

## PRODUCT MONOGRAPH

# MAGNEVIST<sup>®</sup>

Gadopentetate Dimeglumine Injection

Bayer Standard

469 mg/mL (0.5 mmol/mL)

For Intravenous Use

### Therapeutic Classification

Contrast Enhancement Agent  
for Magnetic Resonance Imaging (MRI)

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### Therapeutic Classification

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### ACTION AND CLINICAL PHARMACOLOGY

MAGNEVIST (gadopentetate dimeglumine) was developed as a contrast agent for diagnostic use in magnetic resonance imaging (MRI). Gadolinium is a rare earth element. Its ion ( $Gd^{+++}$ ) has seven unpaired electrons and, therefore, shows paramagnetic properties.  $Gd^{+++}$  has a strong effect on the hydrogen-proton spin-lattice relaxation time ( $T_1$ ), which causes the observed contrast enhancement in MRI scans. By chelation of  $Gd^{+++}$  with diethylenetriamine pentaacetic acid (DTPA), a strongly paramagnetic, well-tolerated, stable complex (gadopentetate dimeglumine salt) is obtained.

The free gadolinium ion is unsuitable for clinical use due to high toxicity; however, the metal chelate is metabolically inert. The organic component of the chelate is not measurably metabolized, and the metal does not dissociate. After intravenous injection of gadopentetate dimeglumine, the meglumine ion completely dissociates from the gadopentetate. The hydrophilic chelate is distributed only in the extracellular water and does not cross the intact blood-brain barrier. Gadopentetate is excreted unchanged in the urine. It is rapidly eliminated by the kidneys with a clearance identical to that of inulin (no tubular reabsorption).

The pharmacokinetic profile of intravenously administered gadopentetate dimeglumine in normal subjects conforms to a two-compartment open model with a mean distribution half-life of about 0.2 hours and a mean elimination half-life of about 1.6 hours. Approximately 80% of the dose was excreted in the urine within 6 hours and 93% within 24 hours post injection of a 0.1 mmol/kg dose. Excretion in the faeces amounted to <0.1% over 5 days. There was no detectable biotransformation, dissociation, or decomposition of gadopentetate.

MAGNEVIST has no pharmacodynamic effect when administered as indicated with the exception of slightly increased plasma osmolality.

### **INDICATIONS AND CLINICAL USE**

MAGNEVIST (gadopentetate dimeglumine), by intravenous injection, is indicated for contrast enhancement during cranial and spinal MRI investigations in adults and children, to detect lesions associated with abnormal vascularity or those thought to alter the blood-brain barrier.

MAGNEVIST is also indicated for use with MRI in adults to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity within the head (extracranial) and neck.

### **CONTRAINDICATIONS**

MAGNEVIST (gadopentetate dimeglumine) should not be administered to patients who are known or suspected of being hypersensitive to it.

## WARNINGS

### Serious Warnings and Precautions

#### 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  $<30 \text{ mL/min/1.73m}^2$ ), or
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

In these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with noncontrast 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 (see **DOSAGE AND ADMINISTRATION** section) and allow a sufficient period of time for elimination of the agent from the body prior to any readministration. (See also **WARNINGS – General**; **WARNINGS – Renal Impairment**; **PRECAUTIONS – Skin**; and **ADVERSE REACTIONS – Postmarket Adverse Drug Reactions**.)

#### General

MRI procedures which involve the use of MAGNEVIST by injection should be carried out by physicians who have the prerequisite training and a thorough knowledge of the particular procedure to be performed.

#### **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  $<30 \text{ mL/min/1.73m}^2$ ), 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 noncontrast-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.

Postmarketing 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<sup>®</sup>), followed by gadopentetate dimeglumine (MAGNEVIST) and gadoversetamide (OptiMARK<sup>®</sup>). NSF has also developed following the sequential administration of gadodiamide with gadobenate dimeglumine (MultiHance<sup>®</sup>) or gadoteridol (ProHance<sup>®</sup>). The number of postmarketing 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 1 retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4%. (1) 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 **ACTION AND CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**.)

A skin biopsy is necessary in order to exclude the diagnosis of similarly presenting skin disorders (eg, scleromyxedema). (See **WARNINGS – Serious Warnings and Precautions**; **WARNINGS – Renal Impairment**; **PRECAUTIONS – Skin**; and **ADVERSE REACTIONS – Postmarket Adverse Drug Reactions**.)

## **Hypersensitivity Reactions**

The decision to use MAGNEVIST (gadopentetate dimeglumine) must be made after careful evaluation of the risk-benefit in patients with a history of allergic disposition or bronchial asthma or with any previous reaction to contrast media (2-4), since experience shows that these patients suffer more frequently than others from hypersensitivity reactions.

Patients who experience hypersensitivity reactions while taking beta blockers may be resistant to treatment effects of beta agonists.

Patients with cardiovascular disease are more susceptible to serious, even fatal outcomes of severe hypersensitivity reactions.

As with other intravenous contrast agents, MAGNEVIST can be associated with anaphylactic reactions, anaphylactoid/hypersensitivity or other idiosyncratic reactions characterized by cardiovascular, respiratory, or cutaneous manifestations, and ranging from mild to severe reactions including anaphylactic shock. (3) These reactions often occur at least within half an hour of administration. However, in rare cases delayed reactions (hours later or up to several days) may occur (see **ADVERSE REACTIONS**). If such a reaction occurs, stop MAGNEVIST administration and immediately begin appropriate therapy, including resuscitation.

It is important for prompt action in the event of such incidents and to be familiar with the practice of emergency measures. To permit immediate counter-measures to be taken in emergencies, appropriate drugs and instruments (eg, endotracheal tube and ventilator) should be readily available.

As with other contrast-enhanced diagnostic procedures, it is important to closely observe patients with a history of drug reactions, allergy or hypersensitivity disorders, during and up to several hours after MAGNEVIST injection. (5, 6)

## **Injection Site Reactions**

Skin and soft tissue necrosis, thrombosis, fasciitis, and compartment syndrome requiring surgical intervention (eg, compartment release or amputation) have occurred very rarely at the site of contrast injection or the dosed limb. Total volume and rate of MAGNEVIST injection, extravasation of contrast agent, and patient susceptibility might contribute to

these reactions. Phlebitis and thrombophlebitis may be observed generally within 24 hours after MAGNEVIST injection and resolve with supportive treatment. Determine the patency and integrity of the intravenous line before administration of MAGNEVIST injection. Assessment of the dosed limb for the development of injection site reactions is recommended.

### **Sickle Erythrocytes**

Deoxygenated sickle cell 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 gadopentetate dimeglumine may possibly potentiate sickle erythrocyte alignment. MAGNEVIST in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

### **Renal Impairment**

In patients with renal insufficiency, acute renal failure requiring dialysis or worsening renal function have occurred, mostly within 48 hours of MAGNEVIST injection. The risk of these events is higher with increasing dose of contrast agent. MAGNEVIST should only be used after careful risk/benefit assessment in these patients, including consideration of possible alternative imaging methods. Use the lowest possible dose and evaluate renal function in patients with renal insufficiency (see **DOSAGE AND ADMINISTRATION**).

- Exposure to GBCAs increases the risk for NSF in patients with:
  - acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m<sup>2</sup>), or
  - acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.
- 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 and Precautions**; **PRECAUTIONS – Skin**; and **ADVERSE REACTIONS – Postmarket Adverse Drug Reactions**.)

No studies have been conducted in children with severe renal or hepatic dysfunction, clinically unstable or uncontrolled hypertension, or in premature infants.

## **PRECAUTIONS**

### **General**

MAGNEVIST (gadopentetate dimeglumine) is to be administered strictly by intravenous injection. MAGNEVIST will cause tissue irritation and pain if administered extravascularly or if it leaks interstitially.

A sweet taste may be experienced briefly by patients receiving a bolus injection of MAGNEVIST intravenously.

As with any paramagnetic contrast agent, MAGNEVIST might impair the visualization of lesions seen on noncontrast MRI. Therefore, caution should be exercised when MAGNEVIST MRI scans are interpreted without a companion noncontrast MRI scan.

### **Hemolytic States**

Gadopentetate dimeglumine alters red blood cell morphology resulting in transient, slight, extravascular (splenic) hemolysis with increased serum iron and total bilirubin levels. Although this effect was of no clinical significance during clinical trials, caution is advised in patients with hepatic disease and/or hemolytic states.

### **Convulsive States**

While there is no evidence suggesting that MAGNEVIST directly precipitates convulsion, the possibility that it may decrease the convulsive threshold in susceptible patients cannot be ruled out. Patients with seizure disorders or intracranial lesions may be at increased risk of seizure activity, as has been reported rarely in association with MAGNEVIST administration. Precautionary measures should be taken with patients predisposed to seizure, eg, close monitoring and availability of injectable anticonvulsants (see **DOSAGE AND ADMINISTRATION**).

### **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 and Precautions; WARNINGS –**

General; **WARNINGS – Renal Impairment**; and **ADVERSE REACTIONS – Postmarket Adverse Drug Reactions**.)

### **Pediatric**

The cautious utilization of the lowest effective dose (0.1 mmol/kg BW) in children is recommended, particularly for neonates and infants, as the pharmacokinetics of MAGNEVIST in neonates and infants with immature renal function have not been studied (see **WARNINGS – Renal Impairment**).

### **Pregnancy**

There are no studies on the use of MAGNEVIST in pregnant women. MAGNEVIST should not be used during human pregnancy unless the potential benefit justifies the potential risk to the fetus.

### **Nursing Mothers**

Transfer of MAGNEVIST into the milk of lactating mothers can occur. Thus breast feeding should be interrupted for 24 hours post administration of MAGNEVIST and the milk discarded during this period.

### **Use in the Elderly**

No special precautions are required for elderly patients (see **WARNINGS – Serious Warnings and Precautions**).

### **Interference with Diagnostic Tests**

The result of serum iron determination employing methods measuring complex formation (eg, bathophenanthroline) within 24 hours of MAGNEVIST examination may result in inaccurately low values due to the free DTPA in MAGNEVIST.

## Patient Counseling Information

Patients scheduled to receive MAGNEVIST should be instructed to inform their physician if they are pregnant, breast feed, or have a history of renal insufficiency, asthma or allergic respiratory disorders.

## ADVERSE REACTIONS

### General

Most adverse reactions to MAGNEVIST (gadopentetate dimeglumine) develop soon after injection; however, the possibility of delayed reactions cannot be ruled out. The most frequently reported adverse reactions following administration of MAGNEVIST were:

Headache	8.7%*
in some cases severe	1.3%
Injection Site Discomfort	6.7%
Nausea	3.2%
Localized Pain in Other Parts	
of the Body (back, ear, eye, teeth)	2.8%
Hypersensitivity-Type Skin	
and Mucosal Reactions	2.1%
Dizziness	1.5%
Vomiting	1.2%
Paresthesia	1.2%

\* 42.3% of all cases of headache were considered unrelated to MAGNEVIST administration.

Adverse reactions occurred in 11 of 319 (3.4%) pediatric patients receiving MAGNEVIST in clinical trials (headache, vasodilatation, dizziness, diarrhea, ear pain, tachycardia, fever, edema, seizure, vomiting, nausea, and urticaria). This adverse reaction profile is consistent with the adverse reaction profile observed in adults.

MAGNEVIST will cause tissue irritation and pain if administered extravascularly.

Transient increases or decreases in blood pressure may occur after the administration of MAGNEVIST. These changes are generally of little consequence although 3 clinically significant cases of hypotension have occurred 2 to 6 hours after MAGNEVIST injection. A relationship to the contrast medium could not be determined; however, caution should be exercised by the patient when driving or operating machinery.

Side effects in association with the use of MAGNEVIST are usually mild to moderate and transient in nature. However, serious or severe and life-threatening reactions as well as death have been reported. Postmarketing anaphylactic reactions have been reported, but are very rare. Convulsions were reported in 4 patients with a history of seizures.

Nausea, vomiting, headache, dizziness, a sensation of pain, a general feeling of warmth and injection site warmth or coldness are the most frequently recorded reactions.

### **Laboratory Changes**

Reversible mild elevations over baseline in serum iron, transaminase, and total bilirubin were observed in clinical trials. Other disturbances in laboratory values (transient increases in liver function tests) have not been associated with the use of MAGNEVIST. MAGNEVIST does not interfere with serum and plasma calcium measurements determined by colorimetric assays.

### **Adverse Drug Reaction Profile**

The following adverse reactions, listed according to body system, have been reported after administration of MAGNEVIST:

**Cardiovascular:** hypotension, vasodilatation, pallor, phlebitis, thrombophlebitis, non-specific ECG changes, substernal pain, angina

**Central nervous system:** headache, dizziness, agitation, paresthesia, tinnitus, visual field defect, convulsions, hyperesthesia, burning sensation

**Gastrointestinal:** nausea, vomiting, gastrointestinal distress, stomach pain, thirst, increased salivation, taste abnormality, oral soft tissue pain, and paresthesia

**Respiratory system:** dry mouth, throat irritation/ throat tightness, pharyngolaryngeal pain/ pharynx discomfort, rhinorrhea, wheezing, sneezing, laryngismus, cough, dyspnea/apnea,

**Cutaneous/mucous membranes:** rash, sweating, urticaria, pruritus

**Miscellaneous:** injection site reactions (coldness, burning, warmth, pain, edema, paresthesia, swelling, irritation, hemorrhage, erythema), teeth pain, pain in extremity, generalized weakness, fever, localised edema, tiredness, anaphylactoid reactions (characterised by cardiovascular, respiratory, and cutaneous symptoms), conjunctivitis

**Laboratory tests:** transient elevation of serum iron and bilirubin levels

The following other adverse events were reported. A causal relationship has neither been established nor refuted:

**Cardiovascular:** hypertension, tachycardia, syncope, death related to myocardial infarction or other undetermined causes, clinically relevant transient disturbance in heart rate, disturbance in cardiac rhythm or function and cardiac arrest, circulatory reactions accompanied by peripheral vasodilatation, dyspnea, confusion, cyanosis possibly leading to unconsciousness.

**Central nervous system:** diplopia, migraine, anxiety, drowsiness, nystagmus, stupor, confusion; disturbed vision, smell, hearing or speech; tremor, coma.

**Gastrointestinal:** constipation, diarrhea, anorexia

**Cutaneous/mucous membranes:** rhinitis, laryngeal/pharyngeal edema, angioedema, flush reaction with vasodilatation, facial edema, erythema, epidermal necrolysis.

**Respiratory:** transient disturbance in respiratory rate, respiratory distress, respiratory arrest, pulmonary edema.

**Renal and Urinary:** urinary incontinence, urinary urgency in patients with pre-existing renal impairment, increased serum creatinine and acute renal failure

**Hepato-biliary:** transitory changes of liver enzyme levels

**Miscellaneous:** localised pain (back, ear, eye), lacrimation, joint pain, chest pain, vasovagal reactions, alterations in body temperature, extravasation, mild warmth, inflammation, and tissue necrosis

### **Postmarket Adverse Drug Reactions**

Postmarketing 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<sup>®</sup>), followed by gadopentetate dimeglumine (MAGNEVIST) and gadoversetamide (OptiMARK<sup>®</sup>). NSF has also developed following the sequential administration of gadodiamide with gadobenate dimeglumine (MultiHance<sup>®</sup>) or gadoteridol (ProHance<sup>®</sup>). Cases of nephrogenic systemic fibrosis (NSF) have been reported with MAGNEVIST. The number of postmarketing 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 1 retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4%. (1) 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 also **WARNINGS – Serious Warnings and Precautions; WARNINGS – Renal Impairment; PRECAUTIONS – General, PRECAUTIONS – Skin**).

In patients with dialysis-dependent renal failure who received MAGNEVIST, delayed and transient inflammatory-like reactions such as fever, chills, and C-reactive protein increase have been commonly observed. These patients had the MRI examination with MAGNEVIST on the day before hemodialysis. (7-9)

Additional adverse drug reactions from postapproval (spontaneous reporting) data: shock, bronchospasm, laryngospasm, anaphylactoid shock, injection site necrosis, injection site thrombophlebitis, injection site phlebitis, injection site inflammation.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

For Management of suspected drug overdose, consult your regional poison control centre.

In the event of inadvertent overdose or in the case of severely impaired renal function, MAGNEVIST (gadopentetate dimeglumine) can be removed from the body by extracorporeal hemodialysis. Renal function should be monitored in patients with renal impairment.

## DOSAGE AND ADMINISTRATION

Special preparation of the patient for examination with MAGNEVIST (gadopentetate dimeglumine) is not required; however, precautionary measures should be taken with patients predisposed to seizure, eg, close monitoring and availability of injectable anticonvulsants (see **PRECAUTIONS**). The usual safety rules for MRI (eg, exclusion of ferromagnetic vascular clips) must be observed.

Young children, infants, and neonates may require sedation prior to undergoing an MRI examination, in order to eliminate movement artifacts.

Use the lowest possible dose and evaluate renal function in patients with renal insufficiency. MAGNEVIST should only be used after careful risk/benefit assessment, including consideration of possible alternative imaging methods, in these patients (see **WARNINGS**).

The following dosage guidelines apply to adults and children (including neonates and infants):

**Recommended Dose:** 0.2 mL/kg (0.1 mmol/kg)

**Route of Administration:** intravenous (into a large vein, if possible)

**Rate of Administration:** 10 mL/min or as a bolus injection at 10 mL/15 sec

**Maximum Single Dose per Injection:** 0.2 mL/kg body weight, to a maximum of 20 mL

To ensure complete injection of the contrast medium, the injection should be followed by a

5 mL normal saline flush.

If strong clinical suspicion of an intracranial or intraspinal lesion persists, despite a normal MRI scan, the diagnostic yield of the examination may be increased by giving another injection of MAGNEVIST equivalent to the original total dose within 30 minutes and performing MRI again.

MAGNEVIST should not be drawn into the syringe until immediately before use. The rubber stopper should never be pierced more than once. Any unused portion must be discarded upon completion of the procedure.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

T<sub>1</sub>-weighted scanning sequences are particularly suitable for contrast-enhanced examinations.

MAGNEVIST has been shown to be effective in a wide range of field strengths (0.14 to 1.5 Tesla).

### **Important Note**

The imaging procedure should be completed within **one hour**. Optimal contrast is generally observed in cranial investigations within 27 minutes following injection of MAGNEVIST and in spinal investigations during the early postadministration phase (10-30 minutes).

In neonates and infants, optimal CNS contrast has been observed to persist for several hours after MAGNEVIST administration. (See **PRECAUTIONS – Pediatric.**)

## **INFORMATION FOR PATIENTS**

### **Nephrogenic Systemic Fibrosis**

There have been postmarket 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 MAGNEVIST 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 MAGNEVIST, if you are considered to be at risk for developing NSF.

## **PHARMACEUTICAL INFORMATION**

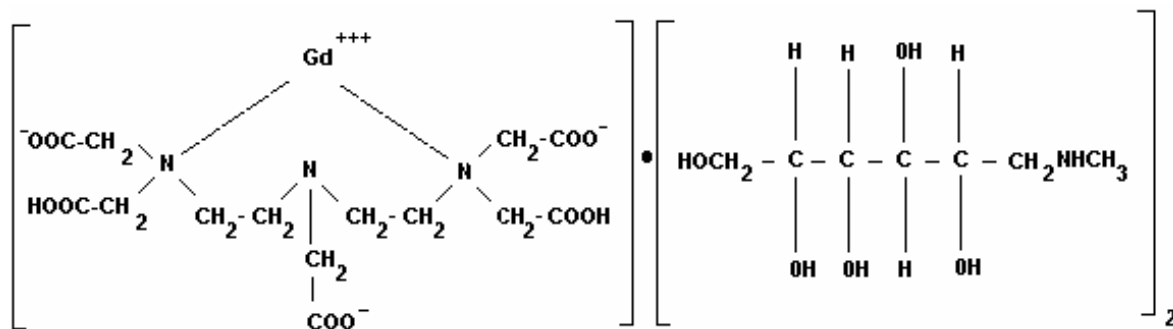
### **Drug Substance**

Trade Name: MAGNEVIST

Proper Name: Gadopentetate dimeglumine (USAN)

Chemical Name: Gadolate(2-),[N,N-bis[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]-, dihydrogen, compound with 1-deoxy-1-(methylamino)-D-glucitol(1:2)

Structural Formula :



Molecular Formula:  $C_{14}H_{20}GdN_3O_{10} \cdot (C_7H_{17}NO_5)_2$

Molecular Weight: 938.02

Solubility: Freely soluble in water

Osmolality: 1960 mOsm/kg H<sub>2</sub>O at 37°C

### Composition

MAGNEVIST for intravenous injection is provided as a sterile, clear, colorless to slightly yellow aqueous solution. Each mL contains 469.01 mg gadopentetic acid dimeglumine salt (equivalent to 0.5 mmol/mL), 0.99 mg meglumine, and 0.40 mg diethylenetriamine pentaacetic acid.

### Stability and Storage Recommendations

MAGNEVIST should be stored at 15°C to 30°C and protected from light.

### AVAILABILITY OF DOSAGE FORMS

MAGNEVIST (gadopentetate dimeglumine) is provided as a sterile, clear, colorless to slightly yellow aqueous solution. Each mL contains 469.01 mg gadopentetic acid dimeglumine salt (equivalent to 0.5 mmol/mL), 0.99 mg meglumine, and 0.40 mg diethylenetriamine pentaacetic acid.

MAGNEVIST is supplied in 20 mL, 15 mL, and 10 mL single-dose vials packaged in individual cartons

MAGNEVIST should be stored at 15°C to 30°C and protected from light.

## PHARMACOLOGY

### Animal Studies

#### Neuropharmacology

The neuropharmacology of gadopentetate dimeglumine was evaluated in rats, following single pericerebral or intracisternal injection. The ED<sub>50</sub>, based on postural anomalies, seizures, or death, and the LD<sub>50</sub> determinations indicated that gadopentetate dimeglumine is considerably less toxic than gadolinium chloride or meglumine diatrizoate. In a similar study, the addition of up to 1.0 mg of free DTPA/mL did not affect the neural tolerance of the gadopentetate dimeglumine (Table 1).

**Table 1: A Comparison of the ED<sub>50</sub> and LD<sub>50</sub> of Gadopentetate Dimeglumine, Gadolinium Chloride, and Meglumine Diatrizoate Following Pericerebral or Intracisternal Administration in Rats**

Compounds	Dose Level ( $\mu\text{mol/kg}$ )	ED <sub>50</sub> ( $\mu\text{mol/kg}$ )	Dose Level ( $\mu\text{mol/kg}$ )	LD <sub>50</sub> ( $\mu\text{mol/kg}$ )
<b>Pericerebral Administration</b>				
Gadopentetate Dimeglumine	25-296.3	96.6 97.1	463-1852	1141.4 1227.3
Gadopentetate Dimeglumine with 1.0 mg DTPA/m	25-296.3	80.2	463-1852	1063.4
Gadolinium Chloride	5-25	10.8	6-100	14.9
Meglumine Diatrizoate	32-53	35.0	32-53	42.8
<b>Intracisternal Administration</b>				
Gadopentetate Dimeglumine	16.7-197.9	74.0 86.2	309-1233 a	654.9 a
Gadopentetate Dimeglumine with 0.15 mg DTPA/mL	16.7-197.9	80.0	a	a
Gadopentetate Dimeglumine with 1.0 mg DTPA/mL	16.7-197.9	85.0	a	a
Gadolinium Chloride	3.3-16.7	5.6	4-17	8.1
Meglumine Diatrizoate	4-21	11.2	32-126	54.9

a - Not evaluated in the study.

#### Cardiovascular and Hemodynamic Effects

The cardiovascular and hemodynamic effects of gadopentetate dimeglumine were assessed in healthy anesthetized dogs following intravenous administration of 0.25 or 1.25 mmol/kg of body weight. A slight increase in peripheral resistance was noted at the low-dose level. Those dogs receiving 1.25 mmol/kg initially displayed reduced peripheral resistance, lower blood pressure and heart rate, and an increase in the left ventricular end-diastolic pressure, stroke volume, and cardiac output. Thereafter, the peripheral resistance increased, and there was a significant increase in blood pressure which persisted at the same level for the remainder of the experiment.

The hemodynamic effects of gadopentetate dimeglumine were also assessed in dogs with

acute ischemia-induced heart failure using doses of 0.25 mmol/kg and 0.75 mmol/kg intravenously. The 0.25 mmol/kg dose elicited a slight decrease in diastolic blood pressure and peripheral resistance and a slight increase in left ventricular dp/dt, cardiac output and stroke index. All parameters returned to the normal range 5 to 10 minutes after administration. The 0.75 mmol/kg dose also elicited a similar transient response in hemodynamic parameters.

### **Renal Tolerance**

The renal tolerance of gadopentetate dimeglumine was examined in rabbits following an intravenous dose of 2 mmol/kg. A slight effect on urinary protein excretion was seen in comparison to a sorbitol control solution; however, gadopentetate dimeglumine exhibited better renal tolerance than other X-ray contrast agents. No effect was seen on serum creatinine or urea-nitrogen levels which served as indicators of renal function. Furthermore, no histological effects could be detected in the kidneys after the 1-week observation period.

### **Physicochemical and Biochemical Properties**

The pharmacological properties of gadopentetate dimeglumine were determined by a battery of *in vitro* and *in vivo* tests following intravenous administration in dogs, rabbits and baboons. Gadopentetate dimeglumine was shown to be highly hydrophilic and, consequently, had no protein binding ability and did not interfere with enzyme activity. In short, the compound was physiologically inert at concentrations anticipated for human use.

### **Effect on Coagulation**

Gadopentetate dimeglumine was evaluated using thromboelastography and citrated dog blood for its *in vitro* effect on the coagulation process. Concentrations up to 29 mmol/L did not affect the coagulation process of citrated dog blood when compared with a control thromboelastogram obtained with normal saline.

### **Efficacy**

The efficacy of gadopentetate dimeglumine was established in rats, rabbits and baboons following intravenous administration for diagnostic MRI. Intravenous doses of 0.01 to 1.0 mmol/kg of body weight enhanced the contrast between healthy and pathological tissue

(infarcts, tumors, and inflammations). Since gadopentetate dimeglumine was excreted in the urine, it also enhanced renal contrast in the rat at doses as low as 0.01 mmol/kg of body weight.

### **Pharmacokinetics**

Gadopentetate dimeglumine was administered orally and/or intravenously in the rat (males, pregnant females or lactating females), rabbit (pregnant females), dog (females), and baboon (males) to investigate absorption, distribution, metabolism, and excretion.

After oral administration, radiolabelled gadopentetate dimeglumine was not absorbed or very poorly absorbed from the gastrointestinal tract of rats and dogs and was excreted almost completely in the faeces (ca. 100% in the rat and 94% in the dog).

After intravenous injection, the compound was excreted primarily in the urine (90% in the rat and >96% in the dog). In renally-impaired rats, biliary excretion of radiolabelled gadopentetate accounted for 2% of the dose in 4 hours when both kidneys were occluded.

Intravenous doses of gadopentetate dimeglumine did not result in any significant accumulation in tissues studied in the rat, rabbit, dog, or baboon. However, in rats with total renal impairment, 3.5% of the radiolabelled gadopentetate dimeglumine dose was secreted into the stomach and bowel 4 hours after intravenous administration. These results suggest that this compound can be secreted into the gastrointestinal tract, particularly when severe renal impairment exists.

Following single intravenous administrations of radiolabelled gadopentetate dimeglumine (0.5 mmol/kg) to pregnant rabbits, peak concentrations of radiolabelled gadolinium in the fetuses appeared after 30 minutes. In the dam plasma, liver, heart, and uterus concentrations remained stable after 15 and 30 minutes. Fetal tissue concentrations were ca. 4% after 15 minutes and 8% after 30 minutes of that in the dams' plasma (corresponding to 0.11% and 0.26% of the total dose, respectively). By 120 minutes, fetal concentrations decreased to 1/4 of peak value. The fetal elimination half-life was 30 to 50 minutes, similar to that of maternal plasma and tissue.

Following intravenous administrations of radiolabelled gadopentetate dimeglumine to pregnant rats, the compound was shown to be rapidly distributed, did not pass the blood-

brain or placental barriers and cleared within 24 hours postadministration.

In lactating rats that were given intravenous administrations of the radiolabelled gadopentetate dimeglumine less than 0.2% of the administered dose was transferred to the offspring via the maternal milk.

Intravenous doses of radiolabelled gadopentetate dimeglumine administered to dogs exhibited no evidence of any metabolism occurring during passage through the body. High performance liquid chromatography did not detect any unchelated gadolinium ion in the animals.

## **Human Studies**

### **Pharmacokinetics**

The pharmacokinetic profile of MAGNEVIST (gadopentetate dimeglumine) was investigated in male volunteers undergoing Magnetic Resonance Imaging (MRI) of the kidneys and urinary bladder during an open label safety and efficacy study conducted in Europe. A single dose of MAGNEVIST was administered intravenously into a cubital vein of each of 20 healthy male volunteers. Four dose levels, ranging from 0.005 mmol/kg to 0.25 mmol/kg, were evaluated in groups of 5 subjects each.

Pharmacokinetic analysis of the plasma concentration versus time data for the 2 highest doses (0.1 and 0.25 mmol/kg) showed that the disposition of gadopentetate dimeglumine in the body follows a 2-compartment model with a mean distribution half-life of 0.2 hour and a mean elimination half-life of 1.6 hours. Dose-dependent kinetics were not observed for the 0.1 and 0.25 mmol/kg doses. Gadopentetate is exclusively eliminated in the urine with an average for all four doses of 83% excreted within 6 hours, and 91% of the dose excreted by 24 hours postinjection. No metabolites of gadopentetate were found in urine, indicating that gadopentetate, which forms the active ingredient of the MRI contrast agent, remains intact.

The urinary and plasma elimination rates ( $111 \pm 19$  mL/min and  $122 \pm 14$  mL/min, respectively) for gadopentetate are essentially identical. The volume of distribution ( $266 \pm 43$  mL/kg) is equal to the calculated volume of extracellular water, and the clearance is similar to that of substances which are subject to glomerular filtration, eg, inulin and CrEDTA. In man, the plasma half-life (1.6 hours) is similar to that reported for dogs and also similar to the elimination characteristics of commonly used x-ray contrast agents for

angio-urography.

### **Clinical Laboratory Evaluations**

Clinical laboratory evaluations revealed elevations in serum iron and, in some cases, serum bilirubin levels, which were considered to be definitely drug-related. In about 15% of female and 30% of male patients, increases in serum iron levels above baseline were noted. The increases appeared within 2 to 4 hours postinjection and declined within 24 hours postinjection. By 48 hours postinjection, the levels had returned to baseline. Hemoglobin, hematocrit, red blood cell count, and liver function enzymes were unaffected. This effect is considered to be due to a slight degree of hemolysis, probably extravascular and too small to result in a change in hemoglobin, hematocrit, or red blood cell count.

Although MAGNEVIST is not a risk for patients with normal hematological status, it is possible that those patients with hemolytic anemia may be at an increased risk, since gadopentetate dimeglumine appears to exert an effect on red blood cell morphology. About 8% of the patients who show a rise in serum iron levels also show a rise in serum bilirubin levels, apparently because these patients are somewhat less efficient in conjugating bilirubin resulting from hemolysis.

### **Clinical Studies in Adults with Cranial and Spinal Lesions**

The efficacy of MAGNEVIST as an MRI contrast enhancement agent in the diagnosis and evaluation of brain lesions and lesions of the spine and associated tissues was demonstrated in 6 pivotal clinical trials and in 3 special studies in which films were read by independent evaluators.

In the 6 clinical trials, a total of 597 patients (571 MAGNEVIST, 26 placebo) were evaluated for efficacy. 196 of these patients (55 brain, 141 spine) were evaluated for inclusion in the radiologist-reader evaluations of MAGNEVIST.

Assessment of efficacy included global efficacy evaluations, intensity scores and film evaluations (including contrast, morphology, and diagnosis).

**Contrast enhancement:** following the injection of MAGNEVIST, an increase in intensity scores was seen for all tissue types evaluated (healthy tissue, lesion, edema, and necrosis). Comparative intensity scores, which showed the relative contrast between tissue

types, were calculated for the pre- and post-MAGNEVIST scan. MAGNEVIST greatly increased the difference in intensity scores between lesion, edema, and healthy tissue compared to the pretreatment difference. Similar increases in contrast were seen for lesion-edema and lesion-necrosis comparisons.

In 5 of the 6 studies (cranial and spinal), contrast enhancement was assessed as an increase in intensity of a lesion compared to its surrounding environment. 292 (86%) of 339 patients showed enhancement after MAGNEVIST. None of the scans from 26 placebo patients showed enhancement.

In 4 of the 6 studies, additional lesions were detected in 113 (24%) of 466 patients following the administration of MAGNEVIST.

**Diagnostic ability:** the diagnostic ability of the investigators was improved or facilitated with MAGNEVIST in 107 (66%) of 162 patients in the cranial studies. In the spinal studies, diagnosis was facilitated in 131 (78%) of 169 patients.

**Change in diagnosis:** in the cranial and spinal studies a change in diagnosis was made by the investigators in 129 (41%) of 317 patients who showed enhancement with MAGNEVIST. Cranial lesions which were enhanced by MAGNEVIST were compatible with presenting symptoms in 95% of cases. The most common diagnostic changes in the cranial studies were: nonspecific neoplasms, meningiomas, metastases, and glial cell tumors. In the spinal studies, the most common change was increased differentiation of scar tissue from abnormal disc material (recurrent postoperative back pain studies) and a better delineation of spinal lesions (changes in lesion size, location, and configuration) in patients with suspected spinal tumors.

**Film evaluations:** film evaluation revealed better contrast in 2/3 of patients with T<sub>1</sub>-weighted scans and more than 1/3 of patients with T<sub>2</sub>-weighted scans. From a group of 167 patients in the cranial studies for whom neither T<sub>1</sub>-weighted nor T<sub>2</sub>-weighted pre-MAGNEVIST scans were diagnostic, diagnosis became possible after the injection of MAGNEVIST in 122 patients (73%).

In the independent radiologist-reader evaluations of the cranial and spinal scans, a significant improvement in the number of lesions detected was observed after

MAGNEVIST. This would have a significant impact on prognosis or treatment, especially in patients where enhanced visualization results in a change of diagnosis, such as a change from negative to positive findings or from a solitary lesion to metastatic disease. The evaluation also showed that MAGNEVIST significantly increased diagnostic accuracy when compared with MRI alone or with computed tomography (CT).

**Diagnostic mode (pulse sequence):** T<sub>1</sub>-weighted scans provided better enhancement in 138 (93%) of 148 patients in the cranial studies. T<sub>2</sub>-weighted was the better diagnostic mode for 10 (7%) patients. In the spinal studies (postoperative back pain), the T<sub>1</sub>-weighted mode provided better enhancement in 55 (95%) of 58 patients and the T<sub>2</sub>-weighted mode provided better enhancement for 3 (5%) patients.

**Time of the best scan:** the time of the best scan in the cranial studies was determined both by global efficacy evaluation and by analysis of contrast score results after film evaluations. Both evaluations demonstrated that early post-injection images are best for diagnosis. Of 148 patients with contrast enhancement, 108 (73%) had the best image within 27 minutes of the injection of MAGNEVIST. Of these, more than half had the best scan within 14 minutes of the injection of contrast agent. In spinal investigations, the early postinjection scans (10-30 minutes) also tended to provide the best images.

### **Clinical Studies in Children with Cranial and Spinal Lesions**

The efficacy of MAGNEVIST was demonstrated in 2 pivotal clinical studies, involving 142 children with a preliminary diagnosis of CNS abnormality, based upon diagnostic methods other than MRI. Their ages ranged from newborn to 18 years. MRI was performed on all patients before and after the administration of 0.2 mL/kg (0.1 mmol/kg) MAGNEVIST. Some patients were given an additional 0.1 mmol/kg dose within 30 minutes of the first dose, if this was necessary to make a diagnosis.

**Contrast evaluations:** after MAGNEVIST injection, the contrast-to-noise ratio of the magnetic resonance images increased notably, with a further increase in those patients receiving a second MAGNEVIST injection. The signal intensity ratio of lesion to normal tissue was significantly increased for head and spinal T<sub>1</sub> scans after MAGNEVIST injection.

Investigator ratings of lesion contrast compared to normal tissue and of lesion demarcation compared to surrounding tissue improved after MAGNEVIST injection. Most ratings progressed from "none" or "poor" to "excellent".

**Diagnostic usefulness:** MAGNEVIST significantly improved the possibility of making a definitive diagnosis. For patients with demonstrated lesions (n=57) with the T<sub>1</sub> or T<sub>2</sub> scan, this possibility increased from 44% prior to MAGNEVIST injection, to 74% after MAGNEVIST injection. The diagnostic quality of both T<sub>1</sub> and T<sub>2</sub> scans significantly improved after MAGNEVIST injection, for patients with both normal and abnormal scans.

Lesion morphology was better characterized after MAGNEVIST administration in 11/70 (16%) patients, allowing a better assessment of cystic, necrotic, tumor, or blood components of the lesion. A gain of diagnostic information was documented for 22/40 (55%) patients, and was statistically significant.

MAGNEVIST was demonstrated to be useful in 40/70 (57%) patients. These include 14 patients who were found to have no abnormality after the final MRI, 14 patients in whom a lesion was observed post-MAGNEVIST only, 6 patients in whom a definitive diagnosis was only made possible post-MAGNEVIST, 3 patients in whom complete tumor resection was confirmed by absence of enhancement, 2 patients in whom the solid, cystic, or necrotic component of the lesion was further characterized, and 1 patient in whom the lesion size was better defined.

### **Clinical Studies in Adults with Head and Neck Lesions**

The efficacy of MAGNEVIST as an MRI contrast enhancement agent was evaluated in 87 patients with head (extracranial) and neck lesions. Film sets from 78 of these patients were additionally assessed by radiologists ("blinded readers") who had not participated in the clinical trials and were not apprised of patient history. Efficacy analyses consisted of comparisons between post-MAGNEVIST scans and corresponding pre-MAGNEVIST scans with respect to contrast enhancement, facilitation of visualization, and contrast scores.

Post-MAGNEVIST contrast enhancement of lesions was demonstrated for 78 of 87 (90%) patients in the clinical trials. When evaluated by blinded readers, contrast enhancement was demonstrated for 56 of the 66 (85%) film sets included in the final data set.

Facilitation of visualization was demonstrated primarily by showing that the post-MAGNEVIST scans provided additional radiologic information concerning parameters such as lesion location, size, configuration, and differentiation from edema or necrosis. Post-MAGNEVIST MR scans provided additional radiologic information for 63 of 87 (72%) patients in the clinical trials. Additionally, there was a significant improvement ( $P<0.001$ ) in lesion visualization of post-MAGNEVIST MR scans versus pre-MAGNEVIST MR scans by the blinded readers. Post-MAGNEVIST scans provided a better visualization of lesion configuration versus pre-MAGNEVIST scans for 40 of the 60 (67%) scans where lesion configuration could be determined. Additional radiologic information was observed in 48 of 66 (73%) post-MAGNEVIST scans viewed by the blinded readers.

Each patient's pre- and post-MAGNEVIST MR images were scored on a 4-point scale, measuring the relative intensity of a lesion in relation to its adjacent tissue (0=no contrast; 1=equivocal; 2=good; 3=excellent). For 63 of 86 (73%) patients in the clinical trials, post-MAGNEVIST contrast scores were higher than pre-MAGNEVIST scores ( $P<0.001$ ). In the blinded reader evaluation, post-MAGNEVIST contrast scores were higher than pre-MAGNEVIST scores in 36 of 66 (55%) patients ( $P<0.001$ ).

## **TOXICOLOGY**

Data from non-clinical studies did not reveal specialized hazard in experimental animals based on conventional studies of safety pharmacology, systemic toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

### **Acute Toxicity**

Acute intravenous studies have been carried out with gadopentetate dimeglumine in mice, rats, and dogs. Acute oral toxicity studies have been carried out in mice and rats.

**Table 2:**

<b>Species Predominant Sex (number of animals / group)</b>	<b>Route of Administration, Dose (mmol/kg)</b>	<b>LD<sub>50</sub> – Range (mmol/kg)</b>	<b>Relevant Prominent Findings</b>
Mice, M (3)	oral, 0.25, 1.0, 5.0	> 5.0	None
Mice, M (3)	IV, 2.5, 5.0, 6.25, 7.5, 10.0	5.0 - 7.5	Apathy, changes in respiration, disturbed gait
Mice, F (3)	IV 6.25, 10.0, 12.5, 15.0	6.25 - 12.5	
Rats, M (3)	oral, 0.2, 0.8, 4.0	> 4.0	None
Rats, M (3)	IV, 10.0, 11.5, 13.5, 15.0	11.5 - 15.0	Prostration, apathy, accelerated respiration, disturbed gait
Rats, F (3)	IV, 7.5, 10.0, 12.5, 15.0	10.0 - 15.0	
Dogs, M+F (3)	IV, 6.0	>6.0	Reddening of mucosa and skin, licking, tremor, hematuria, disturbances of gait, retching, vomiting and bleeding at the injection site.

### Subacute Toxicity

**Table 3:**

<b>Species</b>	<b>Route of Administration, Dose (mmol/kg)</b>	<b>Duration of Administration</b>	<b>Relevant Prominent Findings</b>
Rats 10/sex/dose	IV 1.0, 2.5, 5.0	5 doses/week for 4 weeks	1.0 mmol/kg - without findings. From 2.5 mmol/kg onwards - Dose related apathy, increase in drinking water, consumption, recumbency, respiratory distress, vacuoles in epithelial cells of convoluted tubules and in liver parenchymal cells, slight decrease in hematological parameters, increased absolute and relative liver and kidney weights. Additionally after 5 mmol/kg - Convulsion, decrease in body weight gain, half of the animals died.
Rats 5/males/dose	IV 2.5, 5.0	once or 5 doses/ week for 4 weeks, with 8 and 16 day recovery period	Time-related and dose-related reversibility of renal and hepatic vacuolization. After 5 mmol/kg - atrophy of the spermatogenic cells, not reversible within 15 days.
Dogs, Beagle 2/sex/dose	IV 0.25, 1.0, 2.5	5 doses/week for 4 weeks	0.25 mmol/kg - without findings. From 1.0 mmol/kg onwards - dose related reddening of skin, vacuolization of proximal tubules. 2.5 mmol/kg - elevated kidney weights, decrease in body weight, increase in drinking water consumption.
Rats, pregnant 25/females/dose	IV 0.25, 0.75, 1.25	10 days, day 6-15 of gestation	0.25 - 0.75 mmol/kg - without findings. 1.25 mmol/kg - slight increase in wave-like curved ribs, slight retardation of ossification in the fetuses.
Rabbits, pregnant 21-22 / females/ dose	IV 0.25, 0.75, 1.25	13 days	0.25 mmol/kg - without findings. 0.75 - 1.25 mmol/kg - dose-related retardation of fetal development.

## **Mutagenicity Studies**

Gadopentetate dimeglumine was evaluated for its mutagenic potential in vitro using both bacterial assays (*S. typhimurium*, *E. coli*) and mammalian tests (HGPRT test in V 79 cells, UDS test in hepatocytes, cellular transformation assay in C3H 10T1/2 cells); in vivo, the product was assessed using two different systems, namely the micronucleus test and dominant lethal assay.

There was no indication that gadopentetate dimeglumine possesses any mutagenic potential in vitro or in vivo.

## **Local Tolerance**

Gadopentetate dimeglumine was evaluated for its ability to induce local irritation in rabbits following intravenous, paravenous, intramuscular, and subcutaneous administration. Intravenous administration of gadopentetate dimeglumine elicited only very slight evidence of irritation. However, paravenous, intramuscular or subcutaneous injections resulted in moderate local irritation.

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