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4 Guideline on core SmPC and Package Leaflet for gadoteric 5 acid

6 Draft

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Comments should be provided using this template. The completed comments form should be sent to radiopharmaceuticalsDG@ema.europa.eu.

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Keywords	***Magnetic resonance, contrast media, gadolinium compounds, core SmPC, core Package Leaflet, gadoteric acid***

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Guideline on core SmPC and Package Leaflet for gadoteric acid

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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 gadoteric acid.

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) gadoteric acid [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 contrast agent product containing gadoteric acid 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 gadoteric acid.

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 gadoteric acid

[1]Concept paper on the harmonisation and update of the clinical aspects in the authorised conditions of use for radiopharmaceuticals and other diagnostic medicinal products (EMEA/CHMP/EWP/12052/2008)

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.> [For medicinal products subject to additional monitoring ONLY]

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name 0.5 mmol/mL solution for injection <in prefilled syringe/cartridge>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution for injection contains 279.32 mg gadoteric acid (as meglumine salt), equivalent to 0.5 mmol., equivalent to … mg gadolinium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear colourless to yellow solution

pH		*[Product specific]*
Viscosity [mPa s]	20 °C	*[Product specific]*
	37 °C	*[Product specific]*
Osmolality at 37 °C [mOsm/kg H_2O]		[*Product specific*]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Gadoteric acid is a contrast agent indicated for

Enhancement of the contrast in Magnetic Resonance Imaging (MRI) for a better visualization/delineation:

- MRI of the CNS including lesions of the brain, spine, and surrounding tissues
- Whole body MRI including lesions of the liver, kidneys, pancreas, pelvis, lungs, heart, breast, and musculoskeletal system.
- MR angiography including lesions or stenoses of the non-coronary arteries.

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.

Posology

The recommended dose for intravenous injection in adults is 0.2 mL/kg body weight (BW) (equivalent to 0.1 mmol/kg BW) to provide diagnostically adequate contrast.

Encephalic and spinal MRI

In patients with brain tumors, an additional dose of 0.4 mL/kg BW (equivalent to 0.2 mmol/kg BW) may improve tumor characterisation and facilitate therapeutic decision making.

Angiography
In exceptional circumstances (e.g. failure to gain satisfactory images of an extensive vascular territory) administration of a second consecutive injection of 0.2 mL/kg body weight (BW) (equivalent to 0.1 mmol/kg BW may be justified. However, if the use of 2 consecutive doses of gadoteric acid is anticipated prior to commencing angiography, use of 0.1mL/kg BW (equivalent 0.05 mmol/kg BW) to for each dose may be of benefit, depending on the imaging equipment available.

Renal impairment
The adult dose applies to patients with mild to moderate renal impairment (GFR $\geq$ 30 mL/min/1.73m^2). Gadoteric acid should only be used in patients with severe renal impairment (GFR < 30 mL/min/1.73m^2) and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If it is necessary to use Gadoteric acid, the dose should not exceed 0.2 mL/kg body weight (BW) (equivalent to 0.1 mmol/kg BW). More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Gadoteric acid 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).

Impaired hepatic function
The adult dose applies to these patients. Caution is recommended, especially in the case of perioperative liver transplantation period (see above impaired renal function).
The 0.1 mmol/kg BW dose applies to all indications except angiography.

Children
The 0.2 mL/kg body weight (BW) (equivalent to 0.1 mmol/kg BW) dose applies to all indications except angiography. Gadoteric acid is not recommended for angiography in children under 18 years of age due to insufficient data on efficacy and safety in this indication.
Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Gadoteric acid should only be used in these patients after careful consideration at a dose not exceeding 0.2 mL/kg body weight (BW) (equivalent to 0.1 mmol/kg BW). More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Gadoteric acid injections should not be repeated unless the interval between injections is at least 7 days.
Use for whole body MRI is not recommended in children less than 6 months of age.

<u>Method of administration</u>

The product is indicated for intravenous administration only.

Infusion rate: 3-5 mL/min (higher infusion rates up to 120 mL/min, i.e. 2 mL/sec, may be used for angiographic procedures).

Intravascular administration of contrast media should, if possible, be done with the patient lying down. After the administration, the patient should be kept under observation for at least half an hour, since experience shows that the majority of undesirable effects occur within this time.

For single patient use only, any unused solution should be discarded.

<u>Image acquisition</u>

Contrast enhanced MRI may be initiated immediately after administration of the agent. Optimal imaging: within 45 minutes after injection. Optimal image sequence: T1-weighted

4.3 Contraindications

Previous anaphylactic reaction to gadolinium, to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 agent 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 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 agent 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 agent

- 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 administration of the contrast agent

- competent personnel, drugs and equipment for emergency resuscitation must be available and the patient should remain under 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 gadoteric acid 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.

Impaired renal function
Prior to administration of gadoteric acid, 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 some 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. As there is a possibility that NSF may occur with Gadoteric acid, it should therefore only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI.

Haemodialysis shortly after gadoteric acid administration may be useful at removing gadoteric acid 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.

Paediatric population (Neonates and infants)

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Gadoteric acid should only be used in these patients after careful consideration.
In neonates and infants the required dose should be administered by hand.

Elderly

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

In patients with severe cardiovascular disease Gadoteric acid should only be administrated after careful risk benefit assessment because only limited data are available so far.

CNS disorders

Like with other gadolinium containing contrast agents special precaution is necessary in patients with a low threshold for seizures. Precautionary measures should be taken, e.g. close monitoring. All equipment and drugs necessary to counter any convulsions which may occur must be made ready for use beforehand.

Patient preparation
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.

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, angiotensin receptor antagonists: These medicinal products 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of gadoteric acid in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
Gadoteric acid should not be used during pregnancy unless the clinical condition of the woman requires use of gadoteric acid.

Lactation

Gadolinium containing contrast agents are excreted into breast milk in very small amounts (see section 5.3). At clinical doses, no effects on the infant 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 of Gadoteric acid, should be at the discretion of the doctor and lactating mother.

Fertility

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

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 nausea may incidentally occur.

4.8 Undesirable effects

Summary of the safety profile

The adverse drug reactions (ADRs) associated with the use of gadoteric acid are usually of mild to moderate severity and transient. A sensation of heat, cold and/or pain at the injection site are the most frequently observed reactions.

During clinical trials, headache and paresthesia were very commonly observed (>1/10), and nausea, vomiting and skin reactions such as erythematous rash and pruritus were commonly observed (>1/100 - <1/10). Since post-marketing, the most commonly reported adverse reactions following administration of gadoteric acid are nausea, vomiting, pruritus and hypersensitivity reactions.

Tabulated list of ADRs

The adverse reactions are listed in the table below by SOC (System Organ Class) and by frequency with the following guidelines: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data). The data presented are from clinical trials when available, or from an observational study involving 82,103 patients.

System Organ Class	Frequency: adverse reaction
Immune system disorders	Uncommon: hypersensitivity, anaphylactic reaction, anaphylactoid reaction
Psychiatric disorders	Very rare: agitation, anxiety
Nervous system disorders	Very common: paraesthesia, headache Rare: dysgeusia Very rare: coma, convulsion, syncope, presyncope, dizziness, parosmia, tremor
Eye disorders	Very rare: conjunctivitis, ocular hyperaemia, vision blurred, lacrimation increased, eyelid edema
Cardiac disorders	Very rare: cardiac arrest, bradycardia, tachycardia, arrhythmia, palpitations
Vascular disorders	Very rare: hypotension, hypertension, vasodilatation, pallor
Respiratory, thoracic and mediastinal disorders	Very rare: respiratory arrest, pulmonary oedema, bronchospasm, laryngospasm, pharyngeal oedema, dyspnoea, nasal congestion, sneezing, cough, dry throat
Gastrointestinal disorders	Common: nausea, vomiting Very rare: diarrhoea, abdominal pain, salivary hypersecretion
Skin and subcutaneous tissue disorders	Common: pruritus, erythema, rash Rare: urticaria, hyperhidrosis, Very rare: eczema, angioedema Not known: nephrogenic systemic fibrosis
Musculoskeletal and connective tissue disorders	Very rare: muscle contracture, muscular weakness, back pain
General disorders and administration site conditions	Common: feeling hot, feeling cold, injection site pain Very rare : malaise, thoracic pain, chest discomfort, fever, chills, face oedema, asthenia, injection site discomfort, injection site reaction, injection site oedema, injection site extravasation, injection site inflammation (in case of extravasation), injection site necrosis (in case of extravasation), superficial phlebitis
Investigations	Very rare: decreased oxygen saturation

Description of selected ADRs

In hypersensitivity reactions, the reactions most frequently observed are skin reactions, which can be localized, extended or generalized.
These reactions occur most often immediately (during the injection or within one hour after the start of injection) or sometimes delayed (one hour to several days after injection), presenting as skin reactions in this case.

Immediate reactions include one or more effects, which appear simultaneously or sequentially, which are most often cutaneous, respiratory and/or cardiovascular reactions. Each sign may be a warning sign of a starting shock and go very rarely to death.

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with gadoteric acid, most of which were in patients co-administered other gadolinium-containing contrast agents (see section 4.4).

Adverse events related to gadoteric acid are uncommon in children. The expectedness of these events is identical to that of the events reported in adults (see section 4.2 and 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 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

Gadoteric acid 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: V08CA02

Gadoteric acid is a paramagnetic agent for Magnetic Resonance Imaging (MRI).

The contrast-enhancing effect is mediated by gadoteric acid which is a ionic gadolinium complex composed out of Gadolinium oxide and 1,4,7,10 tetraazacyclododecane- N,N',N'',N''' tetraacetic acid (Dota), and present as meglumine salt.

The paramagnetic effect (relaxivity) is determined from the effect on spin-lattice relaxation time (T1) about 3.4 $mmol^{-1}Lsec^{-1}$ and on the spin-spin relaxation time (T2) about 4.27 $mmol^{-1}Lsec^{-1}$.

Gadoteric acid provides contrast enhancement and facilitates visualisation of abnormal structures or lesions in various parts of the body including the CNS.

5.2 Pharmacokinetic properties

Distribution

After intravenous administration gadoteric acid is rapidly distributed in the extracellular space. The distribution volume was approx. 18 l which is approximately equal to the volume of extra-cellular fluid. Gadoteric acid does not bind to proteins like serum albumin.

Biotransformation

No metabolites were detected.

Elimination

Gadoteric acid is eliminated rapidly (89% after 6 h, 95% after 24 h) in unchanged form through the kidneys by glomerular filtration. Excretion via the feces is negligible. The elimination half life amounts to about 1.6 hours in patients with a normal renal function. In renally impaired patients, the elimination half life was increased to approximately 5 hours for a creatinine clearance between 30 and 60 mL/min and approximately 14 hours for a creatinine clearance between 10 and 30 mL/min.

In animal experiments it has been demonstrated that gadoteric acid can be removed by dialysis.

In patients with normal renal function, the plasmatic half life is about 90 minutes. It is eliminated by glomerular filtration in unchanged form.

Gadoteric acid is poorly excreted in the milk and cross slowly through the placenta barrier.

Special characteristics in patients with restricted kidney function

The plasmatic clearance is reduced in case of renal impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or toxicity to reproduction.

Animal studies have shown negligible (less than 1 % of the administered dose) secretion of gadoteric acid in maternal milk.

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 [...] hours at […]°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 [...] hours at 2 °C 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

[Product specific]

6.6 Special precautions for disposal and other handling

The solution for injection should be inspected visually prior to use. Solutions with visible signs of deterioration (such as particles in the solution, fissures in the vial) must not be used.

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 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.

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}>

<11. DOSIMETRY>

<12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS>

<Any unused medicinal product or waste material should be disposed of in accordance with local requirements.>

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu<, and on the website of {name of MS Agency (link)}>.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

{(Invented) name 500 micromol/mL solution for injection <in prefilled syringe/cartridge>}
{gadoteric acid}

<▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.> [For medicinal products subject to additional monitoring ONLY]

Read all of this leaflet carefully before you start using 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

What is in this leaflet

1. What X is and what it is used for

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

{X} is used used to enhance the contrast of the images obtained in examinations with Magnetic Resonance Imaging (MRI). This contrast enhancement improves the visualisation and delineation of:
- MRI of the CNS including defects (lesions) in brain, spinal cord and adjacent tissue;
- Whole body MRI including defects (lesions) in liver, kidneys, pancreas, pelvis, lungs, heart, breast and musculoskeletal system;
- MR angiography including defects (lesions) and narrowing (stenosis) in arteries, except in coronary arteries.

2. What you need to know before you <take> <use> X

You must not be given {X}:
- if you are allergic (hypersensitive) to gadolinium, gadoteric acid or any of the other ingredients of {X}.

Warnings and precautions

Remove all metallic objects you may wear before the examination.

Tell your radiologist/doctor
- if you have a heart pacemaker, an iron-based (ferromagnetic) clip an implant or an insulin pump, or any suspected metallic foreign bodies, particularly in the eye please. It is a condition where MRI is not suitable.

- if you have, or if you have ever had, bronchial asthma or other allergies (such as seafood allergy, urticaria, hay fever) or a previous allergic reaction to contrast media you may be more likely to have an allergic reaction during the examination. 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). Patients treated with beta-blockers do not necessarily respond to other medicines usually used for the treatment of allergic reactions.
- your kidneys do not work properly. Your doctor or radiologist may decide to take a blood test to check how well your kidneys are working before making the decision to use {X}, especially if you are 65 years of age or older.
- you have a disease affecting your heart or your blood vessels (e. g. severe heart failure, coronary artery disease) you are more susceptible to serious or even fatal outcomes of severe allergic reactions.
- you have had convulsions or you are being treated for epilepsy you may have an increased risk of suffering from one during the examination.
- you have recently had, or soon expect to have, a liver transplant

In all these cases, your doctor or radiologist will assess the benefit-to-risk ratio and decide whether you should be given {X}. If you are given {X}, your doctor or radiologist will take the precautions necessary and the administration of {X} will be carefully monitored.

Children

Neonates and infants

As kidney function is immature in babies up to 4 weeks of age and infants up to 1 year of age, {X} will only be used in these patients after careful consideration by the doctor.

Other medicines and {X}

Tell your doctor or radiologist if you are taking or have recently taken any other medicines. In particular, please inform your doctor, radiologist or pharmacist if you are taking or have recently taken medicines for heart and blood pressure disorders such as beta-blocking agents (such as metoprolol), vasoactive substances (such as doxazosin), angiotensin-converting enzyme inhibitors (such as ramipril), angiontensin II receptor antagonists (such as valsartan).

{X} with food and drink

There are no known interactions between {X} and food and drinks. However, please check with your doctor, radiologist or pharmacist if it is required not to eat anything for 2 hours prior to the investigation.

Pregnancy

You must tell your doctor or radiologist if you think you are or might become pregnant as {X} should not be used during pregnancy unless strictly necessary.

Breast-feeding

Your doctor or radiologist will discuss whether you should continue breast-feeding or interrupt breast-feeding for a period of 24 hours after you receive {X} .

Driving and using machines

Your injection is unlikely to affect your ability to drive a car or to operate machines. However, while driving vehicles or operating machines you should take account that nausea or low blood-pressure may incidentally occur. If you feel unwell after the examination, you should not drive or use machines.

3. How to <take> <use> X

{X} will be given by an authorised healthcare professional directly into a vein (intravenously).

During the examination, you will be under the supervision of a doctor or radiologist. A needle will be left in your vein; this will allow the doctor or radiologist to inject you with appropriate emergency drugs if necessary. If you experience an allergic reaction, the administration of {X} will be stopped.

{X} can be administered by hand or by the mean of an automatic injector. In children, the product will only be administered by hand.

The procedure will be carried out in a hospital, clinic or private practice. The attending staff know what precautions have to be taken for the examination. They are also aware of the possible complications that can occur.

After the examination 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.

Dosage
Your doctor or radiologist will determine the dose you will receive and supervise the injection.

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 0.2 mL/kg body weight for children.

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 medicinal product is for single use only.

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. However if use is required 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, infants, children and adolescents
As kidney function is immature in babies up to 4 weeks of age and infants up to 1 year of age, {X} will only be used in these patients after careful consideration by the doctor. Neonates and infants should only receive one dose of {X} during a scan and should not receive a second injection for at least 7 days.

Use for angiography is not recommended in children less than 18 years of age.

Use for whole body MRI is not recommended in children less than 6 months of age.

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

If you are given more {X} than you should
This medicine will be given to you by a healthcare professional. If you think that you have received too much medicine please tell your doctor or nurse immediately. In case of overdose, {X} can be removed from the body by haemodialysis (blood cleaning).

If you have any further questions on the use of this product, ask your doctor or 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:

Very common side effects (may affect more than 1 in 10 people): headaches, tingling sensation

Common side effects (may affect up to 1 in 10 people): sensation of warmth or cold and/or pain at the injection site, nausea (feeling sick), vomiting (being sick), redness of the skin, itching and rash

Other side effects that may occur have been listed by frequency:

Uncommon side effects (may affect up to 1 in 100 people)	• allergic reactions
Rare side effects (may affect up to 1 in 1,000 people)	• unusual taste in the mouth • hives, increased perspiration
Very rare side effects (may affect up to 1 in 10,000 people)	• agitation, anxiety • coma, seizures, syncope (brief loss of consciousness), faintness (dizziness and feeling of imminent loss of consciousness), dizziness, disorder of smell (perception of often unpleasant odours), tremor • conjunctivitis, red eye, blurred vision, increased tear secretion, eye swelling • cardiac arrest, accelered or slow heart beat, irregular heart beat, palpitations, low or high blood pressure, vascular dilatation, pallor • respiratory arrest, pulmonary oedema, breathing difficulties, feeling of tight throat, wheezing, stuffy nose, sneezing, cough, dry throat • diarrhoea, stomach pain, increased saliva secretion • eczema • muscle contractures, muscle weakness, back pain • malaise, chest pain, chest discomfort, fever, chills, swelling of the face, fatigue, injection site discomfort, injection site reaction, injection site swelling, diffusion of the product outside of blood vessels that can lead to inflammation (redness and local pain) or tissue dying off at the injection site, inflammation of a vein • decrease in oxygen level in blood

There have been reports of nephrogenic systemic fibrosis (which causes hardening of the skin and may affect also soft tissue and internal organs), most of which were in patients who received {X} together with other gadolinium-containing contrast agents. If, during the weeks following the MRI examination, you notice changes in the colour and/or thickness of your skin in any part of your body, inform the radiologist who performed the examination.

After the administration, you will be kept under observation for at least half an hour. Most side effects occur immediately or sometimes delayed. Some effects can occur up to seven days after {X} injection. There is a small risk that you may have an allergic reaction to {X}. Such reactions can be severe and result in shock (case of allergic reaction that could put your life in danger). The following symptoms may be the

first signs of a shock. Inform immediately your doctor, radiologist or health professional if you feel any of them:

- swelling of the face, mouth or throat which may cause you difficulties in swallowing or breathing
- swelling of hands or feet
- lightheadedness (hypotension)
- breathing difficulties
- whistling respiration
- coughing
- itching
- runny nose
- sneezing
- eye irritation
- hives
- skin rash

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 to store X

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> <…> <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.

This medicinal product does not require any special precaution for storage.

Chemical and physical in-use stability has been demonstrated […] hours at […]°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 […] hours at 2°C to 8°C.

This medicine should not be used if any visible signs of deterioration (such as particles in the solution or fissures in the vial) are noticed.

<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 gadoteric acid.

One millilitre of solution for injection contains 279.32 mg of gadoteric acid (as meglumine salt), equivalent to 0.5 mmol of gadoteric acid (as meglumine salt).

The other ingredients are [*product specific*]

What {X} looks like and contents of the pack

Solution for injection.

Clear colourless to yellow 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}>

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<, and on the website of {name of MS Agency (link)}>. <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:

Posology
The recommended dose for intravenous injection in adults is 0.2 mL/kg body weight (BW) (equivalent to 0.1 mmol/kg BW) to provide diagnostically adequate contrast.

- *Encephalic and spinal MRI* In patients with brain tumors, an additional dose of 0.4 mL/kg BW (equivalent to 0.2 mmol/kg BW) may improve tumor characterisation and facilitate therapeutic decision making.
- *Angiography* In exceptional circumstances (e.g. failure to gain satisfactory images of an extensive vascular territory) administration of a second consecutive injection of 0.2 mL/kg body weight (BW) (equivalent to 0.1 mmol/kg BW) may be justified. However, if the use of 2 consecutive doses of gadoteric acid is anticipated prior to commencing angiography, use of 0.1mL/kg BW (equivalent 0.05 mmol/kg BW) to for each dose may be of benefit, depending on the imaging equipment available.
- *Children*: The 0.2 mL/kg body weight (BW) (equivalent to 0.1 mmol/kg BW) dose applies to all indications except angiography due to insufficient data on efficacy and safety in this indication. Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age,

{X} should only be used in these patients after careful consideration at a dose not exceeding 0.1 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {X} injections should not be repeated unless the interval between injections is at least 7 days.
In neonates and infants the required dose should be administered by hand.

- *Patients with renal impairment*: The adult dose applies to patients with mild to moderate renal impairment (GFR $\geq$ 30 mL/min/1.73m^2). See also below "Impaired renal function".
- *Patients with hepatic impairment:* The adult dose applies to these patients. Caution is recommended, especially in the case of perioperative liver transplantation period.

Method of administration

{X} is indicated for intravenous administration only. {X} must not be administered by subarachnoid (or epidural) injection.

Infusion rate: 3-5 mL/min (for angiographic procedures, higher infusion rates up to 120 mL/min, i.e. 2 mL/sec, may be used for angiographic procedures)

Optimal imaging: within 45 minutes after injection

Optimal image sequence: T1-weighted

Intravascular administration of contrast media should, if possible, be done with the patient lying down. After the administration, the patient should be kept under observation for at least half an hour, since experience shows that the majority of undesirable effects occur within this time.

For single patient use only, any unused solution should be discarded.

The solution for injection should be inspected visually prior to use. Only clear solutions free of visible particles should be used.

Impaired renal function

Prior to administration of {X}, 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 some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30mL/min/1.73m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with {X}, it should therefore only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI. If it is necessary to use {X}, the dose should not exceed 0.1 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, {X} injections should not be repeated unless the interval between injections is at least 7 days.

Haemodialysis shortly after {X} administration may be useful at removing {X} 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.

Elderly

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

Neonates and infants

See under Posology, Children

Pregnancy and lactation

{X} should not be used during pregnancy unless the clinical condition of the woman requires use of gadoteric acid.

Continuing or discontinuing breast feeding for a period of 24 hours after administration of {X} , should be at the discretion of the doctor and lactating mother.

Instructions on handling

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.