

PRODUCT MONOGRAPH

OMNISCAN™

(Gadodiamide injection USP)

287 mg/mL (0.5 mmol/mL)
For intravenous Injection Only

Contrast Enhancement Agent for Magnetic Resonance Imaging (MRI)

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THERAPEUTIC CLASSIFICATION

Contrast Enhancement Agent for Magnetic Resonance Imaging (MRI)

ACTIONS AND CLINICAL PHARMACOLOGY

OMNISCAN (gadodiamide) injection was developed as a contrast agent for diagnostic use in magnetic resonance imaging (MRI). Gadodiamide 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.

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 (T_1); and variation of the spin-spin or transverse relaxation time (T_2).

By increasing the relaxation rate, OMNISCAN decreases both the T_1 and T_2 relaxation times in tissues where it is distributed. At clinical doses, the effect is primarily on the T_1 relaxation time, and produces an increase in signal intensity.

OMNISCAN does not cross the intact blood-brain barrier and, therefore, does not accumulate in

normal brain or in lesions that do not have an abnormal blood-brain barrier e.g., cysts, mature post-operative scars etc. [Lack of enhancement need not indicate absence of pathology since some types of low grade malignancies or inactive MS-plaques fail to enhance; it can be used for differential diagnosis between different pathologies.] Disruption of the blood-brain barrier or abnormal vascularity allows accumulation of OMNISCAN in lesions such as neoplasms, abscesses and subacute infarcts. The extended time for OMNISCAN to be accumulated in the lesions is unknown.

Pharmacokinetics:

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

Gadodiamide is eliminated primarily in the urine with $95.4 \pm 5.5\%$ (mean \pm SD) of the administered dose eliminated by 24 hours. There is no detectable biotransformation or decomposition of gadodiamide. 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. No protein binding has been observed.

Plasma clearance and elimination half-life were independent of dose after injection of 0.1 and 0.3 mmol/kg. No metabolites have been detected.

Secondary Pharmacodynamics:

There were no clinically significant deviations from preinjection values in hemodynamic, blood and urine laboratory parameters following intravenous injection of gadodiamide in healthy volunteers. However, a minimal transient increase in serum iron levels 8 to 48 hours after gadodiamide injection was observed.

INDICATIONS

OMNISCAN (gadodiamide) injection is indicated in adults and the pediatric population for contrast enhancement of magnetic resonance imaging (MRI) of lesions of the central nervous system with expected abnormal vascularity or those thought to cause abnormalities in the blood-brain barrier. OMNISCAN has been shown to facilitate visualization of central nervous system lesions including but not limited to tumors.

OMNISCAN is also indicated for intravenous administration for use in MRI in adults to facilitate the visualization of lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities, breast, retroperitoneal space and musculoskeletal system.

OMNISCAN is indicated for intravenous administration for use in magnetic resonance angiography (MRA) for the detection and localization of stenosis in renal arteries and aorto-iliac arteries.

CONTRAINDICATIONS

OMNISCAN (gadodiamide) injection is contraindicated in patients who are known or suspected to be hypersensitive to it or any of its components.

WARNINGS

SERIOUS WARNINGS

NOT FOR INTRATHECAL USE

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

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS

Gadolinium-based contrast agents (GBCAs) increase the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with:

- acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m²), 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 GBCAs 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 GBCA, 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 - General, Skin, Renal, and ADVERSE REACTIONS sections).

General**Nephrogenic Systemic Fibrosis (NSF)**

Gadolinium-based contrast agents (GBCAs) increase the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m²) and in patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. In these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). For patients receiving hemodialysis, healthcare professionals may consider prompt hemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if hemodialysis prevents NSF.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and the degree of renal function impairment at the time of exposure.

NSF development is considered a potential class-related effect of all GBCAs.

Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan™), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK®). NSF has also developed following the sequential administration of gadodiamide with gadobenate dimeglumine (MultiHance®) or gadoteridol (ProHance®). The number of post-marketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific GBCA.

The extent of risk for NSF following exposure to any specific GBCA is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4% (J Am Soc Nephrol 2006;17:2359). The risk, if any for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown, and the cautious utilization of the lowest possible dose of GBCA is preferable.

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a GBCA, 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 PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

A skin biopsy is necessary in order to exclude the diagnosis of similarly presenting skin disorders (e.g. scleromyxedema). (See WARNINGS - Serious Warnings, Renal, Skin, and ADVERSE REACTIONS sections).

Skin

NSF was first identified in 1997 and has so far, been observed only in patients with renal disease. This is a systemic disorder with the most prominent and visible effects on the skin. Cutaneous lesions associated with this disorder are caused by excessive fibrosis and are usually symmetrically distributed on the limbs and trunk. Involved skin becomes thickened which may inhibit flexion and extension of joints and result in severe contractures. The fibrosis associated with NSF can extend beyond dermis and involve subcutaneous tissues, striated muscles, diaphragm, pleura, pericardium, and myocardium. NSF may be fatal. (See WARNINGS - Serious Warnings, General, Renal, and ADVERSE REACTIONS sections).

Renal

- Exposure to GBCAs increases the risk for NSF in patients with:
 - acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m²), or

- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

- Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.
- The risk, if any for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown, and the cautious utilization of the lowest possible dose of GBCA is preferable.

(See WARNINGS - Serious Warnings, General, Skin, and ADVERSE REACTIONS sections).

As with any contrast agent, the possibility of a reaction, including serious, life threatening, fatal, anaphylactoid or other idiosyncratic reactions should always be considered (see **ADVERSE REACTIONS**) especially in those patients with a known clinical hypersensitivity. In the event of hypersensitive reactions, it is essential that medical personnel be familiar with the practice of emergency measures and that adequate equipment and drugs utilized in these situations be readily available for emergency treatment.

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

OMNISCAN injection in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

Patients with other hemolytic anemias have not been adequately evaluated following

administration of OMNISCAN to exclude the possibility of increased hemolysis.

USE IN PREGNANCY

There are no adequate and well-controlled studies in pregnant women. OMNISCAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

OMNISCAN had no effects on fertility or reproductive performance in rats or in teratology studies in rats and rabbits at doses that did not cause maternal toxicity (1.0 mmol/kg).

USE DURING LACTATION

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.

PEDIATRICS

The cautious utilization of the lowest possible dose of Omniscan for children is recommended, particularly for neonates and infants due to their immature renal function (see WARNINGS – General).

No studies have been conducted in pediatric patients with severe renal or hepatic dysfunction; clinically unstable hypertension or uncontrolled hypertension; and in premature infants (see **ADVERSE REACTIONS**).

At this time, there is no data in the pediatric population regarding the minimum period of time before a repeat injection of OMNISCAN; see the **ACTIONS AND CLINICAL PHARMACOLOGY** section for information on the Pharmacokinetics in adults.

PRECAUTIONS

GENERAL

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. OMNISCAN (gadodiamide) injection 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.

Since OMNISCAN is cleared from the body by glomerular filtration, caution should be exercised in patients with impaired renal function. OMNISCAN can be removed from circulation by hemodialysis.

Adequate time should elapse between administration of iodine containing contrast media and enhanced MRI examination, due to the possibility of inducing reversible renal failure. A single case of reversible renal failure occurred in a clinical study when a patient with previously reported normal kidney function, was administered a high dose of OMNISCAN within 24 hours of prior examination with an iodine containing contrast agent.

If, in the clinical judgment of the physician, sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body.

The effect of OMNISCAN on QT prolongation has not been studied in a dedicated QT prolongation clinical study.

CONVULSIVE STATES

While there is no evidence suggesting that OMNISCAN directly precipitates convulsions, the

possibility that it may decrease the convulsive threshold in susceptible patients cannot be ruled out. Appropriate precautionary measures should be taken with patients predisposed to seizure.

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. It may also interfere with determinations of other electrolytes (e.g. iron). Thus it is recommended not to use such methods for 12-24 hours after administration of OMNISCAN.

Elevation of creatine kinase has been observed in clinical trials. The source and clinical significance of this is unknown.

DRUG-DRUG INTERACTION

Administration of iodine-containing contrast agents was restricted to 24 hours pre-injection and 24 hours post OMNISCAN injection. Similarly, administration of other gadolinium-based contrast agents was restricted to 24 hours pre-injection and 24 hours post OMNISCAN injection.

Therefore, safety data of administration of OMNISCAN in conjunction with iodine-containing contrast agents or other gadolinium-based contrast agents are not available.

GERIATRIC PATIENTS

No specific precautions other than those pertinent to MRI and OMNISCAN in general are applicable for elderly patients.

ADVERSE REACTIONS

Adults

The most frequent adverse reactions observed in adult patients during OMNISCAN (gadodiamide) clinical trials were nausea, headache and dizziness with an incidence of 3% or less. This includes all reported adverse events regardless of attribution. The majority of these adverse reactions were of mild to moderate intensity.

The following adverse reactions occurred in less than 1% of the adult 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, feeling hot.

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.

Gastro-Intestinal System Disorders: Abdominal pain, diarrhea, eructation, melena, dry mouth, vomiting.

Hearing and Vestibular Disorders: Tinnitus.

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.

Pediatrics

Three adverse events occurred in 3 of 91 (3%) patients during OMNISCAN clinical trials in pediatric patients. This includes all adverse events regardless of attribution.

Body as a Whole-General Disorders: Fever.

Liver and Biliary System Disorders: Abnormal hepatic function.

Skin and Appendage Disorders: Rash.

The fever and rash were of mild intensity and the abnormal hepatic function was of severe

intensity (although of uncertain relationship to administration of OMNISCAN).

Post-Marketing

Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (OmniscanTM), followed by gadopentetate dimeglumine (Magnevist[®]) and gadoversetamide (OptiMARK[®]). NSF has also developed following the sequential administration of gadodiamide with gadobenate dimeglumine (Multihance[®]) or gadoteridol (ProHance[®]). The number of post-marketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific GBCA. The extent of risk for NSF following exposure to any specific GBCA is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4% (J Am Soc Nephrol 2006; 17:2359). The risk, if any for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown, and the cautious utilization of the lowest possible dose of GBCA is preferable.

(See WARNINGS - Serious Warnings, General, Skin and Renal sections).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Clinical consequences of overdosage have not been reported and acute symptoms of toxicity are unlikely in patients with normal renal function. Treatment is symptomatic. There is no antidote

for this contrast medium. In patients with delayed elimination due to renal insufficiency and in patients who have received excessive doses, the contrast medium may theoretically be eliminated by hemodialysis.

DOSAGE AND ADMINISTRATION

OMNISCAN (gadodiamide) injection 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.

Contrast-enhanced MRI should start shortly after administration of the contrast medium. Optimal enhancement is generally observed within 45 minutes after injection of OMNISCAN. T₁-weighted scanning sequences are particularly suitable for contrast-enhanced examinations with OMNISCAN. In the investigated range of field strengths, from 0.15 Tesla up to 1.5 Tesla, the relative image contrast was found to be independent of the applied field strength.

The recommended dose of OMNISCAN for imaging of the central nervous system is 0.2 mL/kg (0.1 mmol/kg) administered as a bolus intravenous injection. (See the Dosage Chart). If medically indicated, preprocedural medication (e.g., sedatives) may be administered according to the normal routine for MR examinations.

The recommended dose of OMNISCAN for imaging of the body is 0.6 mL/kg (0.3 mmol/kg), administered as a bolus intravenous injection (See the Dosage Chart).

The recommended dose of OMNISCAN for MRA is 0.2 mL/kg (0.1 mmol/kg) administered as a bolus intravenous injection at an injection rate of 1–4 mL/sec.

DOSAGE CHART

BODY WEIGHT		PEDIATRIC 0.1 mmol/kg	ADULT 0.1 mmol/kg 0.3 mmol/kg	
kg	lb	VOLUME (mL)	VOLUME (mL)	
5	11	1.0		
10	22	2.0		
12	26	2.4		
14	31	2.8		
16	35	3.2		
18	40	3.6		
20	44	4.0		
22	48	4.4		
24	53	4.8		
26	57	5.2		
28	62	5.6		
30	66	6.0		
40	88	8.0	8.0	24.0
50	110	10.0	10.0	30.0
60	132	12.0	12.0	36.0
70	154	14.0	14.0	42.0
80	176	16.0	16.0	48.0
90	198	-	18.0	54.0
100	220	-	20.0	60.0
110	242	-	22.0	66.0
120	264	-	24.0	72.0
130*	286	-	26.0	78.0

* 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. 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.

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: (USAN) - gadodiamide

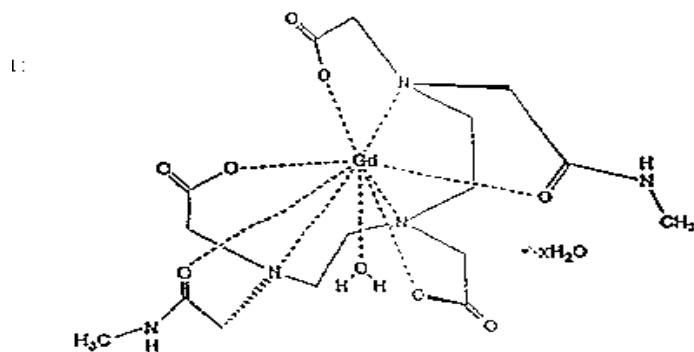
Synonyms: GdDTPA-BMA; gadolinium diethylenetriaminepentaacetic acid bis(methylamide); gadolinium diethylenetriaminepentaacetate bis (methylamide); GdDTPA bis(methylamide)

Chemical Name:

Aqua[5,8-bis(carboxymethyl)-11-[2-(methylamino)-2-oxoethyl]

-3-oxo-2,5,8,11-tetraazatridecane-13-oate(3-)- $\text{N}^5, \text{N}^8, \text{N}^{11}, \text{O}^3, \text{O}^5, \text{O}^8, \text{O}^{11}, \text{O}^{13}$]gadolinium hydrate

Structural Formula:



Molecular Formula: $C_{16}H_{28}GdN_5O_9 \cdot xH_2O$, where x is the number of adsorbed water molecules (the molecular formula includes one water molecule coordinated to gadolinium), or $C_{16}H_{26}GdN_5O_8$ (anhydrous, no adsorbed or coordinated water).

Molecular Weight: 573.66 (anhydrous, no adsorbed or coordinated water)

Physical Form: Gadodiamide is a crystalline solid, appearing as a fine white powder.

Solubility: Gadodiamide is freely soluble in water and methanol, soluble in ethanol and slightly soluble in acetone and chloroform.

pKa: The two most basic groups of the DPTA-BMA ligand have pK_a values of 9.37 and 4.38. The third amine of the ligand has a pK_a of 3.31 and the carboxylates all have pK_a values below 2. The gadolinium ion interferes with the measurement of pK_a values in gadodiamide.

Partition co-efficient: The log of P, the partition co-efficient, between butanol and water is -2.13

Melting Point: Gadodiamide has no discrete melting point. It loses water of hydration below 200 degrees C and shows decomposition at 300 degrees C and above. Melting point behaviour, thermogravimetric analysis and differential scanning calorimetry failed to disclose the presence of polymorphic forms.

Dissociation Constant: The metal-ligand thermodynamic stability constant was determined by competitive titration procedures, with log K equal to 16.85.

Composition

OMNISCAN (gadodiamide) injection is a 0.5 mol/L solution of the gadolinium complex of diethylenetriaminepentaacetic acid bismethylamide. It is a nonionic extracellular enhancing agent for magnetic resonance imaging and is provided as a sterile, clear, colorless to slightly yellow, aqueous solution. Each mL contains 287 mg gadodiamide, 12 mg caldiumide sodium and water for injection. The pH is adjusted between 5.5 and 7.0 with hydrochloric acid and/or sodium hydroxide.

Pertinent physicochemical data for OMNISCAN are noted below:

PARAMETER		
Osmolality (mOsm/kg water)	@ 37°C	789
Viscosity (cp)	@ 20°C	2.0
	@ 37°C	1.4
Density (g/cm ³)	@ 20°C	1.15

OMNISCAN has an osmolality 2.8 times that of plasma (285 mOsm/kg water) at 37°C and is

hypertonic under conditions of use.

Stability and Storage Recommendations

All solutions are sterilized by autoclaving and contain no preservatives. Unused portions must be discarded. Protect from light. Do not freeze. If inadvertently frozen, do not use OMNISCAN solutions, as freezing could cause small cracks in the vials which would compromise the sterility of the product.

OMNISCAN should be stored at controlled room temperature 15°C - 30°C.

AVAILABLE DOSAGE FORMS

OMNISCAN (gadodiamide) injection is supplied in the following sizes:

5 mL fill in 10 mL vial, box of 10

10 mL vial, box of 10

15 mL fill in 20 mL vial, box of 10

20 mL vial, box of 10

50 mL vial, box of 10

INFORMATION FOR PATIENTS

There have been post-market reports of a rare disease called Nephrogenic Systemic Fibrosis (NSF) following gadolinium-based contrast agent (GBCA) use.

NSF is a rare condition which has only been observed so far in patients with severe kidney disease. . At present, there is no evidence that other patient groups are at risk of developing the condition. Due to NSF the skin becomes thickened, coarse and hard, which sometimes makes bending of the joints difficult. NSF may spread to other organs and even cause death.

Patients with severe kidney disease should avoid the use of Omniscan unless the health care professional believes the possible benefits outweigh the potential risks. Those who have already had an MR imaging procedure and who have any of the following symptoms should seek medical attention as soon as possible:

Swelling, hardening and tightening of the skin

Reddened or darkened patches on the skin

Burning or itching of the skin

Yellow spots on the whites of the eyes

Stiffness in the joints, problems moving or straightening arms, hands, legs or feet

Pain deep in the hip bone or ribs

Weakness of the muscles

Your doctor will monitor your health after administering Omniscan, if you are considered to be at risk for developing NSF.

PRECLINICAL PHARMACOLOGY

PHARMACODYNAMICS:

Study type	Animal species (strain; age)	Total no. of animals		Number of dosings (control)	Route	Dose		Results
		M	F			mg/kg	mmol/kg	
Brain tumor imaging	Rat (Fischer 344)	1	0	1	IV inj.	57.4	0.1	Enhancement of tumor in 9L glioma model.
Imaging normal genitourinary system	Rabbit (2-8 months)	1	0	1	IV inj.	57.4	0.1	Enhancement of renal parenchyma.
Genitourinary system imaging: hydronephrosis model	Rabbit (2-8 months)	1	0	1	IV inj.	57.4	0.1	Demonstrated differentiation of the outer and inner medulla, and demonstrated increased water content in the kidney.
Brain tumor imaging	Dog	1 gender unknown		1	IV inj.	57.4	0.1	Enhancement of brain tumor in veterinary referral case.
Brain abscess imaging	Cat (1-3 years)	0	1	1 (on Day 2)	IV inj.	57.4	0.1	Cerebritis detected early; capsular phase detected late.
Brain trauma imaging	Cat (1-3 years)	0	1	2 (on Day 2 and at Week 2 post- trauma)	IV inj.	114.8	0.2	Enhancement consistent with trauma at 2 days; enhancement of areas secondary to trauma.
Imaging normal brain	Cat (1-3 years)	0	1	1	IV inj.	189.42	0.33	Enhancement of intracranial structures lacking a blood-brain barrier.

PRECLINICAL PHARMACOLOGY

BIOCHEMICAL PHARMACOLOGY:

Study type	Animal species (strain; age)	Total no. of animals		Number of dosings (control)	Route	Dose		Results
		M	F			mg/kg	mmol/kg	
*Lysozyme activity	<u>In vitro</u> (<u>Micrococcus</u> <u>lysodeikticus</u>)	5**		1 [buffer]	N/A	0.1, 0.25, 0.50, 1.00, 2.50 and 5.00 mM		Gadodiamide injection and Magnevist ^R caused no change (<5%) in lysozyme activity.
*Cholinesterase activity	<u>In vitro</u>	5**		1 [buffer]	N/A	0.1, 0.25, 0.50, 1.00, 2.50 and 5.00 mM		Gadodiamide injection and Magnevist ^R produced no change in cholinesterase activity.
*Erythrocyte fragility	<u>In vitro</u>	3**		1 [saline]	N/A	50, 100, 150 and 250 mM		Only Magnevist ^R at 250 mM caused significant effects.
*Erythrocyte morphology	<u>In vitro</u>	3**		1 [saline]	N/A	50, 100, 150 and 250 mM		Gadodiamide injection produced macrocytosis (a minor effect) at all concentrations and poikilocytosis at 250 mM. Magnevist ^R caused poikilocytosis at 100, 150 and 250 mM.

* Study in which effects of gadodiamide injection and Magnevist^R (gadopentetate dimeglumine) were compared at equivalent doses.

** Number represents sample size per dose level.

N/A Not applicable (in vitro study).

PRECLINICAL PHARMACOLOGY

CENTRAL NERVOUS SYSTEM:

Study type	Animal species (strain; age)	Total no. of animals		Number of dosings (control)	Route	Dose		Results
		M	F			mg/kg	mmol/kg	
*Intracisternal tolerance	Mouse (NMRI; 4-5 weeks)	5**		1 (Ringer acetate)	Intracis- ternal inj.		0.001 0.003 0.01 0.03 0.1 0.3	Two high dose (gadodiamide 0.3 mmol/kg) animals died under anaesthesia; otherwise, both gadodiamide and Magnevist ^R were well tolerated in doses up to 0.3 mmol/kg.
Neurotoxic potential following blood-brain barrier disruption	Dogs (Labrador or labrador cross-bred; adult)	7		1	IV inj.		0.2	Two dogs did not survive surgical procedure. Three were sacrificed on Days 39, 40 and 43 and showed no clinical evidence of neurotoxicity. One animal was sacrificed 3 days post-BBBD ⁺ due to development of an extensive hematoma and bleeding from the neck wound. One dog developed status epilepticus (plus extensive hematoma) 7 days post-BBBD. Thrombocytopenia (platelet counts <100 x 10 ³ /mm ³) was observed in all 5 dogs with a nadir 3-5 days post-BBBD, and showing evidence of reversibility over 1-6 days.
MRI enhancement following blood-brain barrier disruption		3						Excellent imaging of BBBD, 15 min.-3 hrs. post-surgical procedure. Image enhancement corresponded to Evans blue staining.
*Thrombocytopenia induction potential (Follow-up to above-noted study)	Dogs (Beagle; 10-18 months)	4**		1 (saline)	IV inj.		0.2 2.0	In all dogs, platelet counts were normal (>200,000 per µl) at all time points. No treatment-related effects were observed.

* Study in which effects of gadodiamide injection and Magnevist^R (gadopentetate dimeglumine) were compared at equivalent doses.

** Number represents sample size per dose level.

+ Blood Brain Barrier Disruption

PRECLINICAL PHARMACOLOGY

CARDIOVASCULAR EFFECTS:

Study type	Animal species (strain; age)	Total no. of animals		Number of dosings (control)	Route	Dose		Results
		M	F			mg/kg	mmol/kg	
Cardiovascular	Dog (mongrel; young adult)	11	1	4 (two sequences) [saline]	IV inj.	57.4 172.2 401.8 574.0	0.1 0.3 0.7 1.0	No physiologically significant hemodynamic findings.
*Cardiovascular	Dog (mongrel; young adult)	11	1	4 (six sequences with two doses each of gadodiamide injection and Magnevist ^R) [saline]	IV inj.	574.0 861.0	1.0 1.5	Gadodiamide injection produced 22% and 26% decreases in systemic vascular resistance at 1.0 and 1.5 mmol/kg, respectively. Magnevist ^R produced marked hemodynamic changes in several parameters; including >50% decrease in systemic vascular resistance at both doses.
*Blood pressure	Rat (Wistar)	34	0	1 [saline]	IV inj.	287.0 574.0	0.5 1.0	Neither gadodiamide injection nor Magnevist ^R produced any hemodynamic effects.
*Bovine mesenteric arteries	<u>In vitro</u>	6**		1 (sucrose)	N/A	50mM		Gadodiamide injection produced one-sixth the tension produced by Magnevist ^R .

* Study in which effects of gadodiamide injection and Magnevist^R (gadopentetate dimeglumine) were compared at equivalent doses.

** Number represents sample size per dose level.

N/A Not applicable (in vitro study).

PRECLINICAL PHARMACOLOGY

ABSORPTION, DISTRIBUTION, METABOLISM & EXCRETION:

Study type	Animal species (strain; age)	Total no. of animals		Number of dosings (control)	Route	Dose		Results
		M	F			mg/kg	mmol/kg	
Pharmacokinetics with ¹⁵³ Gd	Rat (Sprague-Dawley; 8 weeks)	30	30	1	IV inj.	57.4	0.1	Data fit two-compartment model with bolus input, first-order output. Distribution half-life . 4.6 min, elimination half-life . 18 min.
Pharmacokinetics	Monkey (Cynomolgus; 2.5-5 years)	3	3	1	IV inj.	57.4	0.1	Data fit two-compartment model with bolus input, first-order output. Distribution half-life . 7 min, elimination half-life . 75 min.
Gadolinium retention 7 and 21 days post-dose	Mouse (NMRI; 4-5 weeks)	21	0	1 (one group killed Day 7 the others on Day 21) [saline]	IV inj.	287	0.5	There was a significant reduction in gadolinium retention in the liver from 7 days post-dosing (0.04% retained) to 21 days post-dosing (0.007% still present).
*Gadolinium retention 7 days post-dose	Rat (Sprague-Dawley; males: 7 weeks and females: 11 weeks)	24	24	1 [saline]	IV inj.	57.4 574	0.1 1.0	In all cases, retained gadolinium was less than 0.14% of the administered gadolinium. Gadolinium from gadodiamide injection was retained at higher levels in the liver and kidneys than was gadolinium from Magnevist [®] .
Distribution and excretion 24 hours post-dose with ¹⁵³ Gd	Rat (Sprague-Dawley; 81-101 days)	3	3	1	IV inj.	57.4	0.1	94.4% of radioactivity excreted in urine. 99.8% mean total recovery. Residual radioactivity accounted for 3.65% of the administered dose, with 0.78% in the solid organs (liver and kidneys) and 2.87% in the GI tract.
Distribution and excretion 6 days post-dose with ¹⁵³ Gd	Rat (Sprague-Dawley; 83-87 days)	3	3	1	IV inj.	57.4	0.1	89.7% of radioactivity excreted in urine. 95.4% mean total recovery. Residual radioactivity was 0.47%; almost all of which was in the liver (0.22%), kidneys (0.14%) or GI tract (0.07%).
Biotransformation	Rat (Wistar)	6 (serum) 6 (urine)		1	IV inj.		0.3	Within 1 hr. after injection, the amount of radiolabelled unknown compound in serum was <1% of the injected dose. Urine samples up to 6 hrs. revealed no higher than 1.3% of total radioactivity in each sample. Biotransformation of gadodiamide injection at a dose of 0.3 mmol/kg is negligible and is excreted unchanged in the urine of rats.

* Study in which effects of gadodiamide injection and Magnevist[®] (gadopentetate dimeglumine) were compared at equivalent doses.

CLINICAL STUDIES

OMNISCAN was evaluated in two controlled clinical trials enrolling a total of 794 patients who were referred for diagnosis of suspected stenosis of the renal or aorto-iliac arteries. These patients (496 men and 298 women) had a mean age of 64 years (range 17 to 94 years). Patients received one dose of OMNISCAN (0.1 mmol/kg, administered as a single bolus at an injection rate of 1–4 mL/sec via power injector) for the detection of stenoses in the renal arteries or aorto-iliac arteries.

The MRA images were evaluated blindly (3 readers) and the results compared to intra arterial digital subtraction angiography (IA DSA), which served as standard of truth, and unenhanced (time-of-flight, TOF) MRA. OMNISCAN-enhanced MRA was shown to be superior to unenhanced MRA and showed comparable results to the standard of truth with sensitivity and specificity values of 86–90% and 85–90%, respectively, for the renal arteries and of 82–90% and 89–96%, respectively, for the aorto-iliac arteries.

However, no conclusions were reached for three of the seven segments (infra-renal aorta; right and left common iliac arteries; right and left external iliac arteries; and right and left common femoral arteries) of the aorto-iliac arteries as the number of subjects with a stenosis in these segments was too small; these were the infra-renal aorta and the left and right common femoral arteries.

In the detection of stenoses in the renal arteries and the aorto-iliac arteries, sensitivity, specificity and accuracy values for OMNISCAN-enhanced (3D CE) MRA and unenhanced (2D TOF) MRA relative to IA DSA are presented below. The respective differences between OMNISCAN-enhanced MRA and unenhanced MRA will also be presented. It should be noted that 3D CE MRA can lead to overestimation of stenosis.

Renal Arteries

	Reader	3D CE MRA		2D TOF MRA		Difference CE – TOF	
		%	95% CI*	%	95% CI*	%	95% CI [§]
Sensitivity	Reader A	87.4	80.3	83.9	66.3	-6.9	-25.8
	Reader B	90.3	83.7	79.8	69.6	12.0	2.2
	Reader C	85.7	78.8	70.6	60.7	16.3	5.9
	Majority Decision	89.1	82.3	78.3	66.7	9.8	-1.9
Specificity	Reader A	87.0	80.8	56.9	44.0	34.5	22.0
	Reader B	89.5	83.9	79.7	72.0	9.0	2.6
	Reader C	85.1	79.3	74.3	66.9	8.4	1.7
	Majority Decision	88.9	83.2	78.6	70.6	8.5	3.0
Accuracy	Reader A	87.2	82.7	65.6	55.2	20.2	8.9
	Reader B	89.8	85.8	79.7	73.8	10.2	4.7
	Reader C	85.4	81.1	72.9	67.1	11.3	5.6
	Majority Decision	89.0	84.9	78.5	72.2	9.0	3.5

NOTE: Sensitivity, specificity and accuracy were calculated for all subjects with evaluable images for a specific modality, following the judgement of the respective reader. Calculation of sensitivity, specificity and accuracy was based on subject level. All efficacy values were calculated based on the standard of truth (IA DSA). Differences between 3D CE MRA and 2D TOF MRA were calculated for those patients who had both 3D CE MRA and 2D TOF MRA results available. The efficacy results in the table are for the main haemodynamically relevant stenosis.

%=degree of sensitivity, specificity or accuracy; 95% CI*=lower limit of the two-sided exact 95% confidence interval; 95% CI[§]=asymptotic lower confidence limit.

Aorto-iliac Arteries:

	Reader	3D CE MRA		2D TOF MRA		Difference CE – TOF	
		%	95% CI*	%	95% CI*	%	95% CI [§]
Sensitivity	Reader A	83.4	78.1	77.9	71.6	6.8	1.0
	Reader B	81.3	75.9	76.3	70.5	4.9	-1.1
	Reader C	89.8	85.2	81.3	75.9	8.7	3.5
	Majority Decision	86.4	81.5	80.3	74.6	6.5	1.0
Specificity	Reader A	94.9	93.7	95.8	94.6	-1.1	-2.4
	Reader B	96.3	95.3	89.9	88.4	6.1	4.6
	Reader C	89.3	87.7	84.0	82.2	4.7	2.7
	Majority Decision	95.2	94.1	92.5	91.1	2.1	0.7
Accuracy	Reader A	84.8	80.4	82.1	77.1	4.0	-1.0
	Reader B	83.5	79.1	78.1	73.1	5.4	0.3
	Reader C	86.1	81.9	79.8	75.0	6.3	1.6
	Majority Decision	86.8	82.6	81.1	76.3	6.3	1.6

NOTE: Sensitivity, specificity and accuracy were calculated for all subjects with evaluable images (sensitivity and accuracy) or segments (specificity) for a specific modality, following the judgement of the respective reader. All efficacy values were calculated based on the standard of truth (IA DSA). Calculation of sensitivity and accuracy was based on a subject level, whereas calculation of specificity was based on all segments combined. Differences between 3D CE MRA and 2D TOF MRA were calculated for those patients who had both 3D CE MRA and 2D TOF MRA results available. The efficacy results in the table are for the main haemodynamically relevant stenosis.

%=degree of sensitivity, specificity or accuracy; 95% CI*=lower limit of the two-sided exact 95% confidence interval; 95% CI[§]= lower limit of the asymptotic 95% confidence interval.

No conclusions were reached for three of the seven segments of the aorto-iliac arteries as the number of subjects with a stenosis in these segments was too small; these were the infra-renal aorta and the left and right common femoral arteries.

TOXICOLOGY

- Acute Toxicity -

Species (sex, number of animals per group)	Route	Dose		Results
		mg/kg	mmol/kg	
Mouse M 5 F 5	IV infusion	2870	5.0	No deaths or signs of toxicity. Minimum lethal dose > 2870 mg/kg (5 mmol/kg)
Mouse M 4 F 4	IV inj.	5740 11480 17220 22960 28700	10 20 30 40 50	LD ₅₀ = 19746 mg/kg (34.4 mmol/kg) Male LD ₅₀ = 38.1 mmol/kg Female LD ₅₀ = 28.0 mmol/kg
Rat M 5 F 5	IV infusion	2870	5.0	No deaths or signs of toxicity. Minimum lethal dose > 2870 mg/kg (5 mmol/kg)
Rat M 10 F 0	IV inj.	229.6 5740 11480	0.4 10 20	One animal died during dosing. The cause of death is not known. The animal was replaced and there were no deaths or signs of morbidity other than a slight decrease in activity in the ten animals dosed at 20 mmol/kg. Dose-related, partially reversible cortical tubule cell vacuolation was observed.

TOXICOLOGY

- Subacute Toxicity -

Species (sex, number of animals per group)	Number of dosings (control)	Route	Dose		Results
			mg/kg	mmol/kg	
Rat M 3 F 3	3 per week for 3 weeks (saline) ****	IV inj.	57.4 574 1722 2870 4305	0.1 1.0 3.0 5.0 7.5	Renal tubular epithelial vacuolation; dose-related in incidence and severity.
Monkey M 3 F 3 *****	10 doses over 22 days (saline)	IV inj.	57.4 2870	0.1 5.0	Moderate vacuolation in proximal tubular cell cytoplasm and increased absolute and relative kidney weights at 5.0 mmol/kg.
Rat M 5	Daily dosing for 14 days (saline)	IV inj.		0.1 0.125 0.25 0.5 1.0 Magnevist ⁷ 1.0	Following 14 consecutive injections, blood appeared in urinary sediments microscopically with positive urinary occult blood for 0.1-1.0 mmol/kg dosing. Histopathologically, cystitis was observed at > 0.1 mmol/kg, and dose related cytoplasmic vacuolation of renal tubular epithelium was seen. These changes were not seen for Magnevist ⁷ .
Rabbit M 3	Daily dosing for 14 days (saline)	IV inj.		0.05 0.1 0.5	Unlike the rat, no occult blood was observed. No clinico-pathological evidence to suggest cystitis was seen. Histopathological findings were stomach edema, testicular tubular degeneration and skin calcinosis all considered to be due to zinc deficiency. No kidney cytoplasmic vacuolation was observed. These results suggest a species-difference between rats and rabbits with regard to cystitis induction.
Monkey M 3 F 3	Daily dosing for 28-30 days (saline)	IV		0.05 0.25 1.25	Renal tubular epithelial changes were noted at the 1.25 mmol/kg/day dose. Serum chemistry revealed a dose related reduction in zinc and phosphate levels. Bone marrow myelograms showed a myeloid left shift in the 1.25 mmol group, corresponding to decreases in group mean myeloblast, neutrophilic myelocyte and neutrophilic polymorph values and an increase in group mean intermediate normoblast values. 0.05 and 0.25 mmol/kg groups also showed reduced mean myeloblast and neutrophilic myelocyte values. Most animal values, however, were within the control ranges. The toxicological significance of these changes is uncertain.

**** Two/sex/group killed on Day 22; one/sex/group killed on Day 29 after 7-day recovery period.

***** One female less than 2.5 years of age.

Carcinogenesis, mutagenesis, teratology, impairment of fertility

No long-term animal studies have been performed to evaluate the carcinogenic potential of gadodiamide.

Gadodiamide did not demonstrate mutagenic potential in three in vitro tests (the Ames test, the CHO/HGPRT forward mutation assay and the Chromosomal Aberration Frequency assay in CHO cells) or in an in vivo mouse micronucleus test.

Teratology studies showed no effects on the fetuses of rats given doses of up to 1.0 mmol/kg/day. In rabbits intravenous administration of 1.0 mmol/kg of gadodiamide injection during the period of major organogenesis (Days 6 through 18 of pregnancy), demonstrated a no-effect level in terms of embryo/fetal toxicity and teratogenicity.

Gadodiamide injection had no effects on fertility and reproductive performance in rats.

Irritancy Studies

Gadodiamide injection was found to be non-irritating following intravenous, and intraarterial administration in rabbits, and paravenous, intramuscular and subcutaneous administration in dogs. Dermal and eye application in rabbits also resulted in a non-irritating effect.

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