SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

OMNISCAN™ 0.5 mmol/ml Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient	Content per ml	Function
GADODIAMIDE (GdDTPA-BMA)	287 mg equiv. 0.5 mmol	MRI-contrast agent

OMNISCAN injection is a linear non-ionic paramagnetic gadolinium-based contrast agent (GBCA) with the following physicochemical properties:

Osmolality (mOsm/kg H^2O) at 37 °C	780
Viscosity (mPa.s) at 20 °C	2.8
Viscosity (mPa.s) at 37 °C	1.9
Density at 20 °C (kg/l)	1.15
Molar relaxivity	
r1 (mM^{-1} . s^{-1}) at 20 MHz and 37 °C	3.9
r1 (mM^{-1} . s^{-1}) at 10 MHz and 37 °C	4.6
r2 (mM^{-1} . s^{-1}) at 10 MHz and 37 °C	5.1
pH 6.0 - 7.0	
Gadodiamide is freely soluble in water.	

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection, for intravenous use.
The product is a clear, colourless to slightly yellow aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.

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

Omniscan is a contrast medium for cranial and spinal magnetic resonance imaging (MRI). Omniscan is also indicated for whole body MRI including head and neck region, thoracic space including the heart, extremities, abdomen and pelvis (prostate and bladder), female breast, abdomen (pancreas and

liver), retroperitoneal space (kidney), musculoskeletal system and vessels (angiography) by intravenous administration.

Omniscan facilitates visualisation of abnormal structures or lesions and helps in the differentiations between healthy and pathological tissue.

4.2 Posology and method of administration

Posology
Omniscan should be drawn into the syringe immediately before use. All the recommended doses below can be administered as bolus intravenous injections. To ensure complete injection of Omniscan, the intravenous line may be flushed with 5 ml sodium chloride 9 mg/ml (0.9 %) solution for injection after injection.

Use the lowest effective dose. Calculate the dose based on the patient's body weight, and do not exceed the recommended dose per kilogram of body weight.

CNS examinations
The recommended dosage to adults and children is 0.2 ml/kg body weight (b.w.) (0.1 mmol/kg b.w.) up to 100 kg. Above 100 kg body weight 20 ml is usually sufficient. When brain metastases are suspected, a dosage of 0.6 ml/kg b.w. (0.3 mmol/kg b.w.) can be administered to adults up to 100 kg. Above 100 kg bodyweight a total of 60 ml is usually sufficient. The dose of 0.6 ml/kg can be administered as a single injection. Alternatively a second bolus injection of 0.4 ml/kg b.w. (0.2 mmol/kg b.w.) may be administered within 20 minutes of the first injection of 0.2 ml/kg b.w. (0.1 mmol/kg b.w.).

Whole body examinations
The recommended dosage to adults and children above 6 months of age is 0.2 ml/kg b.w. (0.1 mmol/kg b.w.) up to 100 kg. Above 100 kg body weight 20 ml is usually sufficient. If needed 0.6 ml/kg b.w. (0.3 mmol/kg b.w.) can be administered to adults up to 100 kg body weight. Above 100 kg body weight a total of 60 ml is usually sufficient.
The MRI examination should start shortly after administration of Omniscan, 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 type of lesion/tissue. Enhancement is generally lasting up to 45 minutes after contrast medium injection. T1-weighted scanning sequences are particularly suitable for contrast enhanced examinations with Omniscan.

The diameter of the pre-filled syringe is too large for accurate measurement of small volumes. The syringe should not be used for volumes below 5 ml.

If this medicinal product is intended to be used with an automatic application system, its suitability for the intended use has to be demonstrated by the manufacturer of the medical device. Instructions for use of the medical device must be followed absolutely.

Special Populations
Patients with renal impairment
Omniscan is contraindicated in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and/or acute kidney injury and in patients in the perioperative liver transplantation period (see section 4.3). Omniscan should only be used after careful risk/benefit evaluation in patients with moderate renal impairment (GFR 30-59 ml/min/1.73m^2) at a dose not exceeding 0.1 mmol/kg body weight (see section 4.4). More than one dose should not be used during a scan. 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 up to 4 weeks of age, infants up to 1 year of age and children
Omniscan is contraindicated in neonates up to 4 weeks of age (see section 4.3).
Due to immature renal function in infants up to 1 year of age, Omniscan 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, Omniscan 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.

Elderly (aged 65 years and above)
No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance gadodiamide or to any of the excipients (see section 6.1).
Omniscan is contraindicated in patients with severe renal impairment ((GFR <30 ml/min/1.73 m^2), and/or acute kidney injury, in patients in the perioperative liver transplantation period and in neonates up to 4 weeks of age (see section 4.4).

4.4 Special warnings and precautions for use

The usual precaution measures for MRI examination should be taken, such as exclusion of pacemakers and ferro-magnetic implants.

Hypersensitivity
Allergoid and other idiosyncratic reactions may occur with all contrast media for intravenous application, also with Omniscan, which could become manifest in form of cardiovascular, respiratory and skin reaction up to shock (see section 4.8). Most of these reactions occur within half an hour after administration of the contrast medium. As with all other contrast media of the same class, late reaction may occur (after hours or days) in rare cases. If hypersensitivity reactions occur, the administration of the contrast medium must be discontinued immediately.

To enable immediate action in emergencies, the necessary medicinal products and equipment for intubation and adequate ventilation support must be immediately available.

The risk of hypersensitivity reactions is increased in the following cases:
- Patients with allergic predisposition
- Patients with bronchial asthma; in these patients especially the risk of bronchospasm is increased
- Patients with a history of severe reactions on contrast agents
- Impaired renal function

Intrathecal administration
OMNISCAN must not be used intrathecally. Intrathecal administration of GBCAs can cause serious adverse reactions including death, coma, encephalopathy, and seizures.

Patients with impaired renal function
Prior to administration of Omniscan, all patients should be screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of Omniscan and some other gadolinum-containing contrast agents in patients with acute or chronic severe renal impairment (GRF < 30ml/min/1.73m^2) and/or acute kidney injury. Omniscan is contraindicated in these patients (see section 4.3). Patients undergoing transplantation are at particular risk since the incidence of acute renal failure is high in this group. Therefore Omniscan must not be used in patients

with severe renal impairment, in patients in the perioperative liver transplantation period and in neonates (see section 4.3).

The risk for development of NSF in patients with moderate renal impairment (GRF 30-59ml/min/1.73m^2) is unknown; therefore, Omniscan should be only used after careful risk-benefit evaluation in patients with moderate 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.

Heamodialysis shortly after Omniscan administration 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.

Neonates and Infants:
Omniscan is contraindicated in neonates up to 4 weeks of age (see section 4.3). Due to immature renal function in infants up to 1 year of age, Omniscan should only be used in these patients after careful consideration.

Experience with Omniscan in children below 6 months with severe liver- or renal disease and in pre-term newborn infants below 4 weeks of age or with gestational age below 30 weeks is not available.

Patients taking beta-blocker
It should be noted that patients using beta-blockers do not necessarily respond to the beta-agonists usually used for the treatment of hypersensitivity reactions.

Patients with cardiovascular disease
In this group of patients hypersensitivity reaction may be more severe. Especially in patients with serious heart diseases (e.g. severe heart failure, coronary artery disease) cardiovascular reactions may deteriorate.

Patients with central nervous system disorders:
In patients suffering from epilepsy or brain lesions the likelihood of convulsions during the examination may be increased, as it was rarely observed with other contrast media of the same class. Precautions are necessary when examining these patients (e.g. monitoring of the patient) and the equipment and medicinal products needed for rapid treatment of possible convulsions should be available.

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

Paediatric patients
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.

<u>Gadolinium retention</u>
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.

Postmarketing 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 minimize potential risks associated with gadolinium retention, it is recommended to use the lowest effective dose (see section 4.2) and to perform a careful benefit risk assessment before administering repeated doses.

This medicinal product contains sodium: 0.62 mg/ml. This needs to be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicaments and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of gadodiamide in pregnant women. Animal studies have shown reproductive toxicity at repeated high doses (see section 5.3).

GBCAs cross the placenta and result in foetal exposure and gadolinium retention. Human data on the association between GBCA and adverse foetal outcomes are limited and inconclusive.

OMNISCAN should therefore only be used during pregnancy if the potential benefit justifies the potential risk to the foetus and the pregnant woman.

Lactation
It is unknown whether gadodiamide is excreted in human milk. Available data in animals have shown excretion of gadodiamide in milk (for details see section 5.3). A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued for at least 24 hours after the administration of Omniscan.

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Ambulant patients while driving vehicles or operating machinery should take account that nausea may incidentally occur.

4.8 Undesirable effects

Adverse reactions have been reported in approximately 6% of the patients in clinical trials.
The most commonly reported spontaneous adverse effects after Omniscan are hypersensitivity reactions, nausea and vomiting. Cases of nephrogenic systemic fibrosis (NSF) have been reported with Omniscan (see section 4.4).

In clinical trials with Omniscan, adverse reactions have been reported with the following frequencies given in the table below (very common ≥ 1/10; common ≥1/100, < 1/10); uncommon (≥ 1/1000, <a 1/100); rare (≥ 1/10000), < 1/1000); very rare < 1/10000). Not known (cannot be estimated from the available data)

Immune system disorders
Uncommon: Allergy-like skin and mucous membrane reactions, hypersensitivity
Not known: Anaphylactic/anaphylactoid reactions, anaphylactic / anaphylactoid shock

Psychiatric disorders
Rare: Anxiety

Nervous system disorders
Common: Headache
Uncommon: Dizziness, paraesthesia, transient perverted sensation of taste
Rare: Convulsions, tremor, somnolence, transient perverted sensation of smell

Eye disorders
Rare: Visual disturbances

Cardiac disorders
Not known: Tachycardia

Vascular disorders
Uncommon: Flushing

Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea, coughing
Not known: Bronchospasm, respiratory distress, throat irritation, sneezing

Gastrointestinal disorders
Common: Nausea
Uncommon: Vomiting, diarrhoea

Skin and subcutaneous tissue disorders
Uncommon: Pruritus
Rare: Oedema including face swelling and angioneurotic oedema, urticaria, rash, skin plaque*
Not known: Nephrogenic systemic fibrosis (NFS)

Musculoskeletal and connective tissue disorders
Rare: Arthralgia

Renal and urinary system disorders
Rare: Acute renal failure

General disorders and administration site conditions
Common: Transient sensation of warmth, coolness or local pressure in connection with injection. Transient sensation of pain at the injection site.
Rare: Chest pain, fever, shivering

* 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

Late adverse reactions can occur hours to days after administration of Omniscan.

Transient changes in serum iron have been observed in some patients but all these patients remained asymptomatic.

4.9 Overdose

In case of an excessive intravenous dose in a patient with renal insufficiency, Omniscan 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.
ATC code: V08CA03

Omniscan is a non-ionic paramagnetic contrast medium for use in magnetic resonance imaging (MRI). Omniscan contains gadodiamide that mainly affects the protons T1-relaxation time. After intravenous injection this yields increased signal intensity and thereby contrast enhancement in MRI-investigations. 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.

The product provides contrast enhancement and facilitates visualisation of abnormal structures or lesions in various parts of the body including the CNS. In cases of blood-brain barrier dysfunction, administration of Omniscan may lead to improved visualisation of pathological changes, and lesions with abnormal vascularity (or those thought to cause abnormalities in the blood-brain barrier) in the brain (intracranial lesions), spine and associated tissues as well as lesions in the thorax, pelvic cavities and the retroperitoneal spaces. It also improves tumour delineation thus determining extent of invasiveness. Signal enhancement is not seen with all types of pathological processes, e.g. some types of low-grade malignancies or inactive MS-plaques fail to enhance. Omniscan can thus be used for differential diagnosis between healthy and pathological tissues, different pathological structures, and in differentiation between tumour and tumour recurrences and cicatricial tissue after treatment.

5.2 Pharmacokinetic properties

Distribution
Gadodiamide is rapidly distributed in the extracellular fluid. The volume of distribution is equivalent to that of extracellular water. The distribution half-life is approximately 4 minutes and the elimination half-life is approximately 70 minutes. In patients with impaired renal function the elimination half-life is prolonged inversely proportional to the impaired renal function. The contrast medium can be eliminated by haemodialysis.

Elimination
Gadodiamide is excreted through the kidneys by glomerular filtration. In patients with normal renal function approximately 85 % of the administered dose is recovered unchanged in the urine by 4 hours and 95-98 % by 24 hours after intravenous injection.

The kinetics is linear after doses of 0.l and 0.3 mmol/kg.

No metabolites have been detected. Gadodiamide is not bound to plasma proteins.

Following GBCA 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

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. After repeated administration of doses of 0.5 and 1.0 mmol/kg/day in pregnant rabbits there were skeletal anomalies indicative of developmental retardation. Carcinogenicity studies have not been performed.

Studies conducted in healthy rats injected repeatedly with GBCAs 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.

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.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The following excipients are included:
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

See expiry date printed on the label.

6.4 Special precautions for storage

OMNISCAN should be stored at 2 - 30 °C protected from
light. Do not freeze.

6.5 Nature and content of containers

The product is filled in injection vials/bottles with a fill volume of 5, 10, 15, 20 and 100 ml, and in polypropylene bottles with a fill volume of 10, 15, 20, 40 and 50 ml, and in pre-filled syringes with a fill volume of 10, 15 and 20 ml. The vials/bottles are made of colourless highly resistant borosilicate glass (Ph.Eur. Type I) and are closed with chlorobutyl rubber stoppers (latex free) grey halo-butyl isoprene blend rubber stoppers (Ph.Eur. Type I), sealed with complete tear off caps of aluminium with coloured plastic "flip-off" tops. The polypropylene bottles are rigid stand-up bottles with a twist-off top. The pre-filled syringes are made of polypropylene, with bromo-butyl rubber plungers, or polycycloolefin, with styrene-butadiene rubber plungers.

The product is supplied as:

1 vial of 5 ml
1 vial of 10 ml
1 vial of 15 ml
1 vial of 20 ml
1 bottle of 100 ml

1 polypropylene bottle of 10 ml
1 polypropylene bottle of 15 ml
1 polypropylene bottle of 20 ml
1 polypropylene bottle of 40 ml
1 polypropylene bottle of 50 ml

1 pre-filled syringe of 10 ml
1 pre-filled syringe of 15 ml
1 pre-filled syringe of 20 m

10 vials of 5 ml
10 vials of 10 ml
10 vials of 15 ml
10 vials of 20 ml
10 bottles of 100 ml

10 polypropylene bottles of 10 ml
10 polypropylene bottles of 15 ml
10 polypropylene bottles of 20 ml
10 polypropylene bottles of 40 ml
10 polypropylene bottles of 50 ml

10 pre-filled syringes of 10 ml
10 pre-filled syringes of 15 ml
10 pre-filled syringes of 20 m

In certain countries some package sizes may not be available.

6.6 Special precautions for disposal and other handling

Vials, polypropylene bottles and prefilled syringes are intended for one patient only. Any unused portions must be discarded.

The peel-off tracking label on the syringe, vial/bottle should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded.

Additional instructions for auto injector/pump
The 100 ml contrast medium bottle should only be used in connection with auto injectors/pumps approved for this volume. A single piercing procedure should be used. The line running from the 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.

7 APPLICANT/MANUFACTURER

Manufactured by:

Applicant

FENSYL MHP CONSULTING LIMITED,
NO. 49, KOFO ABAYOMI STREET,
APAPA NULL NULL, LAGOS

GE Healthcare Ireland Limited
IDA Business Park
Carrigtohill
Co. Cork
IRELAND

8 DATE OF (PARTIAL) REVISION OF THE TEXT

June 2024