Magnevist® 0.5 mmol/ml

Solution for Injection
Gadopentetate dimeglumine

PROFESSIONAL USER'S INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Magnevist 0.5 mmol/ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml aqueous injection solution contains 469.01 mg of gadopentetate dimeglumine (corresponding to 0.5 mmol of gadopentetate dimeglumine, corresponding to 78.63 mg of gadolinium). For the complete listing of excipients, see Section 6.1.

Concentration of gadopentetate dimeglumine		
	(mg/ml)	469.01
	(mmol/ml)	0.5
Content of gadopentetate dimeglumine in (g)		
5-ml vial		2.3
Vial/ready-to-use syringe	with 10 ml	4.7
Vial/ready-to-use syringe	with 15 ml	7.0
Vial/ready-to-use syringe	with 20 ml	9.4
Vial	with 30 ml	14.1
Bottle	with 100 ml	46.9

3. DOSAGE FORM

Injection solution.

Clear, particle-free.

Physicochemical and/or physical properties:

pH		7.0 -7.9
Viscosity (mPa•s or cP)		
	at 20°C	4.9
	at 37°C	2.9
Osmolality		
	(mOsm/kg H2O)	1960
Specific gravity (g/ml)		
	at 20°C	1.210
	at 37°C	1.195

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

This drug is a diagnostic agent for intravenous application.

Intravenous injection of Magnevist provides more conclusive diagnostic information compared with a scan obtained without contrast medium (plain scan). With Magnevist, high-contrast images can be obtained of areas of the brain in which the blood-brain barrier is impaired or absent or of body regions with an altered blood supply (perfusion) or altered extracellular spaces.

Cranial and spinal magnetic resonance tomography (MRT)

In particular for tumour detection and for other differential diagnostics clarification when there is suspicion of

- ▷ meningioma,
- ▷ (acoustic) neurinoma,
- ▷ tumours with infiltrative growth (e.g. glioma) and metastases.

- ▶ For verification of small and/or isointensive tumours,
- ▶ where there is suspicion of recurrence following operations or radiation therapy,
- ▶ for differentiated presentation of rare neoplasias such as hemangioblastomas, ependymomas and small pituitary adenomas,
- ▶ for improved determination of the extent of a tumour in the case of tumours not arising in the brain.

Additionally with spinal MRT:

- ▶ Differentiation between intramedullar and extramedullar tumours
- ▶ Verification of solid tumour parts with known syrinx
- ▶ Determination of intramedullar tumour expansion.

Whole body MRI

Use of Magnevist is recommended in tumour diagnostics particularly

- ▶ for better distinction between malignant and benign tumours of the female breast,
- ▶ to distinguish between tumour and scar tissue after treatment of tumours of the female breast,
- ▶ to distinguish between tumour and scar tissue of the active and passive musculoskeletal system,
- ▶ for differentiating between different portions of tumours of the bone (tumour tissue, decay tissue and inflammatory tissue),
- ▶ to distinguish between different types of liver tumours,
- ▶ to distinguish between tumours located within and outside the kidneys,
- ▶ for determination of the expansion and differentiation of different portions of tumours of the female adnexa.

In addition, the use of Magnevist is recommended for the following special problems:

- ▶ for the depiction of the vessels (angiography) throughout the entire body (except for coronary arteries), particularly for assessment with respect to stenoses, occlusions and collaterals,
- ▶ for carrying out precisely targeted tissue sampling (biopsies) with tumours of the bone,
- ▶ for differentiating between relapses of disc prolapses and scar tissue,
- ▶ for visualisation of acutely damaged heart muscle tissue.

4.2 Posology and method of administration

General information

The usual precautions for magnetic resonance imaging (MRI), e.g. exclusion of cardiac pacemakers and ferromagnetic implants, must be observed.

Between 0.14 Tesla and 1.5 Tesla, the recommended doses are independent of the field strength of the magnet.

The required dose of Magnevist is to be administered by intravenous injection only; it can also be given as bolus injection. Please observe in this connection the «Instructions for handling» in this Section. Contrast-enhanced MRI can start immediately after administration.

The contrast medium should be administered with the patient lying down, if possible, and the patient should be kept under supervision after the administration, as the majority of adverse reactions occur within 30 minutes.

▷ Dietary recommendations

Known undesirable effects of all MR contrast media are queasiness and vomiting. The patient should

therefore not eat anything within two hours prior to the examination in order to avoid any aspiration.

▷ Anxiety

Marked agitation, restlessness and pain can increase the risk of adverse reactions or intensify contrast-medium

induced reactions. A sedative can be administered to such patients.

Dosage

Cranial and spinal MRI

For adults, adolescents and children including infants more than 4 weeks old and small children up to 2 years of age, the following dosage guidelines apply:

The administration of 0.2 ml Magnevist per kg body weight is usually sufficient to provide good contrast enhancement and to answer the relevant clinical questions.

In the event that, despite inconspicuous findings, the strong clinical suspicion of a lesion continues to exist, then the information value of the investigation can be enhanced by a second administration of 0.2 Magnevist/kg of body weight (or in the case of adults even of 0.4 ml Magnevist/kg body weight) within 30 minutes with subsequent MRT.

The administration of 0.6 ml of Magnevist/kg body weight often enhances diagnostic reliability for the exclusion of metastases or tumour relapses among adults.

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

For new-borns up to 4 weeks old and infants up to 1 year of age, see also «Special patient populations».

Whole body MRI

For adults, adolescents and children including infants more than 4 weeks old and small children up to 2 years of age, the following dosage guidelines apply:

The administration of 0.2 ml Magnevist per kg body weight is usually sufficient to provide good contrast enhancement and to answer the relevant clinical questions. There is only limited experience of use for whole body MRI in children under 2 years.

0.4 ml of Magnevist per kg of body weight may be required for sufficient contrasting in special cases, e.g. in the presence of lesions with low vascularisation and/or small extracellular space, particularly in connection with the application of relatively weak T1 weighted imaging sequences.

The administration of 0.6 ml of Magnevist/kg body weight could enhance diagnostic reliability for the exclusion of lesions or tumour relapses among adults.

For visualisation of blood vessels in adults the maximum dose may be necessary, depending on the examination technique and the region to be examined.

Maximum dose: 0.6 ml (adults) or 0.4 ml (children >2 years of age) Magnevist/kg body weight.

For new-borns up to 4 weeks old and infants up to 1 year of age, see also «Special patient populations».

Infants more than 4 weeks old and small children up to 2 years of age

0.2 ml per kg body weight is recommended for infants more than 4 weeks old and small children up to 2 years of age. This corresponds to the maximum dosage.

The required dosage of Magnevist should be administered by hand in order to avoid an accidental overdose, and may not be administered in connection with an autoinjector. See also Section 4.4

Summary - Dosage recommendations/maximum dosage:

0.2 ml Magnevist / kg body weight (corresponding to 0.1 mmol/kg body weight)	Normal dosage for adults, adolescents, children and infants more than 4 weeks old and small children up to 2 years of age for cranial, spinal and whole body MRIs
0.4 ml Magnevist/kg body weight (corresponding to 0.2 mmol/kg body weight)	For difficult questions Maximum dosage for children (age >2 years)
0.6 ml Magnevist/kg body weight (corresponding to 0.3 mmol/kg body weight)	Maximum dosage for adults for the depiction of blood vessels

Special patient populations

▷ Renal function disorder

Magnevist is contraindicated for patients with severe renal function disorder (GFR < 30 ml/min/1.73m²) and/or acute renal damage and for patients in the perioperative liver transplantation phase (see Section 4.3). Magnevist should not be used with patients with moderately impaired kidney function (GFR 30 - 59 ml/min/1.73m²) except after a careful weighing of the associated benefits and risks and then only in a dosage which does not exceed 0.1 mmol/kg body weight (see Section 4.4). Not more than one dosage may be used during an admittance. Because of the absence of information regarding repeated administration, Magnevist injections may not be repeated unless the interval between the injections is at least 7 days in length.

▷ New-borns up to 4 weeks old and infants up to 1 year

Magnevist is contraindicated for new-borns up to 4 weeks of age (see Section 4.3).

Because of the immaturity of kidney function among infants up to 1 year of age, Magnevist may not be used with these patients except after careful evaluation, and then only in a dosage which does not exceed 0.1 mmol/kg body weight. Not more than one dosage may be used during an admittance. Because of the absence of information regarding repeated administration, Magnevist injections may not be repeated unless the interval between the injections is at least 7 days in length.

▷ Older patients (65 years old and older)

No dosage adjustment is regarded as necessary. Caution should be taken with older patients (see Section 4.4).

Type of application:

Magnevist may only be administered intravenously.

Bolus injection is possible.

Instructions for handling

Instructions for the application of the vial:

Magnevist should not be taken up into the syringe until immediately prior to the examination. The rubber plug may not be pierced through more than once. Any contrast medium solution not used in one examination must be discarded.

The following instructions apply to use of the pre-filled syringe:

The ready-to-use syringe should not be taken from the pack and prepared for the injection until immediately prior to the examination. The sealing cap should not be removed until immediately before the ready-to-use syringe is used. Any contrast medium solution not used in one examination must be discarded.

If the preparation is to be given with an automatic administration system the suitability of the system for the intended use must be documented by the medical device manufacturer. The instructions for use of the medical devices must always be observed. In infants and small children use of an automatic administration system is not allowed.

4.3 Contraindications

Hypersensitivity (allergy) to the active substance or to any of the excipients indicated in section 6.1.

Magnevist is contraindicated for patients with severe renal function disorder (GFR <30 ml/min/1.73 m²) and/or acute renal damage, for patients in the perioperative liver transplantation phase and for new-borns up to 4 weeks of age (see Section 4.4).

4.4 Special warnings and precautions for use

Intrathecal administration of Magnevist is not recommended.

▶ Gadolinium Retention

Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (e.g. brain, skin, kidney, liver, and spleen). The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs. At equivalent doses, gadolinium retention varies among the linear agents with Omniscan (gadodiamide) and Optimark (gadoversetamide) causing greater retention than other linear agents [Eovist (gadoxetate disodium), Magnevist (gadopentetate dimeglumine), MultiHance (gadobenate dimeglumine)]. Retention is lowest and similar among the macrocyclic GBCAs [Dotarem (gadoterate meglumine), Gadavist (gadobutrol), ProHance (gadoteridol)].

Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of GBCA administration and retention in skin and other organs have been established in patients with impaired renal function [see section 4.4 - Patients with impaired kidney function]. There are rare reports of pathologic skin changes in patients with normal renal function. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention [see section 4.8].

While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and pediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies, particularly closely spaced studies when possible.

▶ Allergic reaction

As is the case with other contrast media for intravenous application, it is also true for Magnevist that anaphylactoid/allergic or other idiosyncratic reactions can occur, which can manifest themselves in the form of cardiovascular, respiratory and skin reactions, leading all the way to grave reactions, including shock (see also Section 4.8).

The risk of hypersensitivity reactions is increased in the following cases:

- ▷ in patients with previous reactions to contrast media,
- ▷ among patients with bronchial asthma in their anamnesis; the risk of bronchial spasms is particularly elevated among these patients,
- ▷ among patients with predisposition to allergies.

A careful weighing of the associated benefits and risks must be carried out prior to any application of Magnevist with these patients.

The patient should therefore be questioned about existing allergies (e.g. seafood allergy, hay fever, urticaria), oversensitivity to contrast media and bronchial asthma prior to the injection of a contrast medium.

The possibility of administering a premedication with antihistamines and/or glucocorticoids should be taken into consideration.

Most of these reactions occur within half an hour after application of the contrast medium. As is also the case with other diagnostic investigations with contrast media, patient monitoring for at least 30 minutes is recommended subsequent to the investigation procedure (see also Section 4.2).

Delayed reactions can occur in rare cases (after hours or days).

If hypersensitivity reactions occur (see also Section 4.8), administration of the contrast medium must be stopped immediately and - if necessary - specific treatment initiated via an intravenous access. It is advisable to use a flexible intravenous cannula or catheter (for rapid intravenous access) throughout the examination. In order to be able to respond immediately in an emergency appropriate drugs and instruments for emergency treatment (including endotracheal tube and ventilator) should be held ready.

This drug may be used only by authorised professionals with the necessary medical experience and drugs and equipment (e.g. endotracheal tube and ventilator) must be immediately on hand in case of emergency for treating undesirable reactions (e.g. allergy, convulsions).

Patients who are being treated with beta-blockers:

Attention is drawn to the fact that patients taking beta blockers may possibly fail to respond to treatment with beta-agonists in the event of a hypersensitivity reaction.

Patients with cardiovascular diseases:

Patients with cardiovascular diseases (e.g. severe congestive heart failure or coronary heart disease) are more at risk for grave or even fatal consequences of severe allergic reactions.

Patients with disorders of the central nervous system:

In patients with epilepsy or brain lesions there may be an increased risk of seizures during the examination such as has been observed rarely in association with application of Magnevist (see also Section 4.8).

In these patients appropriate precautions should be taken (e.g. careful observation) and the necessary equipment and drugs should be held ready for use in the event of a seizure occurring.

Patients with impaired kidney function

The question of the presence of a renal function disorder must be clarified by laboratory investigations for all patients prior to the administration of Magnevist.

Cases of nephrogenic systemic fibrosis (NSF) have been reported in connection with the use of Magnevist and a few other contrast media containing gadolinium in patients with acute or chronic severely impaired kidney function (GFR < 30 ml/min/1.73 m²) and/or acute renal damage. Magnevist is contraindicated in these patients (see section 4.3). Patients who undergo a liver transplantation are at particular risk, because the occurrence of acute renal failure is high in this patient population. Magnevist is therefore not permitted to be used for patients in the perioperative liver transplantation phase and for new-borns (see Section 4.3).

The risk of the emergence of NSF is unknown in cases of patients with moderately impaired kidney function (GFR 30–59 ml/min/1.73 m²); Magnevist should therefore not be used with patients with moderately impaired kidney function except after a careful weighing of the associated benefits and risks.

A haemodialysis shortly after the application of Magnevist could be useful for removing Magnevist from the body. There is no evidence to suggest that haemodialysis should be initiated among patients who did not previously require dialysis in order to prevent or treat an NSF.

New-borns and infants

Magnevist is contraindicated for new-borns up to 4 weeks of age (see Section 4.3).

Because of the immaturity of kidney function in infants up to 1 year of age, Magnevist is not permitted to be used with these patients except after careful evaluation.

Older patients

Because of the fact that the renal clearance of gadopentetate dimeglumine may be diminished among older patients, it is particularly important to clarify the possibility of the presence of a renal function disorder among patients 65 years of age or older.

▶ Infants more than 4 weeks old and small children up to 2 years of age

The use of an automatic application system is prohibited among infants more 4 weeks of age and small children up to 2 years old in order to avoid the possibility of an accidental overdose. The dosage to be administered is to be administered by hand with this patient population (see also Section 4.2).

4.5 Interactions with other medicinal products and other forms of interaction

No studies have been performed concerning interactions recording.

It is known from the application of contrast media that allergic reactions can occur in intensified form among patients who are receiving beta-blockers (see also Section 4.4).

▶ Influence on diagnostic tests

Serum iron determination with complexometric methods
(e.g. Bathophenanthroline) may yield inaccurately low levels for up to 24 hours after investigations with Magnevist due to the pentetate pentameglumine contained in the contrast media solution.

4.6 Pregnancy and breast-feeding

▶ Pregnancy

There are no data for the use of gadopentetate dimeglumine in pregnant women. Animal experiment studies do not suggest direct or indirect harmful effects with respect to reproduction toxicity (see Section 5.3). Magnevist may not be used during pregnancy unless the clinical condition of the woman makes the use of gadopentetate dimeglumine required.

▶ lactation

Very small amounts of Magnevist (not more than 0.04% of the administered dose) enter the breast milk.

Available data involving animals have shown a transfer of gadopentetate dimeglumine into the milk. The possibility of risk to the infant cannot be excluded. Breast-feeding should be discontinued for at least 24 hours after the administration of Magnevist.

4.7 Effects on the ability to drive and operate machinery

No studies addressing the effects upon driving ability and the ability to operate machinery have been carried out. Ambulant patients who drive vehicles or operate machinery should take into account the fact that delayed reactions (such as queasiness and hypotension) could occasionally occur.

4.8 Side effects

Side-effects occurring in association with the use of Magnevist are usually of mild to moderate severity and of short duration.

Nonetheless, serious and life-threatening reactions, including deaths, have also been reported. The most commonly observed side-effects are nausea, vomiting, headache, dizziness and various types of reactions at the injection site (e.g. pain, sensation of cold, sensation of heat).

Anaphylactic reactions, which could occur independently of both the amount administered and the administration type, could be the first signs of an incipient shock condition.

Delayed reactions in connection with contrast media have been reported on rare occasions (also Section 4.4).

The following categories were used as the basis for the frequency specifications concerning the side effects:

Very common:	≥1/10
Common:	≥1/100 to <1/10
Occasional	≥1/1000 to <1/100
Rare:	≥1/10,000 to <1/1000
Very rare:	<1/10,000
Unknown	(frequency cannot be estimated on the basis of available data)

Frequency of undesirable effects from data prior to and subsequent to the marketing authorisation (spontaneous reports and clinical studies)

The estimations of frequency are based both on data obtained from clinical studies before marketing authorisation was granted as well as on data from spontaneous reports received afterwards.

On the basis of experiences gathered in connection with administration to more than 11,000 patients in clinical studies, the undesirable effects listed in the following table have been judged to be drug-related.

System Organ Class	Uncommon	Rare
diseases of the blood and lymphatic system		Temporary changes in serum iron§ and serum bilirubin levels§
diseases of the immune system		Anaphylactoid reactions§/ allergic reactions§/ anaphylactoid shock§, Quincke's edema, conjunctivitis*, coughing*, pruritus*, rhinitis, sneezing*, urticaria*, Bronchial spasm§, laryngeal spasm§, laryngeal§ or pharyngeal oedema§, hypotension§, shock§
diseases of the nervous system	Vertigo*, headache*	Agitation, disorientation*, confusion, disturbances of speech or smell, seizures* §, paresthesias*, tremor*, asthenia*, coma§, somnolence§, burning sensation*
diseases of the eyes		Watering eyes, eye pain, vision disorders
diseases of ear and inner ear		Ear pain, hearing disorders
diseases of the cardiovascular system		Clinically relevant temporary disturbances of heart rate (tachycardia* §, reflex tachycardia, bradycardia§) and of blood pressure (increase in blood pressure), disturbances of cardiac rhythm (arrhythmia*) and disturbances of cardiac function, as well as cardiac arrest§
diseases of the vascular system		Circulatory system reactions, which are accompanied by peripheral vasodilation*, subsequent hypotension§ and syncope§, reflex tachycardia, agitation, confusion and cyanosis§ and which can lead to unconsciousness§, thrombophlebitis*
diseases of respiratory system, thoracic cavity and mediastinum		Temporary changes in respiratory rate (increase or drop in respiratory rate), shortness of breath* §, difficulty breathing* §, cough*, respiratory arrest§,wheezing*, pulmonary oedema§, throat irritations/feeling of constriction in the throat* §, pharyngolaryngeal pain/ complaints in the pharynx*, sneezing*
diseases of the gastrointestinal tract	Queasiness*, vomiting*, dysgeusia*	Stomach-ache*, gastric complaints*, diarrhoea*, dry mouth*, saliva flow, toothache*, soft tissue pain and paraesthesias in the mouth*
liver and biliary diseases		Temporary changes (increase) in liver enzyme values, elevated blood bilirubin
diseases of skin and subcutaneous cellular tissue		Quincke's oedema§, erubescence* and flush* with vasodilation*, urticaria*, pruritus* and exanthemas*
diseases of skeletal muscels, connective tissue and bones		Pain in the extremities*
diseases of kidneys and urinary tract		Urinary incontinence, an urgent need to pass urine, elevated serum creatinine values and acute kidney failure § in patients who already have poor kidney function
General symptoms	Sensation of heat*, sensation of cold*, pain*	Back pain, joint pain, chest pain*, discomfort*, chills, sweating, vasovagal reactions, changes (increase or drop) in body temperature, fever*, swollen face* §, peripheral oedemas*, fatigue*, thirst*
and		
discomfort at application area	Extravasation, local pain*, sensation of cold*, mild sensation of heat*, oedemas*, Inflammation, tissue necrosis, phlebitis, thrombophlebitis, paresthesias*, swelling*, irritation*, haemorrhagia* erythema*, complaints*	

* Undesirable effects from clinical studies

§ life-threatening cases or fatalities have been reported

Cases of nephrogenic systemic fibrosis (NSF) have been reported in connection with Magnevist (see Section 4.4) §.

Delayed and transient inflammation-like reactions such as fever, chills and an increase in C-reactive protein were frequently observed among patients with renal insufficiency requiring dialysis who received a gadopentetate dimeglumine containing contrast media. These patients had undergone MRI investigation with a gadopentetate dimeglumine containing contrast media on the day before haemodialysis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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4.9 Overdose

No indications of intoxication following overdose have been either observed or reported in clinical applications to date.

In the event of accidental intravascular overdose, the following symptoms and signs are conceivable due to the hyperosmolality of the solution:

▷ Systemic: Elevation of the pulmonary artery pressure, hypovolaemia, osmotic diuresis, dehydratation

▷ Local: vascular pain

In patients with poor kidney function, monitoring of kidney function should be performed.

Magnevist can be eliminated through haemodialysis. There is however no evidence to document that a haemodialysis is suitable for the prevention of nephrogenic systemic fibrosis (NSF).

Poisoning caused by accidental peroral intake of the contrast media is extremely unlikely, in view of the extremely low gastrointestinal resorption rate (<1%) of Magnevist.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group:

Paramagnetic contrast media

ATC Code: V08C A01

Magnevist is a paramagnetic contrast medium for magnetic resonance imaging. The contrast-enhancing effect is provided by the di-N-methylglucamine salt of gadopentetate (GdDTPA) - the gadolinium complex of diethylentriamine penta-acetic acid. The spin-grid relaxation time of excited atomic nucleuses that is shortened by the gadolinium ion leads to an elevation of signal intensity in proton magnet resonance imaging, given the appropriate recording sequence (e.g. T1-weighted spin-echo procedure), and thus as necessary to an increase in image contrast.

Gadopentetate dimeglumine is a strongly paramagnetic compound which leads to a pronounced shortening of relaxation times, even when administered in a low concentration range. The paramagnetic efficiency, the relaxivity - calculated from the effect on the spin-grid relaxation time of the hydrogen protons in plasma - amounts to approximately 4.95 l/(mmol•sec) at pH 7 and 39°C and exhibits only a limited dependency on the strength of the magnetic field.

The paramagnetic gadolinium ion forms a permanent complex with the pentetic acid (DTPA) with an extremely high in vivo and in vitro stability (log K = 22 - 23). The dimeglumine salt of the gadopentetic acid is a readily water-soluble, extremely hydrophilic compound with a partition coefficient between n-Butanol and buffer of around 0.0001 at pH 7.6. The substance exhibits no noteworthy protein formation or inhibitory interaction with enzymes (e.g. myocardial Na+/K+ ATPase). Magnevist does not activate the complement system and therefore has likely very little potential for triggering of anaphylactoid reactions.

Low-grade effects on erythrocyte morphology occur in vitro with prolonged incubation times in the presence of higher concentrations of gadopentetate dimeglumine. This process, which is itself reversible, could lead to weak intravascular haemolysis following intravenous administration of Magnevist to humans and thus explain the slight increase of bilirubin and iron in serum occasionally observed in the first hours following injection.

5.2 Pharmacokinetic properties

Gadopentetate dimeglumine behaves in the organism the same way as other very hydrophilic biologically inert compounds (e.g. mannitol or inulin).

A dosage-independent pharmacokinetics has been observed among humans.

▶ Distribution

The compound becomes rapidly distributed in the extracellular space following intravenous administration.

Seven days following the intravenous administration of radioactively marked gadopentetate dimeglumine, considerably less than 1% of the applied dosage was found in the rest of the body, both in the rat and in the dog. The relatively largest concentrations of the compound were detected thereby in the kidneys in the form of the intact gadolinium complex.

The compound neither penetrates and passes the blood-testis barrier. The small amount which passes through the placenta barrier is rapidly eliminated by the foetus.

With dosages of up to 0.25 mmol of gadopentetate/kg body weight (= 0.5 ml Magnevist/kg), the plasma level falls after the few minutes of the distribution phase, with a half-life of around 90 minutes, which is identical to that of the renal excretion rate. With a dosage of 0.1 mmol gadopentetate/kg (= 0.2 ml Magnevist/kg) body weight, 0.6 mmol of gadopentetate/l plasma were detected 3 minutes after injection, as were 0.24 mmol of gadopentetate/l plasma 60 minutes after injection.

▶ Biotransformation

Neither a splitting-off of the paramagnetic ion nor any biotransformation was documented.

▶ Elimination

Gadopentetate dimeglumine is excreted unchanged via the kidneys by means of glomerular filtration. The proportion of extrarenal excretion is extremely small.

On average, 83% of the dosage is eliminated within up to 6 hours after injection. Around 91% of the dosage is to be found in the urine within 24 hours after the injection. The proportion of the dosage excreted in stool was less than 1 % (up to 5 days after the injection). The renal clearance of gadopentetate dimeglumine is around 120 ml/min/1,73 m^2 and is thus comparable to that of inulin or ^{51}Cr-EDTA.

▶ Anomalies among patients with limited kidney function

Even in the presence of mild to middle-grade limited kidney function (creatinine clearance 20 ml/min), the excretion of gadopentetate dimeglumine is accomplished entirely by the kidneys; the half-life in plasma increases in accordance with the degree of renal insufficiency. No increase of extrarenal excretion was observed.

In cases of severely limited kidney function (creatinine clearance < 20 ml/min), the half-life is prolonged to up to 30 hours.

Magnevist is eliminated through renal excretion, and the clearance diminishes with increasing age, as is to be expected due to age-related physiological decrease of kidney function. The recovery rate of Magnevist in the urine is similar to that found with other age groups.

▶ Paediatric population

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

5.3 Preclinical safety data

Preclinical data from conventional studies concerning safety pharmacology, toxicity with repeated administration, genotoxicity, reproduction toxicology and with respect to carcinogenic potential offers no evidence of any special danger in connection with the administration to humans. Delayed development was observed following repeated administration of gadopentetate dimeglumine to pregnant rabbits.

▶ Systemic toxicity

On the basis of the results of the acute toxicity studies, no acute risk of poisoning exists in connection with the administration of Magnevist.

Experimental systemic tolerance tests with Magnevist following repeated daily intravenous administration revealed no findings which would argue against one-time (as a rule) diagnostic administration to humans.

▶ Genotoxicity, tumourgenicity

Tests for genotoxic effects (tests for genetic, chromosomal and genomic mutations) revealed no indications of any mutagenic potential for gadopentetate dimeglumine, neither in vitro nor in vivo.

No Magnevist-related tumours were observed in a study addressing tumourgenicity in the rat. On the basis of this fact, and on the basis of the absence of genotoxic effects, taking into account the pharmacokinetics, the absence of indications of toxic effects on rapid-growth tissue and the only one-time diagnostic administration of Magnevist, no risk of tumour-causing action in humans is anticipated.

▶ Local tolerance and contact-sensitising potential

Experimental experiments addressing the local tolerance of Magnevist following one-time and repeated intravenous and one-time intra-arterial injection revealed no findings leading to the anticipation of local signs of intolerance in human blood vessels.

Experimental local tolerance tests after one-time paravenous, subcutaneous and intramuscular applications indicated that accidental paravenous application could lead to low-grade local reactions at the application site among humans.

The testing for contact-sensitising effect revealed no indications of a sensitising potential for Magnevist.

Long-term clinical experience with Magnevist does however show that anaphylactoid reactions could occur among humans.

A slight retardation of foetal growth and ossification was to be observed following daily administration of 12.5 times the normal dosage to pregnant rats for a 10-day period and a minimum of 7.5 times the normal dosage to pregnant rabbits for 13 days in comparison with the therapy dosage per kg body weight for humans.

No effect was observed following daily administration of 7.5 times (rat) or 2.5 times (rabbit) the normal therapy dosage for humans, as calculated in terms of body surface.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pentetate pentameglumine

Meglumine

Water for injection purposes

6.2 Incompatibilities

In view of the fact that no compatibility studies have been performed, this drug is not permitted to be mixed with other drugs.

6.3 Shelf-life

Vials 5 years

Ready-to-use syringe 3 years

Chemical and physical stability have been confirmed for 24 hours at 30°C.

From the microbiological point of view the preparation should be used at once unless the container is opened in such a way that a risk of a microbial contamination can be ruled out. If it is not used immediately, then the user is responsible for the duration and conditions of its storage (normally not longer than 24 hours at 2 to 8°C).

6.4 Special precautions for storage

Do not store above 30°C

Vials, bottles and pre-filled syringes should be stored in their cartons in order to protect the contents from light. For storage conditions after drug opening see section 6.3.

6.5 Nature and contents of container

Vial/bottle:

Vial: Glass Type I, colourless

Bottle: Glass Type II, colourless

Seal: Chlorobutyl rubber (Type I)

Sealing cap: Aluminium, coloured plastic cap

Glass ready-to-use syringe:

Glass cylinder: Glass Type I, colourless

Plunger plug: Chlorobutyl rubber black (Type I)

Needle cap: Chlorobutyl rubber

Luer lock adapter: Polycarbonate

Plastic ready-to-use syringe:

Plastic cylinder: Cyclic olefin copolymer, colourless

Plunger plug: Siliconised bromobutyl rubber, grey

Syringe seal: Thermoplastic elastomer (TPE)

Package sizes

5 pre-filled syringes (glass/plastic) containing 10, 15 or 20 ml; syringes in individual blisters are packed in boxes of five syringes.

1 vial of 10, 15 or 20ml

10 vials of 5, 10, 15, 20 or 30 ml.

10 bottles of 100 ml.

Not all packaging sizes are marketed.

6.6 Special precautions for disposal and other instructions on handling

Unused drugs or waste material are to be disposed of in accordance with national requirements.

The tear-off label for tracking purposes on the vials/syringes/bottles is to be glued into the patient's medical records in order to enable precise documentation of the contrast medium containing gadolinium which was used. The dosage used should also be entered. If electronic patient records are used, the name of the medicinal product, the batch name and the dose must be entered here.

7. MANUFACTURER

Bayer AG
Mullerstrasse 178, 13353 Berlin, Germany.

Marketing Authorisation Holder:
Bayer AG,
Kaiser-Wilhelm-Allee 1, 51373 Leverkusen, Germany.

8. DATE OF REVISION OF THE TEXT

May 2016

9. SALES RESTRICTIONS

Prescription-only

This is a medicament

- ▶ A medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- ▶ Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- ▶ The doctor and the pharmacist are experts in medicine, its benefits and risks.
- ▶ Do not by yourself interrupt the period of treatment prescribed.
- ▶ Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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