New Zealand Datasheet

1 PRODUCT NAME
OMNISCAN™

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Gadodiamide injection 287 mg/ml.

Excipient(s) with known effect;
Total sodium content: 0.62 mg/ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
OMNISCAN is a clear, colourless to slightly yellow aqueous solution containing gadodiamide 287 mg/ml equivalent to 0.5 mmol/ml.

Pertinent physiochemical data for OMNISCAN are:

Osmolarity (mOsm/kg water)	@ 37ºC	780
Viscosity (cp)	@ 20ºC	2.8
	@ 37ºC	1.9
Density (g/cm^3)	@ 20ºC	1.15

OMNISCAN has an osmolarity 2.8 times that of plasma (285mOs/kg) at 37ºC and is hypertonic under conditions of use.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
OMNISCAN is indicated as a contrast medium for cranial and spinal resonance imaging (MRI) and for general MRI of the body after intravenous administration.

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

4.2 Dose and method of administration
GBCAs should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI).

No special preparation of the patient is required. OMNISCAN should be drawn into the syringe immediately before use. The vial and pre-filled syringe is intended for one patient only. Contrast medium not used in one examination must be discarded. Calculate the dose based on the patient's body weight, and do not exceed the recommended dose per kilogram of body weight.

The lowest effective dose should be used.

CNS
Dosage for adults and children.
The recommended dosage is 0.1 mmol/kg body weight (equivalent to 0.2 ml/kg b.w,) up to 100 kg. Above 100 kg body weight 20 ml is usually sufficient to provide diagnostically adequate contrast. The required dose should be administered as a single intravenous injection. To ensure complete injection of the contrast medium, the intravenous line may be flushed with 5 ml sodium chloride injection 0.9%.

Adults only.
When brain metastases are suspected, a dosage of 0.3 mmol/kg b.w. (equivalent to 0.6 ml/kg b.w.) can be administered up to 100 kg. Above 100 kg b.w. a total of 60ml is usually sufficient. The dose of 0.3 mmol/kg b.w. can be administered as a bolus intravenous injection. In patients with equivocal scans after administration of the 0.1 mmol/kg b.w. injection, a second bolus injection of 0.2 mmol/kg b.w. (equivalent to 0.4 ml/kg b.w.) may be of additional diagnostic value when administered within 20 minutes of the first injection.

Whole body
Dosage for adults.
The recommended dosage is usually 0.1mmol/kg b.w. (equivalent to 0.2 ml/kg b.w.) or occasionally 0.3 mmol/kg b.w. (equivalent to 0.6 ml/kg b.w.) up to 100 kg. Above 100 kg 20 ml or up to 60 ml is usually sufficient to provide diagnostically adequate contrast.

Dosage for children.
The recommended dosage is 0.1 mmol/kg b.w. (equivalent to 0.2 ml/kg b.w.)

For patients with moderate renal impairment and in infants from 4 weeks to 1 year of age the dose should be restricted to the minimum recommended dose. OMNISCAN is contraindicated in neonates up to 4 weeks of age. Due to immature renal function in infants up to 1 year of age, OMNISCAN should only be used in these patients after careful consideration. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, injections should not be repeated unless the interval between injections is at least 7 days.

For both adults and children, the required dose should be administered as a single intravenous injection. To ensure complete injection of the contrast medium, the intravenous line may be flushed with sodium chloride injection 0.9%.

Contrast-enhanced MRI should start shortly after administration of the contrast medium, depending on the pulse sequences used and the protocol for the examination. Optimal enhancement is observed within the first minutes after injection (time depending on the type of lesion/tissue). Enhancement generally lasts up to 45 minutes after contrast medium injection. T1-weighted scanning sequences are particularly suitable for contrast-enhanced examinations with OMNISCAN. In the investigated range of field strengths, from 0.15 Tesla up to 1.5 Tesla, the relative image contrast was found to be independent of the applied field strength.

Instructions for Use
Additional instructions for auto-injector/pump.
The 100 ml contrast medium bottle should only be used in conjunction with auto injectors/pumps approved for this volume. A single piercing procedure should be used.

The line running from this auto injector/pump to the patient must be exchanged after each patient. Any unused portions of the contrast medium remaining in the bottle and all connecting tubes must be discarded at the end of the day. Instructions from the manufacturer of the auto injector/pump must be followed.

4.3 Contraindications
OMNISCAN should not be used in patients known to have hypersensitivity to OMNISCAN or its constituents.

OMNISCAN is also contraindicated in acute or chronic severe renal insufficiency (a glomerular filtration rate < 30mL/min/1.73m^2) and/or in patients with acute renal insufficiency of any severity due to the hepato-renal syndrome, or in the peri-operative liver transplantation period.

OMNISCAN is also contraindicated in patients with acute kidney injury and neonates up to 4 weeks of age.

4.4 Special warnings and precautions for use

The accepted safety considerations and procedures that are required for magnetic resonance imaging are applicable when OMNISCAN is used for contrast enhancement. Administration of contrast media should be performed by qualified personnel familiar with the procedure and an appropriate technique should be utilised.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular or other idiosyncratic reactions should always be considered, especially in those patients with known clinical hypersensitivity or a history of asthma or other allergic respiratory disorders. A course of action should therefore be planned in advance; with necessary drugs and equipment available for immediate treatment should a serious reaction occur.

Accumulation of Gadolinium in Brain

Trace amounts of Gadolinium may be retained in the brain (particularly in the dentate nucleus and globus pallidus), and in other tissues for months to years after administration of GBCAs. Higher concentrations have been identified in human bone than in skin and brain. Nonclinical evidence suggests that the level of gadolinium retention is higher after repeat administration of linear than after repeat administration of macrocyclic agents.

Increased signal intensity on non-contrast T1 weighted images of the brain has been observed after multiple administrations of GBCAs even in patients with normal renal function. The clinical significance of gadolinium retention in brain is unknown.

There are rare reports of pathologic skin changes including gadolinium associated plaques in patients with normal renal function. Post-marketing reports of adverse events involving multiple organ systems in patients with normal renal function have been received. A causal link to gadolinium retention has not been established. These events include fatigue, asthenia, pain syndromes, and heterogeneous clusters of symptoms in the neurological, cutaneous, and musculoskeletal systems.

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.

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.

Patients with central nervous system disorders

In patients suffering from epilepsy or brain lesions the likelihood of convulsions during the examination may be increased. Precautions are necessary when examining these patients (e.g. monitoring of the patient) and the equipment and medicinal products needed for the rapid treatment of possible convulsions should be available.

Impaired Renal Function (or Nephrogenic Systemic Fibrosis)

Nephrogenic Systemic Fibrosis (NSF) is a debilitating and sometimes fatal disease affecting the skin, muscle and internal organs. There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of gadodiamide and some other gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR <30ml/min/1.73 m^2) and those who have or are undergoing liver transplantation. Therefore, OMNISCAN is contraindicated in patients with severe renal impairment, in patients in the perioperative liver transplantation period and in neonates. Caution should be exercised in use and dose selection of OMNISCAN in patients with

hepatorenal syndrome. All patients should be screened for renal dysfunction using laboratory testing prior to using OMNISCAN.

Patients with renal impairment
Because of the lack of information on repeated administration, Omniscan injections should not be repeated unless the interval between injections is at least 7 days.

Neonates and Infants
Omniscan is contraindicated in neonates up to 4 weeks of age. Due to immature renal function in infants up to 1 year of age, Omniscan should only be used in these patients after careful consideration.

Haemodialysis shortly after OMNISCAN administration in patients currently receiving haemodialysis may be useful at removing OMNISCAN 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.

Transitory changes in serum iron (within the normal range in the majority of cases) have been observed in some patients after administration of OMNISCAN. The clinical significance of this, if any, is not known but all patients in whom this effect was observed remained asymptomatic.

OMNISCAN interferes with serum calcium measurements with some colorimetric (complexometric) methods commonly used in hospitals. It may also interfere with determinations of other electrolytes (e.g. iron). Thus it is recommended that such methods not be used for 12-24 hours after administration of OMNISCAN. If such measurements are necessary, the use of other methods is recommended.

Diagnostic procedures involving the use of contrast agents should be conducted under supervision of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed. If OMNISCAN is drawn into a disposable syringe it should be used immediately. If non-disposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Data on the safety of repeated injections are not available. If the physician determines sequential or repeat examinations are required, a suitable time interval between administrations should be observed to allow for clearance of the drug from the body.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The results of three in vitro and one in vivo short-term genotoxicity assays were negative. No long-term studies have been performed to evaluate the carcinogenic potential of OMNISCAN.

Use in Children
OMNISCAN is contraindicated in neonates up to 4 weeks of age. Due to immature renal function in infants up to 1 year of age, OMNISCAN should only be used in these patients after careful consideration.

The safety and effectiveness of OMNISCAN have been established for whole body magnetic resonance imaging in children from 6 months of age. The safety and effectiveness in infants and neonates have been established in the evaluation of lesions within the brain and spine.

There is no experience with OMNISCAN in children below 6 months of age with severe hepatic or renal disease, or with premature infants below 4 weeks, or those with a post-conceptional age of less than 30 weeks.

Gadolinium is retained in paediatric brains similar in amount and distribution to adults. Developing paediatric brains may be more susceptible to the potential effects of gadolinium exposure.

Use in Elderly Patients
As the renal clearance of OMNISCAN may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

4.5 Interaction with other medicines and other forms of interaction
Asymptomatic transitory increases in serum iron and bilirubin have been reported in patients receiving OMNISCAN.

4.6 Fertility, pregnancy and lactation
OMNISCAN had no effect on the fertility and general reproductive performance in rats or in teratology studies in rats and rabbits at doses that did not cause maternal toxicity. There are no clinical data available with regards to effects on fertility.

Use in Pregnancy
Pregnancy category B3. No effects of OMNISCAN on reproductive performance were seen in rats at doses up to 1.0 mmol/kg. In rabbits, there is an increased incidence of litters with skeletal or visceral abnormalities at doses up to 0.5 and 1.0 mmol/kg. However, these effects are possibly attributable to maternal toxicity rather than a direct effect of the drug. There are no adequate and well-controlled studies of OMNISCAN in pregnant women.

GBCAs administered to pregnant mice (2 mmol/kg daily on gestational days 16 through 19) result in measurable gadolinium concentrations in the pups in bone, brain, kidney, liver, blood, muscle, and spleen at one month postnatal age.

GBCAs cross the placenta and result in foetal exposure and gadolinium retention. Human data on the association between GdCA and adverse foetal outcomes are limited and inconclusive. OMNISCAN should therefore be used in pregnancy only if the potential benefit justifies the potential risk to the foetus and the pregnant woman.

Use in Lactation
It is not known whether OMNISCAN is excreted in human milk. Available data in animals have shown excretion of gadodiamide in milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued prior to administration and should not be recommenced until at least 24 hours after the administration of OMNISCAN.

4.7 Effects on ability to drive and use machines
None known

4.8 Undesirable effects
Discomfort with a general sensation of warmth, coolness or a sensation of local pressure or pain at the injection site were commonly (> 1% and < 10%) observed in clinical studies. Dizziness, nausea, headache and a perverted sense of taste or smell were reported less frequently, but also in > 1% of patients. Uncommon (> 0.1% and < 1%) reactions included vomiting, somnolence, paraesthesia or allergy-like symptoms such as urticaria, itching, irritation in the throat and bronchospasm. Anaphylactoid reactions have occurred. The majority of adverse reactions in clinical studies were of mild intensity.

The following adverse reactions occurred in less than 1% of the patients, and were considered to be possibly related or of unknown relationship to OMNISCAN:

Body as a whole: Body pain, fatigue, malaise, fever, anaphylactoid reaction, anaphylactic/anaphylactoid shock

Cardiovascular: Warmth, chest pain, hypotension (syncope), tachycardia, flushing

Digestive: Melena, dyspepsia, vomiting, diarrhoea, abdominal pain, nausea

Musculoskeletal: Arthralgia

Nervous system: Anxiety, paraesthesia, tinnitus, somnolence, light headedness, trembling, ataxia, personality disorder, convulsions, transient parosmia, taste alteration, headache, dizziness, paraesthesia, tremor.

Skin and appendages: Skin plaque*, urticaria, pruritus, flushing, rash, face oedema, angioedema

Special senses: Visual disturbances

Respiratory, thoracic and mediastinal disorders: Dyspnoea, coughing bronchospasm, respiratory distress, throat irritation, sneezing

General disorders and administration site conditions: chest pain, fever, shivering, feeling hot, injection site pain

* Cases of gadolinium associated skin plaques with demonstrated sclerotic bodies on histology have been reported with gadodiamide in patients who do not otherwise have symptoms or signs of nephrogenic systemic fibrosis.

Cases of nephrogenic systemic fibrosis (NSF) have been reported in patients with severe renal impairment. The causality is still under investigation.

In patients with pre-existing severe renal insufficiency: acute kidney injury, an increase in blood creatinine has been reported.

In very rare cases convulsions have been observed after the administration of OMNISCAN as is the case for other paramagnetic MR contrast media. However, a causal relationship seems to be questionable.

Two cases of transient elevated liver enzymes have been reported. However, in both cases concomitant medication known to cause abnormal results for liver function tests was taken. A causal relationship to OMNISCAN could therefore not be established.

Single cases of relapse of multiple sclerosis, encephalopathy, and hallucinations have been reported.

Transient renal failure was observed in one patient who received an X-ray contrast medium for myelography 22 hours prior to the injection of OMNISCAN. The causality for the reaction has not been established.

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://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Clinical consequences of overdose have not been reported and acute symptoms of toxicity are unlikely in patients with a normal renal function. Treatment is symptomatic. There is no antidote for this contrast medium. In patients with delayed elimination due to renal insufficiency and in patients who have received excessive doses, the contrast medium can be eliminated by haemodialysis.

In case of overdose, immediately contact the Poisons Information Centre for advice, in New Zealand, call 0800 764 766.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Paramagnetic contrast media. ATC code: V08C A03

In magnetic resonance imaging, visualization of normal and pathological brain and spinal tissue depends, in part, on variations in the radiofrequency signal intensity. These variations occur due to: changes in proton density; alteration to spin-lattice or longitudinal relaxation time (T1); and variation of the spin-spin or transverse relaxation time (T2). OMNISCAN is a paramagnetic agent with unpaired electron spins, which generate a local magnetic field. As water protons move through this local magnetic field, the changes in magnetic field experienced by the protons reorient them with the main magnetic field more quickly than in the absence of a paramagnetic agent. Therefore, by increasing the relaxation rate OMNISCAN decreases both the T1 and T2, relaxation times in tissues where it is distributed. At clinical doses, the effect is primarily on the T1 relaxation time, and produces an increase in signal intensity.

Use of OMNISCAN provided contrast enhancement or facilitated visualization of abnormal structures or lesions in 75% (266 of 353) of cases with abnormalities. In comparison with preinjection scans, OMNISCAN allowed visualization of more or smaller lesions in 16% (50/306) of the cases. In 29/96 of the cases OMNISCAN revealed lesions where no lesions were detected prior to OMNISCAN administration.

Clinical Trials

The efficacy of gadodiamide in CNS and whole body imaging of adults and children aged over 6 months of age has been demonstrated in clinical trials.

CNS (Central Nervous System)-Children less than 6 months of age

A total of 7 clinical studies, including 363 patients, have been performed to document the use of gadodiamide injection in paediatric patients undergoing MRI examination of the CNS. Six of these clinical studies included both children and adolescents. The remaining study was designed specifically to demonstrate the safety and effectiveness of OMNISCAN for the enhancement of magnetic resonance images of intracranial and spinal lesions in infants and neonates less than 6 months of age.

In this last study, 61 children below 6 months of age undergoing MRI were included in an open, non-randomised clinical trial conducted at three centres. Forty patients were recruited to receive gadodiamide injection at a dose of 0.1 mmol/kg in the OMNISCAN group (group A) and 21 patients requiring plain MRI examination without contrast were the control group (plain MRI – group B). No patients were withdrawn, however 2 of the children included were older than 6 months and their data excluded from all analyses. In group A, 16 patients were female and 23 male and in group B, 7 were female and 13 male. There were no relevant differences between the two groups regarding age, weight and height. Group A included 8 patients with mass lesions, 7 each with convulsive disorders and hydrocephalus, 6 with infections, 3 with congenital anomalies and 2 each with metabolic disease and hypoxia. Group B included 11 patients with congenital anomalies, 3 with hypoxia, 2 with vascular diseases, one each with convulsive disorders, hydrocephalus and metabolic disease and one with periventricular leukomalacia.

In the comparison of pre- and post-contrast evaluation of the images neither the number of patients with lesions nor the number of lesions in each patient was found to be different. Both the on-site investigator and the independent reader found the quality of lesion delineation to be improved by the injection of contrast medium. There was a discrepancy between investigators in the evaluation of contrast enhancement in the pathological area of interest and was probably due to a different interpretation of the area of interest. In no case was a lesion obscured after administration of the contrast medium. For all patients, the post-contrast images contained at least as much diagnostic information as the pre-contrast images. No serious or significant adverse event occurred. Gadodiamide injection at a dose of 0.1 mmol/kg was shown to be safe, well tolerated and effective in MRI examination of children under 6 months.

5.2 Pharmacokinetic properties

The pharmacokinetics of intravenously administered OMNISCAN in normal subjects conforms to an open, two compartment model with mean distribution and elimination half-lives (reported as mean + SD) of 3.7 + 2.7 minutes and 77.8 + 16 minutes, respectively. Gadodiamide is eliminated primarily in the urine with 95.4 + 5.5% (mean + SD) of the administered dose eliminated by 24 hours. There is no detectable biotransformation or decomposition of gadodiamide. The renal and plasma clearance rates of gadodiamide are nearly identical (1.7 and 1.8 mL/min/kg, respectively) and are similar to that of substances excreted primarily by glomerular filtration.

In patients with impaired renal function (GFR 18-43 mL/min), the mean elimination half-life was 5.8 hours. Gadodiamide is cleared by routine haemodialysis, with 56% of the given dose eliminated during the first haemodialysis session and 72% during four sessions. Gadodiamide is also dialyzable by peritoneal dialysis with 76% of the given dose recovered over 22 days.

Following GdCA administration, trace amounts of gadolinium is present for months or years in brain, bone, skin, and other organs (see section 4.4).

5.3 Preclinical safety data

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.

Studies conducted in healthy rats injected repeatedly with GdCAs demonstrated progressive and persistent T1-weighted hyperintensity on MRI in the deep cerebellar nuclei (DCN) that was higher with linear than with macrocyclic agents. Signal enhancement in the globus pallidus (GP) could not be seen in the animals.

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

Caldiamide sodium
Sodium hydroxide 1 M or hydrochloric acid 1 M
Water for injections.

6.2 Incompatibilities

OMNISCAN should not be directly mixed with other drugs. A separate syringe and needle should be used.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
OMNISCAN should be stored at room temperature (below 30ºC) and protected from light. The vial is intended for one patient only. Any unused portion must be discarded.

6.6 Special precautions for disposal
As for all parenteral products, Omniscan should be inspected visually for particulate matter, discolouration and the integrity of the container prior to use. Do not use if the tamper-evident seal on the outer carton is not intact before use. Any contrast medium or waste material remaining should be immediately discarded after use, in accordance with local requirements.

6.5 Nature and contents of container
Single dose glass vials of 5 ml, 10 ml, 15 ml, 20 ml and 100 ml.

Single dose polypropylene vials of 10 ml, 15 ml, 20 ml, 40 ml and 50 ml.

Pre-filled polypropylene or polycycloolefin syringes of 10 ml, 15 ml, and 20 ml.

Not all presentations are marketed.

7 MEDICINE SCHEDULE
General Sale Medicine

8 SPONSOR
GE Healthcare
8 Tangihua Street
PO Box 106911
Auckland 1010

Ph 0800 659465
Fax (09) 353-6701

9 DATE OF FIRST APPROVAL
21 April 1994

10 DATE OF REVISION OF THE TEXT
10 December 2018

Trademarks

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2	Addition of sodium content
4.2	Dose calculation on body weight
4.4	Updated information on accumulation in the brain
4.6	Updated information on pregnancy and fertility.
4.8	Additional effects: anaphylactic/anaphylactoid shock, nausea, taste alteration, headache, dizziness, paraesthesia, tremor, skin plaque, feeling hot, injection site pain
5.2	Updated information on accumulation
5.3	Updated information