
GE Healthcare Paper on
Nephrogenic Systemic Fibrosis
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Executive Summary

- Limited data are currently available on the causality of Nephrogenic Systemic Fibrosis (NSF); however case reports have associated the administration of gadolinium-containing contrast agents in renally compromised patients with the development of NSF.
- To date GE Healthcare (GEHC) has received 120 reports of NSF after Omniscan™ (gadodiamide) Injection administration, usually associated with exposure at high doses.
- The case reports of NSF from a number of countries indicate that several gadolinium-containing contrast agents have been associated with the development of NSF.
- Spontaneous reports early in an event's history do not imply statistical significance.
- Predictions of *in vivo* stability and toxicity of Gd chelates based on an *in vitro* measure of stability such as thermodynamic stability are inadequate and potentially misleading.
- GEHC 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. Adverse events should be reported to GEHC.

Review of Nephrogenic Systemic Fibrosis (NSF)

Nephrogenic systemic fibrosis (NSF) is a rare, but serious, acquired systemic disease. It has predominantly been reported in patients with renal insufficiency, particularly those with severely impaired renal function with glomerular filtration rate (GFR) < 30 who are on or approaching dialysis. At present, there is no evidence that patients without renal impairment are at risk of developing this disease (Thomsen, 2006). First described in the US in 1997, NSF was initially thought to be confined to the skin and named nephrogenic fibrosing dermopathy (NFD). In some patients, however, there is clinical involvement of other tissues (lung, skeletal muscle, heart diaphragm, esophagus, etc.) and is now more commonly referred to as NSF (Cowper *et al*, 2006). It can be a painful and debilitating condition that can contribute to a fatal outcome.

Risk factors associated with NSF include renal impairment, hypercoagulability states, thrombotic events, recent vascular surgery, recent transplant failure, or sudden onset of kidney disease with severe swelling of the extremities (Cowper, 2007). Case studies indicate that NSF patients commonly have undergone a vascular surgical procedure or have experienced a thrombotic episode about 2 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 8 years old as well as the elderly, but tends to affect the middle-aged.

While the precise cause of NSF is still under investigation, exposure to gadolinium-based (Gd) magnetic resonance (MR) contrast media (CM), particularly Gadodiamide Injection (Omniscan; manufactured by GEHC), was reported in early 2006 to be associated with NSF. While Omniscan was the first agent to be reported in association with cases of NSF, additional cases of NSF have now been reported with other Gd-based CM, indicating the possibility that this may be a Gd class issue.

Cases of NSF have occurred in clusters and the numbers of reported Gd-associated cases have been largely based on spontaneous post-marketing reports, thus making it difficult to calculate a reliable estimate of an incidence rate or to make determinations regarding the relative safety of

Gd-based CM. Deo *et al* have estimated an incidence rate of NSF in renally impaired patients exposed to Gd to be 4.3 cases per 1000 patient-years (Deo *et al*, 2007). The vast majority of renally-impaired patients who receive Gd have not developed NSF.

The published literature indicates that other factors or co-factors to Gd-based contrast agents are likely involved in the pathogenesis of NSF, and no definite causal link has been established for any Gd-based contrast agent to date (Kuo *et al*, 2007). Nevertheless, there is an association between Gd contrast agents and NSF, which must be addressed in the interest of patient safety. Because of the uncertainty surrounding the cause(s) of NSF, and the possible causal role of Gd contrast agents in NSF, it is reasonable to assume, until proven otherwise, that Gd contrast agents may pose a risk of NSF in patients with severe renal impairment. However, it also is important to distinguish between association, which may be coincidental, and actual causation, which is still unknown.

Response to Reports of Contrast Media Involvement in NSF

In April 2006, GEHC initially became aware of, and subsequently reported to health authorities, 25 NSF cases that had occurred during a 4-year period at two European hospitals. In response to these reports, and in close collaboration with GEHC, the Danish Medicines Agency posted a healthcare advisory on its website on May 29, 2006. The Food and Drug Administration (FDA) published a public health advisory on its website, on June 8, 2006 alerting the public to these reported cases of NSF.

In June 2006, 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 gadodiamide. In December 2006, GEHC sent an updated DHP letter in the US reporting additional cases of NSF. As part of these communications, GEHC 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 conjunction with a product license change for all gadolinium agents (described below).

A number of case reports and papers were published throughout 2006. If mentioned, the CM used was Omniscan. Furthermore, GEHC received additional spontaneous post-marketing reports of NSF. Deo *et al* (2007) reported one fatal case associated with Magnevist® (gadopentetate dimeglumine).

To date, the database of NSF cases reported to GEHC includes approximately 120 cases (including the 25 initial cases mentioned above) that have been reported to authorities worldwide. The cases originate predominantly from the US and Denmark, and while only recently reported to GEHC, have occurred over a period of several years. During that time, and until January 2007, no regulatory authority requested changes to the product Summary of Product Characteristics. To date, based on a review of the available scientific information, different regulatory agencies have taken different approaches in dealing with the association between Gd-based contrast agents and NSF.

To date, the FDA has regarded NSF to be an effect of the entire class of Gd-based CM and has issued consistent Public Health Advisories (PHAs) applicable to all such products [FDA, Dec-2006]; this is supported by the following numbers of cases reported to FDA, as of February 1, 2007: Omniscan 85; Magnevist 21, OptiMARK 6, MultiHance 1 (the patient was also exposed to Omniscan).

On the other hand, while European regulators accept that caution should be exercised with the use of all gadolinium contrast agents in certain groups of patients, at this time they regard NSF to be predominantly associated with Omniscan [European Community Pharmacovigilance Working Party (PhVWP, Jan-2007)]. The PhVWP has recommended an urgent safety restriction, i.e., contraindication

of Omniscan in patients with severe renal insufficiency and in liver transplant patients, and a relative warning for all other Gd products.

The different conclusions of the US and European regulators may result from differences in the product-specific safety data at their disposal, which may be attributable to the different safety reporting requirements in the US and EU and the manner in which manufacturers have interpreted and applied them.

Please see attached Prescribing Information.

Epidemiological Considerations

Many of the current data related to NSF come from relatively recent spontaneous reporting. Important considerations common to epidemiological science make drawing certain conclusions from that data difficult for the following reasons:

- **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 manufacturers. For example, GEHC has 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. Other manufacturers use a different standard of evidence before concluding that a case may be related to its product.

GEHC is aware of reports of NSF after the administration of three Gd-based MR contrast agents. These reports indicate that an association with NSF is not limited to just one Gd agent.

GEHC is the only manufacturer so far to distribute “Dear Healthcare Professional” communications. As part of these communications, GEHC actively solicited the reporting of any known or suspected cases of NSF associated with the use of Omniscan. Thus, the number of reports for Omniscan may be attributable, at least in part, to the fact that GEHC has proactively communicated on this issue and encouraged healthcare professionals to report NSF cases.

- **Probable 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 reports of NSF associated with Omniscan may, in part, be 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. This stems from the fact that GEHC is actively soliciting the reporting of cases (see above). It is possible that this imbalance in awareness of products is responsible for under-reporting of cases associated with other Gd-based contrast agents.

Stability of Gadolinium Contrast Agents *In Vivo*

Theoretical Considerations

Grobner (2006) and Broome *et al* (2007), among others, have suggested that one mechanism by which gadolinium contrast media 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 stated that, if the free gadolinium postulate was true, then gadolinium chelates with lower stability constants would be more likely to release gadolinium and trigger NSF. Broome referred to gadodiamide as one agent with a lower stability constant compared to other agents. Several other publications. (Idée *et al*, 2006; Cowper 2006; Khurana *et al*, 2006) have addressed the stability of Gd-based contrast agents and of Omniscan in particular.

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 intense 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_{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.

Cacheris *et al* (1990) attempted to clarify this 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 that takes into account the various possible transmetalation reactions in the body. K_{sel} indicates the selectivity of the ligand for gadolinium over endogenous metal ions (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 (Table 1). It should be noted that gadodiamide (GdDTPA-BMA), with the highest K_{sel} value, has the highest LD_{50} value, i.e., the lowest 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 (Murphy *et al*, 1999). Omniscan also is predicted to be 2 log units (100 times) more stable in relation to zinc transmetalation than gadopentetate. However, this does not correlate with the numbers of reported NSF cases for the two agents.

Table 1: The Logarithmic Selectivity Constant (Log K_{sel}) versus Acute Toxicity (LD₅₀)

Complex	Log K_{sel} at pH 7.4	Toxicity (LD ₅₀) (mmol/kg)
GdDTPA-BMA	9.04	14.8
GdDTPA	7.04	5.6
GdDTPA-BP	5.32	2.8
GdEDTA	4.23	0.3

The LD₅₀ 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 LD₅₀ of gadodiamide from 14 to 34 mmol/kg, and 5% excess (utilized in the commercial Omniscan formulation) optimizes this effect, giving an LD₅₀ of 38 mmol/kg (Cacheris *et al*, 1990). A possible mechanism of how the extra ligand reduces acute toxicity was proposed by these authors. The hypothesis states that the excess ligand improves the 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 1990 paper by Cacheris, the data also indicate that for several gadolinium chelates, despite a 50-fold difference in LD₅₀ values based on administered dosage, all become lethally toxic to half the mice treated (i.e. the LD₅₀), when they release 13-15 μ M gadolinium. This can be taken as an indication of *in vivo* stability and, according to the data, GdDTPA-BMA has a very favorable profile.

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 to free gadolinium (Hals and Høgset, 1990), and show that GdDTPA-BMA is stable in plasma and is excreted unchanged in the urine (Normann and Hals, 1995; Normann *et al*, 1995; Van Wagoner *et al*, 1991).

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, the study by Normann *et al* (2000) showed 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. For instance, the biotransformation of ¹⁴C-gadodiamide was studied in rats after i.v. injection of 0.3 mmol/kg of a radiolabeled formulation of gadodiamide injection. Biotransformation in blood was negligible, and gadodiamide was excreted unchanged in the urine. These findings were supported by autoradiography data, which showed that the tissue distribution of ¹⁵³Gd-labeled gadodiamide was similar to that of ¹⁴C-labeled gadodiamide, demonstrating that both metal and ligand behaved in exactly the same way (Normann *et al*, 1995). Supporting evidence comes from a study showing that the serum concentration of total gadolinium, analyzed by inductive coupled plasma-atomic emission spectroscopy (ICP-AES), was identical to the serum concentration of the gadodiamide complex analyzed by HPLC, indicating that all gadolinium was in the form of the gadodiamide complex (Normann *et al*, 1995).

The serum and peritoneal dialysate samples from end-stage renal disease patients were analyzed for the concentrations of gadolinium and GdDTPA-BMA by ICP-AES and HPLC, respectively (Normann *et al*, 2000). 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 had no evidence of biotransformation (Reinton *et al*, 1994).

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 (Gibby *et al*, 2004; White *et al*, 2006). 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 media (Tweedle *et al*, 1995). The relevance of these findings to humans is not clear. Moreover, a major flaw 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_{sel} values, or the numbers of reported cases of NSF.

Boyd *et al* (2006) reported finding traces of gadolinium in skin biopsy specimens from 4 patients with NSF. They did not report the actual amounts of gadolinium, and did not study control patients who received gadolinium without the development of NSF. Similarly, High *et al* (2007) detected gadolinium in specimens from four of seven patients with documented NSF who were exposed to gadolinium-based contrast. 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 prove that these traces of Gd are only found in patients with NSF and not in other patients exposed to Gd-based contrast media. The relevance of the findings to the aetiology of NSF remains uncertain.

No human studies have ever provided compelling evidence of *in vivo* transmetalation after administration of Gd based contrast agents. Therefore GEHC believes, there is insufficient evidence to support treating Omniscan differently from other gadolinium-based agents. On the contrary, the fact that NSF is associated with other Gd-containing agents makes a compelling case for regarding this as a possible class effect.

Summary of Stability Data

In vivo stability of the Gd chelates is important to limit the release of the toxic Gd metal. Several factors are believed to play roles in influencing the stability of Gd chelates:

- The intrinsic thermodynamic stability constant (K_{therm}), reflecting the affinity of a metal for a ligand, and is dependent on the conditions under which it is measured, and is greatly influenced by pH. Differences in thermodynamic stability constants between gadolinium chelates do not correlate with acute toxicity or reported numbers of cases of NSF.
- The selectivity constant (K_{sel}), the selectivity of the ligand for the bound metal over other endogenous metal ions, particularly zinc. Gadodiamide (GdDTPA-BMA) has a high K_{sel} value. K_{sel} correlates better with acute toxicity (LD_{50}) than does K_{therm} but does not correlate with the reported numbers of NSF cases.
- Kinetics, the rate of the transmetalation reactions which, 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 gadodiamide from patients with renal failure do not provide evidence of dechelation or transmetalation, despite prolonged elimination.

The different measures of stability indicate that the behavior of Gd chelates is complex and that *in vitro* measurement in simple solutions is, of itself, insufficient to predict *in vivo* behavior or toxicity. The *in vivo* stability of the Gd chelates is a result of 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 will play a role in determining the stability of the Gd chelate, the release of Gd, and hence 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 several agents are associated with the development of NSF, and this clearly indicates the possibility of a class effect for all Gd-based contrast agents.

Recommended Actions in the Interest of Patient Safety

GEHC is committed to identifying the best course of action to be taken for patient safety, and in achieving a proper and optimal balance between the benefits and risks of using its product. Having worked in close collaboration with the FDA, and in the interest of patient safety to minimize the risk of NSF, GEHC recommends that *Omniscan and other Gd-based CM should not be used in patients with severe renal impairment (GFR < 30) unless the benefit clearly outweighs the risks*. The decision of whether or not to use these products, and at what dose, should be carefully considered in patients with hepatorenal syndrome.

In its December 2006 Public Health Advisory, the FDA recommends that “*For patients with moderate (GFR < 60 mL/min/1.73m²) to end-stage renal disease (GFR < 15 mL/min/1.73m²): When recommending or performing an MRI or MRA, carefully weigh the benefits and risks associated with using a gadolinium-based contrast agent in light of recent reports of NSF/NFD observed following administration of these agents. Choose an alternative imaging method and/or contrast agent whenever possible.*”

NSF has been reported in patients undergoing or following liver transplantation. To our knowledge, there is no evidence that liver failure *per se* predisposes patients to NSF. A common denominator in this patient group, however, is renal failure caused by liver disease (i.e., hepatorenal syndrome). Therefore, caution should be exercised when using and selecting doses of Gd-based CM in patients with hepatorenal syndrome.

Renal failure in adults is associated with a plethora of biochemical abnormalities, including elevated serum creatinine, serum urea, serum phosphorus, and other abnormalities.

Consistent with the FDA’s Public Health Advisories, GE Healthcare asks all healthcare professionals and patients to report possible cases of NSF to the FDA through the MedWatch program by phone (1-800-FDA-1088) or by the Internet at <http://www.fda.gov/medwatch/index.html> and to also report possible cases to GE Healthcare by contacting Medical and Professional Services directly at 1-800-654-0118.

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

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

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



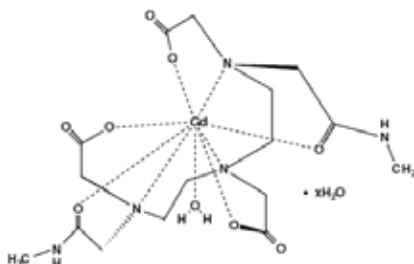
STERILE AQUEOUS INJECTION 287 mg/mL

R_x ONLY

DESCRIPTION

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

OMNISCAN is provided as a sterile, clear, colorless to slightly yellow, aqueous solution. Each mL contains 287 mg gadodiamide, 12 mg caldiamide sodium and water for injection. The pH is adjusted between 5.5 and 7.0 with hydrochloric acid and/or sodium hydroxide. OMNISCAN contains no antimicrobial preservative. OMNISCAN is a 0.5 mol/L solution of aqua[5,8-bis(carboxymethyl)-11-[2-(methylamino)-2-oxoethyl]-3-oxo-2,5,8,11-tetraazatridecan-13-oato (3-)-N⁶, N⁸, N¹¹, O⁵, O⁸, O¹¹, O¹³] gadolinium hydrate, with a molecular weight of 573.66 (anhydrous), an empirical formula of C₁₈H₂₈GdN₆O₉·xH₂O, and the following structural formula:



Pertinent physicochemical data for OMNISCAN are noted below:

PARAMETER		
Osmolality (mOsmol/kg water)	@ 37°C	789
Viscosity (cP)	@ 20°C	2.0
	@ 37°C	1.4
Density (g/mL)	@ 25°C	1.14
Specific gravity	@ 25°C	1.15

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

CLINICAL PHARMACOLOGY

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 3.7 ± 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*.

Pharmacodynamics

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

By increasing the relaxation rate, OMNISCAN decreases both the T₁ and T₂ relaxation times in tissues where it is distributed. At clinical doses, the effect is primarily on the T₁ relaxation time, and produces an increase in signal intensity. OMNISCAN does not cross the intact blood-brain barrier and, therefore, does not accumulate in normal brain or in lesions that do not have an abnormal blood-brain barrier (e.g., cysts, mature postoperative scars, etc). However, disruption of the blood-brain barrier or abnormal vascularity allows accumulation of OMNISCAN in lesions such as neoplasms, abscesses, and subacute infarcts. The pharmacokinetic parameters of OMNISCAN in various lesions are not known.

Metabolism

There is no detectable biotransformation or decomposition of gadodiamide.

Special Populations:

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

CLINICAL TRIALS

CNS (Central Nervous System)

In early clinical trials of 439 adults, OMNISCAN 0.1 mmol/kg was evaluated and found to be useful in providing contrast enhancement in CNS MRI in adults. OMNISCAN was also evaluated in a trial in 57 adults (34 men, 23 women) who had an indication for CNS MRI. These patients had a mean age of 47 years (range 21 to 82 years). Of these, 93% were Caucasian, 2% Black, and 5% other races. All patients were studied with sequential dosing of OMNISCAN 0.1 mmol/kg followed by 0.2 mmol/kg within 20 minutes (for cumulative dose of 0.3 mmol/kg). The results of the noncontrast enhanced MRI, the OMNISCAN 0.1 mmol/kg enhanced, and the cumulative OMNISCAN 0.3 mmol/kg (0.1 followed by 0.2 mmol/kg) enhanced MRIs were compared blindly. In 54/56 (96%) of all patients, contrast enhancement was evident with both the 0.1 mmol/kg and cumulative 0.3 mmol/kg (0.1 mmol/kg followed by 0.2 mmol/kg) doses.

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

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

OMNISCAN was evaluated in two double-blind, parallel studies with MAGNEVIST® (gadopentetate dimeglumine) in a total of 173 children who were referred for CNS MRI. The children received either OMNISCAN or MAGNEVIST in a single 0.1 mmol/kg dose. OMNISCAN was administered to 84 children (45 boys and 39 girls) with a mean age of 8.9 (2-18) years; of these patients, 92% were Caucasian, 7% Black, and 1% other races. The demographics were similar for the 89 children who received MAGNEVIST. Postcontrast MRI results showed that added diagnostic information, diagnostic confidence, and new patient management information were provided in approximately 76%, 67% and 52%, respectively, of children who received OMNISCAN. These findings were similar to those of MAGNEVIST. CT or histopathology was performed in 70/173 (42%) children who received OMNISCAN and MAGNEVIST. Of these, 69/70 (98.6%) were confirmed.

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

OMNISCAN was evaluated in a controlled trial of 276 patients who were referred for MRI of the internal thoracic, abdominal, pelvic or retroperitoneal organs. These patients (170 men and 106 women) had a mean age of 57 (9-88) years. Patients received 0.1 mmol/kg OMNISCAN for imaging body areas that included the internal thorax (noncardiac), abdomen, and pelvis, or a dose of 0.05 mmol/kg for imaging the kidney. Pre- and post-OMNISCAN images were evaluated

blindly for the degree of contrast, diagnostic value, and lesion detection. These were 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. These findings were similar to those of MAGNEVIST 0.1 mmol/kg.

In a dose ranging study of 258 patients who were referred for MRI of the internal thoracic, abdominal, pelvic, or retroperitoneal organs, the evaluated doses included OMNISCAN 0.025, 0.05, 0.1 mmol/kg. The lowest effective dose of OMNISCAN for the kidney was 0.05 mmol/kg.

INDICATIONS AND USAGE

CNS (Central Nervous System)

OMNISCAN is indicated for intravenous use in MRI to visualize lesions with abnormal vascularity (or those thought to cause abnormalities in the blood-brain barrier) in the brain (intracranial lesions), spine, and associated tissues.

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

OMNISCAN is indicated for intravenous administration to facilitate the visualization of lesions with abnormal vascularity within the thoracic (noncardiac), abdominal, pelvic cavities, and the retroperitoneal space.

CONTRAINDICATIONS

None known.

WARNINGS

Deoxygenated sickle erythrocytes have been shown in *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by paramagnetic contrast agents may possibly potentiate sickle erythrocyte alignment. OMNISCAN has not been studied in patients with sickle cell anemia and other hemoglobinopathies.

Patients with other hemolytic anemias have not been adequately evaluated following administration of OMNISCAN to exclude the possibility of increased hemolysis.

Patients with history of allergy or drug reaction should be observed for several hours after drug administration.

PRECAUTIONS

General

Some paramagnetic contrast agents may impair the visualization of existing lesions which are seen on the unenhanced, noncontrast MRI. This may be due to effects of the paramagnetic contrast agent, imaging parameters, misregistration, etc. CAUTION SHOULD BE EXERCISED WHEN A CONTRAST ENHANCED INTERPRETATION IS MADE IN THE ABSENCE OF A COMPANION UNENHANCED MRI.

OMNISCAN is cleared from the body by glomerular filtration. Significant hepatobiliary enteric pathway excretion has not been demonstrated. Dose adjustments in renal or hepatic impairment have not been studied. Caution should be exercised in patients with impaired renal insufficiency with or without hepatic impairment. For elimination of OMNISCAN in pediatric patients, see the Pediatric Use section.

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, a history of asthma, or other allergic respiratory disorders (see ADVERSE REACTIONS).

Repeat procedures: Sequential use during the same diagnostic session has been studied in adult central nervous system use only. Data for sequential injections during the same session or repeated injections for monitoring in other indications are not available. If the physician determines repeat dosing is required in non-CNS use in adults or in CNS pediatric administration, in patients with normal renal function the time interval between repeat doses should be at least 7 hours to allow for normal clearance of the drug from the body (see Pharmacokinetics section).

OMNISCAN should be drawn into the syringe and used immediately. If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Diagnostic procedures involving the use of contrast agents should be conducted under supervision of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed.

INFORMATION FOR PATIENTS

Patients receiving OMNISCAN should be instructed to:

1. Inform their physician if they are pregnant or breast feeding.
2. Inform their physician if they have anemia or diseases that affect red blood cells.
3. Inform their physician if they have a history of renal or hepatic disease, seizure, asthma or allergic respiratory disorders, or hemoglobinopathies.

LABORATORY TEST FINDINGS

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

Omniscan interferes with serum calcium measurements with some colorimetric (complexometric) methods commonly used in hospitals, resulting in serum calcium concentrations lower than the true values. Thus, it is recommended not to use such methods for 12-24 hours after administration of Omniscan. If such measurements are necessary, the use of other methods is recommended. All patients in whom this effect was observed remained asymptomatic.

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: bacterial reverse mutation assay, CHO/HGPRT forward mutation assay, CHO chromosome aberration assay, and the *in vivo* mouse micronucleus assay at intravenous doses up to 27 mmol/kg. Impairment of male or female fertility was not observed in rats after intravenous administration three times per week at 1.0 mmol/kg, the maximum dose tested.

PREGNANCY CATEGORY C

OMNISCAN has been shown to have an adverse effect on embryo-fetal development in rabbits that is observed as an increased incidence of flexed appendages and skeletal malformations at dosages as low as 0.5 mmol/kg/day for 13 days during gestation (approximately 2 times the maximum human cumulative dose of 0.3 mmol/kg based on a mmol/kg comparison or 0.6 times the human dose based on a mmol/m² comparison). Skeletal malformations may be due to maternal toxicity since the body weight of the dams was significantly 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 (8 times the maximum human cumulative dose, or 1.3 times the human dose on a mg/m² 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 at this time. 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.

NURSING MOTHERS

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

PEDIATRIC USE

The safety and efficacy of OMNISCAN at a single dose of 0.05 to 0.1 mmol/kg have been established in the pediatric population over 2 years of age. The safety and efficacy for doses greater than 0.1 mmol/kg and the clinical benefit of repeated procedures have not been studied in pediatric patients. The use of OMNISCAN in these age groups is supported by evidence from adequate and well controlled studies of OMNISCAN in adults, a pediatric study of the MR imaging of the central nervous system and additional safety data obtained in the literature.

Pharmacokinetics of OMNISCAN have not been studied in the pediatric population. Literature reports that the glomerular filtration rate of neonates and infants is much less than that of adults. The pharmacokinetics volume of distribution is different as well. The effect of these differences on the elimination and dosing regimen in pediatric patients under 2 years of age has not been studied. Whether the dose administered or optimal imaging times should be adjusted has not been studied.

However, in the 173 pediatric patients in the central nervous system study with OMNISCAN (see the CLINICAL TRIALS section) and the 144 pediatric patients in the literature, the adverse events were similar to those reported in adults.

GERIATRIC USE

Of the total number of patients in clinical studies of OMNISCAN, 19.3 percent were 65 to 80, while 1.2 percent were over 80. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals 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.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

The most frequent adverse events observed during OMNISCAN clinical trials were nausea, headache, and dizziness that occurred in 3% or less of the patients; other adverse events that occurred in 1% or less of the patients are listed below. This includes all reported adverse events regardless of attribution. The majority of these adverse events were of mild to moderate intensity. Dose and adverse event relationships are not fully clarified.

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

Application Site Disorders: Injection site reaction.

Autonomic Nervous System Disorders: Vasodilation.

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

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

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

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

Hearing and Vestibular Disorders: Tinnitus.

Liver and Biliary System Disorders: Abnormal hepatic function.

Musculoskeletal System Disorders: Arthralgia, myalgia.

Psychiatric Disorders: Anorexia, anxiety, personality disorder, somnolence.

Respiratory System Disorders: Rhinitis, dyspnea.

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

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

Urinary System Disorders: Acute reversible renal failure.

Vision Disorders: Abnormal vision.

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). Gadodiamide has been shown to be dialyzable in an *in vitro* study. Clinical data are not currently available.

DOSAGE AND ADMINISTRATION**CNS (Central Nervous System)**

Adults: The recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg) administered as a bolus intravenous injection. An additional 0.4 mL/kg (0.2 mmol/kg) can be given within 20 minutes of the first dose.
(See the Dosage Chart.)

Pediatric Patients (2-16 years): The recommended dose of OMNISCAN is 0.2 mL/kg (0.1 mmol/kg) administered as a bolus intravenous injection.
(See the Dosage Chart.)

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

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

DOSAGE CHART

BODY WEIGHT		PEDIATRIC		ADULTS		
		0.05 (mmol/kg)	0.1 (mmol/kg)	0.05 (mmol/kg)	0.1 (mmol/kg)	0.2 (mmol/kg)
kg	lb	VOLUME (mL)		VOLUME (mL)		
12	26	1.2	2.4	-	-	-
14	31	1.4	2.8	-	-	-
16	35	1.6	3.2	-	-	-
18	40	1.8	3.6	-	-	-
20	44	2.0	4.0	-	-	-
22	48	2.2	4.4	-	-	-
24	53	2.4	4.8	-	-	-
26	57	2.6	5.2	-	-	-
28	62	2.8	5.6	-	-	-
30	66	3.0	6.0	-	-	-
40	88	4.0	8.0	4.0	8.0	16.0
50	110	5.0	10.0	5.0	10.0	20.0
60	132	6.0	12.0	6.0	12.0	24.0
70	154	7.0	14.0	7.0	14.0	28.0
80	176	8.0	16.0	8.0	16.0	32.0
90	198	-	-	9.0	18.0	36.0
100	220	-	-	10.0	20.0	40.0
110	242	-	-	11.0	22.0	44.0
120	264	-	-	12.0	24.0	48.0
130*	286	-	-	13.0	26.0	52.0

*The heaviest patient in clinical studies weighed 136 kg.

To ensure complete injection of the contrast medium, the injection should be followed by a 5 mL flush of 0.9% sodium chloride, as provided in the Prefill Plus needle-free system. The imaging procedure should be completed within 1 hour of administration of OMNISCAN.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Do not use the solution if it is discolored or particulate matter is present. Any unused portion must be discarded.

HOW SUPPLIED

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

5 mL fill in 10 mL vial, box of 10, (NDC 0407-0690-05)
10 mL vial, box of 10, (NDC 0407-0690-10)
15 mL fill in 20 mL vial, box of 10, (NDC 0407-0690-15)
20 mL vial, box of 10, (NDC 0407-0690-20)
50 mL vial, box of 10, (NDC 0407-0690-55)
10 mL fill in 20 mL prefilled syringe, box of 10, (NDC 0407-0690-12)
15 mL fill in 20 mL prefilled syringe, box of 10, (NDC 0407-0690-17)
20 mL prefilled syringe, box of 10, (NDC 0407-0690-22)

Prefill Plus™ needle-free system

Omniscan 15 mL, box of 10, (NDC 0407-0690-62)
Contains: Omniscan 15 mL fill in 20 mL Single Dose Prefilled Syringe and
5 mL 0.9% Sodium Chloride Injection, USP I.V. Flush Syringe

Prefill Plus™ needle-free system

Omniscan 20 mL, box of 10, (NDC 0407-0690-63)
Contains: Omniscan 20 mL fill in 20 mL Single Dose Prefilled Syringe and
5 mL 0.9% Sodium Chloride Injection, USP I.V. Flush Syringe

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

Protect from light.

Do not freeze. Freezing could cause small cracks in the vials which would compromise the sterility of the product. Do not use if the product is inadvertently frozen.

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