

Data Sheet

MAGNEVIST[®]

Solution for Intravenous Injection

Gadopentetic acid, dimeglumine salt 0.5 mmol/mL

Qualitative and Quantitative Composition

1 mL solution for injection or infusion contains 469 mg (0.5 mmol) gadopentetic acid, dimeglumine salt.

For excipients, see Pharmaceutical Particulars.

Pharmaceutical Form

Solution for injection or infusion.

Clinical Particulars

Therapeutic 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 Method of Administration

General Information

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 magnetic resonance imaging 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.

Between 0.14 Tesla and 1.5 Tesla the recommendations for the use of Magnevist apply, regardless of the field strength of the magnet. T 1 –weighted scanning sequences are particularly suitable for contrast - enhanced examinations.

Magnevist is to be administered strictly by intravenous injection according to the instructions provided in Instructions for use/handling. Contrast-enhanced MRI can be commenced immediately afterwards.

In newborns (< 1 month) and infants (1 month – 2 years) the required dose should be administered by hand.

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

Cranial and Spinal MRI

Adults, adolescents and children (including newborns and babies)

In general, the administration of 0.2 mL Magnevist/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 0.2 or, in adults, of even 0.4 mL Magnevist/kg body weight within 30 minutes with MRI following immediately may increase the diagnostic yield of the examination.

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

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

Whole Body MRI

Adults, adolescents and children

In general, the administration of 0.2 mL Magnevist/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 0.4 mL Magnevist/kg body weight may be necessary for an adequate contrast effect especially on use of relatively slightly T 1 -weighted scanning sequences.

In cases of exclusion of a lesion or tumour recurrences in adults, the injection of 0.6 mL Magnevist/kg body weight may lead to higher diagnostic confidence.

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

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

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

Instructions for use/handling

Parental product should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

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.

Contraindications

Magnevist should not be administered to patients with known sensitivity to dimeglumine gadopentetate, or any of the ingredients listed in Pharmaceutical Particulars.

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); and
- Patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the peri-operative liver transplantation period.

Special Warnings and Special Precautions for Use

Special Warnings

Hypersensitivity

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

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 (see Undesirable Effects).

As with other contrast enhanced diagnostic procedures, post-procedure observation of the patient is recommended.

Medication for the treatment of hypersensitivity reactions as well as preparedness for institution of emergency measures are necessary.

The risk of hypersensitivity reactions is higher in case of:

- previous reaction to contrast media
- history of bronchial asthma
- history of allergic disorders

Therefore, before any contrast medium is injected, the patient should be questioned for a history of allergy (e.g. seafood allergy, hay fever, hives), sensitivity to contrast media and bronchial asthma and premedication with antihistamines and/or glucocorticoids may be considered.

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

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

Special Precautions

Impaired Renal Function

The benefits must be weighed very carefully against the risks in patients with severely 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 use of dimeglumine gadopentetate and some other gadolinium-containing contrast agents in patients with severe renal impairment (GFR < 30 mL/min/1.73m²) and those who have had or are undergoing liver transplantation. Therefore Magnevist should not be used in patients with acute or chronic severe renal insufficiency, 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.

When administering Magnevist (dimeglumine gadopentetate) injection, do not exceed the dose recommended. Allow sufficient time for elimination of the gadolinium-containing contrast agent prior to any re-administration.

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

Magnevist can be removed from the body by haemodialysis. 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.

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. 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.

Newborns and Infants

In newborns and infants the required dose should be administered by hand.

Interaction with Other Medicaments and Other Forms of Interaction

No known interactions with other medicaments.

Interference with Diagnostic Tests

The result of serum iron determination employing methods measuring complexes (e.g. bathophenanthroline) within 24 hours of Magnevist examination may result in inaccurately low values due to the free DTPA contained in the contrast medium formulation.

Pregnancy and Lactation

Pregnancy

For gadopentetic acid, dimeglumine salt no clinical study data on exposed pregnancies are available.

Animal studies do not indicate a teratogenic or other embryotoxic potential following administration of Magnevist during pregnancy.

It has not yet been demonstrated that Magnevist is safe to use during pregnancy. Magnevist should only be used in pregnant women after a clear benefit-to-risk analysis.

Lactation

Minimal amounts of gadopentetic acid, dimeglumine salt (a maximum of 0.04% of the administered dose) enter the breast milk. From experience gained so far, harm to the breast-fed infant is not likely.

Effects on Ability to Drive or Use Machines

Not known.

Undesirable Effects

Adverse reactions with the use of Magnevist are usually mild to moderate and transient in nature. The most frequently reported adverse reactions are nausea, vomiting, headache, dizziness, and injection site reactions (e.g. pain, coldness, warmth).

Severe and life-threatening reactions as well as deaths have been reported.

Delayed contrast medium reactions are rare (see Special Warnings).

Frequency of adverse reactions from clinical trial data:

No individual adverse reaction reached a frequency greater than "uncommon".

Based on experience in more than 11,000 patients, the following undesirable effects have been observed and classified by investigators as medicine-related .

The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs).

System Organ Class	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Psychiatric disorders		Disorientation
Nervous system disorders	Dizziness Headache Dysgeusia	Convulsion Paraesthesia Burning sensation Tremor
Eye disorders		Conjunctivitis
Cardiac disorders		Tachycardia Arrhythmia
Vascular disorders		Thrombophlebitis Flushing Vasodilatation
Respiratory, thoracic and mediastinal disorders		Dyspnoea Throat irritation/throat tightness Pharyngolaryngeal pain/pharynx discomfort Cough Sneezing Wheezing
Gastrointestinal disorders	Vomiting Nausea	Abdominal pain Stomach discomfort Diarrhoea Toothache Dry mouth Oral soft tissue pain and paraesthesia
Skin and subcutaneous tissue		Urticaria Pruritus Rash

System Organ Class	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
disorders		Erythema
Musculoskeletal disorders		Pain in extremity
General disorders and administration site conditions	Pain Feeling hot Feeling cold Various kinds of injection site reactions*	Oedema face Chest pain Pyrexia Oedema peripheral Malaise Fatigue Thirst Asthenia

* Various kinds of injection site reactions (injection site coldness, injection site paraesthesia, injection site swelling, injection site warmth, injection site pain, injection site oedema, injection site irritation, injection site haemorrhage, injection site erythema, injection site discomfort)

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Additional adverse reactions from post-approval (spontaneous reporting) data:

System Organ Class	Rare (< 1/1,000)
Blood and lymphatic system disorders	Iron serum increased
Immune system disorders	Anaphylactoid shock/Anaphylactoid reactions Hypersensitivity reactions
Psychiatric disorders	Agitation Confusion
Nervous system disorders	Coma Loss of consciousness Somnolence Speech disorder Parosmia
Eye disorders	Visual disturbance Eye pain Lacrimation
Ear and labyrinth disorders	Hearing impaired Ear pain
Cardiac disorders	Cardiac arrest Heart rate decreased Reflex tachycardia
Vascular disorders	Shock Syncope

System Organ Class	Rare (< 1/1,000)
	Vasovagal reaction Hypotension Blood pressure increased
Respiratory, thoracic and mediastinal disorders	Respiratory arrest Respiratory distress Respiratory rate increased or respiratory rate decreased Bronchospasm Laryngospasm Laryngeal oedema Pharyngeal oedema Pulmonary oedema Cyanosis Rhinitis
Gastrointestinal disorders	Salivation
Hepatobiliary disorders	Blood bilirubin increased Hepatic enzyme increased
Skin and subcutaneous tissue disorders	Angioedema
Musculoskeletal and connective tissue disorders	Back pain Arthralgia
Renal and urinary disorders	Acute renal failure* Increased serum creatinine* Urinary incontinence Urinary urgency
General disorders and administration site conditions	Chills Sweating Body temperature increased or body temperature decreased Various kinds of injection site reactions**

* in patients with preexisting renal impairment

** Various kinds of Injection site reactions (injection site necrosis, injection site thrombophlebitis, injection site phlebitis, injection site inflammation, injection site extravasation)

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 haemodialysis.

Cases of nephrogenic systemic fibrosis (NSF) have been reported.

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Overdose

No signs of intoxication secondary to an overdose have so far been observed or reported on clinical use.

Accidental overdose may cause the following effects due to the hyperosmolality of Magnevist: increase of pulmonary artery pressure, osmotic diuresis, hypervolaemia, and dehydration.

Renal function should be monitored in patients with renal impairment.

On inadvertent overdosage or in greatly limited renal function, Magnevist can be removed from the body by haemodialysis.

Pharmacological Properties

Pharmacodynamic Properties

Magnevist is a paramagnetic contrast agent for magnetic resonance imaging. The contrast-enhancing effect is mediated by the di-N-methylglucamine salt of gadopentetic acid, dimeglumine - the gadolinium complex of pentetic acid (diethylene triamine pentaacetic acid = DTPA). When a suitable scanning sequence (e.g. T₁-weighted spin-echo technique) is used in proton magnetic resonance imaging, the gadolinium ion-induced shortening of the spin-lattice relaxation time of excited atomic nuclei leads to an increase of the signal intensity and, hence, to an increase of the image contrast of certain tissues.

Gadopentetic acid, dimeglumine is a highly paramagnetic compound which leads to distinct shortening of the relaxation times even at low concentrations. The paramagnetic efficacy, the relaxivity - determined from the influence on the spin-lattice relaxation time of protons in plasma - is about 4.95 l/mmol/sec and displays only slight dependency on the strength of the magnetic field.

DTPA forms a firm complex with the paramagnetic gadolinium ion with extremely high *in-vivo* and *in-vitro* stability (log K = 22 - 23). The dimeglumine salt of gadopentetic acid, dimeglumine is a highly water-soluble, extremely hydrophilic compound with a distribution coefficient between n-butanol and buffer at pH 7.6 of about 0.0001. The substance does not display any particular protein binding¹ or inhibitory interaction with enzymes (e.g. myocardial Na⁺ and K⁺ ATPase). Magnevist does not activate the complement system and, therefore, probably has a very low potential for inducing anaphylactoid reactions.

At higher concentrations and on prolonged incubation, gadopentetic acid, dimeglumine has a slight *in-vitro* effect on erythrocyte morphology. After intravenous administration of Magnevist in man, the reversible process could lead to weak intravascular haemolysis, which might explain the slight increase in serum bilirubin and iron occasionally observed in the first few hours after injection.

The physico-chemical properties of the 0.5 mmol/mL solution Magnevist listed below are:

Magnevist 0.5 mmol/mL	
Contrast medium concentration (mg/mL)	469
Osmolality (Osm/kg H ₂ O) At 37°C	1.96

Viscosity (mPa-s) At 20°C At 37°C	4.9 2.9
Density (g/mL) At 20°C At 37°C	1.210 1.195
pH - value	7.0 - 7.9

Pharmacokinetic Properties

Gadopentetic acid, dimeglumine behaves in the organism like other highly hydrophilic biologically inert compounds (e.g. mannitol or inulin).

The pharmacokinetics observed in man were dose-independent.

Distribution

After intravenous administration, the compound quickly diffuses in the extracellular space. Up to 0.25 mmol gadopentetic acid, dimeglumine/kg body weight (0.5 mL Magnevist/kg), the plasma level fell after an early distribution phase lasting a few minutes with a half-life of about 90 minutes, identical to the renal elimination rate. At a dose of 0.1 mmol gadopentetic acid, dimeglumine/kg (0.2 mL Magnevist/kg body weight), 0.6 mmol gadopentetic acid, dimeglumine/L plasma were measured 3 minutes after the injection and 0.24 mmol gadopentetic acid, dimeglumine/L plasma 60 minutes post injection.

Seven days after intravenous administration of radioactively labeled gadopentetic acid, dimeglumine, distinctly less than 1 % of the dose administered was found in the rest of the body of both the rat and the dog. The relatively highest concentrations of the compound were found in the kidneys in the form of the intact gadolinium complex.

The compound penetrates and passes neither an intact blood-brain nor the blood-testis barrier. The slight amount which overcomes the placental barrier is quickly eliminated by the foetus.

Metabolism

No cleavage of the paramagnetic ion or metabolic break-down was demonstrable.

Elimination

Gadopentetic acid, dimeglumine is eliminated in unchanged form via the kidneys by glomerular filtration. The portion eliminated extrarenally is extremely small.

An average of 83 % of the dose was eliminated via the kidneys by 6 hours p.i. About 91 % of the dose was recovered in the urine within the first 24 hours. By the 5th day after the injection the dose eliminated with the faeces was less than 1 %. The renal clearance of gadopentetic acid, dimeglumine referred to 1.73 m² was about 120 mL/min and is therefore comparable to that of inulin or ⁵¹Cr-EDTA.

Characteristics in Patients

Gadopentetic acid, dimeglumine is completely eliminated via the kidneys even in the presence of impaired renal function (creatinine clearance > 20 mL/min); the plasma half-life

increases in relation to the degree of renal insufficiency, an increase in the extrarenal elimination was not observed.

Because the serum half-life is prolonged (up to 30 hours) in the presence of greatly impaired renal function (creatinine clearance < 20 mL/min), gadopentetic acid, dimeglumine could be eliminated by means of extracorporeal haemodialysis.

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, systemic toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

Systemic Toxicity

Experimental systemic tolerance studies following repeated daily intravenous administration produced no findings which object to a single diagnostic administration of Magnevist to humans.

On the basis of the results of the acute toxicity studies, a risk of acute intoxication is highly unlikely on use of Magnevist in adults.

Genotoxicity, Tumourigenicity

Studies into genotoxic effects (gene, chromosomal and genome mutation tests) of gadopentetic acid, dimeglumine in vivo and in vitro gave no indication of a mutagenic potential.

In a tumourigenicity study with Magnevist in rats no compound-related tumours could be observed. Due to this fact, the absence of genotoxic effects and taking into account the pharmacokinetics and the absence of indications of toxic effects on fast-growing tissues as well as the fact that Magnevist was only administered once, there is no evident risk of a tumourigenic effect on humans.

Reproduction Toxicity

Reproduction-toxicological studies in animals gave no indication of a teratogenic or other embryotoxic potential following an administration of Magnevist during pregnancy.

Local Tolerance and Contact-sensitizing Potential

Experimental local tolerance studies with Magnevist following single as well as repeated intravenous administration and single intraarterial administration gave no indication that adverse local effects are to be expected in blood vessels of humans. Experimental local tolerance studies following a single paravenous, subcutaneous as well as intramuscular administration indicated that slight local intolerance reactions could occur at the injection site after inadvertent paravenous administration.

Studies into contact-sensitizing effect gave no indication of a sensitizing potential of Magnevist.

Pharmaceutical Particulars

Presentation

Magnevist injection is a clear, colourless to slightly yellow solution containing 469 mg/mL of dimeglumine gadopentetate.

List of Excipients

meglumine
pentetic acid
water for injections

Incompatibilities

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

Storage Conditions

Magnevist injection should be stored at controlled room temperature, at or below 30°C and protected from light. Avoid exposure to secondary X-rays. DO NOT FREEZE.

Nature and contents of container

Vials of 5 mL, 10 mL, 15 mL, 20 mL, 30 mL
Bottles of 100 mL for use with an automatic injector
Prefilled syringes of 10 mL, 15 mL, 20 mL

Not all presentations are marketed.

Medicine Classification

General Sales Medicine

Name and Address

Bayer New Zealand Limited
3 Argus Place
Hillcrest
North Shore
Auckland 0627

Free phone 0800 233 988

Date of Preparation

4 September 2007

Ref: Magnevist Labelling Monograph dated 5 June 2007 and Australian Product Information dated 31 July 2007

