (Pediatrics)

In the 97 pediatric patients in CNS studies with OMNISCAN [see *Clinical Studies* (14.1)] and the 144 pediatric patients in published literature, the adverse reactions were similar to those reported in adults.

6.3 Postmarketing Experience

Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during the postmarketing use of OMNISCAN:

Nervous System Disorders: Inadvertent intrathecal use causes seizures, coma, paresthesia, paresis.

General Disorders: Nephrogenic Systemic Fibrosis (NSF) [see *Warnings and Precautions* (5.2)].

7 DRUG INTERACTIONS

Specific drug interaction studies have not been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: OMNISCAN has been shown to have an adverse effect on embryo-fetal development in rabbits at dosages as low as 0.5 mmol/kg/day for 13 days during gestation (approximately 0.6 times the human dose based on a body surface area comparison). These adverse effects are observed as an increased incidence of flexed appendages and skeletal malformations which may be due to maternal toxicity since the body weight of the dams was reduced in response to OMNISCAN administration during pregnancy. In rat studies, fetal abnormalities were not observed at doses up to 2.5 mmol/kg/day for 10 days during gestation (1.3 times the maximum human dose based on a body surface area comparison); however, maternal toxicity was not achieved in these studies and a definitive conclusion about teratogenicity in rats at doses above 2.5 mmol/kg/day cannot be made. Adequate and well controlled studies in pregnant women have not been conducted. OMNISCAN should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when administering OMNISCAN to a nursing woman.

8.4 Pediatric Use

The safety and efficacy of OMNISCAN at a single dose of 0.05 to 0.1 mmol/kg have been established in pediatric patients over 2 years of age based on

adequate and well controlled studies of OMNISCAN in adults, a pediatric CNS imaging study, and safety data in the scientific literature. However, the safety and efficacy of doses greater than 0.1 mmol/kg and of repeated doses have not been studied in pediatric patients.

Pharmacokinetics of OMNISCAN have not been studied in pediatrics. The glomerular filtration rate of neonates and infants is much lower than that of adults. The pharmacokinetics volume of distribution is also different. Therefore, the optimal dosing regimen and imaging times in patients under 2 years of age have not been established.

8.5 Geriatric Use

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 greater in patients with impaired renal function [see *Warnings and Precautions* (5.3)]. Because elderly patients are more likely to have decreased renal function, select dose carefully and consider assessment of renal function before OMNISCAN use.

8.6 Renal/Hepatic Impairment

Dose adjustments in renal or hepatic impairment have not been studied. Caution should be exercised in patients with impaired renal insufficiency [see *Warnings and Precautions* (5.2, 5.3)].

10 OVERDOSAGE

Clinical consequences of overdose with OMNISCAN have not been reported. The minimum lethal dose of intravenously administered OMNISCAN in rats and mice is greater than 20 mmol/kg (200 times the recommended human dose of 0.1 mmol/kg; 67 times the cumulative 0.3 mmol/kg dose). OMNISCAN is dialyzable.

11 DESCRIPTION

OMNISCAN (gadodiamide) Injection is the formulation of the gadolinium complex of diethylenetriamine pentaacetic acid bismethylamide, and is an injectable, nonionic extracellular enhancing agent for magnetic resonance imaging. OMNISCAN is administered by intravenous injection.

OMNISCAN is provided as a sterile, clear, colorless to slightly yellow, aqueous solution. Each 1 mL contains 287 mg gadodiamide and 12 mg calcium chloride in Water for Injection. The pH is adjusted between 5.5 and 7.0 with hydrochloric acid and/or sodium hydroxide. OMNISCAN contains no antimicrobial preservative. OMNISCAN is a 0.5 mol/L solution of aqua[5,8-bis(carboxymethyl)-11-[2-(methylamino)-2-oxoethyl]-3-oxo-2,5,8,11-tetraazatridecan-13-oato (3-)-N⁵, N⁸, N¹¹, O³, O⁵, O⁸, O¹¹, O¹³] gadolinium hydrate, with a molecular weight of 573.66 (anhydrous), an empirical formula of C₁₆H₂₈GdN₄O₉•xH₂O, and the following structural formula:



Pertinent physicochemical data for OMNISCAN are noted below:

PARAMETER			
Osmolality (mOsmol/kg water)	@ 37°C	789	
Viscosity (cP)	@ 20°C	2	
	@ 37°C	1.4	
Density (g/mL)	@ 25°C	1.14	
Specific gravity	@ 25°C	1.15	

OMNISCAN has an osmolality approximately 2.8 times that of plasma at 37°C and is hypertonic under conditions of use.

12 CLINICAL PHARMACOLOGY

12.1 Pharmacodynamics

In magnetic resonance imaging, visualization of normal and pathologic tissue depends in part on variations in the radiofrequency signal intensity. These variations occur due to: changes in proton density; alteration of the spin-lattice or longitudinal relaxation time (T₁); and variation of the spin-spin or transverse relaxation time (T₂). OMNISCAN is a paramagnetic agent with unpaired electron spins which generate a local magnetic field. As water protons move through this local magnetic field, the changes in magnetic field experienced by the protons reorient them with the main magnetic field more quickly than in the absence of a paramagnetic agent.

By increasing the relaxation rate, OMNISCAN decreases both the T_1 and T_2 relaxation times in tissues where it is distributed. At clinical doses, the effect is primarily on the T_1 relaxation time, and produces an increase in signal intensity. OMNISCAN does not cross the intact blood-brain barrier and, therefore, does not accumulate in normal brain or in lesions that do not have an abnormal blood-brain barrier (e.g., cysts, mature postoperative scars). However, disruption of the blood-brain barrier or abnormal vascularity allows accumulation of OMNISCAN in lesions such as neoplasms, abscesses, and subacute infarcts. The pharmacokinetic parameters of OMNISCAN in various lesions are not known. There is no detectable biotransformation or decomposition of gadodiamide.

Pharmacokinetic and pharmacodynamic studies have not been systematically conducted to determine the optimal dose and optimal imaging time in patients with abnormal renal function or renal failure, in the elderly, or in pediatric patients with immature renal function.

12.3 Pharmacokinetics

The pharmacokinetics of intravenously administered gadodiamide in normal subjects conforms to an open, two-compartment model with mean distribution and elimination half-lives (reported as mean \pm SD) of 3.7 ± 2.7 minutes and 77.8 ± 16 minutes, respectively.

Gadodiamide is eliminated primarily in the urine with $95.4 \pm 5.5\%$ (mean \pm SD) of the administered dose eliminated by 24 hours. The renal and plasma clearance rates of gadodiamide are nearly identical (1.7 and 1.8 mL/min/kg, respectively), and are similar to that of substances excreted primarily by glomerular filtration. The volume of distribution of gadodiamide (200 ± 61 mL/kg) is equivalent to that of extracellular water. Gadodiamide does not bind to human serum proteins *in vitro*. Pharmacokinetic and pharmacodynamic studies have not been systematically conducted to determine the optimal dose and imaging time in patients with abnormal renal function or renal failure, in the elderly, or in pediatric patients with immature renal function.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term animal studies have not been performed to evaluate the carcinogenic potential of gadodiamide. The results of the following genotoxicity assays were negative: *in vitro* bacterial reverse mutation assay, *in vitro* Chinese Hamster Ovary (CHO)/Hypoxanthine Guanine Phosphoribosyl Transferase (HGPRT) forward mutation assay, *in vitro* CHO chromosome aberration assay, and the *in vivo* mouse micronucleus assay at intravenous doses of 27 mmol/kg (approximately 7 times the maximum human dose based on a body surface area comparison). Impairment of male or female fertility was not observed in rats after intravenous administration three times per week at the maximum dose tested of 1.0 mmol/kg (approximately 0.5 times the maximum human dose based on a body surface area comparison).

14 CLINICAL STUDIES

14.1 CNS (Central Nervous System)

OMNISCAN (0.1 mmol/kg) contrast enhancement in CNS MRI was evident in a study of 439 adults. In a study of sequential dosing, 57 adults received OMNISCAN 0.1 mmol/kg followed by 0.2 mmol/kg within 20 minutes (for cumulative dose of 0.3 mmol/kg). The MRIs were compared blindly. In 54/56 (96%) patients, OMNISCAN contrast enhancement was evident with both the 0.1 mmol/kg and cumulative 0.3 mmol/kg OMNISCAN doses relative to non-contrast MRI.

In comparison to the non-contrast MRI, increased numbers of brain and spine lesions were noted in 42% of patients who received OMNISCAN at any dose. In comparisons of 0.1 mmol/kg versus 0.3 mmol/kg, the results were comparable in 25/56 (45%); in 1/56 (2%) OMNISCAN 0.1 mmol/kg dose provided more diagnostic value and in 30/56 (54%) the cumulative OMNISCAN 0.3 mmol/kg dose provided more diagnostic value.

The usefulness of a single 0.3 mmol/kg bolus in comparison to the cumulative 0.3 mmol/kg (0.1 mmol/kg followed by 0.2 mmol/kg) has not been established.

OMNISCAN as a single 0.1 mmol/kg dose was evaluated in 97 pediatric patients with a mean age of 8.9 (2-18) years referred for CNS MRI. Postcontrast MRI provided added diagnostic information, diagnostic confidence, and new patient management information in 76%, 67%, and 52%, respectively, of pediatrics.

14.2 Body (Intrathoracic [noncardiac], Intra-abdominal, Pelvic and Retroperitoneal Regions)

OMNISCAN was evaluated in a controlled trial of 276 patients referred for body MRI. These patients had a mean age of 57 (9-88) years. Patients received 0.1 mmol/kg OMNISCAN for imaging the thorax (noncardiac), abdomen, and pelvic organs, or a dose of 0.05 mmol/kg for imaging the kidney. Pre- and post-OMNISCAN images were evaluated blindly for the degree of diagnostic value rated on a scale of "remarkably improved, improved, no change, worse, and cannot be determined." The postcontrast results showed "remarkably improved" or "improved" diagnostic value in 90% of the thorax, liver, and pelvis patients, and in 95% of the kidney patients.

In a dose ranging study 258 patients referred for body MRI received OMNISCAN 0.025, 0.05, 0.1 mmol/kg. The lowest effective dose of OMNISCAN for the kidney was 0.05 mmol/kg.

16 HOW SUPPLIED/STORAGE AND HANDLING

OMNISCAN (gadodiamide) Injection is a sterile, clear, colorless to slightly yellow, aqueous solution containing 287 mg/mL of gadodiamide in in rubber stoppered vials and polypropylene syringes. OMNISCAN is supplied in the following sizes:

5 mL fill in 10 mL vial, box of 10 (NDC 0407-0690-05)

10 mL vial, box of 10 (NDC 0407-0690-10)

15 mL fill in 20 mL vial, box of 10 (NDC 0407-0690-15)

20 mL vial, box of 10 (NDC 0407-0690-20)

50 mL vial, box of 10 (NDC 0407-0690-55)

10 mL fill in 20 mL prefilled syringe, box of 10 (NDC 0407-0690-12)

15 mL fill in 20 mL prefilled syringe, box of 10 (NDC 0407-0690-17)

20 mL prefilled syringe, box of 10 (NDC 0407-0690-22)

Prefill Plus™ needle-free system

OMNISCAN 15 mL, box of 10 (NDC 0407-0691-62)

Contains: OMNISCAN 15 mL fill in 20 mL Single Dose Prefilled Syringe and 5 mL 0.9% Sodium Chloride Injection, USP I.V. Flush Syringe

Prefill Plus™ needle-free system

OMNISCAN 20 mL, box of 10 (NDC 0407-0691-63)

Contains: OMNISCAN 20 mL fill in 20 mL Single Dose Prefilled Syringe and 5 mL 0.9% Sodium Chloride Injection, USP I.V. Flush Syringe

Protect OMNISCAN from strong daylight and direct exposure to sunlight. **Do not freeze.** Freezing can cause small cracks in the vials, which would compromise the sterility of the product. Do not use if the product is inadvertently frozen.

Store OMNISCAN at controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP].

17 PATIENT COUNSELING INFORMATION

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

- are pregnant or breast feeding, or
- have a history of renal 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.

GE Healthcare



Distributed by GE Healthcare Inc., Princeton, NJ
Manufactured by GE Healthcare AS, Oslo, Norway

OMNISCAN is a trademark of GE Healthcare.

GE and the GE Monogram are trademarks of General Electric Company.

OptiMARK® is a registered trademark of Mallinckrodt Inc.

Magnevist® is a registered trademark of Berlex Laboratories, Inc.

MultiHance® is a registered trademark of Bracco International B.V.

ProHance® is a registered trademark of Bracco Diagnostics Inc.

© 2007 General Electric Company

ONC-2S-OSLO/BK

