BERLEX IMAGING®

MAGNEVIST®

(brand of gadopentetate dimeglumine)

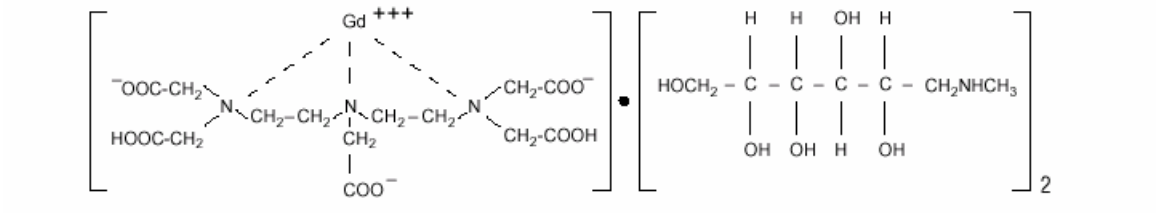
Injection

Rx only

DESCRIPTION

MAGNEVIST® (BRAND OF GADOPENTETATE DIMEGLUMINE) INJECTION IS THE N- METHYLGLUCAMINE SALT OF THE GADOLINIUM COMPLEX OF DIETHYLENETRIAMINE PENTAACETIC ACID, AND IS AN INJECTABLE CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING (MRI). MAGNEVIST® INJECTION IS PROVIDED AS A STERILE, CLEAR, COLORLESS TO SLIGHTLY YELLOW AQUEOUS SOLUTION FOR INTRAVENOUS INJECTION.

MAGNEVIST® INJECTION IS A 0.5-MOL/L SOLUTION OF 1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL DIHYDROGEN [*N*, *N*-BIS[2-[BIS(CARBOXYMETHYL)AMINO]ETHYL]-GLYCINATO-(5$^-$)-]GADOLINATE(2-$^-$) (2:1) WITH A MOLECULAR WEIGHT OF 938, AN EMPIRICAL FORMULA OF $C_{28}H_{54}GdN_5O_{20}$, AND HAS THE FOLLOWING STRUCTURAL FORMULA:



Each mL of MAGNEVIST® Injection contains 469.01 mg gadopentetate dimeglumine, 0.99 mg meglumine, 0.40 mg diethylenetriamine pentaacetic acid and water for injection. MAGNEVIST® Injection contains no antimicrobial preservative.

MAGNEVIST® Injection has a pH of 6.5 to 8.0. Pertinent physicochemical data are noted below:

PARAMETER		
Osmolality (mOsmol/kg water)		
	at 37°C	1,960
Viscosity (CP)		
	at 20°C	4.9
	at 37°C	2.9
Density (g/mL)		
	at 25°C	1.195
Specific gravity		
	at 25°C	1.208
Octanol: H_2O		
	at 25°C and pH7	log P_W = - 5.4

MAGNEVIST® Injection has an osmolality 6.9 times that of plasma which has an osmolality of 285 mOsmol/kg water. MAGNEVIST® Injection is hypertonic under conditions of use.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of intravenously administered gadopentetate dimeglumine in normal subjects conforms to a two compartment open-model with mean distribution and elimination half-lives (reported as mean ± SD) of about 0.2 ± 0.13 hours and 1.6 ± 0.13 hours, respectively.

Upon injection, the meglumine salt is completely dissociated from the gadopentetate dimeglumine complex. Gadopentetate is exclusively eliminated in the urine with 83 ± 14% (mean ± SD) of the dose excreted within 6 hours and 91 ± 13% (mean ± SD) by 24 hours, post-injection. There was no detectable biotransformation or decomposition of gadopentetate dimeglumine.

The renal and plasma clearance rates (1.76 ± 0.39 mL/min/kg and 1.94 ± 0.28 mL/min/kg, respectively) of gadopentetate are essentially identical, indicating no alteration in elimination kinetics on passage through the kidneys and that the drug is essentially cleared through the kidney. The volume of distribution (266 ± 43 mL/kg) is equal to that of extracellular water and clearance is similar to that of substances which are subject to glomerular filtration.

In vitro laboratory results indicate that gadopentetate does not bind to human plasma protein. *In vivo* protein binding studies have not been done.

Pharmacodynamics

Gadopentetate dimeglumine is a paramagnetic agent and, as such, it develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment produced by the paramagnetic

agent results in a relatively large local magnetic field, which can enhance the relaxation rates of water protons in the vicinity of the paramagnetic agent.

In magnetic resonance imaging (MRI), visualization of normal and pathological brain tissue depends in part on variations in the radiofrequency signal intensity that occur with 1) changes in proton density; 2) alteration of the spin-lattice or longitudinal relaxation time (T1); and 3) variation of the spin-spin or transverse relaxation time (T2). When placed in a magnetic field, gadopentetate dimeglumine decreases the T1 and T2 relaxation time in tissues where it accumulates. At usual doses the effect is primarily on the T1 relaxation time.

Gadopentetate dimeglumine 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. However, disruption of the blood-brain barrier or abnormal vascularity allows accumulation of gadopentetate dimeglumine in lesions such as neoplasms, abscesses, and subacute infarcts. The pharmacokinetic parameters of MAGNEVIST® in various lesions are not known.

CLINICAL TRIALS

MAGNEVIST® Injection was administered to 1272 patients in open label controlled clinical studies. The mean age of these patients was 46.4 years (range 2 to 93 years). Of these patients, 55% (700) were male and 45% (572) were female. Of the 1271 patients who received MAGNEVIST® Injection and for whom race was reported, 82.1% (1043) were Caucasian, 9.7% (123) were Black, 5.3% (67) were Hispanic, 2.1% (27) were Oriental/Asian, and 0.9% (11) were other. Of the 1272 patients, 550 patients were evaluated in blinded reader studies. These evaluated the use of contrast enhancement in magnetic resonance imaging of lesions in the head and neck, brain, spine and associated tissues, and body (excluding the heart). Of the 550 patients, all patients had a reason for an MRI and efficacy assessments were based on pre- and post-MAGNEVIST® injection film quality, film contrast, lesion configuration (border, size, and location), and the number of lesions. The protocols did not include systematic verification of specific diseases or histopathologic confirmation of findings.

Of the above 550 patients, 97 patients received 0.1 mmol/kg MAGNEVIST® Injection I. V. in two clinical trials of MAGNEVIST® MRI contrast enhancement for body imaging. Of these 97, 68 had MRIs of the internal organs/structures of the abdomen or thorax (excluding the heart); 8 had breast images and 22 had images of appendages. The results of MRIs before and after MAGNEVIST® use were compared blindly. Overall additional lesions were identified in 22/97 (23%) of the patients after MAGNEVIST® Injection. The mean number of lesions identified before (1.49/patient) and after MAGNEVIST® (1.75/patient) were similar. Seven (8%) of the patients had lesions seen before MAGNEVIST® that were not seen after MAGNEVIST.® Overall, after MAGNEVIST® Injection, 41% of the images had a higher contrast score than before injection; and 18% of the images had a higher contrast score before MAGNEVIST® Injection than after MAGNEVIST® Injection. MAGNEVIST® MRI of the 8 patients with breast images were not systematically compared to the results to mammography, breast biopsy or other modalities. In the 22 patients with appendage images (e. g., muscle, bone and intraarticular structures), MAGNEVIST® MRI was not systematically evaluated to determine the effects of contrast biodistribution in these different areas.

Of the above 550 patients, 66 patients received MAGNEVIST® 0.1 mmol/kg I. V. in clinical trials of MAGNEVIST® MRl contrast enhancement of lesions in the head and neck. A total of 66 MRI images were evaluated blindly by comparing each pair of MRI images, before and after MAGNEVIST®

Injection. In these paired images, 56/66 (85%) had greater enhancement after MAGNEVIST® and 40/66 (61%) had better lesion configuration or border delineation after MAGNEVIST.® Overall, there was better contrast after MAGNEVIST® in 55% of the images, comparable enhancement in 44 (36%) before and after MAGNEVIST,® and better enhancement in 9% without MAGNEVIST®

In the studies of the brain and spinal cord, MAGNEVIST® 0.1 mmol/kg I. V. provided contrast enhancement in lesions with an abnormal blood brain barrier.

In two studies, a total of 108 patients were evaluated to compare the dose response effects of 0.1 mmol/kg and 0.3 mmol/kg of MAGNEVIST® in CNS MRI. Both dosing regimens had similar imaging and general safety profiles; however, the 0.3 mmoL/kg dose did not provide additional benefit to the final diagnosis (defined as number of lesions, location and characterization).

INDICATIONS AND USAGE

Central Nervous System:

MAGNEVIST® Injection is indicated for use with magnetic resonance imaging (MRI) in adults, and pediatric patients (2 years of age and older) to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues. MAGNEVIST® Injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.

Extracranial/Extraspinal Tissues:

MAGNEVIST® is indicated for use with MRI in adults and pediatric patients (2 years of age and older) to facilitate the visualization of lesions with abnormal vascularity in the head and neck.

Body:

MAGNEVIST® Injection is indicated for use in MRI in adults and pediatric patients (2 years of age and older) to facilitate the visualization of lesions with abnormal vascularity in the body (excluding the heart).

CONTRAINDICATIONS

None.

WARNINGS

As with various other intravenous administrations, caution must be used when administering MAGNEVIST® Injection in patients with predisposition to the development of thrombotic syndromes. (See **PRECAUTIONS**).

Deoxygenated sickle erythrocytes have been shown by *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 gadopentetate dimeglumine may possibly potentiate sickle erythrocyte alignment. MAGNEVIST® 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 MAGNEVIST® Injection to exclude the possibility of increased hemolysis.

Hypotension may occur in some patients after injection of MAGNEVIST® Injection. In clinical trials two cases were reported and in addition, there was one case of vasovagal reaction and two cases of pallor with dizziness, sweating and nausea in one and substernal pain and flushing in the other. These were reported within 25 to 85 minutes after injection except for the vasovagal reaction which was described as mild by the patient and occurred after 6-1/2 hours. In a study in normal volunteers one subject experienced syncope after arising from a sitting position two hours after administration of the drug. Although the relationship of gadopentetate dimeglumine to these events is uncertain, patients should be observed for several hours after drug administration.

Patients with a history of allergy, drug reactions, or other hypersensitivity-like disorders, should be closely observed during the procedure and for several hours after drug administration. (See **PRECAUTIONS – General**.)

PRECAUTIONS – General

As with various other injectable products, cases of phlebitis and thrombophlebitis have been reported also in association with MAGNEVIST® Injection. In most cases, symptoms presented during or shortly after injection, and generally within 24 hours of injection and responded to supportive treatment. However, in very rare cases of patients who may have underlying potential to develop thrombotic syndromes, thrombosis with fasciitis and surgical intervention (e. g., compartment release or amputation) of the dosed limb have been reported. The relationship of these events to pre-existing disease, concomitant medications, pre-existing vascular fragility, MAGNEVIST® Injection, or the injection procedure was not established. Patency and integrity of the intravenous line should be determined before administration. As with other intravenous injections, appropriate surveillance of the dosing limb for the development of local injection site reactions following administration of MAGNEVIST® Injection is recommended.

AS WITH ANY PARAMAGNETIC CONTRAST AGENT, MRI WITH MAGNEVIST® CONTRAST ENHANCEMENT MAY IMPAIR THE VISUALIZATION OF EXISTING LESIONS. SOME OF THESE LESIONS MAY BE SEEN ON UNENHANCED, NON-CONTRAST MRI. THEREFORE, CAUTION SHOULD BE EXERCISED WHEN CONTRAST ENHANCED SCAN INTERPRETATION IS MADE IN THE ABSENCE OF A COMPANION UNENHANCED MRI.

Diagnostic procedures that involve the use of contrast agents should be carried out under direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed.

In a patient with a history of grand mal seizure, MAGNEVIST® Injection was reported to induce such a seizure.

Since gadopentetate dimeglumine is cleared from the body by glomerular filtration, caution should be exercised in patients with impaired renal function. MAGNEVIST® is not significantly eliminated by the hepatobiliary enteric pathway, but is dialyzable (See **Pharmacodynamics** Section). Caution should be exercised in patients with either renal or hepatic impairment.

The possibility of a reaction, including serious, life-threatening, or fatal anaphylactoid or cardiovascular reactions or other idiosyncratic reactions (see **ADVERSE REACTIONS**), should

always be considered, especially in those patients with a known clinical hypersensitivity or a history of asthma or other allergic respiratory disorders.

Animal studies suggest that gadopentetate dimeglumine may alter red cell membrane morphology resulting in a slight degree of extravascular (splenic) hemolysis. In clinical trials 15-30% of the patients experienced an asymptomatic transient rise in serum iron. Serum bilirubin levels were slightly elevated in approximately 3.4% of patients. Levels generally returned to baseline within 24 to 48 hours. Hematocrit and red blood cell count were unaffected and liver enzymes were not elevated in these patients. While the effects of gadopentetate dimeglumine on serum iron and bilirubin have not been associated with clinical manifestations, the effect of the drug in patients with hepatic disease is not known and caution is therefore advised.

When MAGNEVIST® Injection is to be injected using nondisposable equipment, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents. After MAGNEVIST® Injection is drawn into the syringe the solution should be used immediately.

Repeat Procedures: Data for repeated procedures are not available. If in the clinical judgment of the physician sequential or repeat procedures are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body.

Repeat Injections: (See **DOSAGE AND ADMINISTRATION**)

Information for Patients:

Patients scheduled to receive MAGNEVIST® Injection should be instructed to inform their physician if the patient:

1. Is pregnant or breast feeding.

2. Has any blood disorders; i. e., anemia, hemoglobinopathies, or diseases that affect red blood cells.

3. Has a history of renal or hepatic disease, seizure, asthma or allergic respiratory disorders.

LABORATORY TEST FINDINGS

Transitory changes in serum iron, bilirubin and transaminase levels have been reported in patients with normal and abnormal liver function (See **PRECAUTIONS – General**).–***Magnevist® Injection does not interfere with serum and plasma calcium measurements determined by colorimetric assay***.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

Long term animal studies have not been performed to evaluate the carcinogenic potential of gadopentetate dimeglumine.

A comprehensive battery of *in vitro* and *in vivo* studies in bacterial and mammalian systems suggest that gadopentetate dimeglumine is not mutagenic or clastogenic and does not induce ***unscheduled*** DNA repair in rat hepatocytes or cause cellular transformation of mouse embryo fibroblasts.

However, the drug did show some evidence of mutagenic potential in vivo in the mouse dominant lethal assay at doses of 6 mmol/kg, but did not show any such potential in the mouse and dog micronucleus tests at intravenous doses of 9 mmol/kg and 2.5 mmol/kg, respectively.

When administered intra-peritoneally to male and female rats daily prior to mating, during mating and during embryonic development for up to 74 days (males) or 35 days (females), gadopentetate caused a decrease in number of corpora lutea at the 0.1 mmol/kg dose level. After daily dosing with 2.5 mmol/kg suppression of food consumption and body weight gain (males and females) and a decrease in the weights of testes and epididymis were also observed.

In a separate experiment in rats, daily injections of gadopentetate dimeglumine over 16 days caused spermatogenic cell atrophy at a dose level of 5 mmol/kg but not at a dose level of 2.5 mmol/kg. This atrophy was not reversed within a 16-day observation period following the discontinuation of the drug.

PREGNANCY CATEGORY C
Gadopentetate dimeglumine retarded fetal development slightly when given intravenously for 10 consecutive days to pregnant rats at daily doses of 0.25, 0.75, and 1.25 mmol/kg (2.5, 7.5 and 12.5 times the human dose based on body weight) and when given intravenously for 13 consecutive days to pregnant rabbits at daily doses of 0.75 and 1.25 mmol/kg (7.5 and 12.5 times the human dose respectively, based on body weight) but not at daily doses of 0.25 mmol/kg. ***No congenital anomalies were noted in rats or rabbits.***

Adequate and well controlled studies were not conducted in pregnant women. MAGNEVIST® Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING WOMEN

Magnevist® Injection is excreted in human milk. Magnevist® Injection was administered intravenously to 18 lactating women with normal renal function at a dose of 0.1 mmol/kg body weight. In these women, less than 0.04% of the administered gadolinium was excreted into the breast milk during the 24-hour period following dosing. Breast milk obtained during the 24 hours following dosing revealed the average cumulative amount of gadolinium excreted in breast milk was 0.57± 0.71 micromol. The amount transferred from a 70 kg woman (receiving 0.1 mmol/kg body weight) to an infant by breast feeding over a period of 24 hrs translates into less than 3 micromol of gadolinium.

The overall duration of excretion of gadolinium into breast milk is unknown. The extent of absorption of Magnevist® Injection in infants and its effect on the breast-fed child remains unknown. Caution should be exercised when Magnevist® Injection is administered to a nursing woman.

PEDIATRIC USE

The use of MAGNEVIST® in imaging the Central Nervous System, Extracranial/ Extraspinal tissues, and Body have been established in the pediatric population from the ages of 2 to 16 years on the basis of adequate and well controlled clinical trials in adults and safety studies in this pediatric population. (See Clinical Trials for details.)

Safety and efficacy in the pediatric population under the age of 2 years have not been established. MAGNEVIST® is eliminated primarily by the kidney. The pharmacokinetics of MAGNEVIST® in neonates and infants with immature renal function have not been studied. (See **INDICATIONS** and the **DOSAGE AND ADMINISTRATION**)

ADVERSE REACTIONS

The mean age of the 1272 patients who received MAGNEVIST® Injection was 46.4 years (range 2 to 93 years). Of these patients, 55% (700) were male and 45% (572) were female. Of the 1271 patients who received MAGNEVIST® Injection and for whom race was reported, 82.1% (1043) were Caucasian, 9.7% (123) were Black, 5.3% (67) were Hispanic, 2.1% (27) were Oriental/ Asian, and 0.9% (11) were other. The most common noted adverse event is headache with an incidence of 4.8%. The majority of headaches are transient and of mild to moderate severity. Nausea is the second most common adverse experience at 2.7%. Injection site coldness/ localized coldness is the third most common adverse experience at 2.3%. Dizziness occurred in 1% of the patients.

The following additional adverse events occurred in fewer than 1% of the patients:

Body as a Whole: Injection site symptoms, namely, pain, localized warmth, and burning sensation; substernal chest pain, back pain, fever, weakness, generalized coldness, generalized warmth, localized edema, tiredness, chest tightness, trembling, shivering, tension in extremities, regional lymphangitis, pelvic pain, and anaphylactoid reactions (characterized by cardiovascular, respiratory and cutaneous symptoms) rarely resulting in death.

Cardiovascular: Hypotension, hypertension, arrhythmia, tachycardia, migraine, syncope, vasodilation, pallor, non-specific ECG changes, angina pectoris, death related to myocardial infarction or other undetermined causes, phlebitis, thrombophlebitis, deep vein thrombophlebitis, compartment syndrome requiring surgical intervention.

Digestive: Gastrointestinal distress, stomach pain, teeth pain, increased salivation, abdominal pain, vomiting, constipation, diarrhea.

Nervous System: Agitation, anxiety, thirst, anorexia, nystagmus, drowsiness, diplopia, stupor, convulsions (including grand mal), paresthesia.

Respiratory System: Throat irritation, rhinorrhea, sneezing, dyspnea, wheezing, laryngismus, cough, respiratory complaints.

Skin: Rash, sweating, pruritus, urticaria (hives), facial edema, erythema multiforme, epidermal necrolysis, pustules.

Special Senses: Tinnitus, conjunctivitis, visual field defect, taste abnormality, dry mouth, lacrimation dis-order (tearing), eye irritation, eye pain, ear pain.

OVERDOSAGE

Systemic consequences associated with overdosage of MAGNEVIST® Injection have not been reported.

DOSAGE AND ADMINISTRATION

The recommended dosage of MAGNEVIST® Injection is 0.2 mL/kg (0.1mmol/ kg) administered intravenously, at a rate not to exceed 10 mL per 15 seconds. Dosing for patients in excess of 286 lbs have not been studied systematically.

DOSE AND DURATION OF MAGNEVIST® INJECTION BY BODY WEIGHT

BODY WEIGHT		Total Volume, mL*
lb	kg	
22	10	2
44	20	4
66	30	6
88	40	8
110	50	10
132	60	12
154	70	14
176	80	16
198	90	18
220	100	20
242	110	22
264	120	24
286	130	26

*Rate of Injection: 10 mL/15 sec

Drug Handling: To ensure complete injection of the contrast medium, the injection should be followed by a 5-mL normal saline flush. The imaging procedure should be completed within 1 hour of injection of MAGNEVIST® Injection.

As with other gadolinium contrast agents, MAGNEVIST® Injection has not been established for use in magnetic resonance angiography.

PARENTERAL PRODUCTS SHOULD BE INSPECTED VISUALLY FOR PARTICULATE MATTER AND DISCOLORATION PRIOR TO ADMINISTRATION. DO NOT USE THE SOLUTION IF IT IS DISCOLORED OR PARTICULATE MATTER IS PRESENT.

Any unused portion must be discarded in accordance with regulations dealing with the disposal of such materials.

HOW SUPPLIED

MAGNEVIST® Injection is a clear, colorless to slightly yellow solution containing 469.01 mg/mL of gadopentetate dimeglumine in rubber stoppered vials. MAGNEVIST® Injection is supplied in the following sizes:

5 mL single-dose vials, rubber stoppered, in individual cartons, Boxes of 20	NDC 50419-188-05
10 mL single-dose vials, rubber stoppered, in individual cartons, Boxes of 20	NDC 50419-188-01
10 mL pre-filled disposable syringe, Boxes of 5	NDC 50419-188-30
15 mL single- dose vials, rubber stoppered, in individual cartons, Boxes of 20	NDC 50419-188-15
15 mL pre- filled disposable syringe, Boxes of 5	NDC 50419-188-31
20 mL single- dose vials, rubber stoppered, in individual cartons, Boxes of 20	NDC 50419-188-02
20 mL pre- filled disposable syringe, Boxes of 5	NDC 50419- 188- 32

STORAGE

MAGNEVIST® Injection should be stored at controlled room temperature, between 15°-30°C (59°-86°F) and protected from light. DO NOT FREEZE. Should freezing occur in the vial MAGNEVIST® Injection should be brought to room temperature before use. If allowed to stand at room temperature for a minimum of 90 minutes, MAGNEVIST® Injection should return to a clear, colorless to slightly yellow solution. Before use, examine the product to assure that all solids are redissolved and that the container and closure have not been damaged. Should solids persist, discard vial.

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