

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Magnevist 0.5mmol/ml Solution for Injection, in pre-filled syringe.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to pale yellow solution.

The physico-chemical properties of Magnevist listed below are:

|   |           |
|---|-----------|
| <b>Osmolality (Osm/Kg H<sub>2</sub>O)</b> |           |
| At 37°C                                   | 1.96      |
| <b>Viscosity (mPa·s)</b>                  |           |
| At 20°C                                   | 4.9       |
| At 37°C                                   | 2.9       |
| <b>pH-value</b>                           | 7.0 – 7.9 |

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

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 space including the heart and abdominal space, the female breast, the pelvis and the active and passive musculoskeletal system, 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 renal function combined with anatomical organ diagnosis.

## 4.2 Posology and 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.

For additional instructions see section “Instructions for use / handling”.

### 4.2.2 Dosage regimen

Wherever possible, intravascular administration of contrast agent is to be given with the patient lying down. T1-weighted scanning sequences are particularly suitable for contrast-enhanced examinations.

#### 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, even of 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 vascularisation 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 T1-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 higher diagnostic confidence.

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

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

## Special Populations

### Renal impairment

Magnevist is contraindicated in patients with severe renal impairment ( $\text{GFR} < 30 \text{ ml/min/1.73m}^2$ ) and/or acute kidney injury, 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 ( $\text{GFR} 30\text{-}59 \text{ ml/min/1.73m}^2$ ) at a dose not exceeding 0.2ml/kg body weight (see section 4.4). More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Magnevist injections should not be repeated unless the interval between injections is at least 7 days.

### Patients 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 5.2).

### Paediatric population

- all indications

Children: 0.2 ml Magnevist per kg body weight.

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

Children below two years of age: limited experience in whole body MRI.

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

### Neonates up to 4 weeks of age and infants up to 1 year of age

Magnevist is contraindicated in neonates up to 4 weeks of age (see section 4.3).

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 of the lack of information on repeated administration, Magnevist injections should not be repeated unless the interval between injections is at least 7 days.

### Elderly (aged 65 years and above)

No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

## **4.3 Contraindications**

Hypersensitivity to any of the ingredients.

Magnevist is contraindicated in patients with severe renal impairment ( $\text{GFR} < 30 \text{ ml/min/1.73m}^2$ ), and/or acute kidney injury, in patients in the perioperative liver transplantation period and in neonates up to 4 weeks of age (see section 4.4).

## **4.4 Special warnings and precautions for use**

- 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.

The risk of hypersensitivity reactions is higher in case of

- previous reaction to contrast media
- history of bronchial asthma

-history of allergic disorders

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, premedication with antihistamines 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 4.8)

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.

- Patients with impaired renal function

**Prior to administration of Magnevist all patients should be screened for renal dysfunction by obtaining laboratory tests.**

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of Magnevist and some other gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment ( $\text{GFR} < 30 \text{ ml/min/1.73m}^2$ ) and/or acute kidney injury. Magnevist is contraindicated in these patients (see section 4.3). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. Therefore Magnevist must not be used in patients in the perioperative liver transplantation period and in neonates (see section 4.3).

The risk for development of NSF in patients with moderate renal impairment ( $\text{GFR } 30\text{--}59 \text{ ml/min/1.73 m}^2$ ) is unknown, therefore, Magnevist should be only used after careful risk-benefit evaluation in patients with moderate renal impairment.

Haemodialysis shortly after Magnevist administration may be useful at removing Magnevist from the body. Approximately 70% of the administered dose is removed with each dialysis session, such that after 3 dialysis sessions of 3 hours each, about 97% of the total administered dose is eliminated from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

- Seizure disorders

Patients with seizure disorders or intracranial lesions may be at increased risk of seizure activity as has been reported rarely in association with Magnevist administration (see section 4.8). 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.

- Neonates and infants

Magnevist is contraindicated in neonates up to 4 weeks of age (see section 4.3). Due to immature renal function in infants up to 1 year of age, Magnevist should only be used in these patients after careful consideration.

- Elderly

As the renal clearance of Magnevist may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions studies with other medicinal products have been conducted.

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

4.6 Fertility, pregnancy and lactation

- Pregnancy
- Adequate and well controlled studies with gadopentetate were not conducted in pregnant women. Animal studies have shown reproductive toxicity at repeated high doses (see section 5.3). The potential risk for humans is unknown. Magnevist should only be used in pregnant women after a clear benefit-to-risk analysis.

- Lactation
- It is unknown whether gadopentetic acid is excreted in human milk. There is insufficient information on the excretion of gadopentetic acid in animal milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued for at least 24 hours after the administration of Magnevist.

4.7 Effects on ability to drive and use machines

Not known.

4.8 Undesirable effects

Summary of the safety profile

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

The most frequently observed adverse drug reaction ( $\geq 0.4\%$ ) 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 reactions in patients receiving Magnevist are:

- Nephrogenic systemic fibrosis
- Anaphylactoid reactions/ - anaphylactoid shock

Delayed hypersensitivity / anaphylactoid reactions (hours later up to several days) have been rarely observed (see section 4.4).

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:  $\geq 1/1,000$  to  $< 1/100$ ; rare:  $\geq 1/10,000$  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 the lymphatic system disorders |                                    |   | Serum iron increased*                                    |
| Immune system disorders                  |                                    | Hypersensitivity /anaphylactoid reaction (e.g. anaphylactoid shock*, Anaphylactoid reaction§ *, Hypersensitivity reactions§ *, Shock§ *, Hypotension§*, Conjunctivitis, Loss of consciousness§*, Throat tightness*, Sneezing, Urticaria, Pruritus, Rash, Erythema, Dyspnea*, Respiratory arrest§*, Bronchospasm§*, Wheezing, Laryngospasm§*, Laryngeal edema§*, Pharyngeal edema§*, Cyanosis§*, Rhinitis§, Angioedema§*, Edema face*, Reflex tachycardia§ |  |
| Psychiatric disorders                    |                                    | Disorientation  | Agitation<br>Confusion                                   |
| Nervous system disorders                 | Dizziness<br>Headache<br>Dysgeusia | Convulsion*<br>Paraesthesia<br>Burning sensation<br>Tremor  | Coma<br>Somnolence*<br>Speech disorder<br>Parosmia       |
| Eye disorders                            |                                    |   | Visual disturbance<br>Eye pain<br>Lacrimation            |
| Ear and labyrinth disorders              |                                    |   | Hearing impaired<br>Ear pain                             |
| Cardiac disorders                        |                                    | Tachycardia*<br>Arrhythmia  | Cardiac arrest*<br>Heart rate decreased/<br>bradycardia* |

|   |   |   |   |
|---|---|---|---|
| Vascular disorders                                    |   | Thrombophlebitis<br>Flushing<br>Vasodilatation  | Syncope*<br>Vasovagal reaction<br>Blood pressure increased  |
| Respiratory, thoracic and mediastinal disorders       |   | Throat irritation<br>Pharynogolaryngeal pain/ Pharynx discomfort<br>Cough   | Respiratory distress<br>Respiratory rate increased or Respiratory rate decreased<br>Pulmonary oedema* |
| Gastrointestinal disorders                            | Vomiting<br>Nausea  | Abdominal pain<br>Stomach discomfort<br>Diarrhoea<br>Toothache<br>Dry mouth<br>Oral soft tissue pain and paraesthesia | Salivation  |
| Hepatobiliary disorders                               |   |   | Blood bilirubin increased<br>Hepatic enzyme increased   |
| Skin and subcutaneous tissue disorders                |   |   | Nephrogenic Systemic Fibrosis (NSF)*  |
| Musculoskeletal, connective tissue and bone disorders |   | Pain in extremity   | Back pain<br>Arthralgia   |
| Renal and urinary disorders                           |   |   | Acute renal failure*, **<br>Increased serum creatinine**<br>Urinary incontinence<br>Urinary urgency   |
| General disorders and administration site conditions  | Pain<br>Feeling hot<br>Feeling cold<br>Injection site reactions (e.g. Injection site coldness, paresthesia, swelling, warmth, pain, edema, irritation, hemorrhage, erythema, discomfort, necrosis§, thrombophlebitis§, phlebitis§, inflammation§, extravasation§) | Chest pain<br>Pyrexia<br>Edema peripheral<br>Malaise<br>Fatigue<br>Thirst Asthenia                                    | Chills<br>Sweating<br>Body temperature increased or Body temperature decreased                        |

\* life-threatening and/or fatal cases have been reported  
\*\* In patients with preexisting renal impairment  
§ Reactions identified only during post-marketing surveillance (frequency not known)

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 with Magnevist (see section 4.4).

#### 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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); e-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

## 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 by haemodialysis (see section 4.4). However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

## 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<sub>1</sub>-weighted scanning sequences are used in proton magnetic resonance imaging, the gadopentetate induced shortening of the spin-lattice relaxation time (T<sub>1</sub>) of excited water protons leads to an increase of the signal intensity and, hence, to an increase of the image contrast of certain tissues.

#### *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 at 37°C, the relaxivity (r<sub>1</sub>) – determined from the influence on the T<sub>1</sub> relaxation time of the water protons in plasma and the relaxivity(r<sub>2</sub>) – determined from the influence on the T<sub>2</sub> 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 (DTPA) forms a complex with the paramagnetic gadolinium ion with high in-vivo and in-vitro stability (thermodynamic stability constant: log K<sub>GdL</sub> = 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 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 per 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 labelled gadopentetate. Less than 1 % of the administered dose was found in the remaining parts of the body of both.

Gadopentetate neither penetrates nor passes the blood-testis barrier. The small amount which overcomes the placental barrier is quickly eliminated by the fetus.

In 18 out of 20 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<sup>2</sup> and is therefore comparable to substances that are exclusively excreted by glomerular filtration (e.g. inulin or <sup>51</sup>Cr-EDTA).

### *Linearity/non-linearity*

Gadopentetate shows linear pharmacokinetics i.e., pharmacokinetic parameters change dose proportionally (e.g. maximum concentration, area under the curve) or are dose independent (e.g. volume of distribution at steady-state, terminal half-life), up to a dose of 0.25 mmol per kg body weight (0.5 ml/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  $\geq 60$  to  $< 90$  ml/min] and 6 patients with moderate renal impairment [creatinine clearance  $\geq 30$  to  $< 60$  ml/min]), mean half-lives were  $2.6 \pm 1.2$  hours and  $4.2 \pm 2.0$  hours for the mildly and moderately impaired patients, respectively, as compared to  $1.6 \pm 0.13$  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  $10.8 \pm 6.9$  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,  $73.3 \pm 16.1\%$  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.

- Paediatric Population

In a study with paediatric patients aged 2 months to  $< 2$  years the pharmacokinetics (body weight normalised clearance, distribution volume, area under the concentration time-curve 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.

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, tumorigenicity

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

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 tumorigenic effect on humans.

- Reproduction toxicity

Repeated intravenous dosing caused retardation of foetal development in rabbits and rats, at doses 2-fold and 2.4-fold (based on body surface area) or 7.5-fold and 12.5-fold (based on body weight) the standard single diagnostic dose in humans.

Magnevist was not teratogenic when given repeatedly during organogenesis in rabbits and rats at the maximum tested doses, which were 9.7-fold and 7.3-fold (based on body surface area) or 30-fold and 45-fold (based on body weight) the standard single diagnostic dose in humans.

Repeated intravenous injections of Magnevist over 16 to 18 days caused spermatogenic cell atrophy/degeneration in male rats at a dose 8-fold (based on body surface area) or 50-fold (based on body weight) the standard single diagnostic dose in humans.

- Local tolerance and contact-sensitizing potential

Experimental local tolerance studies with Magnevist following single as well as repeated intravenous administration and single intraarterial administration did not result in adverse local effects.

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.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Meglumine  
Pentetic 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

Unopened:

- 5 years (glass prefilled syringe)
- 3 years (plastic prefilled syringe)

Once opened: Chemical and physical in-use stability has been demonstrated for 24 hours at temperature not above 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours, below 30°C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Do not store above 30°C. Magnevist is sensitive to light. Keep the container in the outer carton in order to protect from light.

## 6.5 Nature and contents of container

Colourless Type I, glass pre-filled syringes with chlorinated butyl rubber stoppers and combined luer lock adapter, tip cap (chlorobutyl rubber), safety caps.

Pack size: syringes containing 10 ml, 15 ml and 20 ml of Magnevist solution; individual syringes are blister packaged with five syringes per carton.

Plastic prefilled syringes consisting of a colourless cycloolefin polymer plastic barrel with a thermoplastic elastomer tip seal, closed with a siliconized bromobutyl plunger.

Pack size: plastic syringes containing 5 ml, 10 ml, 15 ml and 20 ml of Magnevist solution; individual syringes are blister packaged with five syringes per carton.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No light protection during handling required. For further information see also section 'Special precautions for storage'.

### Visual Inspection

This medicinal product should be visually inspected before use.

Magnevist should not be used in case of severe discoloration, the occurrence of particulate matter or a defective container.

### Pre-filled 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 pre-filled syringe immediately before use. Any contrast medium solution not used in one examination is to be discarded.

The peel-off tracking label on the syringes should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded.

If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record.

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

Unused Magnevist in opened containers must be discarded at the end of the examination day (at maximum 24 hours).

For further information see also section 6.3: Shelf life.

## 7 MARKETING AUTHORISATION HOLDER

Bayer Limited,  
The Atrium,  
Blackthorn Road,  
Dublin 18

**8 MARKETING AUTHORISATION NUMBER**

PA1410/006/002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 13 July 2001

Date of last renewal: 13 July 2006

**10 DATE OF REVISION OF THE TEXT**

June 2016