Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Magnegita 500 micromol/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 469 mg of gadopentetate dimeglumine equivalent to 500 micromol, equivalent to 78.63 mg gadolinium.

5 ml solution for injection contains 2,345 mg of gadopentetate dimeglumine equivalent to 500 micromol/ml, equivalent to 393.15 mg gadolinium.

10 ml of solution for injection contains 4,690 mg of gadopentetate dimeglumine equivalent to 500 micromol/ml, equivalent to 786.30 mg gadolinium.

15 ml of solution for injection contains 7,035 mg of gadopentetate dimeglumine equivalent to 500 micromol, equivalent to 1179.45/ml mg gadolinium.

20 ml of solution for injection contains 9,380 mg of gadopentetate dimeglumine equivalent to 500 micromol/ml, equivalent to 1572.60 mg gadolinium.

30 ml of solution for injection contains 14,070 mg of gadopentetate dimeglumine equivalent to 500 micromol/ml, equivalent to 2358.90 mg gadolinium.

100 ml of solution for injection contains 46,900 mg of gadopentetate dimeglumine equivalent to 500 micromol/ml, equivalent to 7863.00 mg gadolinium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear solution.

pH	7.0 – 7.9
Viscosity [mPas]	
20 °C	4.9
37 °C	2.9
Osmolality at 37 °C [mOsm/kg H_2O]	1960

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.

Magnegita is a contrast medium for cranial and spinal magnetic resonance imaging (MRI).

Magnegita is also indicated for whole body MRI including head and neck region, thoracic space including the heart, female breast, abdomen (pancreas and liver), retroperitoneal space (kidney), pelvis (prostate, bladder and uterus) and musculoskeletal system by intravenous administration.

Gadopentetate dimeglumine facilitates visualisation of abnormal structures or lesions and helps in the differentiation between healthy and pathological tissue.

Gadopentetate dimeglumine can also be used in MR angiography (except for coronary arteries) for the assessment of stenoses, occlusions and collaterals.

Specific applications in the heart include measurement of myocardial perfusion under pharmacological stress conditions and viability diagnostics ("delayed enhancement").

4.2 Posology and method of administration

Method of administration and MRI examination

The required dose of Magnegita should only be administered by intravenous injection. A bolus injection is possible.

Magnegita should be drawn in the syringe immediately before use. If this medicinal product is intended to be used with an automatic application system, its suitability for the intended use has to be demonstrated by the manufacturer of the medical device. Instructions for use of the medical device must be followed absolutely.

Contrast enhanced MRI may be initiated immediately after administration of the medium.

Regardless of the field strength of the magnet, the recommended magnetic flux density for gadopentetate dimeglumine is between 0.14 Tesla and 1.5 Tesla.

The MRI examination should start shortly after administration of Magnegita, depending on the pulse sequences used and the protocol for the examination. Optimal enhancement is observed within the first minutes after injection, time depending on type of lesion/tissue. Enhancement is generally lasting up to 45 minutes after contrast medium injection. T_1-weighted scanning sequences are particularly suitable for contrast enhanced examinations with gadopentetate dimeglumine.

This medicinal product is for single use only.

Only solutions without visible signs of deterioration (such as particles in the solution, fissures in the vial) must be used.

Dietary recommendations

Nausea and vomiting are known possible undesirable effects when using MRI contrast agents. The patient should therefore refrain from eating for 2 hours prior to the investigation.

Anxiety

Pronounced tension, anxiety or pain may increase the risk of undesirable effects or can aggravate the reactions caused by contrast agents. Sedatives may be given to these patients.

Posology

Adults, adolescents and children (over the age of two years)

In general 0.2 ml/kg body weight is sufficient to provide diagnostically adequate contrast to answer clinical questions for cranial and spinal MRI as well as for MRI of other regions.

In special cases, e.g. if a strong clinical suspicion of a lesion persists despite a normal scan or in lesions with poor vascularisation and/or a small extracellular space, an additional 0.2-0.4 ml/kg body weight for adults within 30 minutes, followed by MRI, may be necessary for an adequate contrast, especially with relatively less heavily T_1-weighted scanning sequences.

For the exclusion of metastases or tumour recurrence in adults an initial 0.6 ml/kg body weight may lead to a higher diagnostic confidence.

Depending on the investigation technique and the region to be investigated the maximum dose may be necessary in adults to visualize blood vessels (e.g. angiography).

Maximum dose: 0.6 ml/kg body weight in adults or 0.4 ml/kg body weight in children.

Special Populations

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

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

Toddlers (from 1 - 2 years)

In children less than 2 years of age 0.2 ml/kg body weight is recommended and corresponds to the maximum dose..

The required dose of Magnegita should be administered by hand to avoid overdosage by mistake and must not be administered in combination with an autoinjector.

Please refer also to section 4.4 for Special Warnings and Precautions (newborns and infants).

Elderly (aged 65 years and above)

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

Renal impairment

Magnegita is contraindicated in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and in patients in the perioperative liver transplantation period (see section 4.3). Magnegita 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 (see section 4.4). More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Magnegita injections should not be repeated unless the interval between injections is at least 7 days.

Summary of Dosage recommendations/maximum dose:

0.2 ml/kg body weight	Normal dose in adults, adolescents and children for cranial, spinal and whole body MRI.	Maximum dose in children (< 2 years)
0.4 ml/kg body weight	Difficult diagnostic situations	Maximum dose in children (> 2 years)
0.6 ml/kg body weight	Visualization of blood vessels	Maximum dose in adults

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Magnegita is contraindicated in patients with severe renal impairment (GFR <30ml/min/1.73m2), 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

The usual precautions for MRI should be taken into account, e. g. MRI should not be performed on patients with cardiac pacemakers, ferromagnetic implants or an insulin pump.

Magnegita is not intended for intrathecal use and is for single use only.

Ideally the patient should be recumbent during administration, and should be kept under supervision for at least 30 minutes after the injection, during which time most undesired reactions may occur.

This medicinal product must be administered exclusively by authorised personnel, where the necessary medical expertise, medicinal products and equipment (e.g. endotracheal tube and ventilator) are readily available for the treatment of adverse reactions (e. g. hypersensitivity, seizures).

• Hypersensitivity

As with other intravenous contrast media, Magnegita can be associated with anaphylactoid / hypersensitivity or other idiosyncratic reactions characterised by cardiovascular, respiratory and cutaneous manifestations. Very rarely severe reactions, including shock, may occur.

Most of these reactions occur within half an hour of administration. However, as with other contrast media, in rare cases delayed reactions (after hours or days) may occur.

If hypersensitivity reactions occur, the administration of the contrast medium must be discontinued immediately and, if necessary, intravenous treatment initiated. The insertion of a flexible in-dwelling catheter is recommended during the entire examination. The decision to use gadopentetate dimeglumine must be made after careful evaluation of the risk-benefit ratio in patients with either previous reaction to contrast media, history of bronchial asthma or other allergic disposition, since experience shows that these patients suffer more frequently than others from hypersensitivity reactions.

Premedication with antihistamines and/or glucocorticoids may be considered.

• Patients taking a beta-blocker
It should be noted that patients treated with beta-blockers do not necessarily respond to the beta-agonists usually used for the treatment of hypersensitivity reactions.

• Patients with cardiovascular disease

Patients with cardiovascular disease (e.g. severe heart failure, coronary artery disease) are more susceptible to serious or even fatal outcomes of severe hypersensitivity reactions.

• Patients with central nervous system disorders

Patients suffering from seizure disorders or intracranial lesions may be at increased risk of seizure activity during the examination, although this has rarely been observed in association with gadopentetate dimeglumine administration.

• Impaired renal function

Prior to administration of Magnegita, 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 Magnegita and some other gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 ml/min/1.73m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. Therefore Magnegita must not be used in patients with severe renal impairment, 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 (GFR 30–59 ml/min/1.73 m^2) is unknown, therefore, Magnegita should be only used after careful risk-benefit evaluation in patients with moderate renal impairment.
Haemodialysis shortly after Magnegita administration may be useful at removing Magnegita 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.

• ***Neonates and infants***

Magnegita 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, Magnegita should only be used in these patients after careful consideration.

Elderly
As the renal clearance of gadopentetate dimeglumine 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 interaction studies with other medicinal products have been performed.

The application of contrast media may increase the incidence of hypersensitivity reactions in patients taking beta-blockers (see section 4.4).

Interactions with diagnostic tests:

The results of serum iron determinations using complexometric methods may be reduced for up to 24 hours after the administration of gadopentetate dimeglumine due to free pentetic acid contained in the contrast media solution.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of gadopentetate dimeglumine in pregnant women.

Animal studies have shown reproductive toxicity at repeated high doses (see section 5.3). Magnegita should not be used during pregnancy unless the clinical condition of the woman requires use of gadopentate dimeglumine.

Lactation

It is unknown whether gadopentetate dimeglumine is excreted in human milk. Available data in animals have shown excretion of gadopentetate dimeglumine in milk (for details see section 5.3). A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued for at least 24 hours after the administration of Magnegita.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Ambulant patients while driving vehicles or operating machinery should take into account that delayed reactions (as nausea or hypotension) may incidentally occur.

4.8 Undesirable effects

The undesirable effects associated with the use of gadopentetate dimeglumine are usually mild and transient. Serious, life-threatening and fatal adverse effects have nevertheless been reported.

The most commonly reported undesirable effects are nausea, vomiting, headache, dizziness, pain and a feeling of warmth or coldness at the injection site or a feeling of warmth in general.

Cases of nephrogenic systemic fibrosis (NSF) have been reported with Magnegita (see section 4.4).

Frequency of adverse events from post-approval data (spontaneous and clinical studies):
Frequency estimates are based on data obtained in pre-approval and post-approval studies in more than 13.000 patients as well as data from spontaneous reporting.

MedDRA System organ class	**Uncommon** **(≥1/1,000) to <1/100)**	**Rare** **(≥1/10,000 to <1/1,000)**	**Not known** (cannot be estimated from the available data).
Blood and Lymphatic System Disorders:		transitory increase in serum iron value	

Nervous System Disorders	dizziness, paraesthesia, headache	agitation, confusion, disturbance in speech and smelling, convulsions, tremor, coma, somnolence	
Eye Disorders		eye pain, disturbed vision, lacrimation,	
Ear and Labyrinth Disorders		pain of the ears, disturbed hearing	
Cardiac Disorders		clinically relevant transient disturbance of heart rate and blood pressure, disturbance in cardiac rhythm or function, cardiac arrest	
Vascular Disorders		vasovagal reactions, circulatory reactions accompanied by peripheral vasodilatation, subsequent hypotension and syncope, reflex tachycardia and cyanosis possibly leading to unconsciousness.	
Respiratory, Thoracic and Mediastal Disorders		transitory disturbance in respiratory rate, shortness of breath, dyspnea, respiratory arrest, pulmonary oedema	
Gastrointestinal Disorders	nausea, vomiting	abdominal pain, diarrhoea, disturbance in taste, dry mouth, salivation	
Hepatobiliary Disorders		transitory increases in liver enzyme levels and bilirubine value	
Skin and Subcutaneous Tissue Disorders		erythema and flush associated with vasodilatation, and exanthema	

MedDRA System organ class	**Uncommon (≥1/1,000) to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Not known** (cannot be estimated from the available data).
Musculoskeletal and Connective Tissue Disorders		back pain, arthralgia,	
Renal and Urinary Disorders		urinary incontinence, urinary urgency, in patients with impairment of renal function: elevated serum creatinine values and acute renal failure	

General Disorders and Administration Site Conditions	sensation of heat	chest pain, malaise, chills, sweating, asthenia, changes in body temperature, fever extravasation with local pain, coldness, mild feeling of warmth and oedema, inflammation, tissue necrosis, phlebitis and thrombophlebitis	Cases of Nephrogenic Systemic Fibrosis (NSF) have been reported
Immune System Disorders		Hypersensivity/anaphylactic reaction: Angiooedema, conjunctivitis, coughing, pruritus, rhinitis, sneezing, urticaria, bronchospasm, laryngeal spasm, laryngeal/pharyngeal edema, hypotension, shock	

Anaphylactic reactions which may occur irrespective of the dose and the method of administration, may be symptoms of an incipient shock.
Delayed reactions associated with contrast agents are rare (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; E-mail: medsafety@hpra.ie

4.9 Overdose

No case of overdose has been reported.

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

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

Magnegita can be removed by haemodialysis. If intoxication occurs due to overdose gadopentetate dimeglumine can be removed by haemodialysis. However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

Due to the small amount of active substance used and the very small amount of gastrointestinal absorption (< 1 %) intoxication for an unintentionally oral ingestion is very unlikely.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Paramagnetic contrast media: ATC-Code: V08C A01

Magnegita is a paramagnetic medium for Magnetic Resonance Imaging (MRI). The contrast enhancing effect is produced by the Di-N-methyl glucamine salt of gadopentetate (GdDTPA) — the gadolinium complex of diethylene triamine penta-acetic acid.

The spin grid relaxation time of activated atomic nuclei is shortened by the gadolinium ion and will, in proton MRI with suitable imaging sequence (such as T_1 weighted spin echo procedure), increase the signal intensity and thereby the

image contrast.

Gadopentetate dimeglumine shows only slight dependency on the intensity of the magnetic field.

Gadopentetate dimeglumine does not show significant protein binding or inhibitory interactions with enzymes (such as myocardial Na^+- and K^+-ATPase). The substance is excreted through glomerular filtration by the kidneys. Adverse events on kidney function have not been observed.

Gadopentetate dimeglumine provides contrast enhancement and facilitates visualisation of abnormal structures or lesions in various parts of the body including the CNS. Gadopentetate dimeglumine does not cross the intact blood-brain barrier. In cases of blood-brain barrier dysfunction, administration of gadopentetate dimeglumine may lead to improved visualisation of pathological changes, and lesions with abnormal vascularity (or those thought to cause abnormalities in the blood-brain barrier) in the brain (intracranial lesions), spine and associated tissues as well as lesions in the thorax, pelvic cavities and the retroperitoneal spaces. It also improves tumour delineation thus determining extent of invasiveness. Gadopentetate dimeglumine does not accumulate in normal brain or in lesions that do not have abnormal vascularity (e.g. cysts, mature postoperative scars). Signal enhancement is not seen with all types of pathological processes, e.g. some types of low-grade malignancies or inactive MS-plaques fail to enhance. Magnegita can thus be used for differential diagnosis between healthy and pathological tissues, different pathological structures, and in differentiation between tumour and tumour recurrences and cicatricial tissue after treatment.

In higher concentrations of gadopentate dimeglumine, after a longer incubation period *in vitro*, there will be a slight influence on erythrocyte morphology. This process, which is reversible, may lead to slight intravasal haemolysis after intravenous administration of gadopentetate dimeglumine in humans, which might explain the occasionally observed slight increase in serum bilirubin and iron during the first few hours after injection.

5.2 Pharmacokinetic properties

The behaviour of gadopentetate dimeglumine in the organism is similar to that of other hydrophilic and biologically inert compounds (i.e. Mannitol or Inulin). Dosage independent pharmacokinetics were observed in humans.

Distribution

After intravenous administration the active substance is rapidly distributed in the extracellular spaces.

Seven days after intravenous administration of radioactively marked gadopentetate dimeglumine < 1 % of the applied dosage was found in the residual body of rats and dogs, of which the greatest concentrations were found in their kidneys as the intact gadolinium complex.

Gadopentetate dimeglumine does not appear to penetrate or pass intact blood/brain or blood/testicle barriers. A small percentage passes through the placental barrier but is rapidly eliminated by the foetus.

For dosages of ≤ 250 micromol gadopentetate/kg body weight (= 0.5 ml solution for injection/kg) plasma levels drop after the distribution phase (within a few minutes of administration) with a half-life of about 90 minutes, which is identical to the renal excretion rate. For a dosage of 100 micromol gadopentetate dimeglumine/kg (= 0.2 ml solution for injection/kg) body weight, 3 and 60 minutes after injection 0.6 and 0.24 mmol gadopentetate dimeglumine/l plasma were determined, respectively.

Metabolisation

Metabolisation or splitting of the paramagnetic ion or has not been proven.

Excretion

Gadopentetate dimeglumine is eliminated unchanged by means of glomerular filtration via the kidneys. The share of extrarenal excretion is very low.

An average of 83 % of the initial dosage was eliminated in the urine within 6 hours post injection (p. i.) whilst within 24 hours about 91 % was eliminated. The dosage excreted via the faeces was <1 % (up to 5 days after injection). The renal clearance of gadopentetate dimeglumine was approximately 120 ml/min normalised for 1.73 m^2 body surface and is therefore comparable to that of inulin or ^{51}Cr-EDTA.

Special characteristics in patients with restricted kidney function

Even with slightly to moderately restricted kidney function (creatinine clearance > 20 ml/min), gadopentetate

dimeglumine is entirely excreted by the kidneys. The plasma half-life of gadpentetate dimeglumine increases in relation to the degree of renal insufficiency. An increase in extrarenal excretion was not observed.

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

Pre-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Developmental retardation was observed after repeated administration of gadopentetate dimeglumine in pregnant rabbits. Experimental tests regarding the local tolerability of gadopentetate dimeglumine after single and repeated intravenous and single intra-muscular injection indicated that accidental paravenous application might lead to slight local reactions at the application site.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pentetic acid
Meglumine
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

5 years

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °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 at 2 to 8 °C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Glass vials type I with bromobutyl rubber closure and aluminium caps for single use.

1 x 5 ml	10 x 5 ml
1 x 10 ml	10 x 10 ml
1 x 15 ml	10 x 15 ml
1 x 20 ml	10 x 20 ml
1 x 30 ml	10 x 30 ml

Glass vials type II with bromobutyl rubber closure and aluminium caps for single use.

1 x 100 ml 10 x 100 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused portions and waste material derived from disposal and items which come into contact with the product when administering this product with an automatic application system should be disposed of in accordance with local requirements.

The peel-off tracking label on the vials 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.

7 MARKETING AUTHORISATION HOLDER

Agfa Healthcare Imaging Agents GmbH
Am Coloneum 4
50829 Koln
Germany

8 MARKETING AUTHORISATION NUMBER

PA 1504/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th June 2008

10 DATE OF REVISION OF THE TEXT

March 2015