Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clariscan 279.3 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution for injection contains 279.3 mg gadoteric acid* (as gadoterate meglumine) equivalent to 0.5 mmol

Tetraxetan (DOTA) 202.46 mg
Gadolinium oxide 90.62 mg

* Gadoteric acid: gadolinium complex with1,4,7,10 tetraazacyclododecane N,N′,N″,N‴ tetraacetic acid (tetraxetan (DOTA))

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to slightly yellow solution

Contrast medium concentration	279.3 mg/mL equivalent to 0.5 mmol/mL
Osmolality at 37 °C	1350 $mOsm.kg^{-1}$
Viscosity at 20 °C	3.0 mPa.s
Viscosity at 37 °C	2.1 mPa.s
pH value	6.5 – 8.0

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.

Clariscan should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI).

Clariscan is a contrast agent indicated for enhancement of the contrast in Magnetic Resonance Imaging for a better visualization/delineation.

Adult population and paediatric population (0-18 years):

- lesions of the brain, spine, and surrounding tissues
- whole body MRI (see section 4.2)

Use for whole body is not recommended in children under 6 months.

In adults only:

- lesions or stenoses of the non-coronary arteries (MR Angiography).

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 lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight, and should not exceed the recommended dose per kilogram of body weight detailed in this section.

Adults

MRI of brain and spine
The recommended dose is 0.1 mmol/kg BW, i.e. 0.2 mL/kg BW. In patients with brain tumours, an additional dose of 0.2 mmol/kg BW, i.e. 0.4 mL/kg BW, may improve tumour characterisation and facilitate therapeutic decision making.

Whole body MRI (including lesions of the liver, kidneys, pancreas, pelvis, lungs, heart, breast, and musculoskeletal system)
The recommended dose is 0.1 mmol/kg BW, i.e. 0.2 mL/kg BW to provide diagnostically adequate contrast.

For angiography:
The recommended dose for intravenous injection is0.1 mmol/kg BW, i.e. 0.2 mL/kg BW to provide diagnostically adequate contrast.

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

Special populations

Impaired renal function
Clariscan 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 Clariscan 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, Clariscan 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).

Paediatric population (aged 0-18 years)

Encephalic and Spinal MRI, Whole body MRI:
The recommended and maximum dose of Clariscan is 0.1 mmol/kg body weight. More than one dose should not be used during a scan.

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Clariscan 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, Clariscan 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.

Angiography:
Clariscan is not recommended for angiography in children under 18 years of age due to insufficient data on its efficacy and safety in this indication (see section 4.4).

Method of administration
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). For instructions on preparation and disposal, see section 6.6.

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.

Paediatric population (0-18 years)
Depending on the amount of Clariscan to be given to the child, it is preferable to use Clariscan vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume.

In neonates and infants, the required dose should be administered by hand.

Image acquisition
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

Hypersensitivity to gadoteric acid, to meglumine or to any medicinal products containing gadolinium.

4.4 Special warnings and precautions for use

Clariscan is administered strictly by intravenous injection only. In the event of extravasation local intolerance reactions may be observed, necessitating short term local treatment.

Clariscan must not be administered by subarachnoid (or epidural) injections.

Appropriate facilities should be readily available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself (e.g. hypersensitivity, seizures).

The usual precaution for MRI examination should be taken, such as exclusion of patients with pacemakers, vascular clips, infusion pumps, nerve stimulators, cochlear implants, or suspected intracorporeal metallic foreign bodies, particularly in the eye.

Hypersensitivity

- Hypersensitivity reactions can occur, including life-threatening ones (see section 4.8). Hypersensitivity reactions may be either allergic (described as anaphylactic reactions when serious) or non-allergic. They can be either

immediate (less than 60 minutes), or delayed (up to 7 days). Anaphylactic reactions can occur immediately and can be fatal. Hypersensitivity reactions may be independent of the dose, may occur after even the first dose of the product, and are often unpredictable.

- There is always a risk of hypersensitivity regardless of the dose injected.
- Patients who have already experienced a reaction during previous administration of a gadolinium-containing MRI contrast agent present an increased risk of experiencing another reaction on subsequent administration of the same product, or possibly other products, and are therefore considered to be at high risk.
- The injection of gadoteric acid may aggravate symptoms of an existing asthma. In patients with asthma unbalanced by the treatment, the decision to use gadoteric acid must be made after careful evaluation of the risk/benefit ratio.
- As known from the use of iodinated contrast media, hypersensitivity reactions can be aggravated in patients on beta-blockers, and particularly in the presence of bronchial asthma. These patients may be refractory to standard treatment of hypersensitivity reactions with beta-agonists.
- Before any contrast medium is injected, the patient should be questioned for a history of allergy (e.g. fish and seafood allergy, hay fever, hives), sensitivity to contrast media and bronchial asthma as the reported incidence of adverse reactions to contrast media is higher in patients with these conditions and premedication with antihistamines and/or glucocorticoids may be considered.
- During the examination, supervision by a physician is necessary. If hypersensitivity reactions occur, administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy instituted. A venous access should thus be kept during the entire examination. To permit immediate emergency countermeasures, appropriate drugs (e.g. adrenaline and antihistamines), an endotracheal tube and a respirator should be ready at hand.

Impaired renal function

Prior to administration of Clariscan it is recommended that all patients are 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 particularly high risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur withClariscan, 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 Clariscan administration may be useful at removing Clariscan 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.

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, Clariscan should only be used in these patients after careful consideration.
In neonates and infants, the required dose should be administered by hand.

CNS disorders
Like with other gadolinium containing contrast agents special precaution is necessary in patients with a lowthreshold 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.

Cardiovascular disease

In patients with severe cardiovascular disease Clariscan should only be administered after careful benefit assessment because only limited data are available so far.

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.

4.5 Interaction with other medicinal products and other forms of interactions

No interactions with other medicinal products have been observed. Formal drug interaction studies have not been carried out.

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). Clariscan should not be used during pregnancy unless the clinical condition of the woman requires use of gadoteric acid.

Breastfeeding
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 Clariscan, should be at the discretion of the doctor and lactating mother.

Fertility
There are no clinical data available regarding the 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

Side effects in association with the use of gadoteric acid are usually mild to moderate in intensity and transient in nature. A sensation of heat, cold and/or pain at the injection site are the most frequently observed reactions.

During clinical trials, headaches and paraesthesia were very commonly observed (>1/10), and nausea, vomiting and skin reactions such as erythematous rash and pruritus were commonly observed (>1/100 to <1/10).

Since post-marketing, the most commonly reported adverse reactions following administration of gadoteric acid are nausea, vomiting, pruritus and hypersensitivity reactions.

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).

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 (≥1/10 000 to <1/1 000), very rare (<1/10 000), 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 oedema
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

The following adverse reactions were reported with other intravenous contrast agents for MRI. It is therefore possible that they also occur during examination with Clariscan

System Organ Class	**Adverse reaction**
Blood and lymphatic system disorders	Haemolysis
Psychiatric disorders	Confusion
Eye disorders	Blindness transient, eye pain
Ear and labyrinth disorders	Tinnitus, ear pain
Respiratory, thoracic and mediastinal disorders	Asthma
Gastrointestinal disorders	Dry mouth
Skin and subcutaneous tissue disorders	Dermatitis bullous
Renal and urinary disorders	Urinary incontinence, renal tubular necrosis, renal failure acute
Investigations	Electrocardiogram PR prolongation, blood iron increased, blood bilirubin

	increased, serum ferritin increased, liver function test abnormal

Adverse reaction in children
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.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Clariscan 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: paramagnetic contrast media for magnetic resonance imaging
ATC code: V08 CA 02

This product has no specific pharmacodynamic activity.

Gadoteric acid is a paramagnetic agent for Magnetic Resonance Imaging (MRI). The contrast-enhancing effect is mediated by gadoteric acid which is an 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.

5.2 Pharmacokinetic properties

Distribution
After intravenous injection, Clariscan is distributed in the extracellular fluids of the body. The distribution volume was approximately 18 L which is approximately equal to the volume of extra-cellular fluid. Gadoteric acid does not bind to proteins like serum albumin. Gadoteric acid is poorly excreted in the milk and crosses slowly through the placenta barrier.

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 faeces is negligible. The elimination half-life amounts to about 1.6 hours in patients with a normal renal function.

Special characteristics in patients with renal impairment
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.

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 secretion (less than 1% of the dose) of gadoteric acid in maternal milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Meglumine
Tetraxetan (DOTA)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years

Bottles
Chemical and physical in-use stability has been demonstrated for 48 hours at room temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8° C, unless opening has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Clariscan is filled in the following containers:

Vials

Glass vials (type I, colourless) of 10 mL (filled to 5 or 10 mL) and 20 mL (filled to 15 or 20 mL), closed with halobutyl rubber stopper sealed with caps of aluminium with coloured plastic top.

Packed in outer box of 1 and 10 units.

Bottles

Glass bottles (type I, colourless) of 50 mL (filled to 50 mL) and 100 mL (filled to 100 mL), closed with halobutyl rubber stopper sealed with caps of aluminium with coloured plastic top.

Packed in outer box of 1 and 10 units.

Polypropylene bottles of 50 mL (filled to 50 mL) and 100 mL (filled to 100 mL), closed with halobutyl rubber stopper held in place by a plastic screw cap with pull-off ring and tamper proof ring.

Packed in outer box of 1 and 10 units.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use

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

Vials and bottles
Prepare a syringe with a needle. For vials, remove the plastic disk. For polypropylene bottles remove the plastic screw cap or top plastic lid by pulling the top ring. After cleaning the stopper with a pad soaked in alcohol, puncture the stopper with the needle. Withdraw the quantity of product required for the examination and inject it intravenously.

The remaining contrast medium in the vial/bottle, the connecting lines and all disposable components in the injector system must be discarded after the examination

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

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

7 MARKETING AUTHORISATION HOLDER

GE Healthcare AS
P.O. Box 4220 Nydalen
NO-0401 Oslo
Norway

8 MARKETING AUTHORISATION NUMBER

PA0735/011/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd December 2017
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10 DATE OF REVISION OF THE TEXT

January 2022