GE Healthcare Position Paper on Nephrogenic Systemic Fibrosis
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Executive summary
Executive summary

• Nephrogenic systemic fibrosis (NSF) is a rare, but potentially serious, acquired systemic disease. To date, it has only been reported in patients with severe renal insufficiency (whether chronic or as a result of acute kidney injury), and particularly in patients who are on or are approaching dialysis. At present, there is no evidence that patients without renal impairment, or with only mild or moderate renal insufficiency, 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 severely 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.

• Health authorities have required label changes for all GBCA.

• 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 all adverse events associated with Omniscan™ (gadodiamide) Injection be reported promptly to GE Healthcare and to the appropriate regulatory agencies.

• There have been no reports of cases associated with OMNISCAN with a documented date of onset after July 2007. This may be accounted for by an increase in patient safety management.

• Different numbers of spontaneous reports early in an event’s history do not necessarily imply a difference in risk between agents.

• There is no direct evidence linking stability of agents to the development of NSF. 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 a number of cases in the literature describing NSF in patients with no history of 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.
Current understanding of NSF
Nephrogenic systemic fibrosis (NSF)

Nephrogenic Systemic Fibrosis (NSF) is a rare, but potentially serious, acquired systemic disease. It is characterised by areas of thick, hardened skin commonly associated with brawny hyperpigmentation and preferentially localized to the extremities.¹⁻³ (figure 1).

First described in the US in 2000 identifying a case from 1997, NSF was initially thought to be confined to the skin and was named Nephrogenic Fibrosing Dermopathy (NFD).² 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.⁴⁻⁵ It can be a painful and debilitating condition that can contribute to a fatal outcome.

Figure 1:
The characteristic symptoms of NSF
To date, NSF has only been reported in patients with acute kidney injury and patients with severely impaired renal function with a glomerular filtrate rate (GFR) <30 mL/min/1.73 m², particularly those patients who are on or approaching dialysis. However, the specific origin of the kidney disease does not appear to be related to the incidence of NSF. At present, there is no evidence that patients without renal impairment, or those with mild or moderate renal impairment, are at risk of developing this disease.

Risk factors associated with NSF

The many risk factors shown to be associated with NSF include:

- Edema
- Metabolic acidosis
- Hypercoagulability states
- Thrombotic events
- High dose erythropoietin (EPO)
- Systemic inflammation
- Recent vascular surgery
- Recent transplant failure
- Sudden onset kidney disease with severe swelling of the extremities

Case studies indicate that many NSF patients have undergone a vascular surgical procedure or have experienced a thrombotic episode approximately two weeks before disease onset.

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 eight years old and in the elderly, but the majority of NSF reports are in middle-aged patients. 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 the disease.\textsuperscript{15,16} It also would appear that for cases of NSF associated with GBCA use, among the factors that may increase the risk for NSF is higher than standard single doses of a GBCA in patients with severe or acute renal impairment.\textsuperscript{17,19}

Cases of NSF have been reported with all GBCA approved for use in the US and with the majority of agents available globally, indicating that, to the extent there is an association, NSF may be a class-wide issue, and the FDA has consistently treated it as such.\textsuperscript{10} The mechanistic etiology of the disease is unknown, but the cause of NSF appears to be multifactorial, with the majority of cases involving low GFR (impaired renal function), exposure to GBCA, and additional risk factors such as high-dose EPO, vascular disease, or systemic inflammation.\textsuperscript{10}

In Europe, the number of reported cases of NSF is lower than in the US and the European regulatory bodies have applied different labelling to 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. Information from the American National Kidney Foundation estimates that 0.35\% of the general population has Stage 4 kidney disease and Deo et al have estimated an incidence rate of NSF in renally-impaired patients (CKD Stage 4 and 5) exposed to gadolinium to be 4.3 cases per 1000 patient-years.\textsuperscript{21,22} The vast majority of renally-impaired patients who receive GBCA have not developed NSF.

In addition, 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.\textsuperscript{23} Indeed, there are reports of cases where patients have developed NSF in the absence of any known exposure to GBCA.

One theoretical model addressing the potential role of GBCA in the development of the disease is the ‘cumulative risk factor model’, depicted on page 9 (figure 3). This model, which assumes a contributing role of GBCA in the development of the disease, addresses the diversity in patients’ conditions associated with NSF: patients with greater cumulative risk may only need low dosages of GBCA to trigger NSF, whereas patients with lower cumulative risk may need higher doses of GBCA to trigger NSF.\textsuperscript{10}
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 GBCA 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 acute or severe renal impairment. However, it also is important to distinguish between an association and actual causation, which is still unknown.

Pharmacological class effect: NSF

Due to the lack of prospective randomized clinical data comparing the risk of NSF with the available GBCA, most published discussion and opinion on the relative risk with various GBCA has been based upon the relative number of spontaneous reports associated with them and remains theory and speculation. The rarity of the disorder, the retrospective nature of most case reports, and the relatively short time since an association with gadolinium has been proposed, contribute to the challenges the medical community faces when trying to understand this condition.

Other than avoiding the use of gadolinium agents, especially at high doses, in patients at risk of the condition, there is uncertainty about what can be done to prevent this potentially serious condition.

NSF has only been documented in patients with acute or severe renal impairment, particularly those with end-stage renal disease on dialysis. There also is evidence that higher than standard dosing of GBCA may increase the risk of NSF, with discussions also taking place regarding the potential role of repeated dosing (especially when this repeat dosing takes place over a limited period of time).

In a study to determine the incidence rate of NSF and associated risk factors in patients who underwent gadolinium-enhanced MR imaging at two large medical centers, the highest incidence of NSF (19%) was observed in the patients with acute renal failure who received a high dose of GBCA when their serum creatinine level was increasing, but did not undergo hemodialysis for at least two days after the injection.\(^9\)
In the same study, the incidence of NSF with a standard dose (0.1 mmol/kg) of GBCA was 0 of 74,124 patients examined without being screened for renal function. There also was a lower incidence of NSF – 0 in 5725 patients with multiple 0.1 mmol/kg doses of GBCA administered across multiple examinations compared with the incidence with a single high dose – nine in 5119 patients.

Health authorities’ response

The majority of authorities have approached the issue of NSF as a class effect, and general guidance to clinicians is based upon:

- Screen patients for renal dysfunction by obtaining a history and/or laboratory tests
- In patients with severe renal impairment, avoid the use of GBCA unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI)
- Avoid the use of doses of GBCA exceeding the dose recommended in product labelling
- Allow sufficient time for elimination of the GBCA prior to any re-administration
Understanding the available data

It is always challenging to draw conclusions from data collected through a voluntary spontaneous reporting system. However, taking these considerations into account, it appears that changes in practice may have contributed to a decrease in the number of new cases of NSF being reported since the association was first suggested.

Figure 4 shows the numbers of cases of NSF that have been reported to, or identified by, GE Healthcare through literature and other sources as associated with OMNISCAN by year of onset of NSF (excluding patients for whom the date of onset of NSF is not available). The decrease in the number of cases from 2006 to 2007 is greater than can be explained by any overall decrease in the use of OMNISCAN in the same period. There have been no reports of cases associated with OMNISCAN with a documented date of onset after July 2007.

A similar trend is seen in the number of NSF cases associated with Magnevist® (http://www.imaging.bayerhealthcare.com/html/magnevist/nsf_nfd.html), supporting the view that the decrease in the number of new cases may be the result of changes in clinical practice.

Analysis of spontaneous reports in isolation can lead to misleading conclusions and the numbers of cases reported should be considered in relation to the market share and usage of the various products over the relevant period.

For example, Magnevist® and OMNISCAN were the most commonly used agents in Europe and the US during the time in which NSF cases have occurred; therefore, it is not surprising that the majority of cases have been linked to these products.

It is important to consider the patterns of use of the various products in those patients at greatest risk of NSF, and the doses used:

- How long has a product been available, and was it widely used between 2002 and 2006 when most cases of NSF occurred?
• Was the product available in those markets where most cases were reported?
• Is the product licensed for procedures most likely to be undertaken in patients with renal insufficiency and to involve the use of GBCA at higher doses?
• Does the product have a pre-existing contraindication in patients with severe renal insufficiency in any of the major markets, thus potentially limiting any historical exposure to patients at greatest risk of NSF?

Figure 5 shows that as of end-July 2008 the majority of cases associated with OMNISCAN, as reported to GE Healthcare, have occurred in the US.

Under these circumstances, it might be expected that GBCA that are not licensed or used in the US, such as Dotarem® (gadoterate meglumine) and Gadovist® (gadobutrol), would be associated with fewer cases than those GBCA that have been used in this country.

**Incidence of NSF**

It also is important to consider the underlying incidence of reports of NSF from different countries when different GBCA have had variable geographic use during the period from which the majority of NSF cases were reported. A large percentage of the cases of NSF have occurred in clusters from a relatively small number of healthcare institutions. For example, data from the Danish Medicines Agency in 2008 showed that, in Denmark, which has the second largest number of cases after the US, 33 of the 36 cases reported to the agency had come from a single center (Herlev Hospital). In January 2009, further reports of NSF cases in Danish institutions have been received, although the details of these cases are still being clarified.26

In the US, GE Healthcare has received 366 reports of NSF (as of January 2009); 196 of these have been received from law firms, some of which are likely to be duplicates of reports from other sources.25
Of the healthcare professional and literature reports for which the US administering facility is known, a total of 156 cases of OMNISCAN-associated NSF have been received from 45 imaging centers since NSF was first linked to GBCA in 2006. Of these, 9 of 45 (20%) centers that each reported more than five cases account for 98/156 (63%) cases; of the approximate 2,100 US imaging centers that used OMNISCAN during the period in which NSF emerged, 98% have not reported any cases of NSF.

The relevance of this clustering has yet to be adequately explained, but serves as an example of the lack of understanding that exists about the occurrence of NSF in patients following GBCA. One hypothesis is that NSF has occurred more frequently in those centers performing procedures that often involve relatively large doses of GBCA to patients with severe renal impairment. Only a minority of sites that used OMNISCAN historically have reported any cases of NSF.

Figure 6 compares the percentage of the total number of cases of NSF reported to GE Healthcare as associated with OMNISCAN compared to the percentage of total sales for the product. This analysis shows that the incidence of NSF appears to vary from country to country and appears to have occurred more commonly per exposure to OMNISCAN in some countries (eg Denmark) than in others (eg France).

This is important as it suggests that normal clinical practice in some countries has resulted in a lower risk of NSF than is seen in other countries or in specific institutions, in the same way that changes in practice since 2006 have resulted in a decrease in the incidence of the condition.

This also is pertinent when comparing risk between products. For example, the data show the risk of NSF in relation to OMNISCAN appeared lower in France than in other countries. During the period in which the majority of NSF cases occurred, a significant proportion of the global sales of Dotarem® were in France. If clinical practice in France results in a relatively low risk of NSF then it is expected that there would be a relatively low global incidence of cases associated with Dotarem®.
Potential reporting bias

The relatively high number of reports of NSF associated with OMNISCAN over the first two years of the association being recognized may, in part, be due to reporting bias due to greater physician awareness of the concerns around this product. This may stem from the fact that GE Healthcare was the first GBCA manufacturer to inform healthcare professionals about the association between NSF and OMNISCAN and to actively solicit reports of cases. This could potentially have led to ‘hindsight bias’, where medical notes of patients who had received OMNISCAN, but not other products, were selectively reviewed following ‘Dear Doctor’ letters or media coverage, leading to the reporting of an adverse event.

It is important to note that the number of cases associated with Magnevist® as reported to Bayer has increased from 163 to 314 in the period between April 2008 and July 2008. This increase of 151 cases is not due to new onset cases of NSF but rather largely due to clinicians identifying cases from their records that they had not previously recognised or discovered.

During the same period, the total number of cases associated with OMNISCAN reported to GE Healthcare rose by 76, from 361 to 437. (Only nine of the 76 cases were reported by healthcare professionals). All 76 cases were previously unidentified, historical cases, as distinguished from new-onset cases of NSF.

This serves as an example of the weaknesses of relying on spontaneous reports when such reporting is subject to bias.

<table>
<thead>
<tr>
<th>Agent</th>
<th>April 2006</th>
<th>Feb 2007</th>
<th>April 2008</th>
<th>Latest available data</th>
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</thead>
<tbody>
<tr>
<td>OMNISCAN</td>
<td>25</td>
<td>85</td>
<td>361</td>
<td>517 (January 2009) (including 207 reported from non-HCP sources)</td>
</tr>
<tr>
<td>Magnevist®</td>
<td>0</td>
<td>21</td>
<td>163</td>
<td>314 (Bayer July 31, 2008)</td>
</tr>
<tr>
<td>Gadovist®</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2 (Bayer July 31, 2008)</td>
</tr>
<tr>
<td>ProHance®</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>9 (1 unconfounded – Nov 2007 data – Reilly 2008)</td>
</tr>
<tr>
<td>MultiHance®</td>
<td>0</td>
<td>1</td>
<td>10</td>
<td>10 (2 unconfounded – Nov 2007 data – Reilly 2008)</td>
</tr>
<tr>
<td>Dotarem®</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>9 (Guerbet website Oct 2008)</td>
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</table>

GE Healthcare does not have access to the latest numbers of reports associated with the various GBCA provided by other manufacturers and any comparison we make is dependant on published data from the companies that sell these products or independent authors.
Bracco publishes no such data that we are aware of and the only figures we can draw upon for the number of cases associated with ProHance® (gadoteridol) and MultiHance® (gadobenate dimeglumine) are those published by Reilly in 2008 and taken from FDA Medwatch data in November 2007. This publication lists unconfounded cases for both these products and it is not therefore possible to exclude the risk of NSF when these products are used.

Similarly one cannot exclude the risk of NSF associated with either Dotarem® or Gadovist®. The Bayer website lists two cases of NSF associated with the macrocyclic product Gadovist®, both of which are confounded, within a plausible time period, by another macrocyclic: Dotarem® in one case and ProHance® in the other.

It also should be recognized that in a number of countries certain GBCA were contraindicated in patients with severe renal impairment prior to 2008 when the vast majority of NSF cases occurred. In addition, OMNISCAN is indicated for use at higher dose levels than many other agents. Specific labelling varies by region and needs to be considered. If, in these countries, clinicians were already advised not to use certain GBCA in those patients at greatest risk of NSF, then it is unsurprising that there are differences in the numbers of reports associated with various agents.

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 at-risk population.

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 centers versus imaging centers), and when products have different approved indications and/or contraindications (eg, pre-existing contraindications for use in renally-compromised patients that were present for some products in certain 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. As previously mentioned, Magnevist® and OMNISCAN were the most commonly used agents in Europe and the US during the time in which NSF cases have occurred, and therefore it is not surprising that the majority of NSF cases have occurred in association with these products. In contrast, GBCA such as Dotarem® and Gadovist® are not licensed or used in the US and therefore might be expected to have fewer associated cases under these circumstances.
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 fact that the earliest reports of NSF date to a time 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.

In summary, other than the obvious and significant differences between the historical market share of different GBCA, there are a number of factors that create significant challenges when trying to ascertain relative risk based on differences in numbers of spontaneous reports. In order to estimate the true incidence of NSF associated with different GBCA, it would be necessary to know the actual number of NSF cases associated with each agent, as well as the number of patients at risk of NSF who were exposed to each specific GBCA, and the dose of GBCA administered to these patients. These figures are not known for any GBCA.
Guidance
Guidance

FDA

The FDA issued Public Health Advisories (PHAs) applicable to all GBCA in June and December 2006.\textsuperscript{30}

In May 2007, the FDA requested changes for the entire class of GBCA that included a new boxed warning\textsuperscript{31}:

“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\textsuperscript{2}), or
- Acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any 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.
In 2008, after re-examining the available evidence, the ACR released the sixth edition of its Manual on Contrast Media. Within the manual the ACR states it must be emphasised that the frequency with which NSF has been associated with different GBCA may reflect a combination of differences in agent toxicity and market share. In addition, reported frequency also is likely to be further confounded by the fact that some agents, particularly OMNISCAN, may have been used disproportionately more frequently in patients receiving high doses of GBCA for magnetic resonance angiography. It then goes on to dispense a number of recommendations to help reduce the potential risk of NSF. These guidelines are discussed in more detail on page 32.
Stability of gadolinium contrast agents
Every patient who has developed NSF had abnormal kidney function. Thrombotic events and vascular trauma occur frequently in patients with End Stage Renal Disease (ESRD) and CKD and are conditions commonly associated with NSF. Vascular surgical procedures, DVT, and placement of central catheters are often present before the development of NSF and previously unsuspected hypercoaguable states are sometimes discovered after the diagnosis of NSF.34

It has been speculated that the state of vascular and endothelial dysfunction seen in patients with kidney disease may predispose them for a second event or trigger that puts the fibrosing process into motion.34 Although the trigger for NSF is still unknown, GBCA may be one of the candidates.

Since GBCA are eliminated almost entirely by the kidneys, impaired excretion of GBCA due to CKD can result in an increase in the half-life of GBCA.

One current hypothesis assumes that the increased retention of GBCA, brought about by severely impaired renal function and ESRD, leads to the increased likelihood of Gd³⁺ release from GBCA. Released ‘free’ or dechelated Gd³⁺ is then postulated to trigger NSF.35 Although there is no evidence that inorganic Gd³⁺-species directly trigger NSF, the theoretical rationale that dechelated inorganic Gd³⁺ might cause NSF is based on the following:

1. The elimination half-life of gadolinium chelates increases in normal human volunteers from 1.5 hours to over 30 hours in patients with renal insufficiency. Such protracted retention provides the conditions for the release of Gd³⁺ from GBCA, before the agent can be eliminated
2. Differences in in vitro stability constants control the rate and extent of Gd³⁺ release 35
3. Released gadolinium precipitates and is phagocytosed by tissue macrophages and Gd³⁺ has been identified in the skin of affected patients36,37
4. The phagocytosis of gadolinium triggers inflammatory and fibrotic responses at the site of precipitation

In attempting to explain the difference in reported numbers between the various GBCA, many authors have noted that the majority of cases are with OMNISCAN or Magnevist®, which are both linear molecules, and some have extrapolated from this to argue that the risk of NSF in patients with severe renal impairment is greater with linear GBCA than with macrocyclic agents. The rationale for this argument is largely based on molecular stability, leading to the hypothesis that the stability of gadolinium agents is a factor in the development of NSF – a theory as yet not supported by any clinical evidence.

Theories regarding stability are largely based on a comparison of the thermodynamic stability constant (Kₜ₉₀₀) of the compounds, which is measured at pH 11, and does not reflect physiological conditions.
As shown in a recent article by Ersoy\(^b\), 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>
<thead>
<tr>
<th></th>
<th>Dotarem(^b)</th>
<th>ProHance(^b)</th>
<th>MultiHance(^b)</th>
<th>Magnevist(^b)</th>
<th>OMNISCAN</th>
<th>OptiMARK(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stability</td>
<td>19.0</td>
<td>17.1</td>
<td>18.4</td>
<td>17.7</td>
<td>14.9</td>
<td>15.0</td>
</tr>
<tr>
<td>log K(_{\text{cond}})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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\(^b\) and ProHance\(^b\), 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.

Another constant used in discussions on comparative stability arguments is the kinetic stability but, as with thermodynamic stability, the constant does not reflect physiological conditions and is based on a measurement taken at pH 1 and therefore of questionable relevance to the clinical setting.

As no comparative in vivo stability constants are available, it is impossible to know how the products compare in the truly physiological setting. This is one of a number of areas of research that GE Healthcare is pursuing to better understand the real differences between the available GBCA in clinical practice and to gain further insight into the association with NSF.

In terms of the conditional stability constant, Magnevist\(^b\), a linear GBCA, is currently associated with more than 300 reported cases of NSF, but it is more stable than ProHance\(^b\), a macrocyclic GBCA.

This raises questions about the simplistic message that macrocyclic GBCA are safer than linear GBCA with respect to NSF risk due to their greater stability, especially as there is no evidence that stability is a factor in the development of NSF.

Any discussion regarding risk associated with possible instability should also address a number of as yet unanswered questions:

- How can we explain the small, but increasing, number of reports of cases of NSF with no prior exposure to GBCA?
- Why do the vast majority of patients with end-stage renal disease not develop NSF when exposed to gadolinium agents, even in those centers with the highest incidence of NSF?
- Why are there no reports of symptoms of general gadolinium toxicity, as might be expected if this toxic metal was being released in the bodies of patients developing this condition?
- How can we explain the confirmed and non-confounded case of NSF associated with ProHance\(^b\) – a macrocyclic compound and therefore not thought to be associated with the release of free gadolinium?
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.

It also is important that we do not dismiss confounded cases as irrelevant. For example, in one of the nine confounded cases reported as associated with Dotarem® on the manufacturer’s website, the patient developed NSF in 2005, the same year that they received two macrocyclic agents: Dotarem® and Gadovist®. However, the only exposure listed to a linear product, Magnevist®, was in 1999 and possibly 2000. If it is suggested that the stability of GBCA plays a role in the development of NSF, then it is also important to consider the potential role of the various GBCA administered over the various timescales involved.

Clearly more needs to be considered in evaluating the in vivo stability of contrast agents.
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.\textsuperscript{39-41}

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.\textsuperscript{42,43}

Gadolinium retention in the body

Another area where opinions have been expressed without strong supporting clinical evidence is the differential retention of GBCA in the tissues of the body, with speculation about a possible cumulative dose effect. White and Gibby\textsuperscript{44} reported more gadolinium was detectable in human bone following OMNISCAN administration compared to ProHance\textsuperscript{®} – although both agents resulted in measurable levels of bone retention – and interpreted this as evidence of in vivo dechelation of OMNISCAN. However, no adjustment was made for the different time intervals between administration of the contrast agents and analyses. The mean interval between administration and analysis was shorter for the gadodiamide group, which could result in bias. Furthermore, the analytical method used detects only the gadolinium ion, and cannot distinguish between the intact gadolinium complex and uncomplexed, ‘free’ gadolinium. Hence, it cannot be concluded that this is evidence of gadolinium release from the chelate.

The research by Gibby\textsuperscript{45} did not investigate long-term retention of gadolinium in the tissues. If gadolinium retention is a causal factor in NSF, it may be important to collect clinical information over longer time periods than in this study. Since gadolinium was detected in patients that received a macrocyclic agent, this is not a discussion that should be limited by the structure of the compound. 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, and any conclusions drawn from them, should be treated with caution.

While these observations that precipitated gadolinium can be found in NSF tissue may be important to our understanding of the disease, the studies that identified such species are retrospective and so their conclusions may not necessarily be correct. The basis for the assumption that ‘free’ Gd\textsuperscript{3+} is a trigger of NSF is its cytotoxicity. Indeed, the toxicity of Gd\textsuperscript{3+} (in part) necessitated chelation so that it could be used safely as an MR imaging agent: chelation both shields the body from damage and promotes GBCA rapid elimination.
However, there is now alternative evidence emerging to suggest that even chelated-Gd$^{3+}$ has the ability to initiate pathological processes that were previously attributed to precipitated Gd$^{3+}$ alone.

No human studies have ever provided compelling evidence of in vivo transmetalation or other types of gadolinium release after administration of GBCA. The fact that NSF is associated with most GBCA makes a compelling case for regarding this as a possible class effect.

**Inflammatory and fibrotic responses – new evidence**

New evidence is emerging all the time and recent work by Wermuth, Edward and Varani raises further questions about the role of GBCA stability in NSF. In fact, these data highlight the effect of the chelated gadolinium species rather than the free Gd$^{3+}$ ion.46-48

Wermuth has demonstrated that chelated- Gd$^{3+}$ (Gd$^{3+}$-DTPA-BMA, OMNISCAN and Gd$^{3+}$-DTPA, Magnevist$^\circledR$) can directly stimulate human monocytes and macrophages to release profibrotic cytokines and growth factors capable of initiating and supporting the tissue fibrosis that is characteristic of NSF.46

Likewise, a direct effect of chelated- Gd$^{3+}$ has also been demonstrated on fibroblasts in vitro. In a study by Edward et al (2008)47, OMNISCAN added to culture medium stimulated fibroblast growth and increased levels of hyaluronan secretion. In a separate study by Varani (2009),48 chelated-Gd$^{3+}$ in the form of OMNISCAN, Magnevist$^\circledR$, MultiHance$^\circledR$ and ProHance$^\circledR$ all increased proliferation of human dermal fibroblasts in monolayer culture.

Perhaps more importantly, NSF patient serum stimulated control skin fibroblasts in vitro whilst healthy control serum was without effect.47 This suggests that fibroblasts can be stimulated by substances other than GBCA, eg, proinflammatory and or profibrotic cytokines from blood cells. Thus it is possible that monocytes and macrophages could orchestrate fibroblast activity after GBCA exposure. In a series of follow-up studies, Del Galdo et al49 exposed terminally differentiated human peripheral blood macrophages to either OMNISCAN or saline before isolating and analysing cellular RNA for global gene expression microarray analysis. Analysis of the microarray data revealed that 31 inflammatory and fibrotic genes were up-regulated by more than two-fold in the OMNISCAN treated macrophages (p<0.05). Such observations support the mechanistic relevance of the in vitro studies.

Thus this emerging evidence permits an alternative hypothesis to the ‘free’ Gd$^{3+}$ theory (Figure 7):

1. Protracted retention of GBCA in renal insufficiency provides the conditions for enhanced exposure of tissues to GBCA
2. GBCA could themselves trigger inflammatory and fibrotic responses in the tissues of susceptible cells
3. GBCA interacting with cells may be internalised via receptor driven phagocytosis in macrophages and receptor-mediated endocytosis in fibroblastic cells

Consequently, the formation of tissue retained insoluble Gd$^{3+}$-species may be secondary or a ‘footprint’ of a receptor mediated cell response (Figure 8).
Such a mechanism is entirely consistent with the identification of Gd³⁺-species localized in areas of dermal inflammation rich in macrophages in NSF and the detection of insoluble Gd³⁺-species of <1 μm in diameter confined to areas of fibrosis in NSF tissue.\textsuperscript{37}

The data raise questions about the relevance of dechelated gadolinium as a trigger in the development of NSF and the role of retained gadolinium. Since gadolinium is retained even in normal individuals\textsuperscript{45} and NSF develops only in Severely Impaired Renal Function (SIRF), ESRD and Acute Kidney Injury (AKI), it is difficult to understand how retained gadolinium in bone might play a role. In vitro studies show that chelated gadolinium appears to be capable of stimulating the proinflammatory and profibrotic responses in cells that undergo endocytosis – fibrocytes, fibroblasts, macrophages and monocytes (Figure 7). Clearly such responses do not take place in every patient, thus some form of patient susceptibility is likely. Nevertheless, these data do help explain why cofactors such as high GBCA dose, SIRF and ESRD, dependent edema and pre-existing inflammation might predispose patients receiving GBCA to develop NSF:

- High single dose rather than repeated standard doses of GBCA carries the greatest risk in vivo\textsuperscript{18,19} accords with the concentrations of GBCA that are required to stimulate inflammatory cells and fibroblasts in vitro
- The increased exposure of interstitial tissue to GBCA brought about protracted half-life in ESRD and SIRF\textsuperscript{23} accords with the effect of GBCA on macrophages and fibroblast inflammatory and fibrotic reactions in vitro
- Inflammatory ‘conditions’ in vivo\textsuperscript{11} accord with the observation that macrophages and monocytes can be directly stimulated by GBCA in vitro
- Dependent edema/fluid overload leading to enhanced exposure of interstitial tissue to GBCA in vivo\textsuperscript{8} accords with the observation that fibroblasts can elicit a profibrotic response in vitro
Figure 7: The schematic of the proposed mechanism shows how the retention of chelated gadolinium, occurring after high dose, ESRD and pre-existing inflammation, might stimulate proinflammatory and profibrotic responses that are consistent with those seen in NSF.

Figure 8: The schematic suggests that the release of profibrotic cytokines precedes the formation of tissue-retained insoluble Gd³⁺.
The different measures of stability indicate that \textit{in vitro} measurement in simple solutions is, of itself, insufficient to predict \textit{in vivo} behaviour or toxicity. The \textit{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 \textit{in vivo} stability and toxicity of Gd chelates based on a single \textit{in vitro} measure of stability such as thermodynamic stability are therefore inadequate.

If OMNISCAN were prone to dechelation \textit{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 OMNISCAN 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 the majority of GBCA are associated with the development of NSF, suggesting that, to the extent NSF is associated with the GBCA, it is a class-wide effect.

As has been shown in the above \textit{in vitro} studies, chelated gadolinium appears to be capable of stimulating the proinflammatory and profibrotic responses in cells that undergo endocytosis: fibrocytes, fibroblasts, macrophages and monocytes.
Currently there is no animal model of human NSF. Although a recent publication by Sieber et al claims to have developed such a model, the 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. 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). The lesions, both grossly and histomorphologically, were very similar to those reported 15 years ago in a repeat dose study by Harpur et al. 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.

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. By comparison, the gross and histomorphological characteristics of skin lesions in the Sieber study are consistent with previously published preclinical findings in normal 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.

GE Healthcare has also conducted a recent study in rats. In this study, naive or partially nephrectomised rats received intravenous doses of OMNISCAN, Magnevist®, Caldiamide, GdCl₃, or Gd citrate. Similar responses to treatment were seen in naive and nephrectomised rats. High doses of gadodiamide were toxic, necessitating early termination of the affected animals. Skin lesions appeared in naive and nephrectomised groups treated with gadodiamide or Omniscan®, coinciding with the onset of signs of pruritis, i.e., intensive scratching. The histomorphological features of the skin lesions were also consistent with superficial physical trauma. Dermal fibrosis was not a feature of these skin lesions in any of the groups, i.e., no increased collagen density, CD34+ cells, or increased fibroblasts. The visible skin lesions seen in this study appeared to be caused by excessive scratching in response to pruritis. As there was no evidence of dermal fibrosis—the cardinal feature of human NSF—this did not appear to be a model of human NSF.

Since NSF has only been observed at very low frequencies in patients with SIRF, ESRD and those in ARF in combination with several cofactors, it is possible that a definitive animal model of NSF may be impossible to establish.
Clinical practice
Management of patients at risk of NSF

While NSF is a serious condition, radiologists also must consider the overall safety profile and effectiveness of GBCA for the large majority of patients in whom there is no evidence of a risk of NSF. The adverse events and general patient tolerability for various agents, as well as the differences in licensed indications, need to be fully understood so that a balanced decision is made and the appropriate agent is selected for each patient group.

Key guidelines for the management of at-risk patients in clinical practice include:

- Assume all GBCA carry a risk of NSF until proven otherwise
- Renal function should be assessed before administering GBCA
- Where possible, use of GBCA should be avoided when GFR is <30 ml/min/1.73 m²
- Follow product labelling with regard to administration and dosage
- Post-procedure dialysis may hasten GBCA removal but has not been proven to reduce NSF risk

The most recent guidelines that are available are from the ACR. The table below summarises their recommendations for management of at-risk patients:

<table>
<thead>
<tr>
<th>Stage of renal insufficiency</th>
<th>ACR manual September 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 and 2 (eGFR 60-120 ml/kg)</td>
<td>There is no evidence that patients in these groups are at risk of developing NSF. All GBCA can be used as long as a dose of 0.1 mmol/kg or less is utilized</td>
</tr>
<tr>
<td>Stage 3 (eGFR 30-59 ml/kg)</td>
<td>This group can be considered to be at extremely low or no risk for developing NSF (as long as a dose of GBCA of 0.1 mmol/kg or less is utilized)</td>
</tr>
<tr>
<td>Stage 4 and 5 (eGFR below 30 ml/kg) Acute renal failure</td>
<td>If MRI contrast administration is absolutely essential, judicious use of the lowest possible dose of selected GBCA is probably safest. There is no proof that any GBCA is completely safe in this patient group. However, at the present time, should GBCA use be required in these patients, some have suggested avoiding gadodiamide and consider the use of macrocyclic agents.</td>
</tr>
</tbody>
</table>

The latest ACR guidelines also state that, with respect to patients with stage 1 or 2 renal failure, there is no evidence of an increased risk of developing NSF and that all GBCA can be used as long as no more than a maximum dose of 0.1 mmol/kg is used.
GE Healthcare’s commitment
GE Healthcare’s commitment

GE Healthcare is committed to ensuring the safety of patients who receive our products, and to keeping our customers fully informed about using our products in the safest and most effective manner. GE Healthcare continues to invest in external, as well as internal, research activities and is currently funding multiple investigator-initiated trials at multiple global institutions and will be presenting data as they become available.

Since 2006, GE Healthcare has continuously taken a proactive approach to addressing the risk of NSF associated with GBCA:

• Letters sent to 100,000+ healthcare providers, including radiologists, dermatologists, nephrologists and hospital administrators, informing them of the issues involving NSF through 2006 and 2007
• Ensuring the rapid submission of relevant pharmacovigilance data after receipt of the minimum reporting criteria, thus contributing to rapid signal detection in collaboration with health authorities
• Closely following reported cases and working with hospitals and experts in the field to conduct a thorough investigation of the NSF issue
• Sponsoring research on NSF with the following goals:
  - To develop animal and/or in vitro models to elucidate the NSF mechanism
  - To refine knowledge of risk factors
• Sponsoring scientific meetings and continuing medical education (CME) to discuss NSF with the medical and scientific community

Doctors and departments are strongly encouraged to report any new cases of NSF to the appropriate regulatory authorities and GE Healthcare.
Conclusions

NSF is an increasingly rare disease and one that is still poorly understood, especially in terms of its relationship to the administration of GBCA:

• Data from spontaneous reports suggest that the patients at greatest risk are those with acute or end-stage renal kidney failure, especially when higher than standard doses of GBCA are administered
• Other than differences in the number of spontaneous reports, there is no evidence that any GBCA is more or less safe than any other with respect to NSF
• Emerging ex-vivo data question the role of ‘free gadolinium’ and therefore the role of GBCA stability in the development of NSF
• The large majority of patients undergoing gadolinium-enhanced MR imaging are not at risk of NSF and clinicians should continue to use GBCA with confidence in this majority in accordance with the product labelling
References


44. White GW, Gibby WA, Tweedle MF. Comparison of Gd(DTPA BMA) [Omniscan™] versus Gd(HP DO_A) [ProHance®] relative to gadolinium retention in human bone tissue by inductively coupled plasma mass spectroscopy. *Invest Radiol* 2006; 41: 272-278.


Prescribing information
WARNING: Not for Intrathecal Use and Nephrogenic Systemic Fibrosis (NSF)

Not for Intrathecal Use. Inadvertant intrathecal use of OMNISCAN has caused convulsions, coma, sensory and motor neurologic deficits.

Nephrogenic Systemic Fibrosis (NSF). Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis 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 without-contrast enhanced magnetic resonance imaging. NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration.

The most frequent adverse events observed during OMNISCAN clinical trials in 1,369 patients, at doses between 0.025 mmol/kg and 0.3 mmol/kg, were headache, dizziness, and nausea. The majority of these adverse events were of mild to moderate intensity. The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid, or cardiovascular reactions, or other idiosyncratic reaction, should always be considered, especially in those patients with a known clinical hypersensitivity. Refer to the boxed warning section of the Prescribing Information for acute or chronic severe renal insufficiency since OMNISCAN is cleared from the body by glomerular filtration. Patients with a history of allergy or drug reaction should be observed for several hours after administration.

Please see boxed WARNING and see Full Prescribing Information on following pages.
**GE Healthcare**

**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

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**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 (S.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/1.73 m²), or
  - acute renal insufficiency of any severity due to hepatorenal 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 (S.2).

**RECENT MAJOR CHANGES**

- Based Warning: Nephrogenic Systemic Fibrosis (NSF) 9/2007
- Warnings and Precautions: Hypersensitivity reactions, NSF, acute renal failure, inadvertent intrathecal use (S.1, S.2, S.3, S.4)

**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 (S.1)
- Facilitate the visualization of lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities, and the retroperitoneal space (S.2)

**DOSE AND ADMINISTRATION**

- CNS – Adults and Pediatrics: 0.1 mL/kg (0.1 mmol/kg) (S.1, S.2)
- Body – Adults and Pediatrics: 0.1 mL/kg (0.1 mmol/kg) (S.2, S.4)

**DOSE FORMS AND STRENGTHS**

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

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

- Anaphylactic 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 (S.3).
- Nephrogenic Systemic Fibrosis (NSF) has occurred in patients with severe renal insufficiency. Higher than recommended dosing or repeat dosing appears to increase the risk (S.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 (S.3).

**ADVERSE REACTIONS**

- The most frequent adverse reactions (≥ 3%) observed during OMNISCAN adult clinical trials were nausea, headache, and dizziness (S.1).
- Serious or life-threatening reactions include: cardiac failure, arrhythmia and myocardial infarction (S.1, S.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

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   - Body (Intrathoracic, Intra-abdominal, Pelvic and Retroperitoneal Regions)

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

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**WARNING: NOT FOR INTRATHECAL USE and Nephrogenic Systemic Fibrosis (NSF)**

- Inadvertent intrathecal use of OMNISCAN has caused convulsions, coma, sensory and motor neurologic deficits (S.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/1.73 m²), or
    - acute renal insufficiency of any severity due to hepatorenal syndrome or in perioperative liver transplantation period.

- In these patients, avoid use of gadolinium-based contrast agents unless 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 S.3).

Revised: 9/2007
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 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 Reactions: Injection site reaction.
- Autonomic Nervous System Disorders: Vasodilation.
- Body as a Whole-General Disorders: Anaphylactic reactions (characterized by cardiovascular, respiratory, and cutaneous symptoms), fever, rash, flushing, urticaria, angioedema, or anaphylaxis.

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

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: Rhinorrhea, 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 (14.10)] and the 14% pediatric patients in published literature, the adverse reaction profile was similar to 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, paralysis.

General Disorders: Nephrogenic Systemic Fibrosis (NSF) [see Warnings and Precautions (5.3)].

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 embryofetal development in rabbits at dosages as low as 0.5 mg/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 mg/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 mg/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 mg/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 mg/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 pharmacokinetic 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 minimal lethal dose of intravenously administered OMNISCAN in rats and mice is greater than 20 mg/kg (2000 times the recommended human dose of 0.1 mg/kg; 67 times the cumulative 0.3 mg/kg dose). OMNISCAN is dialyzable.

11. DESCRIPTION

OMNISCAN (gadopentetate dimeglumine) is the formulation of the gadolinium complex of diethylhexamide pentaaacetic acid, dimethylamide, and 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 gadopentetate and 12 mg sodium 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 mL/solution of equil(5-bisterboxymethyl)11-(2-[(methyllamino)-2-oxoethyl]-3-ace-2,3,5,11-tetraazatriaendecan-13-ate [5,5', 5" M, N, O, O', O', O', O', O', O', O'] gadolinium hydrate, with a molecular weight of 573.66 (anhydrous), an empirical formula of C34H41N6O6·H2O, and the following structural formula:

$$\text{C}_{34}H_{41}N_{6}O_{6} \cdot H_2O$$

Pertinent physicochemical data for OMNISCAN are noted below:

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osamine (%)</td>
<td>37°C</td>
</tr>
<tr>
<td>Viscosity (cP)</td>
<td>20°C</td>
</tr>
<tr>
<td>Densit (g/mL)</td>
<td>25°C</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>25°C</td>
</tr>
</tbody>
</table>

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.
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 5% or less of the patients.

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

- Application Site Reactions: 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, rigor, fatigue, malaise, pain, syncope)
- Cardiovascular Disorders: Cardiac failure, rare arrhythmia and myocardial infarction resulting in death in patients with ischemic heart disease, flushing, Nervous System Disorders: 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.
- Gastrintestinal 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.

6.2 Clinical Studies Experience (Pediatrics)
In the 97 pediatric patients in CNS studies with OMNISCAN (see Clinical Studies (24.1)) and the 144 pediatric patients in published literature, the adverse reactions reported are 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, paraphasia.

General Disorders: Nephrogenic Systemic Fibrosis (NSF) (See Warnings and Precautions (5.2, 5.20).

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 33 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 7 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 90 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 the elderly 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 (5.1)). 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 (gadopentetate dimeglumine) Injection is the formulation of the gadolinium complex of diethylenetriamine pentaacetic acid dimethylamide, 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 gadopentetate and 12 mg sodium diacetate in water for injection. The pH is adjusted between 5.5 and 7.0 with hydrochloric acid and/or sodium hydrosulfide. OMNISCAN contains no antimicrobial preservative. OMNISCAN is a 0.5 M MI, solution of aquae5,8-bis(2-mercaptopropionyl)-1,1,12-(methylaminol)-1-oxoethyl)-1,7,9,11-tetraazacyclotetradec-13-ato [1,1',N, N', O, O', O', O''] gadolinium hydrate, with a molecular weight of 573.66 (anhydrous), an empirical formula of C10H14GNO.5·H2O, and the following structural formula:

```
Pertinent physicochemical data for OMNISCAN are noted below:

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Osmolarity (mOsm/kg/h2O)</td>
<td>479</td>
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<tr>
<td>Viscosity (cP)</td>
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<tr>
<td>Density (g/mL)</td>
<td>1.14</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.15</td>
</tr>
</tbody>
</table>
```

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, relative flip angle 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 react with the main magnetic field more quickly than in the absence of a paramagnetic agent.
By increasing the relaxation rate, OMSICAN decreases both the T1 and T2 relaxation times in tissues where it is distributed. At clinical doses, the effect is primarily on T1 relaxation time, and produces an increase in signal intensity. OMSICAN 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 OMSICAN in lesions such as neoplasms, abscesses, and subacute infarcts. The pharmacokinetic parameters of OMSICAN in various lesions are not known. There is no detectable biotransformation or excretion of gadodiamide.

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.

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 ± SD of 5.7 ± 2.7 minutes and 77.8 ± 16 minutes, respectively. Gadodiamide is eliminated primarily in the urine with 95.4 ± 5.5% (mean ± 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)/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 0.3 times the maximum human dose based on a body surface area comparison).

14 CLINICAL STUDIES

14.1 CNS (Central Nervous System)

OMSICAN 0.3 mmol/kg contrast enhancement in CNS MRI was evident in a study of 439 adults. In a study of sequential dosing, 57 adults received OMSICAN 0.1 mmol/kg followed by 0.2 mmol/kg within 20 minutes for cumulative dose of 0.3 mmol/kg. The MRRs were compared blindly. In 54/56 (96%) patients, OMSICAN contrast enhancement was evident with both the 0.1 mmol/kg and cumulative 0.3 mmol/kg OMSICAN 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 OMSICAN at any dose. In comparisons of 0.3 mmol/kg versus 0.3 mmol/kg, the results were comparable, in 22/56 (45%); in 22/56 (42%) OMSICAN 0.1 mmol/kg dose provided more diagnostic value and in 36/55 (64%) the cumulative OMSICAN 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. OMSICAN as a single 0.1 mmol/kg dose was evaluated in 97 pediatric patients with a mean age of 8.9 (±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 (nonsurgical), Intrabdominal, Pelvic and Retropertioneal Regions

OMSICAN was evaluated in a controlled trial of 276 patients referred for body MRI. These patients had a mean age of 57 (±16) years. Patients received 0.1 mmol/kg OMSICAN for imaging the thorax (nonsurgical), abdomen, and pelvic organs; or a dose of 0.05 mmol/kg for imaging the kidney, pre- and post-OMSICAN 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 OMSICAN 0.025, 0.05, 0.1 mmol/kg. The lowest effective dose of OMSICAN for the kidney was 0.05 mmol/kg.

16 HOW SUPPLIED/STORAGE AND HANDLING

OMSICAN (gadodiamide) injection is a sterile, clear, colorless to slightly yellow, aqueous solution containing 297 mg/ml of gadodiamide in water for injection. OMSICAN is supplied in the following sizes:

- 5 mL fill in 10 mL vial, box of 10 (NDC 0047-0690-05)
- 10 mL vial, box of 10 (NDC 0047-0690-10)
- 15 mL fill in 20 mL vial, box of 10 (NDC 0047-0690-15)
- 20 mL vial, box of 10 (NDC 0047-0690-20)
- 50 mL vial, box of 10 (NDC 0047-0690-55)
- 10 mL fill in 20 mL prefilled syringe, box of 10 (NDC 0047-0690-12)
- 15 mL fill in 20 mL prefilled syringe, box of 10 (NDC 0047-0690-17)
- 20 mL prefilled syringe, box of 10 (NDC 0047-0690-22)

Prefill Plus™-needle-free system

OMSICAN 15 mL, box of 10 (NDC 0047-0691-62)
Contains: OMSICAN 15 mL fill in 20 mL Single Dose Prefilled Syringe and
5 mL 0.9% Sodium Chloride Injection, USP (LV Flush Syringe)

Prefill Plus™ needle-free system

OMSICAN 20 mL, box of 10 (NDC 0047-0691-63)
Contains: OMSICAN 20 mL fill in 20 mL Single Dose Prefilled Syringe and
5 mL 0.9% Sodium Chloride Injection, USP (LV Flush Syringe)

Protect OMSICAN 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 OMSICAN at controlled room temperature 25°C (77°F) at excursions permitted to 15°-30°C (59°-86°F) [see USP].

17 PATIENT COUNSELING INFORMATION

Patients receiving OMSICAN should be instructed to inform their physician that they:

- are pregnant or breast feeding,
- 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 hepatitis 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.

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