1.NAME OF THE MEDICINAL PRODUCT

Magnevist 0.5 mmol per ml solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 0.5 mmol gadopentetate dimeglumine (equivalent to 469.01 mg gadopentetate dimeglumine) as active ingredient.

For full list of excipients, see section ‘List of excipients’.

3. PHARMACEUTICAL FORM
Solution for injection.

Clear, colourless to pale yellow solution.
The physio-chemical properties of Magnevist listed below are:

Osmolarity at 37 ºC (osm/l solution)		1.44
Osmolality at 37 ºC (osm/kg H_2O)		1.96
Osmot. pressure at 37 ºC	(atm)	49.8
	(mPa)	5.06
Viscosity (mPa · s or cP)	at 20 ºC	4.9
	at 37 ºC	2.9
pH		7.0-7.9

4. CLINICAL PARTICULARS

4.1 Indication(s)

This medicinal product is for diagnostic use 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.

In particular, Magnevist permits diagnostic information:

- For the demonstration or exclusion of tumours, inflammations 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.

4.2 Dosage and method of administration

4.2.1 Method of administration

This medicinal product is for intravenous administration only.

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

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

For additional instructions see section ‘Instructions for use/handling’.

4.2.2 Dosage regimen

Adults
• Cranial and spinal MRI

In general, the administration of 0.2 ml Magnevist per kg body weight (equivalent to 0.1 mmol gadopentetate dimeglumine per 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 per kg body weight within 30 minutes with immediately following MRI 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 per kg body weight often leads to higher diagnostic confidence.

Maximum single dose: 0.6 ml Magnevist per kg body weight.

• Whole body MRI

In general, the administration of 0.2 ml Magnevist per kg body weight is sufficient for good enhancement and to answer the clinical question.

In special cases, e. g. in lesions with poor vascularization and/or a small extracellular space, the administration of 0.4 ml Magnevist per kg body weight may be necessary for

an adequate contrast effect especially on use of relatively slightly T¡-weighted scanning sequences.

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

Maximum single dose: 0.6ml Magnevist per kg body weight.

4.2.3 Additional information on special populations

4.2.3.1 Pediatric population

- Cranial and spinal MRI

Children: 0.2ml Magnevist per kg body weight.

Due to immature renal function in infants up to 1 year of age, Magnevist should only be used in these patients after careful consideration at a dose not exceeding 0.2 ml/kg body weight. More than one dose should not be used during a scan. 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.

If a strong clinical suspicion of a lesion persists despite a normal scan in patients over 1 year of age, a further injection of 0.2ml Magnevist /kg body weight within 30 minutes may increase the diagnostic yield.

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

- Whole body MRI

Children over 2 years of age: 0.2 ml Magnevist per kg body weight.

Maxmum single dose: 0.4ml Magnevist per kg body weight.

Experience in children under the age of 2 years is limited. However, this limited experience has shown that 0.2ml Magnevist/kg body weight may be used in this particular age group. Due to immature renal function in infants up to 1 year of age, Magnevist should only be used in these patients after careful consideration at a dose not exceeding 0.2ml/kg body weight. More than one dose should not be used during a scan. 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.

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

4.2.3.2 Elderly population (aged 65 years and above)

No dosage adjustment is considered necessary in elderly (aged 65 years and above). Caution should be exercised in elderly patients (see also section ‘Pharmacokinetic properties’).

4.2.3.3 Patient with 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 also section 'Pharmacokinetic properties').

4.2.3.4 Patient with renal impairment

Magnevist is contraindicated in patients with severe renal impairment (GFR <30 ml/min/ 1.73 m^2) and in patients in the perioperative liver transplantation period (see section 4.3). Magnevist should only be used after careful risk/benefit evaluation in patients with moderate renal impairment (GFR 30-59 ml/ min/ 1.73m^2) at a dose not exceeding 0.2 ml/kg body weight. More than one dose should not be used during a scan. 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 (see "Special Warnings and Precautions for use").

4.3 Contraindications

Use of Magnevist is contraindicated in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2) and in patients in the perioperative liver transplantation period.

4.4 Special warnings and precautions for use

- Hypersensitivity

Particularly careful risk-benefit assessment in patients with known hypersensitivity to Magnevist or any of its ingredients.

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.

The risk of hypersensitivity reactions is higher in case of:

- Previous reaction to contrast media
- History of bronchial asthma
- History of allergic disorder

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.

Most of these reactions occur within at least half an hour of administration. Therefore, post-procedure observation of the patient is recommended.

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

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

Delayed reactions after hours up to several days have been rarely observed (see section ‘Undesirable effects’).

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 or even fatal outcomes of severe hypersensitivity reactions.

- Impaired renal function

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

Magnevist must not be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period.

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 Magnevist.

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 also section ‘Pharmacokinetic properties’).

Magnevist can be removed from the body by hemodialysis.

After 3 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.

There is no evidence to support the initiation of hemodialysis for prevention or treatment of NSF in patients not already undergoing hemodialysis.

There have been reports of nephrogenic systemic fibrosis (NSF) including nephrogenic fibrosing dermapathy (NFD) associated with the use of contrast agents containing gadolinium including Magnevist in patients with

-Acute or chronic severe renal impairment (GFR < 30 ml/min/1.73m^2)
-Acute renal insufficiency of any severity due to the hepatic-renal syndrome or in the perioperative liver transplantation period.

Therefore Magnevist must not be used in patients with severe renal impairment and in

patients in the perioperative liver transplantation period.

The risk for the development of NSF in patients with moderate renal impairment is unknown; therefore Magnevist should be used with caution in patients with moderate renal impairment (GFR 30-59 ml/min/1.73m^2).

Due to immature renal function in infants up to 1 year of age, Magnevist should only be used in these patients after careful consideration.

- Seizure disorders

Patients with seizures disorders or intracranial lesions may be at increased risk of seizure activity as has been reported rarely in association with Magnevist administration (see section 'Undesirable effects').

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

- Accumulation of gadolinium in the brain

The current evidence suggests that gadolinium may accumulate in the brain after multiple administrations of gadolinium-based contrast agents (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. In order to minimise 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.

4.5 Interaction with other medicaments and other forms of interaction

No interaction studies with other medicinal products have been conducted.

- Interference with diagnostic tests

Serum iron determinations using methods measuring complexes (e.g. bathophenanthroline) may result in falsely low values for up to 24 hours after the administration of Magnevist because of the free DTPA contained in Magnevist.

4.6 Pregnancy and lactation

4.6.1 Pregnancy

Adequate and well controlled studies with gadopentetate were not conducted in pregnant women.

The safe use of Magnevist during pregnancy has not yet been demonstrated. Magnevist

should only be used in pregnant woman after a clear benefit-to-risk ratio.

Animal studies at clinically relevant doses have not shown reproductive toxicity after repeated administration (see section 'Preclinical safety data').
The potential risk for humans is unknown.

4.6.2 Lactation

Minimal amounts of gadopentetate (a maximum of 0.04% of the dose administered intravenously) enter the human breast milk. There is evidence from non-clinical data that the absorption via the gastrointestinal tract is poor with about 4% (see section 'Pharmacokinetic properties').

From experience gained so far, harm to the nursing infant is not likely, nonetheless, caution should be exercised when Magnevist is administered to a nursing woman.

4.7 Effects on ability to drive or use machines

Not known.

4.8 Undesirable effects

4.8.1 Summary of the safety profile

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

The most frequent observed adverse drug reactions (≥ 0.4%) in patients receiving Magnevist in clinical trials are

- Various injection site reactions
- Headache
- Nausea

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

Overall, the most serious adverse drug reaction 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 'Special warnings and special precautions for use'). Severe and life-threatening reactions as well as deaths have been reported.

4.8.2 Tabulated list of adverse reactions

The adverse drug reactions observed with Magnevist are represented in the table below. 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: uncommon:
≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000. The adverse drug reactions identified only during post-marketing surveillance, and for which a frequency could not be

estimated, are listed under ‘not known’.

Table 1: Adverse drug reactions reported in clinical trials or during post-marketing surveillance in patients treated with Magnevist.

System Organ Class (MedDRA)	Uncommon	Rare	Not known
Blood and lymphatic system disorders			Serum iron increased*
Immune system disorders		Hypersensitivity /anaphylactoid reaction(e.g. anaphylactoid shock*, anaphylactoid reaction[α]*,	
		Hypersensitivity reactions [α]*, Shock [α]*, Hypotension [α]*, Conjunctivitis, Loss of consciousness [α]* Throat tightness*, Sneezing, Urticaria, Pruritus, Rash, Erythema, Dyspnea*, Respiratory arrest[α]*, Bronchospasm [α]*, Wheezing, Laryngospasm [α]*, Laryngeal edema [α]*, Pharyngeal edema [α]*, Cyanosis [α]*, Rhinitis [α], Angioedema [α]*, Edema face*, Reflex tachycardia [α]	
Psychiatric disorders		Disorientation	Agitation Confusion
Nervous system disorders	Dizziness Headache Dysgeusia	Convulsion* Paresthesia Burning sensation Tremor	Coma* Somnolence* Speech disorder Parosmia
Eye disorders			Visual disturbance Eye pain Lacrimation
Ear and labyrinth disorders			Hearing impaired Ear pain

Cardiac disorders		Tachycardia* Arrhythmia	Cardiac arrest* Heart rate decreased/ bradycardia*
Vascular disorders		Thrombophlebitis Flushing Vasodilatation	Syncope* Vasovagal reaction Blood pressure increased
Respiratory, thoracic and mediastinal disorders		Throat irritation Pharyngolaryngeal pain/ Pharynx discomfort Cough	Respiratory distress Respiratory rate increased or Respiratory rate decreased Pulmonary edema*
Gastrointestinal disorders	Vomiting Nausea	Abdominal pain Stomach discomfort Diarrhea Toothache Dry mouth Oral soft tissue pain and paresthesia	Salivation
Hepatobiliary disorders			Blood bilirubin increased Hepatic enzyme increased
Skin and subcutaneous tissue disorders			Nephrogenic Systemic Fibrosis (NSF)
Musculoskeletal and connective tissue disorders		Pain in extremity	Back pain Arthralgia
Renal and urinary disorders			Acute renal failure*,** Increased serum creatinine** Urinary incontinence Urinary urgency

General disorders and administration site conditions	Pain Feeling hot Feeling cold Injection site reactions(e.g. Injection site coldness, paresthesia, swelling, warmth, pain, edema, irritation, hemorrhage, erythema, discomfort, necrosis [α], thrombophlebitis [α], phlebitis [α], inflammation [α], extravasation [α]	Chest pain Pyrexia Edema peripheral Malaise Fatigue Thirst Asthenia	Chills Sweating Body temperature increased or Body temperature decreased

* Life-threating and/or fatal cases have been reported

** In patients with pre-existing renal impairment

α Reactions identified only during post-marketing surveillance (frequency not known)

4.8.3 Description of selected adverse reactions

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.

4.9 Overdose

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

In case of inadvertent overdose, renal function should be monitored in patients with renal impairment.

Magnevist can be removed from the body by hemodialysis (see section ‘Special warnings and special precautions for use’).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: paramagnetic contrast media
ATC code: V08CA01

Mechanism of action

Magnevist is a paramagnetic contrast agent for magnetic resonance imaging.

When T_1-weighted scanning sequences are used in proton magnetic resonance imaging, the gadopentetate-induced shortening of the spin lattice relaxation time(T1) of excited water protons leads to an increase of the signal intensity and, hence, to an increase of the image contrast of certain tissues.

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

Pharmacodynamic effects

Gadopentetate is a highly paramagnetic compound which leads to distinct shortening of the relaxation times even at low concentrations. The paramagnetic efficacy at a magnetic field strength of 1.5T and 37°C, the relaxivity (r_1) – determined from the influence on the T1 relaxation time of the water protons in plasma and the relaxivity (r_2)- determined from the influence on the T2 relaxation time- is about 4.1 ± 0.2l/ (mmol.sec) and 4.6 ±0.8 l/(mmol.sec) respectively. The relaxivities display only slight dependency on the strength of the magnetic field.

Diethylene triamine pentaacetic acid (DPTA) forms a complex with the paramagnetic gadolinium ion with high *in-vivo* and *in-vitro* stability (thermodynamic stability constant: log K_{GdL} = 22-23). Gadopentetate dimeglumine is a highly water-soluble, hydrophilic compound with a partition coefficient between n-butanol and buffer at pH 7.6 of about 0.0001. The substance does not display significant inhibitory interaction with enzymes e.g. acetylcholinesterase and lysozyme at clinically relevant concentrations.

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, gadopentetate 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 hemolysis, which might explain the slight increase in serum bilirubin and iron occasionally observed in the first few hours after injection.

5.2 Pharmacokinetic properties

General introduction

Gadopentetate behaves in the organism like any other highly hydrophilic biologically inert compounds (e.g. mannitol or inulin).

Absorption and distribution

After intravenous administration of Magnevist, plasma levels decline rapidly bi-exponentially with a terminal half-life of about 90 minutes.

Gadopentetate is rapidly distributed in the extracellular space.

The total distribution volume of gadopentetate is about 0.26 L /kg. Protein binding is negligible.

In studies in rats and dogs, relatively high concentrations of the intact gadolinium complex were found in the kidneys amounting to about 0.15% of administered dose seven days after intravenous administration of radioactively labeled gadopentetate. Less than 1% of the administered dose was found in the remaining parts of the body of both.

Gadopentetate does not penetrate or pass the blood-testis barrier. The small amount which overcomes the placental barrier is quickly eliminated by the fetus.

In lactating women (aged 23-38 years), less than 0.04% of administered gadopentetate is excreted into human breast milk. In rats, absorption from the gastrointestinal tract after oral administration was found to be small with about 4%

Metabolism

Gadopentetate is not metabolized.

Elimination

Gadopentetate is eliminated in unchanged form via the kidneys by glomerular filtration. The fraction eliminated extra-renally is less than 1% of the administered dose.

An average of 83% of the dose was eliminated within 6 hours post-injection. About 91% of the dose was recovered in the urine within the first 24 hours. The renal clearance of gadopentetate was about 120 ml/min/1.73 m^2 and is therefore comparable to substances that are exclusively excreted by glomerular filtration (e.g. inulin or Cr-EDTA).

Linearity/non-linearity

The pharmacokinetics of gadopentatete dimeglumine in humans were dose-proportional and dose-independent, respectively. Gadoxetate disodium shows linear pharmacokinetics, i.e. pharmacokinetic parameters change dose proportionally (e.g. C_{max}, AUC) or are dose independent (e.g. V_{ss}, $t_{1/2}$), between the doses of 0.1 and 0.25 mmol/kg).

Characteristics in special patient populations

A phase I study with 0.3 mmol Magnevist per kg body weight compared subjects with moderate hepatic impairment, healthy matched subjects, healthy non-elderly males and females, and healthy elderly subjects.

A phase II study of 0.1 mmol Magnevist per kg body weight compared subjects with various levels of impaired renal function with healthy subjects.

- 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.

- Gender

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

- 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.

- 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 could be eliminated by means of hemodialysis. In a clinical study, patients with renal impairment received a dose of 0.1 mmol per kg gadopentetate dimeglumine. 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.

- Pediatric population

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

5.3 Preclinical safety data

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

- 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.

- Genotoxicity, tumorigenicity

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

In a tumorigenicity 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

Repeated intravenous dosing in reproductive toxicology studies caused retardation of fetal development at a dose of 0.75 mmol per kg (rabbits) and 1.25 mmol per kg (rats) and being 2 to 2.4 times (based on body surface area) or 7.5 to 12.5 times (based on body weight) above the standard single diagnostic dose in humans.

Magnevist was not embryotoxic in rats and rabbits when given repeatedly during organogenesis at doses of 0.25 mmol per kg (rabbits) or 0.75 mmol per kg(rats) being 2.5 or 7.5 times(based on body weight) above the standard single diagnostic dose in humans.

Magnevist was not teratogenic in rats and rabbits when given repeatedly during organogenesis at maximum tested dose levels of 3 mmol per kg (rabbits) or 4.5 mmol per kg (rats) being 9.7 or 7.3 times (based on body surface area) or 30 to 45 times (based on body weight) above the standard single diagnostic dose in humans.

Daily intravenous injections of Magnevist over 16 to 18 days cause spermatogenic cell atrophy / degeneration in male rats at a dose of 5 mmol per kg being 8 times (based on body surface area) or 50 times (based on body weight) above the standard single diagnostic dose in humans. This atrophy was not reversible. Spermatogenesis was not affected in rats and dogs at a dose of 2.5 mmol per kg given repeatedly over 4 weeks.

- Local tolerance and contact-sensitizing potential

Experimental local tolerance studies with Magnevist following a single paravenous, subcutaneous as well as intramuscular application indicated that slight local intolerance reactions could occur at the administration site after inadvertent paravenous administration.

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

6.1 List of excipients
Meglumine
Diethylenetriamine pentaacetic acid
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

Please refer to labels.

6.4 Special precautions for storage

Magnevist is sensitive to light. Keep the container in the outer carton in order to protect from light.

6.5 Instructions for use/handling

Visual inspection

This medicinal product should be visually inspected before use.
Magnevist should not be used in case of severe discolouration, the occurrence of particulate matter or a defective container.

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.

Pre-filled syringes

The pre-filled syringe must be taken from the pack and prepared for the injection immediately before the examination.
The tip cap should be removed from the pre-filled 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 the use of the bottle containing 50 or 100ml:

The contrast medium must only be administered by means of an automatic injector, or by other approved procedure which ensures sterility of the contrast medium. Instructions of the device manufacturer must be followed.

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

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

6.6 Presentation

Vial of 5, 10, 15, 20, 30 ml
Bottle
Pre-filled syringe
Not all presentations may be available locally.

6.7 Manufactured by
Bayer AG
Müllerstraße 178
13353 Berlin
Germany

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