DATA SHEET

MAGNEVIST®

Solution for Intravenous Injection
Dimeglumine gadopentetate 0.5 mmol/mL

PRESENTATION

Magnevist injection is a sterile, clear, colourless to slightly yellow solution for intravenous injection. Each mL contains 0.5 mmol dimeglumine gadopentetate.

INDICATIONS

For diagnostic use by intravenous administration only.

Cranial and Spinal Magnetic Resonance Imaging (MRI)
In particular for the demonstration of tumours and for further differential-diagnostic clarification in suspected meningioma, (acoustic) neurinoma, invasive tumours (e.g. glioma) and metastases; for the demonstration of small and/or isointense tumours; in suspected recurrence after surgery or radiotherapy; for the differentiated demonstration of rare neoplasms such as haemangioblastomas, ependymomas and small pituitary adenomas; for improved determination of the spread of tumours not of cerebral origin.

Additionally in spinal MRI: Differentiation of intra- and extramedullary tumours; demonstration of solid tumour areas in known syrinx; determination of intramedullary tumour spread.

Whole Body MRI
Including the facial skull, the neck region, the thoracic and abdominal space, the female breast, the pelvis and the active and passive locomotive apparatus and imaging of vessels throughout the body.

In particular, Magnevist permits diagnostic information:
- For the demonstration or exclusion of tumours, inflammation and vascular lesions;
- For determination of the spread and demarcation of these lesions;
- For the differentiation of the internal structure of lesions;
- For assessment of the circulatory situation of normal and pathologically changed tissues;
- For the differentiation of tumour and scar tissue after therapy;
- For the recognition of recurrent prolapse of a disk after surgery.
- For the semi-quantitative evaluation of the renal function combined with anatomical organ diagnosis.

DOSAGE AND ADMINISTRATION

Method of Administration
Magnevist is to be administered only by intravenous injection.
Nausea and vomiting are known possible adverse events of all MRI contrast media. The patient should therefore refrain from eating for two hours prior to the investigation to reduce the risk of aspiration.

The safety rules customary for MRI must be observed, e.g. exclusion of cardiac pacemakers, ferromagnetic implants.

Wherever possible, intravascular administrations of contrast agent are to be given with the patient lying down; after the end of the injection the patient should be kept under supervision for at least half an hour since the majority of undesirable effects occur in this time.

Pronounced states of excitement, anxiety and pain may increase the risk of side effects or intensify contrast medium-related reactions. These patients may be given a sedative.

**Dosage regimen**

**Cranial and Spinal MRI**
The recommended dosage of Magnevist Injection in both adults and children is 0.2 mL/kg body weight is sufficient for good enhancement and to answer the clinical question. If a strong clinical suspicion of a lesion persists despite a normal contrast enhanced MRI, a further injection of Magnevist 0.2 mL/kg or, in adults, of even 0.4 mL/kg body weight within 30 minutes immediately following MRI may increase the diagnostic yield of the examination.

For the exclusion of metastases or recurrent tumours in adults the injection of Magnevist 0.6 mL/kg body weight often leads to higher diagnostic confidence.

*Maximum single dose:* Magnevist 0.6 mL/kg (for adults) or 0.4 mL/kg (for children) body weight.

**Whole Body MRI**
In general, the administration of Magnevist 0.2 mL/kg body weight is sufficient for good enhancement and to answer the clinical question.

In special cases, e.g. in lesions with poor vascularisation and/or a small extracellular space, the administration of Magnevist 0.4 mL/kg body weight may be necessary for an adequate contrast effect especially on use of relatively slightly T<sub>1</sub> -weighted scanning sequences. In cases of exclusion of a lesion or tumour recurrences in adults, the injection of Magnevist 0.6 mL /kg body weight may lead to higher diagnostic confidence.

For the visualisation of vessels, depending on the region to be investigated and the examination technique, in adults the injection of up to Magnevist 0.6 mL/kg body weight may be required.

*Maximum single dose:* Magnevist 0.6 mL/kg (for adults) or 0.4 mL/kg (for children) body weight.

*Children (under two years):* Limited experience in whole body MRI.

**CONTRAINDICATIONS**

Magnevist should not be administered to patients with known sensitivity to any of the ingredients.

Use of Magnevist (dimeglumine gadopentetate) is contraindicated in patients with:
- Acute or chronic severe renal insufficiency (a glomerular filtration rate < 30 mL/min/1.73m²); or
- Patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the peri-operative liver transplantation period.

WARNINGS AND PRECAUTIONS

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

Hypersensitivity reactions
Magnevist should not be administered to patients with known sensitivity to any of the ingredients (see Contraindications).

As with other intravenous contrast agents, Magnevist can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions characterised by cardiovascular, respiratory or cutaneous manifestations, and ranging to severe reactions including shock (see Adverse Effects).

Most of these reactions occur within at least half an hour of administration. However, in rare cases delayed reactions (hours later or up to several days) may occur. Post-procedure observation of the patient is recommended.

In patients with an allergic disposition (especially with a history of the above mentioned conditions), the decision to use Magnevist must be made after particularly careful evaluation of the risk-benefit-ratio in patients.

The risk of hypersensitivity reactions is higher in case of:
- previous reaction to contrast media
- history of bronchial asthma
- history of allergic disorders

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

In patients with allergic disposition, pre-medication with antihistamines and/or glucocorticoids may be considered.

Medication for the treatment of hypersensitivity reactions as well as preparedness for institution of emergency measures is necessary (e.g. appropriate drugs, an endotracheal tube and a ventilator should be at hand).

Patients taking beta blockers who experience such reactions may be resistant to treatment with beta agonists.

Management of anaphylaxis and emergency measures:
- As hypersensitivity/anaphylaxis is a medical emergency the number of symptoms and/or signs that has been documented for each case may vary considerably
- If hypersensitivity reactions occur, administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy instituted via a venous access. It is therefore advisable to use a flexible indwelling cannula for intravenous contrast medium administration
- Prompt and early treatment of anaphylaxis may prevent the development of symptoms in other organ systems.

Anaemia

Patients receiving Magnevist Injection should be instructed to inform their physician if they have anaemia or any disease that affects red blood cells.

The accepted safety considerations and procedures that are required for MRI are applicable when Magnevist Injection is used for contrast enhancement. In addition, deoxygenated sickle erythrocytes have been shown in *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by dimeglumine gadopentetate may possibly potentiate sickle erythrocyte alignment. Magnevist Injection in patients with sickle cell anaemia and other haemoglobinopathies has not been studied.

Patients with other haemolytic anaemias have not been adequately evaluated following administration of Magnevist Injection to exclude the possibility of increased haemolysis.

Hypotension

Hypotension may occur in some patients after injection of Magnevist. In clinical trials, two cases were reported and in addition, there was one case of a vasovagal reaction and two cases of pallor with dizziness, sweating and nausea in one and substernal pain and flushing in the other. These were reported within 25 to 85 minutes after injection except for the vasovagal reaction which was described as mild by the patient and occurred after 6½ hours. In a study in normal volunteers one subject experienced syncope after arising from a sitting position two hours after administration of the drug. Although the relationship of dimeglumine gadopentetate to these events is uncertain, patients should be observed for several hours after drug administration.

Impaired Renal Function

In these patients acute renal failure requiring dialysis or worsening renal function have occurred rarely. The risk of these events is higher with increasing dose of contrast medium.

Nephrogenic Systemic Fibrosis (NSF): There have been reports of nephrogenic systemic fibrosis (NSF) associated with the use of contrast agents containing gadolinium, including Magnevist in patients with acute or chronic severe renal insufficiency (GFR < 30 ml/min/1.73m²) or acute renal insufficiency of any severity due to the hepato-renal syndrome or in the peri-operative liver transplantation period (see Contraindications).

NSF is a debilitating and sometimes fatal disease affecting the skin, muscle and internal organs.

Prior to administration of Magnevist all patients should be screened for renal dysfunction by obtaining a history and/or laboratory tests.

When administering Magnevist injection, do not exceed the dose recommended in the product labelling.

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 (see Pharmacology, Pharmacokinetics).
Magnevist can be removed from the body by haemodialysis. After 3 dialysis sessions of 3 hours each, about 97% of the administered dose is eliminated from the body. With each dialysis session, about 70% of the administered dose is eliminated.

For patients receiving haemodialysis, prompt initiation of haemodialysis following the administration of Magnevist should be considered, in order to enhance the contrast agent’s elimination (see Adverse Effects).

**Seizure Disorders**

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 Adverse Effects).

For patients predisposed to seizures, precautionary measures should be taken, e.g. close monitoring, all equipment and medicines necessary to manage convulsions should they occur must be made ready for use beforehand.

**General**

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

**Use in Pregnancy – Category B2**

Dimeglumine gadopentetate has been shown to retard development slightly in rats when given in doses of 0.25 mmol/kg and in rabbits when given in doses of 0.75 mmol/kg and 1.25 mmol/kg. The drug did not exhibit this effect in rabbits when given in doses of 0.25 mmol/kg. No congenital anomalies were noted in either species. The potential risk for humans is unknown.

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

**Effects on Fertility**

The results of a reproductive study in rats showed that dimeglumine gadopentetate administered in daily doses of 0.1 - 2.5 mmol/kg did not cause a significant change in the pregnancy rate in comparison to a control group. However, suppression of body weight gain and food consumption and a decrease in the mean weights of testis and epididymis occurred in male rats at the 2.5 mmol/kg dose.

In a separate experiment, 16 daily intravenous injections were administered to male rats. At a dose of 5 mmol/kg of dimeglumine gadopentetate, spermatogenic cell atrophy was observed. This atrophy was not reversed within a 16 day observation period following the discontinuation of the drug. This effect was not observed at a dose of 2.5 mmol/kg.

**Use in Lactation**

Patients receiving Magnevist Injection should be instructed to inform their physician if they are pregnant or if they are breastfeeding.
Intravenous administration of Magnevist to 18 lactating women with normal renal function demonstrated that most probably, gadopentetic acid - dimeglumine salt is excreted in human milk. Analysis of milk samples (n = 18) indicated excretion of Magnevist equivalent to 0.052 to 3 μmol of gadolinium during a 24 hour period. This led to excretion of a maximum of 0.04% of the administered gadolinium dose into the breast milk during a 24 hour period (overall duration of excretion not studied). There is evidence from non-clinical data in rats that indicate the absorption via the gastrointestinal tract is poor; however, the extent of the absorption of dimeglumine gadopentetate in infants and its effects on the breast-fed child remains unknown. Caution should be exercised when Magnevist is administered to a nursing mother.

**Paediatric Use**
Safety and effectiveness of Magnevist Injection in children including neonates and infants, has been established in the evaluation of lesions within the brain and spine. However, caution should be exercised with neonates and infants up to 1 year of age, due to their immature renal function.

**Use in the Elderly**
No dosage adjustment is considered necessary in the elderly (aged 65 years and above). In clinical studies, no overall differences in safety or efficacy were observed between the 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 Pharmacology, Pharmacokinetics).

**Effects on Ability to Drive or Use Machines**
Not known.

**Genotoxicity**
Dimeglumine gadopentetate did not evoke any evidence of mutagenic potential in a number of *in vivo* and *in vitro* tests.

**Carcinogenicity**
In a tumourigenicity study in which rats were administered up to 15 intravenous doses of dimeglumine gadopentetate 0.5 mmol/kg/day over 3 weeks, and observed for 1 or 2 years, no compound-related tumours were observed.

**Effect on Laboratory Tests**
Transitory changes in serum iron and bilirubin levels have been reported in patients with normal and abnormal liver function (see Warnings and Precautions, General).

Interference with diagnostic tests: Serum iron determination using methods measuring complexes (e.g. bathophenanthroline) may result in falsely low values for up to 24 hours after the administration of Magnevist due to the free DTPA contained in Magnevist.

**ADVERSE EFFECTS**

**Summary of the Safety Profile**
The overall safety profile of Magnevist is based on data from post-marketing surveillance and from more than 11,000 patients in clinical trials.

The most frequently observed adverse drug reactions in patients receiving Magnevist in clinical trials are:
- Various injection site reactions
- Headache
• Nausea
• Dizziness
• Vomiting
• Dysgeusia

Most of the adverse drug reactions in the clinical trials were of mild to moderate intensity.

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 observed rarely (see Warnings and Precautions – Hypersensitivity reactions). Severe and life threatening reactions as well as deaths have been reported.

Localised pain and vomiting occurred in less than 2% of the patients.

**Adverse Drug Reactions from Clinical Trial Data**

Adverse drug reactions observed with Magnevist in clinical trials are represented in Table 1. They are classified according to System Organ Class (MedDRA version 12.1). The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Adverse drug reactions from clinical trials are classified according to their frequencies. Frequency groupings are defined according to the following convention:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>(\geq 1/1,000 ) to (&lt; 1/100)</td>
</tr>
<tr>
<td>Rare</td>
<td>(\geq 1/10,000 ) to (&lt; 1/1,000)</td>
</tr>
</tbody>
</table>

**Table 1: Adverse drug reactions reported in clinical trials**

<table>
<thead>
<tr>
<th>System Organ Class (MedDRA)</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity /anaphylactoid reaction</td>
<td>(e.g. anaphylactoid shock*, conjunctivitis,</td>
</tr>
<tr>
<td></td>
<td>(e.g. anaphylactoid shock*, conjunctivitis,</td>
<td>throat tightness*, sneezing, urticaria, pruritus,</td>
</tr>
<tr>
<td></td>
<td>throat tightness*, sneezing, urticaria, pruritus,</td>
<td>rash, erythema, dyspnoea*, wheezing,</td>
</tr>
<tr>
<td></td>
<td>throat tightness*, sneezing, urticaria, pruritus,</td>
<td>oedema face*)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Disorientation</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>Convulsion*</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Paraesthesia</td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
<td>Burning sensation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tremor</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Tachycardia*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>Thrombophlebitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flushing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vasodilatation</td>
</tr>
<tr>
<td>Respiratory, thoracic and</td>
<td></td>
<td>Throat irritation</td>
</tr>
<tr>
<td>mediastinal</td>
<td></td>
<td>Pharyngolaryngeal pain/pharynx discomfort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cough</td>
</tr>
<tr>
<td>System Organ Class (MedDRA)</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Stomach discomfort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toothache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral soft tissue pain and paraesthesia</td>
</tr>
<tr>
<td>Musculoskeletal,</td>
<td></td>
<td>Pain in extremity</td>
</tr>
<tr>
<td>connective tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and bone disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders</td>
<td>Pain</td>
<td>Chest pain</td>
</tr>
<tr>
<td>and administration site</td>
<td>Feeling hot</td>
<td>Pyrexia</td>
</tr>
<tr>
<td>conditions</td>
<td>Feeling cold</td>
<td>Oedema peripheral</td>
</tr>
<tr>
<td></td>
<td>Injection site reactions (e.g. injection</td>
<td>Malaise</td>
</tr>
<tr>
<td></td>
<td>site coldness, paraesthesia, swelling,</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>warmth, pain, oedema, irritation, haemorrhage,</td>
<td>Thirst</td>
</tr>
<tr>
<td></td>
<td>erythema, discomfort)</td>
<td>Asthenia</td>
</tr>
</tbody>
</table>

* Life threatening and/or fatal cases have been reported

Adverse drug reactions from post-marketing experience

Adverse drug reactions identified only during post-marketing surveillance are shown in Table 2.

Table 2: Adverse drug reactions identified only during post-marketing surveillance (spontaneous reporting)

<table>
<thead>
<tr>
<th>System Organ Class (MedDRA)</th>
<th>Frequency Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Iron serum increased*</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity/anaphylactoid reactions (e.g. anaphylactoid reaction*,</td>
</tr>
<tr>
<td></td>
<td>hypersensitivity reactions*, shock*, hypotension*, loss of consciousness*,</td>
</tr>
<tr>
<td></td>
<td>respiratory arrest*, bronchospasm*, laryngospasm*, laryngeal oedema*,</td>
</tr>
<tr>
<td></td>
<td>pharyngeal oedema*, cyanosis*, rhinitis, angioedema*, reflex tachycardia)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Agitation</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Coma</td>
</tr>
<tr>
<td></td>
<td>Somnolence*</td>
</tr>
<tr>
<td></td>
<td>Speech disorder</td>
</tr>
<tr>
<td></td>
<td>Parosmia</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Visual disturbance</td>
</tr>
<tr>
<td>System Organ Class (MedDRA)</td>
<td>Frequency Not known</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Eye pain</td>
<td></td>
</tr>
<tr>
<td>Lacrimation</td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Hearing impaired</td>
</tr>
<tr>
<td></td>
<td>Ear pain</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac arrest*</td>
</tr>
<tr>
<td></td>
<td>Heart rate decreased/bradycardia*</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Syncope*</td>
</tr>
<tr>
<td></td>
<td>Vasovagal reaction</td>
</tr>
<tr>
<td></td>
<td>Blood pressure increased</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Respiratory distress</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate increased or respiratory rate decreased</td>
</tr>
<tr>
<td></td>
<td>Pulmonary oedema*</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Salivation</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Blood bilirubin increased</td>
</tr>
<tr>
<td></td>
<td>Hepatic enzyme increased</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Nephrogenic Systemic Fibrosis (NSF)*</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>Back pain</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Acute renal failure* ,**</td>
</tr>
<tr>
<td></td>
<td>Increased serum creatinine**</td>
</tr>
<tr>
<td></td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td></td>
<td>Urinary urgency</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Chills</td>
</tr>
<tr>
<td></td>
<td>Sweating</td>
</tr>
<tr>
<td></td>
<td>Body temperature increased or body temperature decreased</td>
</tr>
<tr>
<td></td>
<td>Injection site reactions (e.g. necrosis, thrombophlebitis, phlebitis, inflammation, extravasation)</td>
</tr>
</tbody>
</table>

* Life threatening and/or fatal cases have been reported
** In patients with pre-existing renal impairment

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 observed commonly. These patients had the MRI examination with Magnevist on the day before haemodialysis.

**INTERACTIONS**

No interaction studies with other medicinal products have been conducted.
OVERDOSE
There is currently no information on the clinical consequences of Magnevist overdosage. In case of inadvertent overdose, renal function should be monitored in patients with renal impairment.

Magnevist can be removed from the body by haemodialysis (see Warnings and Precautions).

For information on the management of overdose, contact the Poisons Information Centre on 0800 POISON or 0800 764 766 (New Zealand) for recommendations on the treatment and management of overdosage.

FURTHER INFORMATION

PHARMACOLOGY

Pharmacodynamics

Mechanism of Action
Dimeglumine gadopentetate is a paramagnetic agent and, as such, it develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment produced by the paramagnetic agent results in a relatively large local magnetic field, which can enhance the relaxation rates of water protons in the vicinity of the paramagnetic agent.

In MRI, visualisation of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occur with 1) changes in proton density; 2) alteration of the spinlattice or longitudinal relaxation time (T_1); and 3) variation of the spin-spin or transverse relaxation time (T_2). When placed in a magnetic field, dimeglumine gadopentetate decreases the T_1 and T_2 relaxation time in tissues where it accumulates. At usual doses the effect is primarily on the T_1 relaxation time. Optimal signal enhancement occurs with a dose of 0.1 mmol/kg (0.2 mL/kg).

Pharmacokinetics

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

Dimeglumine gadopentetate does not cross the intact blood-brain barrier and, therefore, does not accumulate in normal brain or in lesions that do not have an abnormal blood-brain barrier, e.g. cysts, mature post-operative scars, etc. However, disruption of the blood-brain barrier or abnormal vascularity allows accumulation of dimeglumine gadopentetate in lesions such as neoplasms, abscesses, subacute infarcts.

The extent of protein binding and blood cell partitioning of dimeglumine gadopentetate is not known.
Metabolism
Dimeglumine gadopentetate is not metabolised.

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

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

Characteristics in Special Patient Populations

Renal Impairment
In patients with impaired renal function, the serum half-life of gadopentetate is prolonged due to the reduced glomerular filtration rate. After administration of a single intravenous dose to 10 patients with impaired renal function (4 patients with mild renal impairment [creatinine clearance ≥ 60 to < 90 mL/min] and 6 patients with moderate renal impairment [creatinine clearance ≥ 30 to < 60 mL/min]), mean half-lives were 2.6 ± 1.2 hours and 4.2 ± 2.0 hours for the mildly and moderately impaired patients, respectively, as compared to 1.6 ± 0.13 hours in healthy subjects. In patients with severe renal impairment (creatinine clearance < 30 mL/min) but not on dialysis, mean half-life further increased to 10.8 ± 6.9 hours.

Gadopentetate is completely renally excreted within two days in patients with slightly to moderately impaired renal function (creatinine clearance > 30 mL/min). In patients with severe renal impairment, 73.3 ±16.1% of the administered dose was recovered in the urine within two days.

In patients with renal impairment gadopentetate can be eliminated by means of hemodialysis. In a clinical study patients with renal impairment received a dose of 0.1 mmol/kg dimeglumine gadopentetate. The patients underwent a 3-hour dialysis session per day on three consecutive days. The plasma concentration of gadopentetate decreased by 70% with each dialysis session. After the last session, the plasma concentration was less than 5% of the original value.

Hepatic Impairment
In line with the almost exclusive renal elimination pathway, pharmacokinetics of gadopentetate were not altered in patients with hepatic impairment (as studied in patients with Child-Pugh B) as compared to healthy matched subjects. Data on patients with severe hepatic impairment (Child-Pugh C) are not available.

Elderly population (aged 65 years and above)
In accordance with the physiological changes in renal function with age, the systemic exposure and terminal half-life were increased from 3.3 mmol•h/L to 4.7 mmol•h/L and from 1.8 h to 2.2 h, respectively, in elderly healthy subjects (males aged 65 years and above) compared to non-elderly healthy subjects (males age range 18-57 years). Total clearance was reduced from 117 mL/ min in non-elderly subjects to 89 mL/min in elderly subjects.
**Paediatric Population**

In a study with paediatric patients aged 2 months to < 2 years the pharmacokinetics (body weight-normalised clearance and distribution volume and terminal half-life) of gadopentetate were similar to adults.

**Gender**

The pharmacokinetics of gadopentetate in non-elderly healthy male and female subjects (aged 18-57 years) were similar.

**OTHER**

Magnevist (dimegulime gadopentetate) solution for intravenous injection is the N-methylglucamine salt of the gadolinium complex of diethylenetriamine pentaacetic acid, and is an injectable contrast medium for magnetic resonance imaging (MRI).

**Chemical structure**

Magnevist Injection is a 0.5 mmol/mL solution of 1-deoxy-1-(methylamino)-D-glucitol dihydrogen \([\text{N,N-bis[2-[bis(carboxymethyl)amino]ethyl]}\text{glycinato-(5-)]gadolinate (2-) (2:1) with a molecular weight of 938 and has the following structural formula:}

![Chemical Structure Diagram]

Dimegulime Gadopentetate (USAN)
Gadopentetate Dimegulime (INN)
Molecular Formula: C_{28}H_{54}GdN_{5}O_{20}
CAS Registry No.: 86050-77-3

The physico-chemical properties of Magnevist are listed below:

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolality (Osm/kg H_{2}O)</td>
<td>1.96</td>
</tr>
<tr>
<td>Viscosity (mPa·s)</td>
<td></td>
</tr>
<tr>
<td>At 20°C</td>
<td>4.9</td>
</tr>
<tr>
<td>At 37°C</td>
<td>2.9</td>
</tr>
<tr>
<td>pH - value</td>
<td>7.0 - 7.9</td>
</tr>
</tbody>
</table>
**Excipients**
Each mL contains 469 mg dimeglumine gadopentetate, meglumine, pentetic acid and water for injections. Magnevist Injection contains no antimicrobial preservative.

**PHARMACEUTICAL PRECAUTIONS**

**Instructions for use and handling**
Parenteral product should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Magnevist should not be used in case of severe discolouration, the occurrence of particulate matter or a defective container.

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

**Vials**
Magnevist should only be drawn into the syringe immediately before use. The rubber stopper should never be pierced more than once.

Any contrast medium solution not used in one examination must be discarded.

**Prefilled Syringes**
The prefilled syringe must be taken from the pack and prepared for the injection immediately before the examination. The tip cap should be removed from the prefilled syringe immediately before use.

Any contrast medium solution not used in one examination must be discarded.

**Large Volume Containers**
In addition, the following applies to use of the infusion bottle containing 100 mL. The contrast medium must only be administered by means of an approved procedure which ensures sterility of the contrast medium. If using a device, instructions of the device manufacturer must be followed.

Unused Magnevist in opened containers must be discarded at the end of the examination day.

**Incompatibilities**
In the absence of compatibility studies, Magnevist Injection must not be mixed with other medicinal products.

**Shelf life**
Glass bottle, vial and prefilled syringe - 5 years
Plastic prefilled syringe – 3 years

**Storage Conditions**
Magnevist injection should be stored at controlled room temperature, at or below 30°C.

Glass prefilled syringe, vial and bottle - Magnevist is sensitive to light when packed in the glass presentations. Keep the container in the outer carton to protect from light. Avoid exposure to secondary X-rays. Do not freeze.

Plastic prefilled syringe - Protect from secondary X-rays and do not freeze.
PACKAGE QUANTITIES

Magnevist is registered as:
- 15 mL and 20 mL glass vials, packs of 1
- 10 mL and 30 mL glass vials, packs of 1 or 10
- 100 mL glass bottles, packs of 1
- 10 mL, 15 mL and 20 mL prefilled glass syringes, packs of 5
- 10 mL and 15 mL prefilled plastic syringes, packs of 5

Not all pack sizes are marketed.

MEDICINE SCHEDULE

General Sales Medicine

SPONSOR DETAILS

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Hillcrest, North Shore
Auckland 0627
Free phone 0800 233 988

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