

GE Healthcare

# GE Healthcare Position Paper on NSF

February 2008

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### Executive Summary

- Nephrogenic systemic fibrosis (NSF) is a rare, but serious, acquired systemic disease. To date, it has only been reported in patients with renal insufficiency, particularly those 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 have associated the administration of gadolinium-containing contrast agents [GBCA] 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 300 reports of NSF after Omniscan™ (Gadodiamide Injection) administration. This is usually associated with exposure to high doses. These 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 provide a unique patient identifier 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.
- Different 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 and to appropriate regulatory agencies.

# Review of Nephrogenic Systemic Fibrosis (NSF)

Nephrogenic systemic fibrosis (NSF) is a rare, but serious, acquired systemic disease. To date, it has only been reported in patients with renal insufficiency, particularly those with severely impaired renal function with glomerular filtration rate (GFR) < 30 mL/min/1.73m<sup>2</sup>, 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.<sup>1</sup> First described in the US in 2000,<sup>2</sup> 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, oesophagus, etc)<sup>3</sup> and it is now commonly referred to as NSF<sup>4</sup>. 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<sup>5</sup>. 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<sup>6</sup>. There appears to be no predilection for any race/ethnic group or geographic location. Also, gender and age do not appear to be risk factors. NSF has been reported in children as young as 8 years old<sup>7</sup> and in the elderly, but the majority of NSF reports are in middle-aged patients.<sup>5</sup> 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 pathological.

While the precise cause of NSF is still under investigation, exposure to GBCA has been reported to be 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<sup>8</sup>. In Europe, the number of reported cases of NSF is lower than that in the US and the European regulatory bodies have applied different labeling to the different GBCA. Currently the majority of available GBCA have been associated with NSF either as the sole agent administered or in confounded cases.

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 Gd to be 4.3 cases per 1,000 patient-years<sup>9</sup>. The vast majority of renally impaired patients who receive Gd have not developed NSF. Information from the American National Kidney Foundation estimates that 0.35% of the general population has Stage IV kidney disease.

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<sup>10</sup>. 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. However, it is also 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 NSF<sup>11</sup>.

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 were also sent in many European countries in February 2007 in connection with a product licence change for all gadolinium agents (see "Response of health authorities").

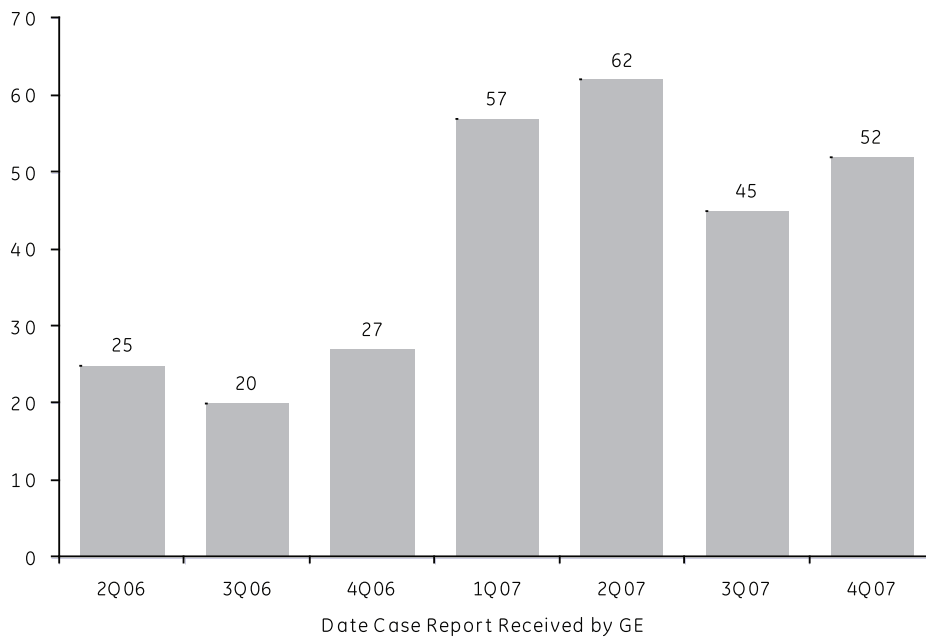
To date, the database of NSF cases identified by GE Healthcare includes approximately 300 cases. These have been reported by GE Healthcare to regulatory authorities worldwide. Most cases originate from the US, and while only recently reported to GE Healthcare, have occurred over a period of several years (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, this has also been reported by at least one other GBCA manufacturer.

GE Healthcare actively seeks out cases and logs all cases that provide a unique patient identifier and appear to be NSF associated with Omniscan. Biopsy confirmation is not required for a case to be included in our reported figures, which are the same as those submitted to the regulatory authorities. Approximately 57% of cases logged included a biopsy confirmation and approximately 20% of the logged cases have been reported by non-healthcare professionals.

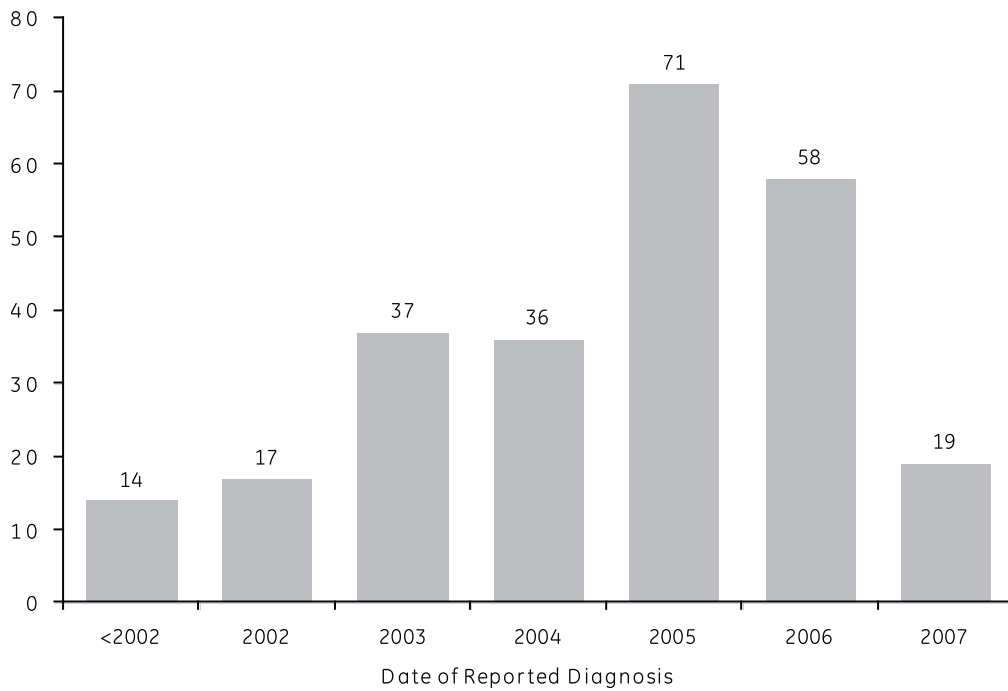
GE Healthcare is currently supporting efforts by the American College of Radiology (ACR) to develop a standard definition for NSF and we continue to seek additional information on the cases logged to make these data as accurate as possible. Until such time that a definition exists and all cases have 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-quarter reported to GE Healthcare**



**Figure 2**  
**Number of NSF cases by year of diagnosis**

There are 36 cases where no diagnosis dates have been reported



# 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<sup>11</sup>. In May 2007, the FDA requested label changes for the entire class of GBCA that included a new boxed warning<sup>12</sup>:

“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/1.73m<sup>2</sup>), 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 effected 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) have 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](http://ajronline.org)) the "ACR Guidance Document for Safe MR Practices: 2007"<sup>13</sup>. At the time this was published in AJR (June 2007), it was accompanied by an editorial from Dr van Moore<sup>14</sup>, 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 10 for MultiHance™[gadobenic acid]<sup>15</sup>.

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<sup>12</sup>.

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<sup>16</sup>. 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.”<sup>12</sup>

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 GBCA<sup>9</sup> 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 an effort to harmonize 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 does not require biopsy confirmation or an exclusive link to Omniscan administration before reporting a case to regulatory authorities.

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).

- **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 that this imbalance in awareness of products is responsible for under-reporting of cases associated with other GBCA.

- **Patient populations exposed to different GBCA.**

In addition to needing reliable numbers of reported cases, 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 possible at present 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 eg. tertiary medical centres versus imaging centres, 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 is also 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 to be used at a higher dose level than many other agents. Specific labelling 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 validity of spontaneous reporting. 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

Grobner<sup>17</sup> and Broome et al,<sup>18</sup> among others, have suggested that one mechanism by which a gadolinium contrast agent 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 that 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<sup>19,20</sup>

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 gadolinium contrast agents for proper interpretation.

- The intrinsic thermodynamic stability constant ( $K_{\text{therm}}$ ), 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 ( $K_{\text{sel}}$ ), indicates the selectivity of the ligand for the bound metal over other endogenous ions, particularly zinc. Omniscan has a high  $K_{\text{sel}}$  value.  $K_{\text{sel}}$  correlates better with acute toxicity ( $\text{LD}_{50}$ ) than does  $K_{\text{therm}}$ , and though related to stability, but does not correlate 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. Studies of the recovery of Omniscan from patients with renal failure do not provide evidence of dechelation or transmetalation, despite prolonged elimination.

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

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

As shown in the recent article by Ersoy<sup>21</sup>, 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.

	Dotarem®	ProHance®	MultiHance®	Magnevist®	OMNISCAN™	OptiMARK®
Stability log $K_{\text{therm}}$	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.

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 associated with one case of NSF unconfounded with any other GBCA.

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 evidence linking the stability of GBCA to NSF. The claims for 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 safer with respect to NSF, especially as there is no evidence that GBCA stability is a factor in the development of NSF.

As no comparative in-vivo constants are available, it is impossible to know how the stability of the products would compare in the truly physiological setting. What is clear is that the difference in numbers of reported cases can not 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<sup>22</sup> Regardless of this, GE Healthcare is continuing to invest in research to fully understand the stability of agents in-vivo and determine if there is any relevance to NSF.

Subject to the caveats described above with regard to the unreliability of spontaneous adverse event reporting, it is clear that stability measures alone do not explain the patterns of NSF reporting to date. The stability measure by itself implies two broad groups of agents with very different stability levels, and yet the numbers of cases reported for some agents are higher than reported for other agents with similar stability values. Further complications are evident when the conditional values are considered: Magnevist is suggested to be more stable than ProHance by this measure, which again is not consistent with the current numbers of reported cases.

Clearly more needs to be considered in evaluating in vivo stability of contrast agents. Cacheris et al<sup>23</sup> 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).

The selectivity constants of several Gd chelates indicate a good correlation with toxicity in animal studies<sup>23</sup> It should be noted that Omniscan with a high  $K_{sel}$  also has a high  $LD_{50}$  value, i.e., low acute toxicity. These results are also consistent with clinical studies that have indicated that Omniscan is well tolerated and, apart from the recently reported association with NSF in renally impaired patients, is similarly well tolerated when compared with other commercially available gadolinium-based contrast agents.<sup>24</sup> Using  $K_{sel}$ , Omniscan is also predicted to be 2 log units (100 times) more stable in relation to gadolinium exchange than Magnevist, weakening the case that stability measures correlate with the numbers of reported NSF cases.

GBCA in general have a very high overall safety record. Even so, the LD<sub>50</sub> of gadodiamide – the gadolinium chelate in the commercial formulation of Omniscan – can be made even higher (less toxic) through the addition of extra ligand (caldiamide sodium [CaNaDTPA-BMA]). A 1% excess of caldiamide sodium increases the LD<sub>50</sub> of gadodiamide from 14 to 34 mmol/kg, and a 5% excess (utilized in the commercial Omniscan formulation) optimizes this effect, giving an LD<sub>50</sub> of 38 mmol/kg<sup>23</sup>. A possible mechanism of how the extra ligand reduces acute toxicity was proposed by these the same authors. The hypothesis states that the excess ligand reduces the potential toxicity of gadodiamide by reducing Gd-Zn transmetalation in vivo since endogenous zinc will displace Ca from CaNaDTPA-BMA and is therefore no longer available for displacing gadolinium from gadodiamide. It may also simply drive the chelation reaction more to completion. In the paper by Cacheris, the data also indicate that for several gadolinium chelates, despite a 50-fold difference in LD<sub>50</sub> values based on administered dosage, all become lethally toxic to half the mice treated (i.e. the LD<sub>50</sub>), when they release 13-15 µM gadolinium. This can be taken as an indication of in vivo stability and, according to the data, GdDTPA-BMA has a very favourable profile (Murphy et al., 1999)<sup>24</sup>

## Pharmacokinetic studies

Several studies have investigated the pharmacokinetics of Omniscan in vivo. These indicate that 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.<sup>25-27</sup>

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.<sup>28,29</sup> Similarly in experimental animals the biotransformation of <sup>14</sup>C-gadodiamide was studied after i.v. injection in rats of 0.3 mmol/kg of a radiolabelled formulation of gadodiamide injection. Biotransformation in blood was negligible, and gadodiamide was excreted unchanged in the urine<sup>27</sup>. In further studies in rodents, the distribution of gadodiamide was shown to be quantitatively and qualitatively different to that of the free Gd metal.<sup>25,30</sup> These findings were supported by autoradiography data, which showed that the tissue distribution of <sup>153</sup>Gd-labelled gadodiamide was similar to that of <sup>14</sup>C-labelled gadodiamide, demonstrating that both metal and ligand behaved in exactly the same way.<sup>31</sup> Supporting evidence comes from a study showing that the serum concentration of total gadolinium, analysed by inductive coupled plasma-atomic emission spectroscopy (ICP-AES), was identical to the serum concentration of the gadodiamide complex analysed by HPLC, indicating that all gadolinium was in the form of the gadodiamide complex.<sup>31</sup>

The serum and peritoneal dialysate samples from end-stage renal disease patients were analysed for the concentrations of gadolinium and GdDTPA-BMA by ICP-AES and HPLC, respectively.<sup>29</sup> 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.<sup>32</sup>

## Retention in tissues

Two studies have suggested that more gadolinium was detectable in human bone following Omniscan administration compared to ProHance, and interpreted this as evidence of greater in vivo dechelation of Omniscan.<sup>33,34</sup> However, the measured amounts of gadolinium were not adjusted for the different time intervals between administration of the contrast agents and analyses. In fact, the Omniscan group had a considerably shorter interval for elimination, which would bias the results against Omniscan. Furthermore, it should be noted that the analytical methods used in that study can only detect the gadolinium ion and cannot distinguish between the intact gadolinium complexes of the different contrast agents and uncomplexed "free" gadolinium. Finally, the relative amounts of retained gadolinium do not correlate with stability constants, or with the numbers of reported cases of NSF. Consequently, the results of such studies should be treated with caution.

Tweedle reported that more gadodiamide was retained in mice and rats compared to other contrast agents.<sup>35</sup> The relevance of these findings to humans is not clear. Moreover, a major concern with this article is that the measured amounts of gadolinium-153 were not corrected for the number of elimination half-lives that elapsed between administration and analysis. Another caveat is that the gadolinium chelates were prepared in the laboratory of the investigators and may not be reflective of the chemical composition or purity of the commercial formulations. The ratios of retained amounts do not correlate with stability constants, K<sub>sel</sub> values, or the numbers of reported cases of NSF.

Boyd et al reported finding traces of gadolinium in skin biopsy specimens from 4 patients with NSF<sup>36</sup>. They did not report the actual amounts of gadolinium, and did not study any control patients who received gadolinium without the development of NSF. Similarly, High et al detected gadolinium in specimens from 4 of 7 patients with documented NSF who were exposed to gadolinium-based contrast.<sup>37</sup> No gadolinium was detected in a paraffin-embedded specimen from a patient without NSF (it was not stated whether this patient had ever been exposed to gadolinium before). These pilot studies have methodological limitations, namely detection method, low number of specimens and choice of controls. The finding of gadolinium by High et al in the tissues was not consistent and does not establish that these traces of Gd are only found in patients with NSF and not in other patients exposed to GBCA. The relevance of the findings to the aetiology of NSF remains uncertain.

No human studies have ever provided compelling evidence of in vivo transmetalation or other type of gadolinium release after administration of GBCAs.

Therefore, GE Healthcare believes, there is insufficient evidence to support treating Omniscan differently from other GBCA. On the contrary, the fact that NSF is associated with other GBCA makes a compelling case for regarding this as a possible class effect.

## Stability data: Conclusions

The different measures of stability indicate that in vitro measurement in simple solutions is, of itself, insufficient to predict in vivo behaviour 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 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, 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, threats in that study had normal renal function and the key feature of dermal fibrosis was not present in those rats with reported skin changes.<sup>38</sup> The paper<sup>38</sup> 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). The lesions, both grossly and histomorphologically, were very similar to those reported 15 years ago in a repeat dose study by Harpur et al.<sup>39</sup> 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.<sup>40</sup>

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.<sup>39</sup> By comparison the gross and histomorphological characteristics of skin lesions in the Sieber study are consistent with previously published preclinical findings in rats exposed to repeated treatment with high doses of Omniscan, 50-100 times the standard clinical dose. The pruritus, excessive scratching and, as a consequence, superficial abrasions of the skin could 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 has only been reported in patients with renal insufficiency, particularly those 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 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.
- Different 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 and to appropriate regulatory agencies.

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# Prescribing information Omniscan (gadodiamide)

Indications and approvals may vary in different countries. Please refer to the local Summary of Product Characteristics (SPC) before prescribing. Further information available on request.

**PRESENTATION** Non-ionic, paramagnetic aqueous solution containing 287mg/ml gadodiamide (GdDTPA-BMA) as active ingredient, equivalent to 0.5mmol/ml.

**INDICATIONS** Contrast medium for cranial and spinal magnetic resonance imaging (MRI) and for general MRI of the body after intravenous administration. The product provides contrast enhancement and facilitates visualisation of abnormal structures or lesions in various parts of the body including the CNS. For cardiac MRI, the product is indicated for the evaluation of coronary artery disease (CAD) by myocardial perfusion imaging MRI (stress/rest and late enhancement examination) for the detection and localization of coronary artery disease (CAD) and differentiation between areas of ischaemia and infarction in subjects with known or suspected CAD.

**DOSAGE AND METHOD OF ADMINISTRATION** Adults and children: Dosage varies depending on patient weight and type of examination. Angiography and the CAD indication have not been studied in children.

**CONTRAINDICATIONS** Gadodiamide is contraindicated in patients with severe renal impairment (GFR<30 ml/min/1.73m<sup>2</sup>), and those who have had or are undergoing liver transplantation. OMNISCAN should not be used in patients known to have hypersensitivity to OMNISCAN or its constituents.

**PRECAUTIONS, WARNINGS ETC.** The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered, especially in those patients with a known clinical hypersensitivity or a history of asthma or other allergic respiratory disorders. A course of action should therefore be planned in advance, with necessary drugs and equipment available for immediate treatment should a serious reaction occur. Transitory changes in serum iron (within the normal range in the majority of cases) have been observed. OMNISCAN interferes with serum calcium measurements with some complexometric methods. Such methods should not be used for 12-24 hours after administration. Elimination of OMNISCAN is prolonged in patients with impaired renal function. Due to lack of information on such patients the interval between repeated administration should be at least seven days. Severe renal impairment and liver transplant patients: There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of gadodiamide and some other gadolinium-containing contrast agents in patients with severe renal impairment (GFR <30ml/min/1.73m<sup>2</sup>) and those who have had or are undergoing liver transplantation. Therefore OMNISCAN should not be used in these populations. Cases of NSF have also been reported in patients with moderate renal impairment (GFR <60 ml/min/1.73m<sup>2</sup>) with gadodiamide. OMNISCAN should be used in these patients with caution. Haemodialysis shortly after OMNISCAN administration in patients currently receiving haemodialysis may be useful at removing OMNISCAN from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis. Neonates and Infants: Due to immature kidney function in neonates and infants up to 1 year of age, OMNISCAN should only be used in these patients after careful consideration.

**PREGNANCY AND LACTATION** There is no experience of the use of OMNISCAN during pregnancy or lactation. The product should not be used in pregnancy unless essential. Breast feeding should be discontinued prior to administration and should not be re-commenced until at least 24 hours after OMNISCAN administration.

**UNDESIRABLE EFFECTS** Discomfort, with a general sensation of warmth or coolness, and pressure or pain at the injection site are occasionally seen. Less frequently reported are dizziness, nausea, headache and a perverted sensation of taste or smell. Rare reactions are vomiting, somnolence, paraesthesia, visual disturbances, diarrhoea, anxiety, dyspnoea, chest pain, tachycardia, trembling, arthralgia or allergy-like symptoms such as urticaria, itching or an irritation in the throat. Anaphylactoid reactions may occur. Cases of nephrogenic systemic fibrosis (NSF) have been reported with OMNISCAN. In very rare cases convulsions have been observed after the administration of OMNISCAN as is the case for other paramagnetic MR contrast media. However, a causal relationship seems to be questionable. Transient renal failure was observed in one patient included in the clinical trials. The patient had received an X-ray contrast medium for myelography 22 hours prior to the injection of OMNISCAN. The causality for the reaction has not been established.

**INSTRUCTIONS FOR USE AND HANDLING** The product should be drawn into the syringe immediately before use. Containers are intended for single use only, any unused portions must be discarded. The product in glass vials and polypropylene bottles

should be drawn into the syringe immediately before use.

**MARKETING AUTHORISATION HOLDER** GE Healthcare AS, Nycoveien 1-2, Postboks 4220 Nydalen, NO-0401 Oslo, Norway.

**CLASSIFICATION FOR SUPPLY** Subject to medical prescription (POM).

**UK MARKETING AUTHORISATION NUMBERS** 00637/0015 (glass vials), 00637/0025 (polypropylene bottles), 00637/0030 (pre-filled syringes).

**PRICE** 20ml: £59.24.

**DATE OF REVISION OF THE TEXT** 13 April 2007

Information about adverse event reporting can be found at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk). Adverse events should also be reported to GE Healthcare.

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