SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCTS

Clariscan

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of solution :

Gadoteric acid* .....279.3 mg

corresponding to gadoterate meglumine.....376.9 mg

corresponding to gadolinium oxide.....90.62 mg

corresponding to tetraxetan…….202.46 mg

*Gadoteric acid: complex of gadolinium with 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid.

Concentration in the contrast agent: 0.5 mmol/mL

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for I.V injection in pre-filled syringe, vial or bottles (glass and polypropylene).

Clear, colourless to slightly yellow solution.

Osmolality: 1350 $mOsm.kg^{-1}$

Viscosity at 20°C: 3.0 mPa.s

Viscosity at 37°C: 2.1 mPa.s

pH: 6.5 to 8.0.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Enhancement of contrast in magnetic resonance imaging.
- Encephalic and spinal pathologies: brain tumours, tumours of the spine and the surrounding tissue, intervertebral disk prolapse infectious diseases.
- Abdominal pathologies: primary and secondary liver tumours.
- Osteo-articular pathology: bone and soft tissue tumours synovial diseases.
- Magnetic resonance imaging for angiography.

4.2. Posology and method of administration

Posology

The lowest dose that provides sufficient enhancement for diagnostic purposes should be used.

The recommended dose is 0.1 mmol/kg, i.e., 0.2 mL/kg, in adults, children and infants.

In angiography, depending on the results of the examination being performed, a second injection may be administered during the same session if necessary.

In some exceptional cases, as in the confirmation of isolated metastasis or the detection of leptomeningeal tumours, a second injection of 0.2 mmol/kg can be administered.

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-contras 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.

Paediatric population

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

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.

Clariscan is not recommended for angiography in children under the age of 18 because of insufficient data on the efficacy and safety in this indication.

Elderly (aged 65 years and above)

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

Method of administration

The product must be administered by strict intravenous injection.

4.3. Contraindications

Hypersensitivity to gadoteric acid 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. Serious, life-threatening and fatal cases, primarily with neurological reactions (e.g. coma, encephalopathy, seizures), have been reported with intrathecal use. Take care to maintain strictly intravenous injection: extravasation may result in local intolerance reactions, requiring the usual local care.

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

Hypersensitivity

- As with other gadolinium-containing contrast media, hypersensitivity reactions can occur, including life-threatening ones (see 4.8 "Undesirable effects"). 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 occur immediately and can be fatal. They are independent of the dose, can 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 more difficult to treat 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. 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. epinephrine and antihistamines), an endotracheal tube and a respirator should be ready at hand.

Impaired renal function

Prior to administration of gadoteric acid, 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 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.

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

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

Depending on the amount of gadoteric acid to be given to the child, it is preferable to use gadoteric acid vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume.

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.

Gadolinium retention

Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (e.g. brain, skin, kidney, liver, and spleen). The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs.

The current evidence suggests that gadolinium may accumulate in the brain after multiple administrations of GBCAs. Increased signal intensity on non-contrast T1-weighted images of the brain has been observed after multiple administrations of GBCAs in patients with normal renal function. Gadolinium has been detected in brain tissue after multiple exposures to GBCAs, particularly in the dentate nucleus and Globus pallidus. The evidence suggests that the risk of gadolinium accumulation is higher after repeat administration of linear than after repeat administration of macrocyclic agents. The clinical significance of gadolinium accumulation in the brain is presently unknown; however, gadolinium accumulation may potentially interfere with the interpretation of MRI scans in the brain. In order to minimize potential risks associated with gadolinium accumulation in the brain, it is recommended to use the lowest effective dose and perform a careful benefit risk assessment before administering repeated doses.

While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and paediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies, particularly closely spaced studies when possible.

4.5. Interaction with other medicinal products and other forms of interaction

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

Concomitant medications to be taken into account

Beta-blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists: these medicinal products decrease the efficacy of the mechanisms of cardiovascular compensation for blood pressure disorders: the radiologist must be informed before injection of gadolinium complexes, and resuscitation equipment must be at hand.

4.6. Fertility, pregnancy and lactation

Pregnancy

Data on the use of gadolinium-based contrast agents including gadoteric acid in pregnant women is limited. Gadolinium can cross the placenta. It is unknown whether exposure to gadolinium is associated with adverse effects in the fœtus. 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.

Breast-feeding

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.

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.

Patients received as outpatients who drive vehicles or use machines should be made aware of the potential onset of nausea.

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. Injection site reactions, nausea and headache are the most frequently observed reactions.

During clinical trials uncommon adverse reactions (≥ 1/1000 to < 1/100) were nausea, headache, injection site reactions, feeling cold, hypotension, somnolence, dizziness, feeling hot, burning sensation, rash, asthenia, dysgeusia and hypertension.

Post-marketing the most commonly reported adverse reactions following administration of gadoteric acid have been nausea, vomiting, pruritus and hypersensitivity reactions.

In hypersensitivity reactions, the reactions most frequently observed are skin reactions, which can be localised, extended or generalised. 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, and are most often cutaneous, respiratory, gastrointestinal, joint and/or cardiovascular reactions.

Each sign may be a warning sign of shock and may very rarely lead 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 according to the following categories: very common (≥1/10), common (≥1/100 to 1<1/10), uncommon (≥1/1,000 to 1<1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), undetermined frequency (cannot be estimated on the basis of available data). The data presented are from clinical trials involving 2822 patients when available, or from a pool of observational studies involving 185,500 patients.

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

The following adverse reactions have been reported with other intravenous contrast agents for MRI:

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, acute renal failure
Investigations	Electrocardiogram PR prolongation, blood iron increased, blood bilirubin increased, serum ferritin increased, liver function test abnormal

Adverse reactions in children

Safety of paediatric patients was considered in clinical trials and post-marketing studies. As compared to adults, the safety profile of gadoteric acid did not show any specificity in children. The most common reactions are gastrointestinal symptoms or signs of hypersensitivity.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
And emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

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: paramagnetic contrast media for MRI, ATC code: V08 CA02.
Macrocyclic form of Gadolinium. Gadoteric acid has paramagnetic properties allowing MRI contrast enhancement. It has no specific pharmacodynamic activity and is biologically very inert.

5.2. Pharmacokinetic properties
Following intravenous injection, gadoteric acid is mainly distributed throughout the extracellular fluid. It is not bound to plasma albumin.
In patients with normal renal function, the plasma half-life is about 90 minutes. Gadoteric acid is eliminated in unchanged form by glomerular filtration.
Plasma clearance is delayed in patients with impaired renal function.
A small amount of gadoteric acid is excreted in breast milk, and it crosses the placenta slowly.

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.
In acute toxicity studies of intravenous gadoteric acid in mice and rats, adverse effects (seizures, transient respiratory disorders) were only reported at doses much higher than those used in humans.
Administration of gadoteric acid at daily doses of up to 15 times the recommended dose in clinical practice and for 28 days did not induce any marked effect apart from reversible vacuolization of renal proximal tubule cells.
Animal studies showed negligible (less than 1% of the administered dose) secretion of gadoteric acid in maternal milk.
No teratogenic effect was demonstrated in rats and rabbits.
No mutagenic effect was demonstrated on the reagent systems used.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Meglumine
DOTA
Water for injection

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

6.3. Shelf life
The expiry date of the product is indicated on the packaging materials.

Shelf life after opening, for 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

Pre-filled syringe: Store below 30°C. Protect from freezing.
Vial: Store below 30°C
Bottles: Store below 30°C
Poly-propylene bottles: Store below 30°C

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 halo-butyl rubber stopper sealed with caps of aluminium with coloured plastic top. Packed in outer box of 1 and 10 units.

Pre-filled syringes
Polymer syringe: Poly-cycloolefin, Crystal Clear Polymer (CCP) syringe of 20 mL (filled to 10, 15, and 20 mL), label graduated per mL with tip cap and halo-butyl plunger stopper attached to a plunger rod.
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 halo-butyl rubber stopper sealed with caps of aluminium with coloured plastic top.
Packed in outer box of 1 and 10 units.

Poly-propylene bottles
Polypropylene bottles of 50 ml (filled to 50 ml) or 100 ml (filled with 100 ml), closed with rubber stopper and a screw cap.
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. 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.
For Poly-propylene bottles, remove the plastic screw cap or top plastic lid by pulling the top ring.

Pre-filled syringes: Inject intravenously the quantity of product required for the examination.

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 syringes/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. MANUFACTURER

GE Healthcare AS
Nycoveien 1 NO-0485, Oslo, Norway

8. REGISTRATION NUMBERS

35367

9. REGISTRATION OWNER

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