New Zealand Datasheet

1. PRODUCT NAME
Clariscan 279.3 mg/ml solution for injection
Clariscan 279.3 mg/ml solution for injection in pre-filled syringes
Clariscan 279.3 mg/ml solution for injection in bottles

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: composition of gadolinium complex with1,4,7,10 tetraazacyclododecane N,N',N",N"' tetraacetic acid (tetraxetan (DOTA)).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Clariscan is a clear, colourless to slightly yellow solution available in glass vials, polypropylene bottles or pre-filled syringes intended for intravenous injection. Each vial, bottle or pre-filled syringe contains the active ingredient gadoteric acid 279.32 mg/mL (0.5 M).

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. Magnetic resonance imaging for:
- cerebral and spinal disease,
- diseases of the vertebral column,
- and other whole body pathologies (including angiography of the non-coronary arteries).

4.2. Dose and method of administration
Dose
The lowest effective dose should be used. Adult population
The recommended dose is 0.1 mmol/kg, i.e. 0.2 mL/kg, in adults.

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 when confirming isolated metastasis or detecting leptomeningeal tumours, a second injection of 0.2 mmol/kg can be administered.

Use of Clariscan in a single-use setting
Vials and bottles containing contrast medium solutions are not intended for the withdrawal of multiple doses.
The rubber stopper of the vial or bottle should never be pierced more than once.

Each vial or bottle should be used in one patient on one occasion only and any residue should be discarded. Clariscan contains no preservatives.
If a single-use injector system is used, Instructions For Use (IFU) of the device manufacturer must be followed, including connecting tubes and all disposable parts. Ensure the single-use disposables are replaced after each patient.

Use of Clariscan with a multi-patient use injector system and/or large volume containers (50 and 100mL)
The transmission of viral infections and bacterial contamination are recognised but rare potential complications of multi-use containers and administration devices. The following measures should be strictly adhered to when using Clariscan:
The multiple withdrawal and administration of contrast medium must be done utilising a device and disposables system validated and approved for multiple-patient use, such as an automatic injector system.
The rubber stopper of the bottle should never be pierced more than once.
Instructions For Use (IFU) of the device manufacturer must be followed, including connecting tubes and all disposable parts of the injector system. Ensure the single-use disposables are replaced after each patient.

Special populations
Impaired renal function

The adult dose applies to patients with mild to moderate renal impairment (GFR ≥ 30 ml/min/1.73m^2).
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.

Paediatric population (0-18years)

MRI of brain and spine / whole-body MRI: the recommended and maximum dose of Gadoteric acid 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. 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.

Angiography: Gadoteric acid is not recommended for angiography in children under 18 years of age due to insufficient data on its efficacy and safety in this indication.

Method of administration
The product is indicated for intravenous administration only.

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.

Paediatric population (0-18 years)
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.

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

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

4.4. Special warnings and precautions for use
Gadoteric acid must not be used intrathecally. Serious, life-threatening and fatal cases, primarily with neurological reactions (e.g. coma, encephalopathy, seizures), have been reported with intrathecal use. Gadoteric acid should be strictly administered via intravenous injection. 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 (see section 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 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. 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 medicines (e.g. epinephrine and antihistamines), an endotracheal tube and a respirator should be ready at hand.

Accumulation of Gadolinium in Brain
The current evidence suggests that gadolinium may accumulate in the brain after multiple administration 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 of the brain. In order to minimise 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.

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.

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 medicines necessary to counter any convulsion which may occur must be made ready for use beforehand.

4.5. Interaction with other medicines 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 foetus.. 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
No data is available.

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

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

Since 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 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, gastrointestinal, articular and/or cardiovascular reactions.

Each sign may be a warning sign of a starting shock, however, it is very rarely fatal.

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 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, somnolence, paraesthesia (including burning sensation) Rare: presyncope Very rare: coma, convulsion, syncope, tremor, parosmia
Eye disorders	Rare: eyelid edema Very rare: conjunctivitis, ocular hyperaemia, vision blurred, lacrimation increased
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: 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),
Investigations	Very rare: decreased oxygen saturation

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

Organ Class System	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
Investigations	Electrocardiogram PR prolongation, blood iron increased, blood bilirubin increased, serum ferritin increased, liver function test abnormal

Adverse reaction in Children
Safety of paediatric patients was considered in clinical trials and postmarketing studies. As compared to adult, the safety profile of gadoteric acid did not show any specificity in children. Most of reactions are gastrointestinal symptoms or signs of hypersensitivity.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

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).

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Pharmacotherapeutic group: paramagnetic contrast media for MRI, ATC code: V08 CA02.

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 in 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 crosses the placenta.

The current evidence suggests that gadolinium may accumulate in the brain after repeated administration of gadolinium based contrast agents (GBCAs) although the exact mechanism of gadolinium passage into the brain has not been established.

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 man.

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.

Recent studies conducted in healthy rats injected repeatedly with linear or macrocyclic GBCAs demonstrated that linear agents were associated with progressive and persistent T1-weighed hyperintensity on MRI in the deep cerebellar nuclei (DCN). Signal enhancement in the globus pallidus (GP) could not be seen in the animals. No changes in signal intensities in either DCN or GP were observed for the macrocyclic GBCAs.

Quantitative results using mass spectrometry demonstrated that the total gadolinium concentrations were significantly higher with the linear GBCAs than with the macrocyclic GBCAs. These studies reported no abnormal behavioural changes suggestive of neurological toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Meglumine, tetraxetan (DOTA) and 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.

6.4. Special precautions for storage

Vials: Store below 30°C.
Pre-filled syringes: Store below 30°C. Protect from light. Do not freeze.
Bottles: Store below 30°C
In-Use: Unused Clariscan in opened containers must be discarded immediately. Unused Clariscan in a 50mL or 100mL bottle and used with a multi-patient injector system must be discarded within 24 hours after first opening the container.

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 20 ml), closed with halobutyl rubber stopper sealed with caps of aluminium with coloured plastic top.

Packed in outer box of 10 units.

Bottles
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, a top plastic lid and tamper proof ring.

Packed in outer box of 10 units

Pre-filled syringes
Polymer syringe: Poly-cycloolefin, Crystal Clear Polymer (CCP) syringe of 20 ml (filled to 10 and 15 ml), label graduated per ml, with tip cap and halobutyl plunger stopper attached to a plunger rod.

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

Vials
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.

Prefilled syringes
Inject intravenously the quantity of product required for the examination.

The remaining contrast medium in the vial, 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 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. MEDICINE SCHEDULE

General Sale Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

13 August 2020

10. DATE OF REVISION OF THE TEXT

16 October 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Additional warning on intrathecal administration
4.6	Updated information on use in pregnancy