Product Monograph
Including Patient Medication Information

MAGNEVIST®

Gadopentetate dimeglumine injection

(solution, 469 mg/mL (0.5 mmol/mL), for intravenous use)

Bayer Standard

Contrast Enhancement Agent
for Magnetic Resonance Imaging (MRI)

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Date of Authorization:

2025-09-04

Submission Control Number: 296001

Recent Major Label Changes

7 Warnings and Precautions, 7.1.1 Pregnancy	05/2024
3 Serious Warning and Precautions Box, NOT FOR INTRATEHCAL USE	09/2025
4 Dosage and Administration, 4.1 Dosing Considerations	09/2025
7 Warnings and Precautions, Risk of Intrathecal Use	09/2025

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Certain sections (as indicated in section 2.1 of the PM Guidance) or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed

Part 1: Health Professional Information

1 Indications

MAGNEVIST (gadopentetate dimeglumine injection), 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.
- use with MRI in adults to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity within the head (extracranial) and neck.

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of MAGNEVIST (gadopentetate dimeglumine injection) in pediatric patients has been established.
Therefore, Health Canada has authorized an indication for pediatric use (see 1 Indications).

Use of macrocyclic agents may be preferable in potentially vulnerable patients such as children.

1.2 Geriatrics

Geriatrics (65 years of age and over)**:** In clinical studies, no overall differences in safety or efficacy were observed between elderly (aged 65 years and above) and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

2 Contraindications

Gadolinium-based contrast agents (GBCAs) increase risk for Nephrogenic Systemic Fibrosis (NSF) in patients with renal insufficiency. Gadopentetate dimeglumine injection is contraindicated:

- In patients with chronic severe kidney insufficiency (glomerular filtration rate <30 mL/min/1.73m^2)
- In patients with acute kidney injury
- In neonates up to 4 weeks of age due to their immature renal function

Gadopentetate dimeglumine injection should not be administered to patients who are known or suspected of being hypersensitive to it.

3 Serious Warnings and Precautions Box

Nephrogenic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF in patients with renal insufficiency. MAGNEVIST is contraindicated in:

- Chronic severe kidney insufficiency where glomerular filtration rate is <30 mL/min/1.73m^2 (See 2 Contraindications)
- Acute kidney injury (See 2 Contraindications)
- Neonates up to 4 weeks of age (See 2 Contraindications)

The use of MAGNEVIST in patients with mild to moderate renal impairment (GFR ≥30 to <89 mL/min/1.73m^2) needs to be weighed against the risk of performing alternative medical imaging by health care professionals.

MAGNEVIST should be used with caution in infants less than 1 year of age.

NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs. Before administering MAGNEVIST, screen patients for acute kidney injury and any other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g., age >60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

In these patients described above, avoid use of MAGNEVIST unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). When administering MAGNEVIST, do not exceed the recommended dose (see 4 Dosage and Administration section) and allow a sufficient period of time for elimination of the agent from the body prior to any readministration. (see 7 Warnings and Precautions, General, Renal Impairment, Skin; and 8.5 Post-Market Adverse Reactions).

NOT FOR INTRATHECAL USE

Intrathecal administration of GBCAs can cause serious, life-threatening, and fatal reactions. MAGNEVIST is not approved for intrathecal use (see 7 Warning and Precautions, Risks of Intrathecal Use).

4 Dosage and Administration

4.1 Dosing Considerations

- MAGNEVIST is for intravenous administration, only.
- Special preparation of the patient for examination with MAGNEVIST (gadopentetate dimeglumine injection) is not required; however, precautionary measures should be taken with patients predisposed to seizure, e.g., close monitoring and availability of injectable anticonvulsants (see 7 Warnings and Precautions). The usual safety rules for MRI (e.g., 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.
- The lowest effective dose should be used. Use of macrocyclic agents may be preferable in certain patients such as those for whom repeated GBCA doses may need to be

considered due to individual clinical circumstances and in other potentially vulnerable patients such as children and pregnant women (see 7 Warnings and Precautions).

- 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 7 Warnings and Precautions).

4.2 Recommended Dose and Dosage Adjustment

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

Pediatrics (< 18 years of age):

Health Canada has authorized an indication for pediatric use (1.1 Pediatrics).

Geriatrics (aged 65 years and above):

No dosage adjustment is considered necessary in elderly (aged 65 years and above). In clinical studies, no overall differences in safety or efficacy were observed between elderly (aged 65 years and above) and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients (see 10.3 Pharmacokinetics).

Hepatic impairment:

Since gadopentetate is exclusively eliminated in an unchanged form via the kidneys, no dosage adjustment is considered necessary in patients with moderate hepatic impairment. Data on patients with severe hepatic impairment are not available (see 10.3 Pharmacokinetics).

4.4 Administration

In children below two years of age the required dose should be administered manually and not in combination with an autoinjector to avoid injury.

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.

No light protection during handling is required. For further information see 11 Storage, Stability and Disposal.

MAGNEVIST should be visually inspected before use. MAGNEVIST should not be used in case of severe discoloration, the occurrence of particulate matter or a defective container.

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.

T1-weighted scanning sequences are particularly suitable for contrast-enhanced examinations.

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 7.1.3 Pediatrics).

4.5 Missed Dose

Not applicable.

5 Overdose

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

It is unknown if hemodialysis reduces the risk of NSF.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Composition

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

Availability of Dosage Forms

MAGNEVIST is provided as a sterile, clear, colorless to slightly yellow aqueous solution. Each mL contains 469.01 mg gadopentetate 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. MAGNEVIST is sensitive to light. Keep the container in the outer carton in order to protect from light.

7 Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

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.

MAGNEVIST 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.

Accumulation of Gadolinium in the Brain

The current evidence suggests that gadolinium may accumulate in the brain after multiple administrations of GBCAs. Increased signal intensity on non-contrast T1-weighted images of the brain has been observed after multiple administrations of GBCAs in patients with normal renal function. Gadolinium has been detected in brain tissue after multiple exposures to GBCAs, particularly in the dentate nucleus and globus pallidus. The evidence suggests that the risk of gadolinium accumulation is higher after repeat administration of linear than after repeat administration of macrocyclic agents.

The clinical significance of gadolinium accumulation in the brain is presently unknown; however, gadolinium accumulation may potentially interfere with the interpretation of MRI scans in the brain. In order to minimize potential risks associated with gadolinium accumulation in the brain, it is recommended to use the lowest effective dose and perform a careful benefit risk assessment before administering repeated doses.

Risk of Intrathecal Use

Serious, life-threatening and fatal cases, primarily with neurological reactions (e.g. coma, encephalopathy, seizures), have been reported with off-label intrathecal use of GBCAs. MAGNEVIST is not approved for intrathecal use (see 3 Serious Warnings and Precautions Box, 4.1 Dosing Considerations).

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

(see 8.1 Adverse Reaction Overview). Precautionary measures should be taken with patients predisposed to seizure, e.g., close monitoring and availability of injectable anticonvulsants (see 4 Dosage and Administration).

Driving and Operating Machinery

Transient increases or decreases in blood pressure may occur after the administration of MAGNEVIST. Caution should be exercised by the patient when driving or operating machinery.

Hematologic

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.

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.

Immune

Hypersensitivity Reactions

The decision to use MAGNEVIST 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, 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 idiosynchratic reactions characterized by cardiovascular, respiratory, or cutaneous manifestations, and ranging from mild to severe reactions including anaphylactic shock. If such a reaction occurs, stop MAGNEVIST administration and immediately begin appropriate therapy, including resuscitation. These reactions often occur at least within half an hour of administration. Therefore, post-procedure observation of the patient is recommended. In rare cases delayed reactions (hours later or up to several days) may occur (see 8 Adverse Reactions).

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 (e.g., 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.

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 MAGNEVIST. MAGNEVIST should only be used after careful risk/benefit assessment in these patients, including consideration of possible alternative imaging methods, since contrast medium elimination is delayed in such cases. Use the lowest possible dose and evaluate renal function in patients with renal insufficiency (see 4 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^2)
- 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 3 Serious Warnings and Precautions Box; 7 Warnings and Precautions, Skin; and 8.5 Post-Market Adverse Reactions.)

MAGNEVIST is contraindicated for use in patients with acute or chronic severe kidney insufficiency (glomerular filtration rate <30 mL/min/1.73m^2) (See 2 Contraindications).

Evaluate all patients for renal dysfunction prior to administration of MAGNEVIST. For patients at risk for chronically reduced renal function (e.g., age >60 years, diabetes mellitus or chronic hypertension) estimate the GFR through laboratory testing.

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. MAGNEVIST should only be used after careful risk-benefit evaluation in patients with mild to moderate renal impairment (GFR ≥30 to <89 mL/min/1.73m^2) (See 7 Warnings and Precautions).

Because gadopentetate is renally excreted, a sufficient period of time for elimination of the contrast agent from the body should be ensured prior to any re-administration in patients with renal impairment. Elimination half-life in patients with mild or moderate renal impairment is 3 to 4 hours. Elimination half-life in patients with severe renal impairment is about 11 hours, and about 75% of the administered dose was recovered in the urine within two days.

MAGNEVIST can be removed from the body by hemodialysis. (See 5 Overdose.)

After 3 consecutive daily dialysis sessions of 3 hours each, about 97% of the administered dose is eliminated from the body, by about 70% with each dialysis session.

For patients already receiving hemodialysis at the time of MAGNEVIST administration, prompt initiation of hemodialysis following the administration of MAGNEVIST should be considered, in order to enhance the contrast agent's elimination.

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

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 3 Serious Warnings and Precautions Box; Warnings and Precautions, General, Renal Impairment; and 8.5 Post-Market Adverse Reactions.)

Nephrogenic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) may increase the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with acute or chronic renal insufficiency of any severity. 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.

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®), 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 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%. 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 acute kidney injury, renal dysfunction and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury.

For patients at risk for chronically reduced renal function (e.g., age >60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

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 10 Clinical Pharmacology, 7 Warnings and Precautions, Renal Impairment and Dosage and Administration.)

A skin biopsy is necessary in order to exclude the diagnosis of similarly presenting skin disorders (e.g., scleromyxedema). (See 3 Serious Warnings and Precautions Box; 7 Warning and Precautions, Renal Impairment, Skin; and 8.5 Post-Market Adverse Reactions.)

Injection Site Reactions

Skin and soft tissue necrosis, thrombosis, fasciitis, and compartment syndrome requiring surgical intervention (e.g., 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. Phlebetis 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.

7.1 Special Populations

7.1.1 Pregnancy

MAGNEVIST should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use of macrocyclic agents may be preferable in certain patients such as those for whom repeated GBCA doses may need to be considered due to individual clinical circumstances and in other potentially vulnerable patients such as pregnant women.

Traces of GBCAs can cross the placenta barrier and result in fetal exposure and may be detected in organs and tissues for an extended period of time. 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.

The potential risks of an abnormal pregnancy outcome are unknown, as adequate and well controlled clinical studies with MAGNEVIST were not conducted in pregnant women. A retrospective cohort study, comparing pregnant women who had a GBCA MRI to pregnant women who did not have an MRI, reported a higher occurrence of stillbirths and neonatal deaths in the group receiving GBCA MRI. However, no increased risk of congenital anomalies was observed. Limitations of this study include a lack of comparison with non-contrast MRI, lack of information about the maternal indication for MRI, and the type of GBCA used. These limitations were further addressed in another retrospective cohort study that found no increased risk for fetal or neonatal death or Neonatal Intensive Care Unit (NICU) admission when comparing pregnancies exposed to GBCA MRI and non-contrast MRI.

7.1.2 Breastfeeding

MAGNEVIST is excreted in human milk. MAGNEVIST was administered intravenously to 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 µmols.

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

7.1.3 Pediatrics

Use of macrocyclic agents may be preferable in potentially vulnerable patients such as children. The cautious utilization of the lowest effective dose (0.1 mmol/kg BW) in children is recommended, particularly for neonates and infants less than 1 year of age, as the pharmacokinetics of MAGNEVIST in neonates and infants with immature renal function have not been studied (see 7 Warnings and Precautions, Renal Impairment, 3 Serious Warnings and Precautions Box).

MAGNEVIST is contraindicated in neonates up to 4 weeks of age.

7.1.4 Geriatrics

No special precautions are required for elderly patients (see 3 Serious Warnings and Precautions Box).

8 Adverse Reactions

8.1 Adverse Reaction Overview

Side effects in association with the use of MAGNEVIST (gadopentetate dimeglumine injection) are usually mild to moderate and transient in nature. However, serious or severe and life-threatening reactions as well as death have been reported.

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.

MAGNEVIST will cause tissue irritation and pain if administered extravascularly.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reaction observed in the clinical trials, may not reflect the frequencies observed in clinical practice and should not be compared to the frequencies reported in clinical trials of another drug.

Most adverse reactions to MAGNEVIST 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% [a]
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%

[a] 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.

Transient increases or decreases in blood pressure have been observed to occur after the administration of MAGNEVIST in clinical trials. Three cases of clinically significant hypotension have occurred 2 to 6 hours after MAGNEVIST injection. A relationship to the contrast medium could not be determined. (See 7 Warning and Precautions, General.)

Convulsions were reported in 4 patients with a history of seizures.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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 in clinical trials.

MAGNEVIST does not interfere with serum and plasma calcium measurements determined by colorimetric assays.

8.5 Post-Market Adverse Reactions

Nephrogenic Systemic Fibrosis

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®), 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®). 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%. 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 3 Serious Warnings and Precautions Box, 7 Warnings and Precautions, General, Renal Impairment, Skin.)

Additional Postmarket Adverse Drug Reactions

Overall, the most serious adverse drug reactions in patients receiving MAGNEVIST are:

- Nephrogenic systemic fibrosis
- Anaphylactoid reactions / anaphylactoid shock

Delayed hypersensitivity / anaphylactoid reactions (hours later up to several days) have been rarely observed. (See 7 Warnings and Precautions, Hypersensitivity Reactions.)

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

Cardiovascular: heart rate decreased / bradycardia [a], vasodilatation, pallor, thrombophlebitis, non-specific ECG changes, substernal pain, angina, blood pressure increased, tachycardia [a], syncope [a], arrhythmia, disturbance of cardiac function, cardiac arrest [a].

Central nervous system: headache, dizziness, agitation, paresthesia, tinnitus, visual field defect, convulsions [a], hyperesthesia, disorientation, somnolence [a], burning sensation, visual disturbance, parosmia, speech disorder, hearing impaired, coma [a], tremor.

Gastrointestinal: nausea, vomiting, abdominal pain, stomach discomfort, thirst, increased salivation, dysgeusia, oral soft tissue pain and paresthesia, diarrhea.

[a] Life-threatening and/or fatal cases have been reported.

Respiratory system: dry mouth, throat irritation, pharyngolaryngeal pain / pharynx discomfort, rhinorrhea, cough, apnea, respiratory rate increased or respiratory rate decreased, respiratory distress, pulmonary edema [a].

Cutaneous / mucous membranes: sweating, nephrogenic systemic fibrosis (NSF) [a], flushing.

Miscellaneous: injection site reactions (e.g. injection site coldness, paresthesia, swelling, warmth, burning, pain, edema, irritation, hemorrhage, erythema, discomfort, necrosis, thrombophlebitis, phlebitis, inflammation, extravasation), toothache, pain in extremity, asthenia, pyrexia, edema peripheral, fatigue, chills, malaise, back pain, ear pain, eye pain, lacrimation, arthralgia, vasovagal reactions, body temperature increased or body temperature decreased, feeling hot, feeling cold, chest pain.

Laboratory tests: serum iron increased [a] and blood bilirubin increased.

Immune system: hypersensitivity / anaphylactoid reaction (e.g. anaphylactoid shock [a], anaphylactoid reaction [a], hypersensitivity reactions [a], shock [a], hypotension [a], loss of consciousness [a], throat tightness [a], sneezing, urticaria, pruritus, rash, erythema, dyspnea [a], respiratory arrest [a], bronchospasm [a], wheezing, laryngospasm [a], laryngeal edema [a], pharyngeal edema [a], cyanosis [a], rhinitis, angioedema [a], edema face [a], reflex tachycardia, conjunctivitis).

Renal and Urinary: urinary incontinence, urinary urgency, increased serum creatinine [b], acute renal failure [a,b].

Hepato-biliary: hepatic enzyme increased.

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

Cardiovascular: death related to myocardial infarction or other undetermined causes, clinically relevant transient disturbance in heart rate.

Central nervous system: anxiety, nystagmus, confusion.

Gastrointestinal: constipation, anorexia.

Postmarket ADRs in Patients with Dialysis-dependent Renal Failure

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.

9 Drug Interactions

9.2 Drug Interactions Overview

No specific drug interaction studies have been done for MAGNEVIST during the development of this product.

[b] In patients with preexisting renal impairment.

9.3 Drug-Behaviour Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

No interactions studies with other medicinal products have been conducted.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interference with Diagnostic Tests

Serum iron determination using methods measuring complexes (e.g. Bathophenanthroline) may result in low values for up to 24 hours after the administration of MAGNEVIST. This value may be a falsely low value due to the free DTPA contained in MAGNEVIST.

10 Clinical Pharmacology

10.1 Mechanism of Action

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 paramagnetic efficacy at a magnetic field strength of 1.5 T and at 37°C, as indicated by the relaxivity (r1) (determined from the influence on the T1 relaxation time of the water protons in plasma) and the relaxivity (r2) (determined from the influence on the T2 relaxation time), is about 4.1 ± 0.2 L/(mmol•sec) and 4.6 ± 0.8 L/(mmol•sec), respectively. The relaxivities display only slight dependency on the strength of the magnetic field.

The free gadolinium ion is unsuitable for clinical use due to high toxicity; however, the metal chelate is metabolically inert and does not display significant inhibitory interaction with enzymes (e.g. acetylcholinesterase and lysozyme) at clinically relevant concentrations. 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).

10.2 Pharmacodynamics

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

10.3 Pharmacokinetics

The pharmacokinetic profile of 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+19 mL/min and 122+14 mL/min, respectively) for gadopentetate are essentially identical. The volume of distribution (266+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, e.g., inulin and ^{51}Cr-EDTA. 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.

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 feces amounted to <0.1% over 5 days. There was no detectable biotransformation, dissociation, or decomposition of gadopentetate.

Special populations and conditions

- **Pregnancy and breastfeeding:** In lactating women (aged 23-38 years), less than 0.04% of administered gadopentetate is excreted into human breast milk.

The current evidence suggest that gadolinium may accumulate in the brain after repeated administrations of GBCAs although the exact mechanism of gadolinium passage into the brain has not been established.

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 hematolytic 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.

11 Storage, Stability, and Disposal

MAGNEVIST should be stored at 15°C to 30°C. MAGNEVIST is sensitive to light. Keep the container in the outer carton in order to protect from light. After the vial has been opened, MAGNEVIST remains chemically, physically and microbiologically stable for 24 hours at temperatures not exceeding 30°C and must be discarded thereafter.

12 Special Handling Instructions

MAGNEVIST should be visually inspected before use. MAGNEVIST should not be used in case of severe discoloration, the occurrence of particulate matter or a defective container.

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.

The imaging procedure should be completed within one hour.

For more information, see 4.1 Dosing Considerations and 4.4 Administration.

Part 2: Scientific Information

13 Pharmaceutical Information

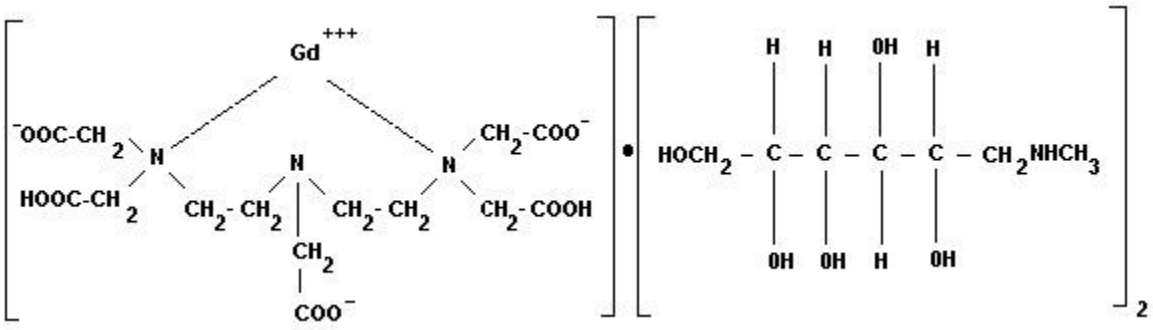
Drug Substance

Non-proprietary name of the drug substance: Gadopentetate dimeglumine (USAN)

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

Molecular formula and molecular mass: $C_{14}H_{20}GdN_3O_{10}A(C_7H_{17}NO_5)_2$ 938.02

Structural formula:



Solubility: Freely soluble in water

Osmolality: 1960 mOsm/kg H2O at 37°C

14 Clinical Trials

14.1 Clinical Trials by Indication

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_1-weighted scans and more than 1/3 of patients with T_2-weighted scans. From a group of 167 patients in the cranial studies for whom neither T_1-weighted nor T_2-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_1-weighted scans provided better enhancement in 138 (93%) of 148 patients in the cranial studies. T_2-weighted was the better diagnostic mode for 10 (7%) patients. In the spinal studies (postoperative back pain), the T_1-weighted mode provided better enhancement in 55 (95%) of 58 patients and the T_2-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_1 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_1 or T_2 scan, this possibility increased from 44% prior to MAGNEVIST injection, to 74% after MAGNEVIST injection. The diagnostic quality of both T_1 and T_2 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 ($P<0.001$).

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

General 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.

Recent studies conducted in healthy rats injected repeatedly with linear or macrocyclic GBCAs demonstrated that linear agents were associated with progressive and persistent T1-weighted hyperintensity on MRI in the deep cerebellar nuclei (DCN). Signal enhancement in the globus pallidus (GP) could not be seen in animals. No changes in signal intensities in either DCN or GP were observed for the macrocyclic GBCAs.

Quantitative results using mass spectrometry demonstrated that the total gadolinium concentrations were significantly higher with the linear GBCAs than with the macrocyclic GBCAs. These studies reported no abnormal behavioural changes suggestive of neurological toxicity.

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 1:

Species Predominant Sex (number of animals / group)	Route of Administration, Dose (mmol/kg)	LD_{50} – Range (mmol/kg)	Relevant Prominent Findings
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 2:

Species	Route of Administration, Dose (mmol/kg)	Duration of Administration	Relevant Prominent Findings
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.

Species	Route of Administration, Dose (mmol/kg)	Duration of Administration	Relevant Prominent Findings
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.

Carcinogenicity

No long-term animal studies have been performed to evaluate carcinogenic potential of MAGNEVIST (gadopentetate dimeglumine injection).

Genotoxicity

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.

Reproductive and developmental toxicology

MAGNEVIST was investigated in mice to detect potential effects of gadopentetate dimeglumine (0.6, 1.2, or 2.5 mmol/kg/day) on the F1 offspring of Crl:CD1(ICR) F0 generation female mice consequent to exposure of the female from implantation throughout the fetal period via intravenous bolus injection on Gestation Day (GD) 6 through 18. Observations, including learning and memory testing, were continued through sexual maturity of the F1 generation mice until Day 70 postpartum.

Administration of gadopentetate dimeglumine was tolerated at doses up to and included 1.2 mmol Gd/kg/day. At 2.5 mmol Gd/kg/day, there was an increase in mortality in the F0 generation dams and renal tubular vacuolation observed in the early deaths. These early deaths in the F0 generation dams at 2.5 mmol Gd/kg/day may have been associated with the overall injection rate of the test item and the volume of test item that was administered (5 mL/kg). Therefore, the general toxicity and maternal no-observed-adverse-effect level (NOAEL) was 1.2 mmol Gd/kg/day. This NOAEL corresponds to a C_{max} of 5380 µmol/L and an AUC_{Tlast} of 3440 hr*µmol/L on GD 6 and a C_{max} of 7260 µmol/L and AUC_{Tlast} of 6020 hr*µmol/L on GD 17. There were no adverse effects observed in the F1 generation mice; therefore, the developmental no-observed-adverse-effect level (NOAEL) was 2.5 mmol Gd/kg/day corresponding to 25-fold the recommended diagnostic dose per day (representing in total the 325-fold Gd dose compared to the single diagnostic dose). In the F1 generation mice, the highest systemic exposure was observed on Day 1 postpartum (5.86 µmol/L in males and 2.67 µmol/L in females). Corresponding Gadolinium concentrations in brain were 17.6 nmol/g in males and 20.2 nmol/g in females on Day 1 postpartum which did not relate to any effects on brain development or impact of functional parameters such as behavior, learning and memory.

Special toxicology

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.

PHARMACOLOGY

Animal Studies

Neuropharmacology

The neuropharmacology of gadopentetate dimeglumine was evaluated in rats, following single pericerebral or intracisternal injection. The ED_{50}, based on postural anomalies, seizures, or death, and the LD_{50} 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 3).

Table 3: A Comparison of the ED50 and LD50 of Gadopentetate Dimeglumine, Gadolinium Chloride, and Meglumine Diatrizoate Following Pericerebral or Intracisternal Administration in Rats

Compounds	Dose Level (µmol/kg)	ED_{50} (µmol/kg)	Dose Level (µmol/kg)	LD_{50} (µmol/kg)
Pericerebral Administration				
Gadopentetate Dimeglumine	25-296.3	96.6	463-1852	1141.4
		97.1		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
Intracisternal Administration				
Gadopentetate Dimeglumine	16.7-197.9	74.0	309-1233	654.9
		86.2	a	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 very poorly absorbed from the gastrointestinal tract of rats and dogs and was excreted almost completely in the faeces (ca. 96% 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 radiolabellled 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. In rats, absorption from the gastrointestinal tract after oral administration was found to be small with about 4% absorbed.

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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

MAGNEVIST®

Gadopentetate dimeglumine injection, 469 mg/mL (0.5 mmol/mL)

For Intravenous Use

This Patient Medication Information is written for the person who will be taking **MAGNEVIST**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary and will not tell you everything about this medication. If you have more questions about this medication or want more information about **MAGNEVIST** talk to a healthcare professional.

Serious warnings and precautions box

Nephrogenic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (such as MAGNEVIST) increase the risk of a rare disease called Nephrogenic Systemic Fibrosis (NSF) in patients with kidney disease. MAGNEVIST should not be used in:

- **Patients with chronic, severe kidney disease**
- **Patients with acute kidney injury**
- **New-borns up to 4 weeks of age due to their developing kidneys**

If you have mild to moderate kidney disease, you should only be given MAGNEVIST after a careful assessment by your healthcare professional.

MAGNEVIST should be used with caution in infants less than 1 year of age.

Your healthcare professional will monitor your health before and after giving you MAGNEVIST if you are at risk for developing NSF (see "Other warnings that you should know about", below).

Not for Intrathecal use

If injected into the spinal canal (by intrathecal injection), gadolinium-based contrast agents such as MAGNEVIST can cause serious life-threatening side effects such as:

- Coma (prolonged loss of consciousness)
- Encephalopathy (changes in how your brain works)
- Seizures (temporary loss of consciousness and muscle control)
- Death

MAGNEVIST is for intravenous (IV) use only.

What MAGNEVIST is used for:

- MAGNEVIST is used during magnetic resonance imaging (MRI) of the head, neck and spine. This helps with the diagnosis of various conditions.

How MAGNEVIST works:

- MRI is a form of medical diagnostic imaging that creates detailed images of the organs and tissues inside your body.
- MAGNEVIST makes certain areas appear brighter in your MRI. This helps your healthcare professional identify any potential issues.

The ingredients in MAGNEVIST are:

Medicinal ingredient(s): gadopentetate dimeglumine

Non-medicinal ingredients: diethylenetriamine pentaacetic acid and meglumine

MAGNEVIST comes in the following dosage form:

MAGNEVIST is a ready-to-use solution (corresponding to 0.5 mmol/mL) for rapid injection into a vein.

Do not use MAGNEVIST if:

Gadolinium-based contrast agents (such as MAGNEVIST) increase the risk of a rare disease called Nephrogenic Systemic Fibrosis (NSF) in patients with kidney disease. MAGNEVIST should not be used in:

- Patients with chronic, severe kidney disease
- Patients with acute kidney injury
- New-borns up to 4 weeks of age due to their developing kidneys
- You are allergic (hypersensitive) to gadopentetate dimeglumine or to any of the other ingredients of MAGNEVIST (see “What are the ingredients in MAGNEVIST” section)
- You have previously had a life-threatening reaction to MAGNEVIST.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MAGNEVIST. Talk about any health conditions or problems you may have, including if:

- You have or have had a previous reaction to contrast media
- You suffer or have suffered from an allergy (e.g., hay fever, hives) or asthma.
- You have very poor kidney function.
- You have recently had, or soon expect to have, a liver transplant.
- You have epilepsy or suffer from brain conditions with seizures.
- You are pregnant or are planning to become pregnant, as it is not known if MAGNEVIST may harm your unborn baby. MAGNEVIST will only be given to you during pregnancy if your doctor decides it is absolutely necessary. You are breast-feeding or intend to breast-feed. MAGNEVIST passes in breast milk.

- You suffer from heart or blood circulation problems. This is because in the rare event that you do have an allergic reaction, it is more likely to be serious or fatal.
- You have sickle cell anemia, hemolytic conditions (destruction of red blood cells), or related blood disorders of hemoglobin in the blood (hemoglobinopathies).
- You have heart problems, breathing difficulties, or skin reactions may occur with the use of MAGNEVIST. Severe reactions may occur. Most of these reactions occur within half an hour of administration. Therefore, your attending healthcare professional may observe you in this period. Delayed reactions may occur hours or even days later.

Other warnings you should know about:

MAGNEVIST may increase or decrease blood pressure and may make you feel dizzy or faint. See how you feel after you are given MAGNEVIST and before driving or operating machinery.

Accumulation of Gadolinium in the Brain

Recent information shows that gadolinium (as in **MAGNEVIST**) may build up in the brain after multiple uses and:

- The effect on the brain is unknown right now.
- Your healthcare professional will:
  - Carefully consider whether to use repeated doses
  - Use the lowest dose

Kidney Impairment

Before you receive MAGNEVIST, your healthcare professional will check how well your kidneys are working. Patients with severe kidney disease should not be given MAGNEVIST (See Serious Warnings and Precautions). Patients with mild to moderate kidney disease should only be given MAGNEVIST after a careful assessment by their healthcare professional. Your doctor may decide to take a blood test to check this before making the decision to use MAGNEVIST.

If you have poor kidney function, your healthcare professional will make sure that MAGNEVIST has been eliminated from your body before you receive a second injection of MAGNEVIST.

MAGNEVIST can be removed from the body by dialysis. If you are already undergoing regular dialysis, your healthcare professional will decide if you should receive dialysis after you have been given MAGNEVIST.

Nephrogenic Systemic Fibrosis

Receiving MAGNEVIST may cause Nephrogenic Systemic Fibrosis (NSF). This is a rare condition which has only been observed so far in patients with severe kidney disease. NSF causes the skin to become thickened, coarse, and hard, which sometimes makes bending of the joints difficult. NSF may spread to other organs and even cause death.

Before you receive MAGNEVIST, your healthcare professional will evaluate your kidney function. This will help determine if you should be given MAGNEVIST.

If you have already had an imaging procedure and experience any of the following symptoms, you 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 healthcare professional will monitor your health after administering MAGNEVIST, if you are considered to be at risk for developing NSF.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Drug interaction studies have not been done for MAGNEVIST.

Before you have any blood tests, tell your healthcare professional you have been given MAGNEVIST. This is because some tests for iron levels in the blood may be affected for up to 24 hours after MAGNEVIST has been given.

How to take MAGNEVIST:

- MAGNEVIST will be given to you by a healthcare professional before your MRI.

Usual dose:

Your healthcare professional will determine your dose based on your body weight. The recommended dose of MAGNEVIST is 0.2 millilitres per kg body weight.

If you receive a bolus injection of MAGNEVIST (a large dose quickly) you may notice a temporary sweet taste in your mouth.

Overdose:

If you think you, or a person you are caring for, has been given too much MAGNEVIST, contact your healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Possible side effects from using MAGNEVIST:

These are not all the possible side effects you may have when taking MAGNEVIST. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, MAGNEVIST can cause side effects, although not everybody gets them.

Common side effects observed in clinical trials (between 1 and 10 in every 100 patients are likely to get these):

- Headache (in some cases severe)
- Injection site discomfort
- Nausea (feeling sick)
- Pain (back, ear, eye, teeth)
- Dizziness
- Vomiting
- Paresthesia ("pins and needles")

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Rare			
Serious allergy-like reactions: swelling of the face, lips, tongue, eyes or throat, difficulty breathing, blueness in the lips, coughing, runny nose, low blood pressure, chest pain, rash / hives, and flushing (redness) or paleness in the skin. This can sometimes be fatal. Reactions may occur after you are given the drug but can also happen within hours or days after taking MAGNEVIST.		✓	
Unknown			
Acute kidney failure (severe kidney problems): confusion; itchiness or rashes; puffiness in your face and hands; swelling in your feet or ankles; urinating less or not at all; weight gain.		✓	
Cardiac arrest (heart stops beating)		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Coma: loss of consciousness, feeling unresponsive.		✓	
Fainting		✓	
Fits or seizures		✓	
Heart problems: slow, fast, or irregular heartbeat. Chest pain.		✓	
Nephrogenic Systemic Fibrosis (NSF) (a disease mainly involving thickening of the skin and connective tissues): severe joint immobility, muscle weakness, or may affect the normal working of internal organs which may potentially be life-threatening.		✓	
Pulmonary edema (fluid in lungs): difficulty breathing that worsens with activity or when lying down, shortness of breath, wheezing or gasping for breath, irregular heartbeat.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

MAGNEVIST should be stored at temperatures between 15°C to 30°C. MAGNEVIST is sensitive to light. Keep the container in the outer carton in order to protect from light.

Keep out of reach and sight of children.

If you want more information about MAGNEVIST:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.bayer.ca), or by calling Bayer Medical Information at 1-800-265-7382 or Canada.medinfo@bayer.com.

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Date of Authorization: 2025-09-04