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Guideline on core SmPC and Package Leaflet for gadopentetate dimeglumine

Draft

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Executive summary

This guideline describes the information to be included in the Summary of Products Characteristics (SmPC) and package leaflet for gadopentetate dimeglumine.

1. Introduction (background)

The purpose of this core SmPC and package leaflet is to provide applicants and regulators with harmonised guidance on the information to be included in the Summary of product characteristics (SmPC) gadopentetate dimeglumine [1]. This guideline should be read in conjunction with the QRD product information templates and the guideline on Summary of Product Characteristics.

This Core SmPC has been prepared on the basis, and taking into account the available published scientific literature. However, any new application or extension of indications for a radiopharmaceutical product containing gadopentate dimeglumine should be submitted with all the required data in order to be valid. For any new indication that is not in the core SmPC, it should be supported by appropriate efficacy and safety data.

2. Scope

This core SmPC and package leaflet covers gadopentetate dimeglumine.

3. Legal basis

This guideline has to be read in conjunction with Article 11 of Directive 2001/83 as amended, and the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended.

4. Core SmPC and Package Leaflet for gadopentetate dimeglumine

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

< ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.>

1. NAME OF THE MEDICINAL PRODUCT

{X} 500 micromol/mL solution for injection <in prefilled <syringe><cartridge>>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL solution for injection contains 469 mg of gadopentetate dimeglumine equivalent to 500 micromol, equivalent to 78.63 mg gadolinium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear solution

pH		[Product specific]
Viscosity [mPa s]	20 °C	[Product specific]
	37 °C	[Product specific]
Osmolality at 37 °C [mOsm/kg H2O]		[Product specific]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
Gadopentetate dimeglumine is a contrast medium magnetic resonance imaging (MRI) indicated for visualisation of abnormal structures or lesions and differentiation between healthy and pathological tissue in

- Cranial and spinalMRI.
- Whole body MRI including head and neck region, thoracic space (including the heart and female breast), abdomen (pancreas and liver), retroperitoneal space (kidney), pelvis (prostate, bladder and uterus) and musculoskeletal system.
- Specific applications in the heart include measurement of myocardial perfusion under pharmacological stress conditions and viability diagnostics ("delayed enhancement").
- MR angiography (except for coronary arteries) for the assessment of stenoses, occlusions and collaterals.

4.2 Posology and method of administration

This medicinal product should only be administered by trained healthcare professionals with technical expertise in performing and interpreting gadolinium enhanced MRI.

<u>Posology</u>

Adults, adolescents and children over the age of two years
The recommended dose in adults and children and adolescents is 0.2 mL/kg body weight of the 0.5 M solution (0.1 mmol/kg).

If a strong clinical suspicion of a lesion persists despite an unremarkable scan or in lesions with poor vascularisation and/or a small extracellular space, a further injection of 0.2 mL/kg body weight for adults may be performed within 30 minutes of the first injection.

Maximum dose in children over the age of two years: 0.4 mL/kg body weight.

For the exclusion of metastases or tumour recurrence in adults, an initial dose of 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 of 0.6 mL/kg may be necessary in adults to visualize blood vessels (e.g.MR angiography).
Maximum dose in adults: 0.6 mL/kg body weight.

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

Renal impairment / Hepatic impairment
Gadopentetate dimeglumine is contraindicated in patients with severe renal impairment (GFR < 30 mL/min/1.73 m2) and in patients in the perioperative liver transplantation period (see section 4.3).

Gadopentetate dimeglumine should only be used after careful risk/benefit evaluation in patients with moderate renal impairment (GFR 30 59 mL/min/1.73 m^2) at a dose not exceeding 0.2 mmol/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, gadopentetate dimeglumine injections should not be repeated unless the interval between injections is at least 7 days.

Paediatric population (up to 2 years of age)
Gadopentetate dimeglumine 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, gadopentetate dimeglumine should only be used in these patients after careful consideration.

More than one dose should not be used during a scan. Because of the lack of information on repeated administration, gadopentetate dimeglumine injections should not be repeated unless the interval between injections is at least 7 days.

The conduct of a whole-body MRI is not recommended in infants under 6 months of age. The product should be used only after careful consideration in these patients.

The required dose of gadopentetate dimeglumine 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 for use (neonates and infants).

Method of administration
{X} is to be administered by intravenous injection. A bolus injection is possible.

Gadopentetate dimeglumine should be drawn in the syringe immediately before use. In order to guarantee full injection of the contrast product, the injection should be followed by a bolus of 5 mL of sodium chloride 9 mg/mL (0.9 %) solution for injection. Ideally the patient should be recumbent during administration.

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 exactly. This medicinal product is for single use only. Multiple injections are possible.

<For patient preparation, see section 4.4.>

Image acquisition
Contrast enhanced MRI may be initiated immediately after administration of the medium and should be performed within 45 minutes following injection. The optimal improvement of the contrast media is generally observed after 15 minutes after injection.

4.3 Contraindications

Previous anaphylactic reaction to the gadopentatate dimeglumine or to any of the excipients listed in section 6.1.
Severe renal dysfunction (GFR < 30 mL/min/1.73 m^2).
Patients in the perioperative liver transplantation period.
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.
Do not use by intrathecal route. Take care to maintain strictly intravenous injection: extravasation may result in local intolerance reactions, requiring the usual local care.
Appropriate facilities should be readily available for coping with any complication of the procedure, as well as for emergency treatment of severe reaction to the contrast medium itself (e.g. hypersensitivity, seizures).

Potential for hypersensitivity or anaphylactic reactions
All MRI contrast products can cause minor or major hypersensitivity reactions, characterised by cardiovascular, respiratory and cutaneous manifestations, which can be life-threatening. Most of these reactions occur immediately (within 30min) or in rare cases are delayed (after hours or days).

Severe reactions, including anaphylactic shock, occur very rarely. Anaphylactic reactions are immediate and can lead to death. They are independent of the dose, may occur upon the first administration of the product, and are often unforeseeable. The risk of a major reaction makes it necessary to have immediate access to the resources necessary for emergency life support.

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. Medication and equipment for the treatment of hypersensitivity reactions must be ready for use.

Patients with either previous reaction to contrast media, history of bronchial asthma or other allergic disposition have an increased risk of hypersensitivity reactions.

Before administration of the contrast medium
- ask the patient about previous reactions to contrast media or allergies,
- consider premedication with antihistamines and/or glucocorticoids in patients with the highest risk / known intolerance. However, they cannot prevent the occurrence of serious or fatal anaphylactic shock.

Throughout the examination
- provide medical monitoring

- maintain a venous access for emergency treatment in the event of a reaction.

After the examination

- competent personnel, drugs and equipment for emergency resuscitation must be available and the patient should remain in observation at least 30 minutes, because the majority of serious adverse effects occur within this interval.
- The patient should be informed of the possibility of delayed reactions.

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 central nervous system disorders

Patients with a history of convulsions 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. Precautionary measures should be taken, e.g. close monitoring, all equipment and drugs necessary to manage convulsions should they occur, must be ready for use.

Renal impairment

Prior to administration of gadopentetate dimeglumine, 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 gadopentetate dimeglumine and some other gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 mL/min/1.73 m2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. Therefore gadopentetate dimeglumine 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 m2) is unknown, therefore, gadopentetate dimeglumine should be only used after careful risk-benefit evaluation in patients with moderate renal impairment.

Haemodialysis shortly after gadopentetate dimeglumine administration may be useful at removing gadopentetate dimeglumine 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.

In patients with renal impairment, acute renal failure requiring dialysis or worsening renal function has been reported after application of gadopentetate dimeglumine. The risk of these events is higher with increasing dose of gadopentetate dimeglumine. Because gadopentetate is renally excreted, a sufficient period of time for elimination of the contrast agent from the body should be ensured prior to any re-administration in patients with renal impairment. Elimination half-life in patients with mild or moderate renal impairment is 3 to 4 hours.

Paediatric population (Neonates and infants)

For information on the use in paediatric population, see sections 4.2. or 5.1.

Gadopentetate dimeglumine 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, gadopentetate dimeglumine should only be used in these patients after careful consideration.

Patient preparation

<The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the examination in order to reduce radiation.
[or, in case of administration of higher activities:] Patients should be encouraged to increase oral fluids and urged to void as often as possible to reduce bladder radiation, especially after high activities e.g. for

radionuclide therapy. Patients with bladder voiding problems should be catheterised after high activity […] administration.>

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.

Patient preparation
Physicians should consider the possibility of nausea and vomiting as possible undesirable effects when using MRI contrast agents and recommend fasting if considered necessary.

<Excipients>
<This medicinal product contains sodium. The level of sodium is less than 1 mmol per bottle, essentially "sodium-free".>

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with other medicinal products have been performed.

Beta-blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, and angiotensin receptor antagonists induce decreased efficacy of cardiovascular compensation mechanisms of blood pressure changes. 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 adequate data from the use of gadopentetate dimeglumine in pregnant women. Animal studies at clinically relevant doses have not shown direct or indirect harmful effects with respect to reproductive toxicity after repeated administration whereas animal studies at repeated high doses have shown reproductive toxicity (see section 5.3).

Gadopentetate dimeglumine should not be used during pregnancy unless the clinical condition of the woman requires use of gadopentetate dimeglumine.

Breast-feeding
Very small amounts of gadopentetate dimeglumine are excreted into breast milk (a maximum of 0.04% of the dose administered intravenously). At clinical doses, no effects on the breast feeding child are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing or discontinuing breast feeding for a period of 24 hours after administration should be at the discretion of the doctor and breast feeding mother.

Fertility
There are no clinical data available with regard to effects on fertility.

4.7 Effects on ability to drive and use machines

Gadopentetate dimeglumine has minor influence on the ability to drive and use machines. Ambulant patients while driving vehicles or operating machines should take into account that delayed reactions (as nausea or hypotension) may incidentally occur.

4.8 Undesirable effects

Summary of the safety profile

The adverse drug reactions (ADRs) associated with the use of gadopentetate dimeglumine are usually of mild to moderate severity and transient. Serious, life-threatening and fatal adverse reactions have nevertheless been reported.

The most commonly reported ADRs are: Nausea, vomiting, headache, dizziness, various injection site reactions (e.g. pain, sensation of coldness, sensation of warmth) or a feeling of warmth in general.

The most serious ADRs in patients receiving are:

- Nephrogenic systemic fibrosis (NSF) (see section 4.4)
- Anaphylactic reactions which may occur irrespective of the dose and the method of administration and which may be symptoms of an incipient shock

Tabulated list of ADRs

Frequency of adverse reactions 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. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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 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, Dyspnoea*, Respiratory arrest[§]*, Bronchospasm[§]*, Coughing, Wheezing, Laryngospasm[§]*, Laryngeal oedema[§]*, Pharyngeal oedema[§]*, Cyanosis[§]*, Rhinitis[§], Angioedema[§]*, Oedema face*, Reflex tachycardia[§])	

Psychiatric disorders		Disorientation	Agitation, Confusion
Nervous system disorders	Dizziness, Headaches, Dysgeusia	Convulsion*, Paraesthesia, Burning sensation, Tremor	Coma*,Somnolence*,S peech disorder, Parosmia
Eye disorders			Visual disturbance, Eye pain, Lacrimation
Ear and labyrinth disorders			Hearing impaired, Ear pain
Cardiac disorders		Tachycardia*, Arrhythmia	Cardiac arrest*, Heart rate decreased/bradycardia*
Vascular disorders		Thrombophlebitis, Flushing, Vasodilation	Syncope*, Vasovagal reaction, Blood pressure increased
Respiratory, thoracic and mediastinal disorders		Throat irritation, Pharyngolaryngeal pain/ Pharynx discomfort, Cough	Respiratory distress, Respiratory rate increased or Respiratory rate decreased Pulmonary oedema*
Gastrointestinal disorders	Nausea, Vomiting	Abdominal pain, Stomach discomfort, Diarrhoea, Toothache, Dry mouth, Oral soft tissue pain and paraesthesia	Salivation
Hepato-biliary disorders			Blood bilirubin increased, Hepatic enzyme increased
Skin and subcutaneous tissue disorders			Nephrogenic Systemic Fibrosis (NSF)*
Musculoskeletal, connective tissue and bone disorders		Pains in extremity	Back pain, Arthralgia
Renal and urinary disorders			Acute renal failure*,**, Increased serum creatinine**, Urinary incontinence, Urinary urgency
General disorders and administration site conditions	Pain, Feeling hot, Feeling cold, Injection site reactions (e.g. Injection site coldness, paresthesia, swelling, warmth,	Chest pain, Pyrexia, Oedema peripheral, Malaise Fatigue Thirst, Asthenia	Chills, Sweating, Body temperature increased or Body temperature decreased

	pains, oedema, irritation, haemorrhage, erythema, discomfort, necrosis[§], thrombophlebitis[§], phlebitis[§], inflammation[§], extravasation[§])		

* life-threatening and/or fatal cases have been reported
** in patients with previously diagnosed kidney damage
[§] Reactions identified only during post-marketing surveillance (frequency not known)

Description of selected ADRs

Delayed reactions associated with contrast agents are rare. In patients with dialysis-dependent renal failure who received gadopentetate dimeglumine, 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 gadopentetate dimeglumine on the day before haemodialysis.

Injection site reactions and vascular disorders: Skin and soft tissue necrosis, thrombosis, fasciitis, and compartment syndrome requiring surgical intervention (e.g., compartment release or amputation) have occurred very rarely at the site of contrast injection or the dosed limb. Total volume and rate of injection, extravasation of contrast agent, and patient susceptibility might contribute to these reactions. Phlebitis and thrombophlebitis may be observed generally within 24 hours after injection and resolve with supportive treatment.

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 the national reporting system listed in Appendix V*.
*[*For the printed material, please refer to the guidance of the annotated QRD template.]*

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 gadopentetate dimeglumine: increased pulmonary artery pressure, osmotic diuresis, hypervolaemia, dehydration, local vascular pain and/or injection site pain.

Gadopentetate dimeglumine can be removed by haemodialysis. 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: Magnetic resonance imaging contrast media, paramagnetic contrast media, ATC code: V08CA01

Mechanism of action

Gadopentetate dimeglumine is a paramagnetic medium for 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 T1 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.

Clinical efficacy and safety
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. Gadopentetate dimeglumine 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.

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.

Gadopentetate dimeglumine does not show significant protein binding or inhibitory interactions with enzymes (such as myocardial Na+- and K+ ATPase).

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

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.

Elimination
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 m2 body surface and is therefore comparable to that of inulin or 51Cr-EDTA.

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.

Renal/Hepatic impairment

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 gadopentetate dimeglumine increases in relation to the degree of renal insufficiency. An increase in extrarenal excretion was not observed.

5.3 Preclinical safety data

Preclinical 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 intra-venous 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

[Product specific]

6.2 Incompatibilities

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

6.3 Shelf life

[Product specific]

Chemical and physical in-use stability has been demonstrated for {X} 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 {X} hours at 2 °C to 8 °C.

6.4 Special precautions for storage

Do not store above 30 °C.

Keep the <vial><bottle> in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

<Not all pack sizes may be marketed.>

[General description of primary and protective shielded secondary container should be included]

[Product specific]

6.6 Special precautions for disposal and other handling

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

The <vial><bottle> should not be used if its integrity is compromised at any time in the preparation of this product.

The peel-off tracking label on the <vials><bottles> should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded.
Any unused product and waste material derived from disposal, as well as items that come into contact with the product when administering it with an automatic application system should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

<Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu>

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

{X} 500 micromol/mL solution for injection <in prefilled <syringe><cartridge>>
gadopentetate dimeglumine

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your radiologist/doctor who will supervise the procedure.
- If you get any side effects, talk to your radiologist/doctor. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What X is and what it is used for
2. What you need to know before X is used
3. How X is used
4. Possible side effects
5. How X is stored
6. Contents of the pack and other information

1. What X is and what it is used for

{X} contains gadopentetate dimeglumine, a product which enhances contrast. It is for diagnostic use only.

{X} is used in examinations with Magnetic Resonance Imaging (MRI).

It is used during cranial (head), spinal and whole body MRI scans including head and neck region, the chest including heart and female breast, the belly including pancreas and liver, the kidneys, the pelvis including prostatic gland, bladder and womb, the muscles and the bones.

It may be used to facilitate the visualization, detection and characterisation of several different types of tumours (growths) or lesions in the head, spine and various sites of the body.

In addition, the visualisation of all blood vessels (MR-angiography) is possible (with exception of the arteries of the heart), especially for diagnosis of narrowing or obstructions of the vessels.

The blood supply to the heart muscle under stress conditions, for example induced by medicines, can be measured and viability of the heart muscle can be diagnosed ("delayed enhancement").

2. What you need to know before X is used

X must not be used
- if you had a severa allergic reaction to gadopentetate dimeglumine or any of the other ingredients of {X}.
- if you suffer from severe kidney problems, or if you are a patient who is about to have or has recently had a liver transplant, as use of {X} in patients with these conditions has been associated with a disease called nephrogenic systemic fibrosis (NSF). NSF is a disease involving thickening of the skin and connective tissues. NSF may result in severe joint immobility, muscle weakness or may affect the normal working of internal organs which may potentially be life-threatening.

Warnings and precautions

Take special care with X

- if you have a heart pacemaker, an iron-based (ferromagnetic) clip or an implant or an insulin pump, please inform your radiologist/doctor about this. It is a condition where MRI is not suitable.
- {X} may trigger allergic or other specific individual reactions that may have consequences on your heart, on your respiratory tract or on your skin.

If an allergic reaction occurs, the radiologist/doctor will stop the administration of the contrast medium at once and, if necessary, will start appropriate treatment of the allergic reactions.

Therefore, it is recommended that you have a flexible in-dwelling catheter during the examination, to enable immediate action in case of emergencies.

Very rarely, severe reactions, including shock, may occur. Therefore, you should read the following very carefully:

- if you have, or if you have ever had, bronchial asthma or other allergies or a previous allergic reaction to contrast media you may be more likely to have an allergic reaction during the examination. Tell your radiologist/doctor if you suffer from these conditions. You may be given another medicine before the examination to prevent them.
- if you are taking a beta-blocker (medicines used against high blood pressure, heart problems and other conditions) you should tell your radiologist/doctor. Patients treated with beta-blockers do not necessarily respond to other medicines usually used for the treatment of allergic reactions.
- if you have any heart problems (e. g. severe heart failure, coronary artery disease) **you are more susceptible to serious or even fatal outcomes of severe allergic reactions.**
- if you have fits or seizures you may have an increased risk of suffering from one during the examination.
- if you suffer from moderate renal impairment (GFR 30-59 mL/min/1.73 m^2) you should tell your radiologist/doctor. Your doctor will screen your renal function before administering {X}.

Before administration of X you should tell your radiologist/doctor if::

- your kidneys do not work properly
- you have recently had, or soon expect to have, a liver transplant

Before you receive {X}, you will need to have a blood test to check how well your kidneys are working.

Children and adolescents

{X} should not be used in newborn babies up to the age of 4 weeks. As kidney function is immature in infants up to 1 year of age, {X} will only be used in infants after careful consideration by the doctor.

Other medicines and X

Tell your radiologist / doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Especially tell your doctor if you take beta blockers (medicines used for high blood pressure, heart problems and other conditions).

X with food and drink

It is very important that you do not eat anything for 2 hours prior to the investigation.

Pregnancy

You must inform the radiologist/ doctor before the administration of X if there is a possibility you might be pregnant, if you have missed your period or if you are breast-feeding.
When in doubt, it is important to consult your radiologist/doctor who will supervise the procedure.

If you are pregnant
[*product specific]*

The radiologist/doctor will only administer this product during pregnancy if a benefit is expected which would outweigh the risks.

If you are breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Breast-feeding should be discontinued for at least 24 hours after you receive {X}.

Driving and using machines
Your injection is unlikely to affect your ability to drive or to operate machines. However, while driving vehicles or operating machines, you should take account that nausea or low blood-pressure may incidentally occur.

X contains {name the excipient(s)}

3. How X is used

{X} will be given by an authorised healthcare professional directly into a vein (intravenously).
Ideally you should be recumbent during administration, and you will be kept under supervision for at least 30 minutes after the injection by your radiologist/doctor. This is the time where most undesired reactions (e. g. allergic reactions) may occur. However, in rare cases, reactions may occur after hours or days.

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.

This medicine is for single use only.

Adults, adolescents and children (over the age of two years)
The dose for cranial, spinal and whole body MRI used will depend on the type of lesion that is being investigated but it is usually between 0.2 and 0.6 mL/kg body weight for adults and between 0.2 and 0.4 mL/kg body weight for children.

Dosage in special patient groups
Patients with impaired renal function
You should not be given {X} if you suffer from severe kidney problems or if you are a patient who is about to have or has recently had a liver transplant.
{X} should also not be used in newborn babies up to the age of 4 weeks.
If you have moderate kidney problems, you should only receive one dose of {X} during a scan and you should not receive a second injection for at least 7 days.

Neonates and infants
As kidney function is immature in neonates and infants up to 1 year of age, they should only receive one dose of {X} during a scan and should not receive a second injection for at least 7 days.

Elderly
It is not necessary to adjust your dose if you are 65 years of age or older but you will have a blood test to check how well your kidneys are working.

If you have been given more X than you should
An overdose is unlikely.

This medicine will be given to you by a healthcare professional. If you think that you have received too much medicine, tell your doctor or nurse immediately.
If you have any further questions on the use of this product, ask your doctor, radiographer or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The most commonly reported side effects with {X} are nausea, vomiting, headache, dizziness, pain and a feeling of warmth or coldness at the injection site or a feeling of warmth in general.
There have been reports of nephrogenic systemic fibrosis (which causes hardening of the skin and may affect also soft tissue and internal organs).
Other side effects that may occur have been listed by frequency:

Frequency	**Adverse reaction**
Uncommon (affects 1 to 10 users in 1,000)	Dizziness, numbness (paraesthesia), headache Nausea, vomiting Sensation of heat
Rare (affects 1 to 10 users in 10,000)	Short term increase in blood iron Hypersensivity/anaphylactic reaction: angioedema, inflammation of the eye (conjunctivitis), coughing, itching, runny nose, sneezing, skin rashes (urticaria), wheeziness, tightness of the voicebox (larynx), swelling of the voice box (larynx) and the throat (pharynx), low blood pressure, shock
Very rare (affects less than 1 user in 10,000)	Agitation, confusion, speech or smelling disturbance, fits, tremor, coma, sleepiness Eye pain, sight disturbance, eyes watering Pain of the ear, hearing disturbance Changes in heart rate or rhythm, blood pressure changes, heart stops beating Widening of the blood vessels and changes in blood flow causing low blood pressure followed by fainting, fast heart rate (tachycardia), difficulties in breathing and turning blue possibly leading to unconsciousness and shock Short term changes in breathing rate, shortness of breath, difficulty in breathing, stopping breathing, fluid in the lungs Abdominal pain, diarrhoea, taste disturbance, dry mouth, excess saliva Short-term increase in liver enzymes and bilirubine value Swelling of eyelids, face or lips, redness of the skin, itchiness Back pain or joint pain Urinary incontinence (urine leaking) or urgency, short term changes in kidney function values or acute renal failure in patients with disturbed kidney function Chest pain, chills, sweating, changes in body temperature, fever Pain at the administration site, feeling of coldness or warmth, swelling, inflammation, degeneration of tissue (tissue necrosis), inflammation of the veins at the injection site
Not known (frequency cannot be estimated from the available data)	Cases of nephrogenic systemic fibrosis/ nephrogenic fibrosing dermophathy (a condition in patients with kidney disease with hardening of the skin and other organs)

Some people may have an allergic reaction to {X}. Tell your doctor immediately if any of the following rare severe allergy symptoms occur:

- Sudden wheeziness and tightness of the chest
- Swelling of eyelids, face or lips

- Skin rashes (urticaria), itchiness, fever
- Collapse
- Turning blue (cyanosis)

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Reporting of side effects

If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

*[*For the printed material, please refer to the guidance of the annotated QRD template.]*

5. How X is stored

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date that is stated on the label<carton> <bottle> <vial> <after {abbreviation used for expiry date}.>. The expiry date refers to the last day of that month.

Keep the <vial><bottle> in the outer carton in order to protect from light.

Do not store above 30 °C.

Chemical and physical in-use stability has been demonstrated 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°C to 8°C.

Do not use this medicine if you notice any visible signs of deterioration (such as particles in the solution or fissures in the vial).

<Do not throw away any medicines via wastewater <or household waste>. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What X contains

The active substance is gadopentetate dimeglumine.

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

The other ingredients are [*product specific*]

What X looks like and contents of the pack

Solution for injection.

Clear solution.

[*Nature and contents of the container - product specific*]

{X} is presented in the following packs:

[*Product specific*]

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

<For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:>

België/Belgique/Belgien
{Nom/Naam/Name}
<{Adresse/Adres/Anschrift }
B-0000 {Localité/Stad/Stadt}>
Tél/Tel: + {N° de téléphone/Telefoonnummer/ Telefonnummer}
<{e-mail}>

Luxembourg/Luxemburg
{Nom}
<{Adresse}
L-0000 {Localité/Stadt}>
Tél/Tel: + {N° de téléphone/Telefonnummer}
<{e-mail}>

България
{Име}
<{Адрес}
{Град} {Пощенски код}>
Тел.: + {Телефонен номер}
<{e-mail}>

Magyarország
{Név}
<{Cím}
H-0000 {Város}>
Tel.: +Telefonszám}
<{e-mail}>

Česká republika
{Název}
<{Adresa}
CZ {město}>
Tel: +{telefonní číslo}
<{e-mail}>

Malta
{Isem}
<{Indirizz}
MT-0000 {Belt/Raħal}>
Tel: + {Numru tat-telefon}
<{e-mail}>

Danmark
{Navn}
<{Adresse}
DK-0000 {by}>
Tlf: + {Telefonnummer}
<{e-mail}>

Nederland
{Naam}
<{Adres}
NL-0000 XX {stad}>
Tel: + {Telefoonnummer}
<{e-mail}>

Deutschland
{Name}
<{Anschrift}
D-00000 {Stadt}>
Tel: + {Telefonnummer}
<{e-mail}>

Norge
{Navn}
<{Adresse}
N-0000 {poststed}>
Tlf: + {Telefonnummer}
<{e-mail}>

Eesti
(Nimi)
<(Aadress)
EE - (Postiindeks) (Linn)>
Tel: +(Telefoninumber)

Österreich
{Name}
<{Anschrift}
A-00000 {Stadt}>
Tel: + {Telefonnummer}

<{e-mail}>

Ελλάδα
{Όνομα}
<{Διεύθυνση}
GR-000 00 {πόλη}>
Τηλ: + {Αριθμός τηλεφώνου}
<{e-mail}>

España
{Nombre}
<{Dirección}
E-00000 {Ciudad}>
Tel: + {Teléfono}
<{e-mail}>

France
{Nom}
<{Adresse}
F-00000 {Localité}>
Tél: + {Numéro de téléphone}
<{e-mail}>

Ireland
{Name}
<{Address}
IRL - {Town} {Code for Dublin}>
Tel: + {Telephone number}
<{e-mail}>

Ísland
{Nafn}
<{Heimilisfang}
IS-000 {Borg/Bær}>
Sími: + {Símanúmer}
<{Netfang }>

Italia
{Nome}
<{Indirizzo}
I-00000 {Località}>
Tel: + {Numero di telefono}>
<{e-mail}>

Κύπρος
{Όνομα}
<{Διεύθυνση}
CY-000 00 {πόλη}>
Τηλ: + {Αριθμός τηλεφώνου}
<{e-mail}>

Latvija
{Nosaukums}
<{Adrese}
{Pilsēta}, LV{Pasta indekss }>
<{e-mail}>

Polska
{Nazwa/ Nazwisko:}
<{Adres:}
PL – 00 000{Miasto:}>
Tel.: + {Numer telefonu:}
<{e-mail}>

Portugal
{Nome}
<{Morada}
P-0000–000 {Cidade}>
Tel: + {Número de telefone}
<{e-mail}>

România
{Nume}
<{Adresă}
{Oraş} {Cod poştal} – RO>
Tel: + {Număr de telefon}
<{e-mail}>

Slovenija
{Ime}
<{Naslov}
SI-0000 {Mesto}>
Tel: + {telefonska številka}
<{e-mail}>

Slovenská republika
{Meno}
<{Adresa}
SK-000 00 {Mesto}>
Tel: + {Telefónne číslo}
<{e-mail}>

Suomi/Finland
{Nimi/Namn}
<{Osoite/Adress}
FIN-00000 {Postitoimipaikka/Stad}>
Puh/Tel: + {Puhelinnumero/Telefonnummer}
<{e-mail}>

Sverige
{Namn}
<{Adress}
S-000 00 {Stad}>
Tel: + {Telefonnummer}
<{e-mail}>

United Kingdom
{Name}
<{Address}
{Town} {Postal code} – UK>

Tel: + {Telefona numurs}
<{e-mail}>

Tel: + {Telephone number}
<{e-mail}>

Lietuva
{pavadinimas}
<{adresas}
LT {pašto indeksas} {miestas}>
Tel: +370{telefono numeris}
<{e-mail}>

This leaflet was last revised in {MM/YYYY} {month YYYY}

<Other sources of information>

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu <There are also links to other websites about rare diseases and treatments.>

<This leaflet is available in all EU/EEA languages on the European Medicines Agency website.>

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The following information is intended for medical or healthcare professionals only:
Prior to administration of gadopentetate dimeglumine, 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 gadopentetate dimeglumine and some other gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 mL/min/1.73 m2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. Therefore gadopentetate dimeglumine must not be used in patients with severe renal impairment, in patients in the perioperative liver transplantation period.

Gadopentetate dimeglumine should also not be given to newborn babies up to the age of 4 weeks.
The risk for development of NSF in patients with moderate renal impairment (GFR 30 - 59 mL/min/1.73 m2) is unknown, therefore, gadopentetate dimeglumine should be only used after careful risk-benefit evaluation in patients with moderate renal impairment at a dose not exceeding 0.2 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, gadopentetate dimeglumine injections should not be repeated unless the interval between injections is at least 7 days.

Due to immature renal function in infants up to 1 year of age, gadopentetate dimeglumine should only be used in these patients after careful consideration at a dose not exceeding 0.2 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, gadopentetate dimeglumine injections should not be repeated unless the interval between injections is at least 7 days. Gadopentetate dimeglumine should not be given to newborn babies up to age of 4 weeks.

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.

Haemodialysis shortly after gadopentetate dimeglumine administration may be useful at removing gadopentetate dimeglumine 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.

Gadopentetate dimeglumine should not be used during pregnancy unless the clinical condition of the woman requires use of gadopentetate dimeglumine.

Breast-feeding should be discontinued for at least 24 hours after the administration of gadopentetate dimeglumine.

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

The complete SmPC of {(Invented) name} is provided <as a separate document> <as a tear-off section at the end of the printed leaflet> in the product package, with the objective to provide healthcare professionals with other additional scientific and practical information about the administration and use of this radiopharmaceutical.

Please refer to the SmPC [SmPC should be included in the box].