ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Optimark 500 micromol/ml solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 330.9 mg gadoversetamide, equivalent to 500 micromol.

Each 10 ml syringe contains 3309 mg gadoversetamide equivalent to 5 millimol.
Each 15 ml syringe contains 4963.5 mg gadoversetamide equivalent to 7.5 millimol.
Each 20 ml syringe contains 6618 mg gadoversetamide equivalent to 10 millimol.
Each 30 ml syringe contains 9927 mg gadoversetamide equivalent to 15 millimol.

Excipient(s) with known effect:
20 ml of the solution contain 28.75 mg of sodium.
30 ml of the solution contain 43.13 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.
Clear, colourless to pale yellow solution.
pH: 6.0 – 7.5
Osmolality (37°C): 1000 – 1200 mOsm/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Optimark is indicated for use with magnetic resonance imaging (MRI) of the central nervous system (CNS) and liver. It provides contrast enhancement and facilitates visualization and helps with the characterization of focal lesions and abnormal structures in the CNS and liver in adult patients and in children of two years and older with known or highly suspected pathology.

4.2 Posology and method of administration

Optimark should only be administered by physicians experienced in clinical MRI practice.
To enable immediate action in emergencies, the necessary medicinal products (e.g. epinephrine/ adrenaline, theophylline, antihistamines, corticosteroids and atropines), endotracheal tube and ventilator must be immediately available.

Posology
The agent should be administered as a bolus peripheral intravenous injection at a dose of 0.2 ml/kg (100 micromol/kg) body weight. To ensure complete injection of the contrast medium, the injection should be followed by a 5 ml flush of sodium chloride 9 mg/ml (0.9 %) solution for injection. The imaging procedure should be completed within 1 hour of administration of the contrast medium.

Repeat dose
In cranial MRI, if a strong clinical suspicion of a lesion persists despite a single dose contrast-enhanced MRI or when more accurate information on the number, size or extent of lesions might influence management or therapy of the patient, in subjects with normal renal function, a second bolus injection of 0.2ml/kg (100 micromol/kg) may be administered within 30 minutes of the first injection as it may increase the diagnostic yield of the examination.
The safety of repeat doses has not been established in children and adolescents (2 years and older), in patients with renal impairment, or the elderly. The repeat dose is not recommended in these populations.
Limited data with other gadolinium contrast agents suggests that for the exclusion of additional cranial metastases in a patient with a known solitary resectable metastasis, an MR exam with the injection of the dose of 300 micromol/kg body weight of Optimark may lead to higher diagnostic confidence.

Paediactric population
No dose adjustment is considered necessary in children more than 2 years of age.
Optimark is contraindicated in neonates up to 4 weeks of age (see section 4.3).
Use of Optimark is not recommended in children less than 2 years of age because the safety, efficacy, and impact of immature kidney function have not been studied in this age group.

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

Renal and hepatic impairment
Optimark is contraindicated in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and/or acute renal injury and in patients who have had liver transplantation or in patients in the perioperative liver transplantation period (see section 4.3). Optimark 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 100 micromol/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, Optimark injections should not be repeated unless the interval between injections is at least 7 days.

Method of administration
The agent should be administered as a bolus peripheral intravenous injection. To ensure complete injection of the contrast medium, the injection should be followed by a 5 ml flush of sodium chloride 9 mg/ml (0.9 %) solution for injection. Insertion of a flexible in-dwelling venous catheter is recommended, see section 4.4.
Optimark must not be administered with an autoinjector to children of 2 to 11 years (see section 4.4).

Precautions to be taken before handling or administering the medicinal product
The container and the solution should be inspected prior to use as described in section 6.6.

4.3 Contraindications

Hypersensitivity to gadoversetamide or to other gadolinium containing products, or to any of the excipients listed in section 6.1.

Optimark is contraindicated
- in patients with severe renal impairment (GFR <30ml/min/1.73m^2) and/or acute kidney injury,
- in patients who have had liver transplantation or
- 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

As with any paramagnetic contrast agent, enhancement of MRI with gadoversetamide may impair the visualization of existing lesions. Some of these lesions may be seen on unenhanced, non-contrast MRI.

Therefore, caution should be exercised when contrast enhanced scan interpretation is made in the absence of a companion unenhanced MRI.
Before the examination, care must be taken that patients are sufficiently hydrated.

Hypersensitivity
Allergoid and other idiosyncratic reactions also may occur with gadoversetamide, which could become manifest in form of cardiovascular, respiratory and skin reactions (see section 4.8). Most of these reactions occur within half an hour after administering the contrast medium. As with all other contrast media of the same class, late reactions may occur (after hours or days) in rare cases; however, none were reported in the completed clinical trials.
If hypersensitivity reactions occur, the administration of the contrast medium must be discontinued immediately and intravenous treatment initiated, if necessary.
During the examination, supervision by a physician is necessary and insertion of a flexible in-dwelling catheter is recommended. To enable immediate action in emergencies, the necessary medicinal products (e.g. epinephrine/adrenaline, theophylline, antihistamines, corticosteroids and atropines), endotracheal tube and ventilator 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 it is especially the risk of bronchospasm which is increased
- patients with a history of reactions to contrast agents, including a previous history of reaction to iodine-based contrast agents

Before the injection of contrast media, patients should be asked whether they have any allergies (e.g. allergies to seafood or medicinal products, hay fever, urticaria), whether they are hypersensitive to contrast media and whether they have bronchial asthma. Premedication with antihistamines and/or glucocorticoids may be considered.

Patients taking beta-blockers
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 reactions may be severe. Especially in patients with serious heart diseases (e.g. severe heart failure, coronary artery disease) cardiovascular reactions may deteriorate. However, these were not evident from clinical trials with Optimark.

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.

Patients with impaired renal function
Prior to administration of Optimark, 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 Optimark and some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR <30ml/min/1.73m^2) and/or acute kidney injury. Optimark is contraindicated in these patients (see section 4.3). Patients who have had or are undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. Therefore, Optimark must not be used in patients who have had or are undergoing liver transplantation and in neonates (see section 4.3).
The risk for development of NSF in patients with moderate renal impairment (GFR 30–59 ml/min/1.73 m²) is unknown; therefore Optimark should only be used after careful risk-benefit evaluation in patients with moderate renal impairment.
Gadoversetamide is dialysable. Haemodialysis shortly after Optimark administration may be useful at removing Optimark 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.

Children and adolescents
Optimark must not be administered with an autoinjector. The required dose should be administered by hand to children of 2 to 11 years to avoid overdosage by mistake.

Neonates and infants
Optimark should not be used in children below the age of two years. Safety and efficacy have not been studied in this age group.

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

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose of up to 17 ml, i.e. it is essentially 'sodium-free'.
10 ml vials and 15 ml vials contain less than 1mmol sodium; i.e. they are essentially sodium free.
Higher doses contain 1 mmol of sodium or more, which should be taken into consideration for patients on a controlled sodium diet.
20 ml of the solution contain 28.75 mg of sodium.
30 ml of the solution contain 43.13 mg sodium.

Serum iron and zinc
Caution should be exercised because transient decreases in serum iron and zinc parameters have been observed in clinical trials. The clinical significance of this is unknown.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed.

Optimark has been shown to cause interference in the measurement of serum calcium using the ortho-cresolphthalein complexone (OCP) colorimetric method. However, the administration of gadoversetamide does not cause a true decrease in serum calcium. In the presence of gadoversetamide, the OCP technique produces an erroneous, low value for plasma calcium. The magnitude of this measurement artefact is proportional to the concentration of gadoversetamide in the blood, and in patients with normal renal clearance accurate values can be obtained approximately 90 minutes following injection. In patients with compromised renal function, clearance of gadoversetamide will be slowed and the interference with calcium determination by OCP prolonged. Gadoversetamide does not affect other methods of measuring serum calcium, such as the arsenazo III colorimetric method, atomic absorption spectroscopy, and inductively coupled plasma mass spectroscopy.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of gadoversetamide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Optimark should not be used during pregnancy unless the clinical condition of the woman requires use of gadoversetamide.

Breast-feeding
It is unknown whether gadoversetamide is excreted in human milk. There is insufficient information on the excretion of gadoversetamide in animal milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued for at least 24 hours after the administration of Optimark.

Fertility
Non-clinical data did not reveal special hazards for humans based on conventional studies of reproductive toxicity. Clinical studies on fertility have not been performed

4.7 Effects on ability to drive and use machines

Optimark has no or negligible influence on the ability to drive and use machines.
Ambulant patients while driving vehicles or operating machinery should take into account that acute dizziness may uncommonly (≥1/1,000 to <1/100) occur (see section 4.8).

4.8 Undesirable Effects

Summary of the safety profile
Most of the adverse reactions were of mild to moderate intensity and transient in nature. The most common adverse reactions were dysgeusia, feeling hot, headache and dizziness.
The majority of adverse reactions observed after the use of gadoversetamide were found to be adverse reactions of the nervous system, followed by general adverse reactions, gastrointestinal disorders/skin and subcutaneous tissue disorders.
Serious adverse reactions have been reported and include anaphylactic reactions, cardiovascular reactions, and allergic respiratory disorders. Treatment should be symptomatic and immediate access to necessary medicinal products and emergency equipment should be available should a serious event occur.

Tabulated list of adverse reactions
The following adverse reactions have been reported from clinical trials and from post-marketing use of gadoversetamide. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class (MedDRA)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very Rare (<1/10,000)**	**Not known**
Immune System Disorders		Anaphylactic reaction			
Metabolism and Nutrition Disorders			Decreased appetite		
Psychiatric Disorders			Anxiety, Sleep disorder, Confusion and disorientation		
Nervous System Disorders	Headache, Dysgeusia	Dizziness, Hypoaesthesia, Paraesthesia, Parosmia	Convulsion, Tremor, Somnolence, Burning sensation	Syncope	
Eye Disorders			Erythema of eyelid, Eye pain, Vision blurred, Conjunctivitis, Ocular hyperaemia		
Ear and Labyrinth Disorders			Tinnitus, Vertigo		
Cardiac Disorders			Palpitations, AV block first degree, Extrasystoles, Tachycardia, Arrhythmia		
Vascular Disorders		Flushing	Hypotension, Hypertension		
Respiratory, Thoracic and Mediastinal Disorders		Nasal congestion, Throat irritation	Dyspnoea, Dysphonia, Rhinorrhoea, Throat tightness, Bronchospasm, Cough, Laryngeal/pharyngeal oedema, Pharyngitis, Rhinitis, Sneezing		
Gastrointestinal Disorders		Nausea, Diarrhoea	Salivary hypersecretion,, Abdominal pain, Constipation, Dry mouth	Vomiting	
Skin and Subcutaneous Tissue Disorders		Pruritus, Rash	Urticaria, Cold sweat, Erythema, Hyperhidrosis	Periorbital oedema	Nephrogenic systemic fibrosis (NSF)
Renal and Urinary Disorders			Blood creatinine increased, Haematuria		

System Organ Class (MedDRA)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Not known
General Disorders and Administration Site Conditions	Feeling hot	Chest discomfort, Chest pain, Feeling cold (including peripheral coldness), Administration site reactions	Chills, Pain, Face oedema, Asthenic conditions including asthenia, fatigue, and malaise, Fever, Oedema peripheral, Feeling abnormal		
Investigations		Blood calcium abnormal	ALT increased, Urine analysis abnormal, Urine electrolytes abnormal, albumin in urine, CPK Increased, Haemoglobin decreased	Electrocardiogram QT prolonged	

Local reactions have occurred at the injection site and may lead to local irritation type reactions.

Cases of nephrogenic systemic fibrosis (NSF) have been reported with Optimark (see section 4.4).

Paediatric population
Optimark has been studied in children of 2 years and older with a similar safety profile as shown in the adult population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Gadoversetamide has been tested in humans in doses up to 700 micromol/kg (seven times the standard dose). Clinical consequences of an overdose have not been reported. Acute toxicity symptoms are unlikely to occur in patients with normal renal function. Optimark 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: MRI contrast media, ATC code: V08CA06

Gadoversetamide is a chelate containing gadolinium - which has paramagnetic properties and is responsible for the contrast enhancement effect in MRI - and the ligand versetamide.

The purpose of an MRI contrast agent is to induce signal intensity changes within the lesion thereby facilitating its recognition from the surrounding normal structures. The use of a contrast agent may therefore reduce the threshold for lesion detection and visualization. Gadolinium containing MRI contrast agents (gadolinium-based chelates) are designed to act indirectly on the local magnetic environment by altering proton T1 (spin-lattice) and T2 (spin-spin) relaxation times and at the usual concentration of 100 micromol/kg, the T1 shortening predominates, and the T2 shortening is not significant using T1-weighted sequences.

Gadoversetamide, an extracellular gadolinium chelate, after intravenous administration, equilibrates rapidly within the extracellular fluid/space and is eliminated primarily by glomerular filtration.
As a result of these characteristics, the timing of the image acquisition after contrast administration is critical in liver imaging. For liver metastases, the signal difference between the tumour and surrounding liver tissue is significantly improved during the first 90 seconds after an extracellular gadolinium contrast agent is administered. Therefore, a rapid imaging sequence should be initiated 20 seconds after bolus injection of the contrast agent when the agent is predominately in the hepatic arteries and then again at 60 seconds after injection during the dominant portal venous phase. Since the hepatic artery and portal venous system supply approximately 20% and 80% of the hepatic blood supply, respectively, the earlier (hepatic arterial phase) images provide optimal lesion conspicuity for hypervascular lesions and the portal venous phase images are useful for hypovascular lesions (most metastatic lesions are relatively hypovascular and are better demonstrated during the portal venous phase, manifesting as areas of lower signal intensity compared with the markedly enhanced liver). Lesion conspicuity of hypo- and hypervascular lesions may be reduced if imaging is delayed more than 3 minutes due to the diffusion of the contrast agent into the interstitial spaces of both the liver parenchyma and lesion (e.g. metastasis) making the lesion isointense with the normal liver parenchyma. Delayed post-contrast or equilibrium images (> 5 minutes after dosing) assist in the

characterization of lesions, e.g. the centre of a metastasis may accumulate contrast in the interstitial space of the lesion and become hyperintense to the normal liver. This difference in enhancement pattern is useful in formulating a differential diagnosis based on lesion characterization and diagnostic confidence.

The enhancement of brain tumours using a gadolinium (or iodine) containing contrast agent depends on the disruption of the blood brain barrier (BBB). As a result, these agents have been referred to as markers for sites of abnormal BBB breakdown. When the BBB is disrupted, the gadoversetamide molecules diffuse into the interstitial compartment thereby producing the characteristic paramagnetic effect of T1 and T2 shortening. In general, the addition of contrast to MRI, at the standard clinical dose of 100 micromol/kg, has led to a significantly improved lesion detection, sensitivity and diagnostic accuracy.

5.2 Pharmacokinetic properties

Distribution
The pharmacokinetics of gadoversetamide conforms to a two compartment open-model. At the 100 micromol/kg dose, the mean distribution half life in normal subjects calculated by the method of residuals in 12 normal volunteers is 13.3 ± 6.8 min. Mean volume of distribution at the 100 micromol/kg dose in non-renally impaired patients (including both normal subjects and patients with CNS or liver pathology) was 158.7 ± 29.0 to 214.3 (range 116.4 to 295.0) ml/kg. This volume of distribution (approximately 10-15 l for a body weight of 70 kg) is consistent with a medicinal product which distributes into the extracellular fluid. Dose level has no consistent effect on the volume of distribution in any of the studies. Gadoversetamide does not undergo protein binding in vitro.

Elimination
The elimination half life at the 100 micromol/kg dose ranges from 1.49 ± 0.15 h in healthy volunteers to 2.11 ± 0.62 h in non-renally impaired patients (including normal subjects and patients with CNS or liver pathology).

The mean plasma clearance of gadoversetamide in healthy subjects (111.0 ± 14.1 ml/min/1.73m² BSA) is not significantly different from the mean renal clearance. Similar results are obtained in normal subjects and patients with various combinations of liver, CNS and renal dysfunctions with renal clearance of gadoversetamide being approximately 95% of the total plasma clearance. Such results (ratio renal clearance/total plasma clearance close to 1) indicate that gadoversetamide is essentially cleared through the kidneys.

There was no systematic difference in any of the kinetic parameters as a function of dose level (100 to 700 micromol/kg). Therefore, within this dose range, the kinetics of gadoversetamide appear to be linear.

Metabolism
The high accountability for the dose as intact complex in urine suggests that no significant metabolism of gadoversetamide occurs in humans.

Special Populations

Effect of Gender:
Adult male and female subjects were enrolled in two pharmacokinetic studies. No significant differences in pharmacokinetics based on gender were identified.

Effects of Age:
When corrected for body weight, the total body clearance of gadoversetamide is greater in the 2 to 11 year age group (143 ± 27.9 ml/h/kg) than that observed in the 12 to 18 year age group (117 ± 26.1 ml/h/kg) and the two adult populations (82.1 ± 16.8 and 56.5 ± 9.7 ml/h/kg in the 19 to 64 and ≥ 65 year of age groups, respectively).

The elimination half life in the 2 to 11 and 12 to 18 year age groups (1.4 ± 0.3 and 1.6± 0.3 h^{-1}, respectively) is shorter than that observed in the two adult populations (1.9 ± 0.5 and 2.5± 0.5 h^{-1} in the 19 to 64 and ≥ 65 year of age groups, respectively). The number of elderly patients in whom the pharmacokinetics were determined was limited (over 65 years, N=3).

Effect of Renal Impairment
Gadoversetamide plasma levels increase linearly with decreasing renal function; in patients with severe renal impairment (Cr_{Cl}<30 ml/min) this even leads to a six-fold decreased gadoversetamide clearance and a corresponding six-fold increased extent of exposure AUC and $t_{½}$. Since gadoversetamide is only administered as a single dose this will lead to a longer and higher exposure for a limited duration. Still, after 72 hours even in patients with severe renal impairment nearly the whole dose is recovered in the urine and in healthy populations up to 500 micromol/kg doses were administered without safety issues. Nevertheless, because of reported cases of NSF that may be associated with renal impairment for other gadolinium containing contrast agents and for gadoversetamide, Optimark should not be used in these patients.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute toxicity, reproductive toxicity, local tolerance, antigenicity, and genotoxicity. No carcinogenicity studies were performed.

Repeated-dose toxicity studies in rats and dogs revealed vacuolation of the tubular cells of the kidneys, with strong evidence for reversibility of the effect. No functional impairment was observed.

The elimination of Optimark in dogs younger than 3 months of age was significantly delayed because of immature renal function and resulted in a high systemic exposure to Optimark. Weekly repeated dosing of two to twenty times the clinical dose from one week of age through maturation resulted in extensive mineralization of tissues, which produced localized effects, such as ulcerative dermatitis, compromised circulation and hepatic dysfunction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Versetamide
Calcium hydroxide
Calcium chloride dihydrate
Sodium hydroxide and/or hydrochloric acid for pH adjustment
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, Optimark should not be mixed with other medicinal products.

6.3 Shelf-life

3 years.

Chemical and physical in-use stability has been demonstrated for 24 hours at up to 25°C.
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.

6.4 Special precautions for storage

Keep the syringe in the outer carton in order to protect from light.
Do not refrigerate or freeze.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Optimark is filled in pre-filled syringes made of polypropylene. Syringe tip cap and piston are made of bromobutyl rubber.

Pack sizes:

1 x 10 ml	10 x 10 ml
1 x 15 ml	10 x 15 ml
1 x 20 ml	10 x 20 ml
1 x 30 ml	10 x 30 ml

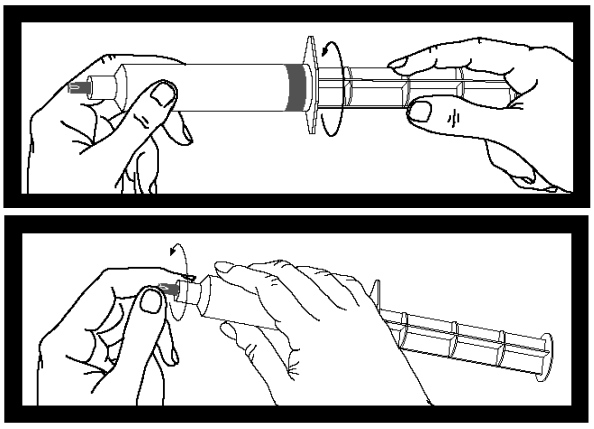
Not all pack-sizes may be marketed**.**

6.6 Special precautions for disposal and other handling

Optimark is intended for single use only; any unused portions should be discarded.

Do not use the solution if it is discoloured or particulate matter is present. If non-disposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Pre-filled syringes:
Assembly and Inspection
Inspect the syringe for signs of leakage. Do not use if leakage is observed.



After screwing the push rod into the syringe piston, it is important to **turn the push rod an additional ½ turn** so that the grey piston rotates freely

Prior to using the syringe, twist off grey tip cap and discard. Syringe is now ready for needle or infusion tubing attachment.

Discard syringe and unused portion of the solution after use.
Any unused product or waste material should be disposed of in accordance with local requirements.
The peel-off tracking label on the pre-filled syringes 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.

7. MARKETING AUTHORISATION HOLDER

Mallinckrodt Deutschland GmbH
Josef-Dietzgen-Str.1
53773 Hennef
Germany

8. MARKETING AUTHORISATION NUMBER(S)

1 x 10 ml: EU/1/07/398/007
10 x 10 ml: EU/1/07/398/008
1 x 15 ml: EU/1/07/398/009
10 x 15 ml: EU/1/07/398/010
1 x 20 ml: EU/1/07/398/011
10 x 20 ml: EU/1/07/398/012
1 x 30 ml: EU/1/07/398/013
10 x 30 ml EU/1/07/398/014

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 July 2007
Date of latest renewal: 15 June 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Optimark 500 micromol/ml solution for injection in vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 330.9 mg gadoversetamide, equivalent to 500 micromol.

Each 10 ml vial contains 3309 mg gadoversetamide equivalent to 5 millimol.
Each 15 ml vial contains 4963.5 mg gadoversetamide equivalent to 7.5 millimol.
Each 20 ml vial contains 6618 mg gadoversetamide equivalent to 10 millimol.

Excipient(s) with known effect:
20 ml of the solution contain 28.75 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in vial.
Clear, colourless to pale yellow solution.
pH: 6.0 – 7.5
Osmolality (37°C): 1000 – 1200 mOsm/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Optimark is indicated for use with magnetic resonance imaging (MRI) of the central nervous system (CNS) and liver. It provides contrast enhancement and facilitates visualization and helps with the characterization of focal lesions and abnormal structures in the CNS and liver in adult patients and in children of two years and older with known or highly suspected pathology.

4.2 Posology and method of administration

Optimark should only be administered by physicians experienced in clinical MRI practice.
To enable immediate action in emergencies, the necessary medicinal products (e.g. epinephrine/ adrenaline, theophylline, antihistamines, corticosteroids and atropines), endotracheal tube and ventilator must be immediately available.

Posology
The agent should be administered as a bolus peripheral intravenous injection at a dose of 0.2 ml/kg (100 micromol/kg) body weight. To ensure complete injection of the contrast medium, the injection should be followed by a 5 ml flush of sodium chloride 9 mg/ml (0.9 %) solution for injection. The imaging procedure should be completed within 1 hour of administration of the contrast medium.

Repeat dose
In cranial MRI, if a strong clinical suspicion of a lesion persists despite a single dose contrast-enhanced MRI or when more accurate information on the number, size or extent of lesions might influence management or therapy of the patient, in subjects with normal renal function, a second bolus injection of 0.2ml/kg (100 micromol/kg) may be administered within 30 minutes of the first injection as it may increase the diagnostic yield of the examination.
The safety of repeat doses has not been established in children and adolescents (2 years and older), in patients with renal impairment, or the elderly. The repeat dose is not recommended in these populations.

Limited data with other gadolinium contrast agents suggests that for the exclusion of additional cranial metastases in a patient with a known solitary resectable metastasis, an MR exam with the injection of the dose of 300 micromol/kg body weight of Optimark may lead to higher diagnostic confidence.

Paediactric population
No dose adjustment is considered necessary in children more than 2 years of age.
Optimark is contraindicated in neonates up to 4 weeks of age (see section 4.3). Use of Optimark is not recommended in children less than 2 years of age because the safety, efficacy, and impact of immature kidney function have not been studied in this age group.

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

Renal and hepatic impairment
Optimark is contraindicated in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and/or acute renal injury and in patients who have had liver transplantation or in patients in the perioperative liver transplantation period (see section 4.3). Optimark 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 100 micromol/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, Optimark injections should not be repeated unless the interval between injections is at least 7 days.

Method of administration
The agent should be administered as a bolus peripheral intravenous injection. To ensure complete injection of the contrast medium, the injection should be followed by a 5 ml flush of sodium chloride 9 mg/ml (0.9 %) solution for injection. Insertion of a flexible in-dwelling venous catheter is recommended, see section 4.4.
Optimark must not be administered with an autoinjector to children of 2 to 11 years (see section 4.4).

Precautions to be taken before handling or administering the medicinal product
The container and the solution should be inspected prior to use as described in section 6.6.

4.3 Contraindications

Hypersensitivity to gadoversetamide or to other gadolinium containing products or to any of the excipients listed in section 6.1.

Optimark is contraindicated
- in patients with severe renal impairment (GFR <30ml/min/1.73m²) and/or acute kidney injury,
- in patients who have had liver transplantation or
- 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

As with any paramagnetic contrast agent, enhancement of MRI with gadoversetamide may impair the visualization of existing lesions. Some of these lesions may be seen on unenhanced, non-contrast MRI. Therefore, caution should be exercised when contrast enhanced scan interpretation is made in the absence of a companion unenhanced MRI.
Before the examination, care must be taken that patients are sufficiently hydrated.

Hypersensitivity
Allergoid and other idiosyncratic reactions also may occur with gadoversetamide, which could become manifest in form of cardiovascular, respiratory and skin reactions (see section 4.8). Most of these reactions occur within half an hour after administering the contrast medium. As with all other contrast media of the same class, late reactions may occur (after hours or days) in rare cases; however, none were reported in the completed clinical trials.
If hypersensitivity reactions occur, the administration of the contrast medium must be discontinued immediately and intravenous treatment initiated, if necessary.
During the examination, supervision by a physician is necessary and insertion of a flexible in-dwelling catheter is recommended. To enable immediate action in emergencies, the necessary medicinal products (e.g. epinephrine/adrenaline, theophylline, antihistamines, corticosteroids and atropines), endotracheal tube and ventilator 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 it is especially the risk of bronchospasm which is increased
- patients with a history of reactions to contrast agents, including a previous history of reaction to iodine-based contrast agents

Before the injection of contrast media, patients should be asked whether they have any allergies (e.g. allergies to seafood or medicinal products, hay fever, urticaria), whether they are hypersensitive to contrast media and whether they have bronchial asthma. Premedication with antihistamines and/or glucocorticoids may be considered.

Patients taking beta-blockers
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 reactions may be severe. Especially in patients with serious heart diseases (e.g. severe heart failure, coronary artery disease) cardiovascular reactions may deteriorate. However, these were not evident from clinical trials with Optimark.

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.

Patients with impaired renal function
Prior to administration of Optimark, 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 Optimark and some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR <30ml/min/1.73m^2) and/or acute kidney injury. Optimark is contraindicated in these patients (see section 4.3). Patients who have had or are undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. Therefore, Optimark must not be used in patients who have had or are undergoing liver transplantation and in neonates (see section 4.3).

The risk for development of NSF in patients with moderate renal impairment (GFR 30–59 ml/min/1.73 m^2) is unknown; therefore Optimark should only be used after careful risk-benefit evaluation in patients with moderate renal impairment.
Gadoversetamide is dialysable. Haemodialysis shortly after Optimark administration may be useful at removing Optimark 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.

Children and adolescents
Optimark must not be administered with an autoinjector. The required dose should be administered by hand to children of 2 to 11 years to avoid overdosage by mistake.

Neonates and infants
Optimark should not be used in children below the age of two years. Safety and efficacy have not been studied in this age group.
Elderly
As the renal clearance of gadoversetamide may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose of up to 17 ml, i.e. it is essentially 'sodium-free'.
10 ml vials and 15 ml vials contain less than 1mmol sodium; i.e. they are essentially sodium free.
Higher doses contain 1 mmol of sodium or more, which should be taken into consideration for patients on a controlled sodium diet.
20 ml of the solution contain 28.75 mg of sodium.

Serum iron and zinc
Caution should be exercised because transient decreases in serum iron and zinc parameters have been observed in clinical trials. The clinical significance of this is unknown.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed.

Optimark has been shown to cause interference in the measurement of serum calcium using the ortho-cresolphthalein complexone (OCP) colorimetric method. However, the administration of gadoversetamide does not cause a true decrease in serum calcium. In the presence of gadoversetamide, the OCP technique produces an erroneous, low value for plasma calcium. The magnitude of this measurement artefact is proportional to the concentration of gadoversetamide in the blood, and in patients with normal renal clearance accurate values can be obtained approximately 90 minutes following injection. In patients with compromised renal function, clearance of gadoversetamide will be slowed and the interference with calcium determination by OCP prolonged. Gadoversetamide does not affect other methods of measuring serum calcium, such as the arsenazo III colorimetric method, atomic absorption spectroscopy, and inductively coupled plasma mass spectroscopy.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of gadoversetamide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Optimark should not be used during pregnancy unless the clinical condition of the woman requires use of gadoversetamide.

Breast-feeding
It is unknown whether gadoversetamide is excreted in human milk. There is insufficient information on the excretion of gadoversetamide in animal milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued for at least 24 hours after the administration of Optimark.

Fertility
Nonclinical data did not reveal special hazards for humans based on conventional studies of reproductive toxicity. Clinical studies on fertility have not been performed.

4.7 Effects on ability to drive and use machines

Optimark has no or negligible influence on the ability to drive and use machines.
Ambulant patients while driving vehicles or operating machinery should take into account that acute dizziness may uncommonly (≥1/1,000 to <1/100) occur (see section 4.8).

4.8 Undesirable Effects

Summary of the safety profile
Most of the adverse reactions were of mild to moderate intensity and transient in nature. The most common adverse reactions were dysgeusia, feeling hot, headache and dizziness.
The majority of adverse reactions observed after the use of gadoversetamide were found to be adverse reactions of the nervous system, followed by general adverse reactions, gastrointestinal disorders/skin and subcutaneous tissue disorders.
Serious adverse reactions have been reported and include anaphylactic reactions, cardiovascular reactions, and allergic respiratory disorders. Treatment should be symptomatic and immediate access to necessary medicinal products and emergency equipment should be available should a serious event occur.

Tabulated list of adverse reactions
The following adverse reactions have been reported from clinical trials and from post-marketing use of gadoversetamide. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class (MedDRA)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very Rare (<1/10,000)**	**Not known**
Immune System Disorders		Anaphylactic reaction			
Metabolism and Nutrition Disorders			Decreased appetite		
Psychiatric Disorders			Anxiety, Sleep disorder, Confusion and disorientation		
Nervous System Disorders	Headache, Dysgeusia	Dizziness, Hypoaesthesia, Paraesthesia, Parosmia	Convulsion, Tremor, Somnolence, Burning sensation,	Syncope	
Eye Disorders			Erythema of eyelid, Eye pain, Vision blurred, Conjunctivitis, Ocular hyperaemia		
Ear and Labyrinth Disorders			Tinnitus, Vertigo		
Cardiac Disorders			Palpitations, AV block first degree, Extrasystoles, Tachycardia, Arrhythmia		
Vascular Disorders		Flushing	Hypotension, Hypertension		
Respiratory, Thoracic and Mediastinal Disorders		Nasal congestion, Throat irritation	Dyspnoea, Dysphonia, Rhinorrhoea, Throat tightness, Bronchospasm, Cough, Laryngeal/pharyngeal oedema, Pharyngitis, Rhinitis, Sneezing		
Gastrointestinal Disorders		Nausea, Diarrhoea	Salivary hypersecretion,, Abdominal pain, Constipation, Dry mouth	Vomiting	
Skin and Subcutaneous Tissue Disorders		Pruritus, Rash	Urticaria, Cold sweat, Erythema, Hyperhidrosis	Periorbital oedema	Nephrogenic systemic fibrosis (NSF)
Renal and Urinary Disorders			Blood creatinine increased, Haematuria		

System Organ Class (MedDRA)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Not known
General Disorders and Administration Site Conditions	Feeling hot	Chest discomfort, Chest pain, Feeling cold (including peripheral coldness), Administration site reactions	Chills, Pain, Face oedema, Asthenic conditions including asthenia, fatigue, and malaise, Fever, Oedema peripheral, Feeling abnormal		
Investigations		Blood calcium abnormal	ALT increased, Urine analysis abnormal, Urine electrolytes abnormal, albumin in urine, CPK Increased, Haemoglobin decreased	Electrocardiogram QT prolonged	

Local reactions have occurred at the injection site and may lead to local irritation type reactions.

Cases of nephrogenic systemic fibrosis (NSF) have been reported with Optimark (see section 4.4).

Paediatric population
Optimark has been studied in children of 2 years and older with a similar safety profile as shown in the adult population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Gadoversetamide has been tested in humans in doses up to 700 micromol/kg (seven times the standard dose). Clinical consequences of an overdose have not been reported. Acute toxicity symptoms are unlikely to occur in patients with normal renal function. Optimark 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: MRI contrast media, ATC code: V08CA06

Gadoversetamide is a chelate containing gadolinium - which has paramagnetic properties and is responsible for the contrast enhancement effect in MRI - and the ligand versetamide.

The purpose of an MRI contrast agent is to induce signal intensity changes within the lesion thereby facilitating its recognition from the surrounding normal structures. The use of a contrast agent may therefore reduce the threshold for lesion detection and visualization. Gadolinium containing MRI contrast agents (gadolinium-based chelates) are designed to act indirectly on the local magnetic environment by altering proton T1 (spin-lattice) and T2 (spin-spin) relaxation times and at the usual concentration of 100 micromol/kg, the T1 shortening predominates, and the T2 shortening is not significant using T1-weighted sequences.

Gadoversetamide, an extracellular gadolinium chelate, after intravenous administration, equilibrates rapidly within the extracellular fluid/space and is eliminated primarily by glomerular filtration.
As a result of these characteristics, the timing of the image acquisition after contrast administration is critical in liver imaging. For liver metastases, the signal difference between the tumour and surrounding liver tissue is significantly improved during the first 90 seconds after an extracellular gadolinium contrast agent is administered. Therefore, a rapid imaging sequence should be initiated 20 seconds after bolus injection of the contrast agent when the agent is predominately in the hepatic arteries and then again at 60 seconds after injection during the dominant portal venous phase. Since the hepatic artery and portal venous system supply approximately 20% and 80% of the hepatic blood supply, respectively, the earlier (hepatic arterial phase) images provide optimal lesion conspicuity for hypervascular lesions and the portal venous phase images are useful for hypovascular lesions (most metastatic lesions are relatively hypovascular and are better demonstrated during the portal venous phase, manifesting as areas of lower signal intensity compared with the markedly enhanced liver). Lesion conspicuity of hypo- and hypervascular lesions may be reduced if imaging is delayed more than 3 minutes due to the diffusion of the contrast agent into the interstitial spaces of both the liver parenchyma and lesion (e.g. metastasis) making the lesion isointense with the normal liver parenchyma. Delayed post-contrast or equilibrium images (> 5 minutes after dosing) assist in the

characterization of lesions, e.g. the centre of a metastasis may accumulate contrast in the interstitial space of the lesion and become hyperintense to the normal liver. This difference in enhancement pattern is useful in formulating a differential diagnosis based on lesion characterization and diagnostic confidence.

The enhancement of brain tumours using a gadolinium (or iodine) containing contrast agent depends on the disruption of the blood brain barrier (BBB). As a result, these agents have been referred to as markers for sites of abnormal BBB breakdown. When the BBB is disrupted, the gadoversetamide molecules diffuse into the interstitial compartment thereby producing the characteristic paramagnetic effect of T1 and T2 shortening. In general, the addition of contrast to MRI, at the standard clinical dose of 100 micromol/kg, has led to a significantly improved lesion detection, sensitivity and diagnostic accuracy.

5.2 Pharmacokinetic properties

Distribution
The pharmacokinetics of gadoversetamide conforms to a two compartment open-model. At the 100 micromol/kg dose, the mean distribution half life in normal subjects calculated by the method of residuals in 12 normal volunteers is 13.3 ± 6.8 min. Mean volume of distribution at the 100 micromol/kg dose in non-renally impaired patients (including both normal subjects and patients with CNS or liver pathology) was 158.7 ± 29.0 to 214.3 (range 116.4 to 295.0) ml/kg. This volume of distribution (approximately 10-15 l for a body weight of 70 kg) is consistent with a medicinal product which distributes into the extracellular fluid. Dose level has no consistent effect on the volume of distribution in any of the studies. Gadoversetamide does not undergo protein binding in vitro.

Elimination
The elimination half life at the 100 micromol/kg dose ranges from 1.49 ± 0.15 h in healthy volunteers to 2.11 ± 0.62 h in non-renally impaired patients (including normal subjects and patients with CNS or liver pathology).

The mean plasma clearance of gadoversetamide in healthy subjects (111.0 ± 14.1 ml/min/1.73m² BSA) is not significantly different from the mean renal clearance. Similar results are obtained in normal subjects and patients with various combinations of liver, CNS and renal dysfunctions with renal clearance of gadoversetamide being approximately 95% of the total plasma clearance. Such results (ratio renal clearance/total plasma clearance close to 1) indicate that gadoversetamide is essentially cleared through the kidneys.

There was no systematic difference in any of the kinetic parameters as a function of dose level (100 to 700 micromol/kg). Therefore, within this dose range, the kinetics of gadoversetamide appear to be linear.

Metabolism
The high accountability for the dose as intact complex in urine suggests that no significant metabolism of gadoversetamide occurs in humans.

Special Populations

Effect of Gender:
Adult male and female subjects were enrolled in two pharmacokinetic studies. No significant differences in pharmacokinetics based on gender were identified.

Effects of Age:
When corrected for body weight, the total body clearance of gadoversetamide is greater in the 2 to 11 year age group (143 ± 27.9 ml/h/kg) than that observed in the 12 to 18 year age group (117 ± 26.1 ml/h/kg) and the two adult populations (82.1 ± 16.8 and 56.5 ± 9.7 ml/h/kg in the 19 to 64 and ≥ 65 year of age groups, respectively).

The elimination half life in the 2 to 11 and 12 to 18 year age groups (1.4 ± 0.3 and 1.6± 0.3 h^{-1}, respectively) is shorter than that observed in the two adult populations (1.9 ± 0.5 and 2.5± 0.5 h^{-1} in the 19 to 64 and ≥ 65 year of age groups, respectively). The number of elderly patients in whom the pharmacokinetics were determined was limited (over 65 years, N=3).

Effect of Renal Impairment
Gadoversetamide plasma levels increase linearly with decreasing renal function; in patients with severe renal impairment (Cr_{Cl}<30 ml/min) this even leads to a six-fold decreased gadoversetamide clearance and a corresponding six-fold increased extent of exposure AUC and $t_{½}$. Since gadoversetamide is only administered as a single dose this will lead to a longer and higher exposure for a limited duration. Still, after 72 hours even in patients with severe renal impairment nearly the whole dose is recovered in the urine and in healthy populations up to 500 micromol/kg doses were administered without safety issues. Nevertheless, because of reported cases of NSF that may be associated with renal impairment for other gadolinium containing contrast agents and for gadoversetamide, Optimark should not be used in these patients.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute toxicity, reproductive toxicity, local tolerance, antigenicity, and genotoxicity. No carcinogenicity studies were performed.

Repeated-dose toxicity studies in rats and dogs revealed vacuolation of the tubular cells of the kidneys, with strong evidence for reversibility of the effect. No functional impairment was observed.

The elimination of Optimark in dogs younger than 3 months of age was significantly delayed because of immature renal function and resulted in a high systemic exposure to Optimark. Weekly repeated dosing of two to twenty times the clinical dose from one week of age through maturation resulted in extensive mineralization of tissues, which produced localized effects, such as ulcerative dermatitis, compromised circulation and hepatic dysfunction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Versetamide
Calcium hydroxide
Calcium chloride dihydrate
Sodium hydroxide and/or hydrochloric acid for pH adjustment
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, Optimark should not be mixed with other medicinal products.

6.3 Shelf-life

3 years.
Chemical and physical in-use stability has been demonstrated for 24 hours at up to 25°C.
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.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.
Do not refrigerate or freeze.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Optimark is filled in vials made of colourless highly resistant borosilicate glass (EP Type I). The vials are fitted with bromobutyl rubber closures, aluminium cap seals, and plastic flip caps.

Pack sizes:
1 x 10 ml 10 x 10 ml
1 x 15 ml 10 x 15 ml
1 x 20 ml 10 x 20 ml

Not all pack-sizes may be marketed**.**

6.6 Special precautions for disposal and other handling

Optimark is intended for single use only; any unused portions should be discarded.

Do not use the solution if it is discoloured or particulate matter is present. If non-disposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Optimark should be drawn into the syringe and used immediately.
The product must be examined before use to confirm that all solids are dissolved and that the container and closure are undamaged. If solids remain, the vial must be discarded.

Discard syringe and unused portion of the solution after use.
Any unused product or waste material should be disposed of in accordance with local requirements.

The peel-off tracking label on the 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.

7. MARKETING AUTHORISATION HOLDER

Mallinckrodt Deutschland GmbH
Josef-Dietzgen-Str.1
53773 Hennef
Germany

8. MARKETING AUTHORISATION NUMBER(S)

1 x 10 ml: EU/1/07/398/001
10 x 10 ml: EU/1/07/398/002
1 x 15 ml: EU/1/07/398/003
10 x 15 ml: EU/1/07/398/004
1 x 20 ml: EU/1/07/398/005
10 x 20 ml: EU/1/07/398/006

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 July 2007
Date of latest renewal: 15 June 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Mallinckrodt Medical Imaging Ireland
Damastown
Mulhuddart
Dublin 15
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription. (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSURs
The PSUR cycle for the medicinal product should follow a yearly cycle until otherwise agreed by the CHMP.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Prior to the launch, the MAA shall provide to all potential prescribers a copy of the SPC with a cover letter highlighting the safety information included in Sections 4.3 and 4.4. The text shall be agreed by the CHMP and shall also contain the following key element:

- Optimark is not recommended for use in children below the age of two years because the safety, efficacy, and impact of immature kidney function have not been studied in this age group. Optimark has been studied in children of 2 years and older with a similar safety profile as shown in the adult population.

- **OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES**

The MAH shall complete, within the stated timeframe, the following measures:

Obligation to conduct Post-Authorisation Measures

Description	**Due date**
The MAH shall submit **annual** cumulative reviews on nephrogenic systemic fibrosis (NSF) cases.	July of each year until the results of the study in bone have been submitted.
The MAH shall conduct a study evaluating the potential for long-term accumulation of gadolinium in the bone based on a CHMP agreed protocol.	Final Study Report: June 2016

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Text for the outer packaging of 10 ml, 15 ml, 20 ml and 30 ml pre-filled syringes

1. NAME OF THE MEDICINAL PRODUCT

Optimark 500 micromol/ml solution for injection in pre-filled syringe
Gadoversetamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 330.9 mg gadoversetamide, equivalent to 500 micromol.

3. LIST OF EXCIPIENTS

Excipients: versetamide, calcium hydroxide, calcium chloride dihydrate, sodium hydroxide and/or hydrochloric acid, water for injections.
Please see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
10 ml (1, 10 syringes)
15 ml (1, 10 syringes)
20 ml (1, 10 syringes)
30 ml (1, 10 syringes)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contrast medium for magnetic resonance imaging

For recording: stick the peel-off tracking label onto the patient record. For electronic records: enter product name, batch no. and dose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the syringe in the outer carton in order to protect from light.
Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only. Discard any remaining solution after first use.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mallinckrodt Deutschland GmbH, Josef-Dietzgen-Str.1, 53773 Hennef, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/398/007 (1 x 10 ml)
EU/1/07/398/008 (10 x 10 ml)
EU/1/07/398/009 (1 x 15 ml)
EU/1/07/398/010 (10 x 15 ml)
EU/1/07/398/011 (1 x 20 ml)
EU/1/07/398/012 (10 x 20 ml)
EU/1/07/398/013 (1 x 30 ml)
EU/1/07/398/014 (10 x 30 ml)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Text for the immediate packaging of 15 ml, 20 ml and 30 ml pre-filled syringes

1. NAME OF THE MEDICINAL PRODUCT

Optimark 500 micromol/ml solution for injection in pre-filled syringe
Gadoversetamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 330.9 mg gadoversetamide, equivalent to 500 micromol.

3. LIST OF EXCIPIENTS

Excipients: versetamide, calcium hydroxide, calcium chloride dihydrate, sodium hydroxide and/or hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

15 ml
20 ml
30 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

This sticky label should be stuck on patient records.
For electronic records: enter product name, batch no. and dose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the syringe in the outer carton in order to protect from light.
Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only. Discard any remaining solution after first use.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mallinckrodt Deutschland GmbH, Josef-Dietzgen-Str.1, 53773 Hennef, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/398/007 (1 x 10 ml)
EU/1/07/398/008 (10 x 10 ml)
EU/1/07/398/009 (1 x 15 ml)
EU/1/07/398/010 (10 x 15 ml)
EU/1/07/398/011 (1 x 20 ml)
EU/1/07/398/012 (10 x 20 ml)
EU/1/07/398/013 (1 x 30 ml)
EU/1/07/398/014 (10 x 30 ml)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Text for the immediate packaging of the 10 ml pre-filled syringe

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Optimark 500 micromol/ml solution for injection in pre-filled syringe
Gadoversetamide
IV use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

Keep the syringe in the outer carton in order to protect from light.
Do not refrigerate or freeze.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Text for the outer packaging of 10 ml, 15 ml and 20 ml vials

1. NAME OF THE MEDICINAL PRODUCT

Optimark 500 micromol/ml solution for injection in vial
Gadoversetamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 330.9 mg gadoversetamide, equivalent to 500 micromol.

3. LIST OF EXCIPIENTS

Excipients: versetamide, calcium hydroxide, calcium chloride dihydrate, sodium hydroxide and/or hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in vial
10 ml (1, 10 vials)
15 ml (1, 10 vials)
20 ml (1, 10 vials)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contrast medium for magnetic resonance imaging

For recording: stick the peel-off tracking label onto the patient record. For electronic records: enter product name, batch no. and dose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.
Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only. Discard any remaining solution after first use.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mallinckrodt Deutschland GmbH, Josef-Dietzgen-Str.1, 53773 Hennef, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/398/001 (1 x 10 ml)
EU/1/07/398/002 (10 x 10 ml)
EU/1/07/398/003 (1 x 15 ml)
EU/1/07/398/004 (10 x 15 ml)
EU/1/07/398/005 (1 x 20 ml)
EU/1/07/398/006 (10 x 20 ml)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Text for the immediate packaging of 15 ml and 20 ml vials

1. NAME OF THE MEDICINAL PRODUCT

Optimark 500 micromol/ml solution for injection in vial
Gadoversetamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 330.9 mg gadoversetamide, equivalent to 500 micromol.

3. LIST OF EXCIPIENTS

Excipients: versetamide, calcium hydroxide, calcium chloride dihydrate, sodium hydroxide and/or hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in vial
15 ml
20 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

This sticky label should be stuck on patient records.
For electronic records: enter product name, batch no. and dose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.
Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only. Discard any remaining solution after first use.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mallinckrodt Deutschland GmbH, Josef-Dietzgen-Str.1, 53773 Hennef, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/398/001 (1 x 10 ml)
EU/1/07/398/002 (10 x 10 ml)
EU/1/07/398/003 (1 x 15 ml)
EU/1/07/398/004 (10 x 15 ml)
EU/1/07/398/005 (1 x 20 ml)
EU/1/07/398/006 (10 x 20 ml)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Text for the immediate packaging of the 10 ml vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Optimark 500 micromol/ml solution for injection in vial
Gadoversetamide
IV use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

Keep the vial in the outer carton in order to protect from light.
Do not refrigerate or freeze.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Optimark 500 micromol/ml solution for injection in pre-filled syringe
Gadoversetamide

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are being given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Optimark is and what it is used for

Optimark contains the active substance gadoversetamide. Gadoversetamide is used as a 'contrast agent' in magnetic resonance imaging.

Optimark is for diagnostic use, only. It is used in adult patients and children of two years and older, who are undergoing magnetic resonance imaging (MRI), a type of scan where images of the internal organs are taken. Optimark is used to obtain a clearer scan in patients who have or are thought to have abnormalities in the brain, spine or liver.

2. What you need to know before you are given Optimark

Do not use Optimark
if you are allergic
- to the active substance gadoversetamide or
- to any of the other ingredients of Optimark (see section 6), or
- to other gadolinium contrast agents

You must not be given Optimark if
- you suffer from severe and/or acute kidney impairment, or
- if you are a patient who is about to have or has had a liver transplant as use of Optimark in patients with these conditions has been associated with a disease called nephrogenic systemic fibrosis (NSF). NSF is a disease involving thickening of the skin and connective tissues. NSF may result in debilitating joint immobility, muscle weakness or may affect the normal working of internal organs which may potentially be life-threatening.
- Optimark must not be used in newborn babies up to the age of 4 weeks.

Before you receive Optimark, you will need to have a blood test to check how well your kidneys are working.

Warnings and precautions
Talk to your doctor before Optimark is used, if:

- you suffer from allergies (e.g. medicinal products, seafood, hay fever, hives) or asthma
- you had any reactions to previous injections of a contrast agent, including a previous history of reaction to iodine-based contrast agents
- your kidneys do not work properly
- you have recently had, or soon expect to have, a liver transplant
- you are feeling thirsty and/or if you have only had small quantities or nothing to drink before the examination
- you are taking a special kind of antihypertensive medicine, i.e. a beta-blocker
- you have heart disease
- you suffer from epilepsy or brain lesions
- you are on a controlled sodium diet

If any of these apply to you, your doctor will decide whether the intended examination is possible or not.

Children and adolescents
Optimark is not recommended in children who are below the age of two years.

Other medicines and Optimark
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Optimark should not be used during pregnancy unless strictly necessary.
Breast-feeding should be discontinued for at least 24 hours after you receive Optimark.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines
If you are an ambulant patient and plan to drive or use tools or machines, take into account that dizziness may incidentally occur after you undergo a procedure involving the injection of Optimark. Up to 1 in 100 people may be affected.

Optimark contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose of up to 17 ml, i.e. it is essentially ‘sodium-free’.
10 ml vials and 15 ml vials contain less than 1mmol sodium; i.e. they are essentially sodium free.
Higher doses contain 1 mmol of sodium or more, which should be taken into consideration for patients on a controlled sodium diet.
20 ml of the solution contain 28.75 mg of sodium.
30 ml of the solution contain 43.13 mg sodium.

3. How Optimark is given

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.

The usual dose
The usual dose of 0.2 ml/kg body weight is the same in adults and children of 2 years and older. It would account for 14 ml for a 70 kg individual, and this volume would be injected over about 7 -14 seconds into a vein, usually a vein in an arm. The injection is then flushed through with a saline injection to make sure none is left in the needle or tube used for the injection. In adults, a second dose may be given within 30 minutes of the first injection. When looking at certain abnormalities in the brain, Optimark may need to be used at three times the usual dose in one injection in adults. The

doctor will decide how much Optimark is needed for your examination. You must tell the doctor or nurse/technologist immediately if you feel pain around the area where the needle is placed.

Dosage in special patient groups
In patients with moderate kidney problems, more than one dose of Optimark should not be used during a scan. Optimark injections should not be repeated unless the interval between injections is at least 7 days.

It is not necessary to adjust your dose if you are 65 years of age or older but you will have a blood test to check how well your kidneys are working.

If you are given more Optimark than you should have been
If too much Optimark was injected it is unlikely that it will do you much harm, as much higher doses did not lead to any problems when some people received them. If your kidneys are working normally it is unlikely you will have any problems. Optimark can be removed using dialysis. If you think you have been injected with too much Optimark, tell the doctor or nurse/technologist immediately.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You must report any of the following symptoms immediately to the doctor or nurse/technologist, and get immediate treatment as they can be or can become very serious:
side effects affecting the heart (fainting, extra heart beats, chest pain) or the respiratory system (shortness of breath, tightening of the airways, swollen or tight throat, itchy or runny nose, sneezing).

Most of the side effects observed after the use of Optimark were of mild to moderate intensity and transient in nature. The most common side effects were a strange taste in the mouth, feeling hot, headache and dizziness.
Possible side effects are described in greater detail below.

The frequencies below and the following symptoms are based on clinical trials, and on the experience in using Optimark after it was on the market:

Frequency	**Possible side effects**
Common (may affect up to 1 in 10 people)	headache, strange taste in the mouth, feeling hot
Uncommon (may affect up to 1 in 100 people)	allergic/hypersensitivity reaction, dizziness, tingling sensation, numbness, reduced sense of smell, skin red and warm, nasal congestion, sore throat, nausea, diarrhoea, itching, rash, chest discomfort, chest pain, feeling cold including cold feeling in extremities, administration site reactions, changes in blood calcium levels

Frequency	Possible side effects
Rare (may affect up to 1 in 1000 people)	decreased appetite, feeling anxious, sleep disorder, drowsy feeling, burning sensation, a sensation of movement or spinning, ringing in the ears, eyelid redness, eye pain, vision blurred, bloodshot eyes, awareness of the heartbeat, irregular heartbeats, extra heartbeats, low blood pressure, shortness of breath, hoarseness, runny nose, throat constriction, mouth watering, abdominal pain, constipation, dry mouth, hives, cold sweat, redness, higher blood level of a substance (creatinine) usually eliminated by the kidneys, blood in urine, face swollen, weakness and similar symptoms like fatigue and general feeling of being unwell, fever, swelling in limbs, chill, pain, cold feeling in extremities, liver enzyme increased, urine analysis abnormal, mineral values in urine increased, protein in urine, heart and muscle enzyme increased, decreased haemoglobin, feeling confused and disoriented, shaking, convulsion, pink eye, fast heart beat, high blood pressure, tightening of the airways, swollen throat or voice box, raw throat, cough, itchy nose, sneezing, sweating
Very rare (may affect up to 1 in 10,000 people)	swelling around the eyes, abnormal ECG heart tracing, fainting, vomiting
Not known (frequency cannot be estimated from the available data)	hardening of the skin which may affect also soft tissue and internal organs (nephrogenic systemic fibrosis), feeling unwell

There have been reports of nephrogenic systemic fibrosis (which causes hardening of the skin and may affect also soft tissue and internal organs).

When Optimark was used in children aged 2 or older they had similar side effects as in adults.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Optimark

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and on the syringe label after EXP.
Keep the syringe in the outer carton in order to protect from light.

Do not refrigerate or freeze.

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.

Do not use the solution if it is discoloured or particulate matter is present.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Optimark contains

- The active substance is gadoversetamide.
  1 ml contains 330.9 mg gadoversetamide, equivalent to 500 micromol.
  Each 10 ml syringe contains 3309 mg gadoversetamide.
  Each 15 ml syringe contains 4963.5 mg gadoversetamide.
  Each 20 ml syringe contains 6618 mg gadoversetamide.
  Each 30 ml syringe contains 9927 mg gadoversetamide.
- The other ingredients are: versetamide, calcium hydroxide, calcium chloride dihydrate, sodium hydroxide and/or hydrochloric acid, water for injections.

What Optimark looks like and contents of the pack

Optimark syringes contain a clear, colourless to pale yellow solution.
Optimark is supplied in pre-filled syringes made of polypropylene. Syringe tip cap and piston are made of bromobutyl rubber.

Optimark pre-filled syringes are supplied in the following package sizes:

1 x 10 ml	10 x 10 ml
1 x 15 ml	10 x 15 ml
1 x 20 ml	10 x 20 ml
1 x 30 ml	10 x 30 ml

Not all package sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Mallinckrodt Deutschland GmbH
Josef-Dietzgen-Str.1
53773 Hennef
Germany

For any information about this medicine, please contact the Marketing Authorisation Holder.

Manufacturer

Mallinckrodt Medical Imaging Ireland
Damastown
Mulhuddart, Dublin 15
Ireland

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Therapeutic indications

Optimark is indicated for use with magnetic resonance imaging (MRI) of the central nervous system (CNS) and liver. It provides contrast enhancement and facilitates visualization and helps with characterization of focal lesions and abnormal structures in the CNS and liver in adult patients and in children of two years and older with known or highly suspected pathology.

Contraindications

- Hypersensitivity to gadoversetamide or to other gadolinium containing products or to any of the excipients.

- Optimark is contraindicated in patients with severe renal impairment (GFR <30ml/min/1.73m^2) and/or acute kidney injury, in
- patients who have had liver transplantation or in
- patients in the perioperative liver transplantation period and in
- neonates up to 4 weeks of age.

Special warnings and precautions for use
As with any paramagnetic contrast agent, enhancement of MRI with Optimark may impair the visualization of existing lesions. Some of these lesions may be seen on unenhanced, non-contrast MRI. Therefore, caution should be exercised when contrast enhanced scan interpretation is made in the absence of a companion unenhanced MRI.
Before the examination, care must be taken that patients are sufficiently hydrated.

Hypersensitivity
Allergoid and other idiosyncratic reactions also may occur with gadoversetamide, which could become manifest in form of cardiovascular, respiratory and skin reactions. Most of these reactions occur within half an hour after administering the contrast medium. As with all other contrast media of the same class, late reactions may occur (after hours or days) in rare cases; however, none were reported in the completed clinical trials.
If hypersensitivity reactions occur, the administration of the contrast medium must be discontinued immediately and intravenous treatment initiated, if necessary.
During the examination, supervision by a physician is necessary and insertion of a flexible in-dwelling catheter is recommended. To enable immediate action in emergencies, the necessary medicinal products (e.g. epinephrine/adrenaline, theophylline, antihistamines, corticosteroids and atropines), endotracheal tube and ventilator 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 it is especially the risk of bronchospasm which is increased
- patients with a history of reactions to contrast agents, including a previous history of reaction to iodine-based contrast agents

Before the injection of contrast media, patients should be asked whether they have any allergies (e.g. allergies to seafood or medicinal products, hay fever, urticaria), whether they are hypersensitive to contrast media and whether they have bronchial asthma. Premedication with antihistamines and/or glucocorticoids may be considered.

Patients taking beta-blockers
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 reactions may be severe. Especially in patients with serious heart diseases (e.g. severe heart failure, coronary artery disease) cardiovascular reactions may deteriorate. However, these were not evident from clinical trials with Optimark.

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.

Patients with impaired renal function
Prior to administration of Optimark, 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 Optimark and some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR <30ml/min/1.73m²) and/or acute kidney injury. Optimark is contraindicated in these patients

(see section 4.3). Patients who have had or are undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. Therefore, Optimark must not be used in patients who have had or are undergoing liver transplantation and in neonates. The risk for development of NSF in patients with moderate renal impairment (GFR 30–59 ml/min/1.73 m²) is unknown; therefore, Optimark should only be used after careful risk-benefit evaluation in patients with moderate renal impairment. Gadoversetamide is dialysable. Haemodialysis shortly after Optimark administration may be useful at removing Optimark 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.

Children and adolescents
Optimark must not be administered with an autoinjector. The required dose should be administered by hand to children of 2 to 11 years to avoid overdosage by mistake.

Neonates and infants
Optimark should not be used in children below the age of two years. Safety and efficacy have not been studied in this age group.

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

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose of up to 17 ml, i.e. it is essentially 'sodium-free'.
10 ml vials and 15 ml vials contain less than 1mmol sodium; i.e. they are essentially sodium free.
Higher doses contain 1 mmol of sodium or more, which should be taken into consideration for patients on a controlled sodium diet.
20 ml of the solution contain 28.75 mg of sodium.
30 ml of the solution contain 43.13 mg sodium.

Serum iron and zinc
Caution should be exercised because transient decreases in serum iron and zinc parameters have been observed in clinical trials. The clinical significance of this is unknown.

Fertility, pregnancy and lactation
Pregnancy
There are no data from the use of gadoversetamide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Optimark should not be used during pregnancy unless the clinical condition of the woman requires use of gadoversetamide.

Breast-feeding
It is unknown whether gadoversetamide is excreted in human milk. There is insufficient information on the excretion of gadoversetamide in animal milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued for at least 24 hours after the administration of Optimark.

Fertility
Nonclinical data did not reveal special hazards for humans based on conventional studies of reproductive toxicity. Clinical studies on fertility have not been performed.

Posology and method of administration
Optimark should only be administered by physicians experienced in clinical MRI practice.
To enable immediate action in emergencies, the necessary medicinal products (e.g. epinephrine/ adrenaline, theophylline, antihistamines, corticosteroids and atropines), endotracheal tube and ventilator must be immediately available.

Posology

The agent should be administered as a bolus peripheral intravenous injection at a dose of 0.2 ml/kg (100 micromol/kg) body weight. To ensure complete injection of the contrast medium, the injection should be followed by a 5 ml flush of sodium chloride 9 mg/ml (0.9 %) solution for injection. The imaging procedure should be completed within 1 hour of administration of the contrast medium.

Repeat dose
In cranial MRI, if a strong clinical suspicion of a lesion persists despite a single dose contrast-enhanced MRI or when more accurate information on the number, size or extent of lesions might influence management or therapy of the patient, in subjects with normal renal function, a second bolus injection of 0.2ml/kg (100 micromol/kg) may be administered within 30 minutes of the first injection as it may increase the diagnostic yield of the examination.
The safety of repeat doses has not been established in children and adolescents (2 years and older), in patients with renal impairment, or the elderly. The repeat dose is not recommended in these populations.

Limited data with other gadolinium contrast agents suggests that for the exclusion of additional cranial metastases in a patient with a known solitary resectable metastasis, an MR exam with the injection of 300 micromol/kg body weight of Optimark may lead to higher diagnostic confidence.

Paediatric population
No dose adjustment is considered necessary in children more than 2 years of age.
Optimark is contraindicated in neonates up to 4 weeks of age. Use of Optimark is not recommended in children less than 2 years of age because the safety, efficacy, and impact of immature kidney function have not been studied in this age group.

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

Renal and hepatic impairment
Optimark is contraindicated in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and/or acute renal injury and in patients who have had liver transplantation or in patients in the perioperative liver transplantation period. Optimark 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 100 micromol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Optimark injections should not be repeated unless the interval between injections is at least 7 days.

Method of administration
The agent should be administered as a bolus peripheral intravenous injection. To ensure complete injection of the contrast medium, the injection should be followed by a 5 ml flush of sodium chloride 9 mg/ml (0.9 %) solution for injection. Insertion of a flexible in-dwelling venous catheter is recommended.
Optimark must not be administered with an autoinjector to children of 2 to 11 years.

Precautions to be taken before handling or administering the medicinal product
The container and the solution should be inspected prior to use.

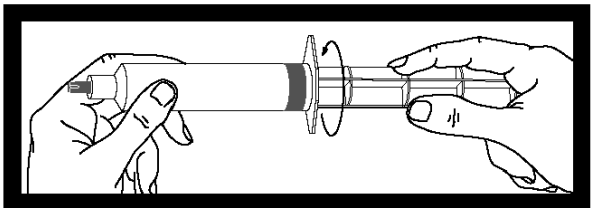
Interaction with other medicinal products and other forms of interaction
No formal interaction studies have been performed.
Gadoversetamide has been shown to cause interference in the measurement of serum calcium using the ortho-cresolphthalein complexone (OCP) colorimetric method. However, the administration of gadoversetamide does not cause a true decrease in serum calcium. In the presence of gadoversetamide, the OCP technique produces an erroneous, low value for plasma calcium. The magnitude of this measurement artefact is proportional to the concentration of gadoversetamide in the blood, and in patients with normal renal clearance accurate values can be obtained approximately 90 minutes following injection. In patients with compromised renal function, clearance of gadoversetamide will be slowed and the interference with calcium determination by OCP prolonged. Gadoversetamide does

not affect other methods of measuring serum calcium, such as the arsenazo III colorimetric method, atomic absorption spectroscopy, and inductively coupled plasma mass spectroscopy.

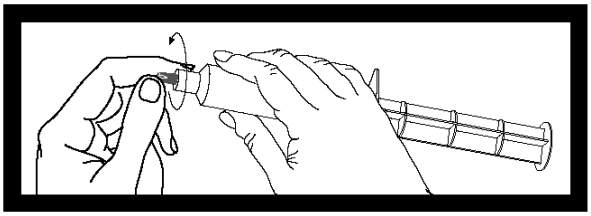
Special precautions for disposal and other handling
Optimark is intended for single use only; any unused portions should be discarded.

Do not use the solution if it is discoloured or particulate matter is present. If non-disposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Pre-filled syringes:
Assembly and Inspection
Inspect the syringe for signs of leakage. Do not use if leakage is observed.



After screwing the push rod into the syringe piston, it is important to **turn the push rod an additional ½ turn** so that the grey piston rotates freely.



Prior to using the syringe, twist off grey tip cap and discard. Syringe is now ready for needle or infusion tubing attachment.

Discard syringe and unused portion of the solution after use.
Any unused product or waste material should be disposed of in accordance with local requirements.
The peel-off tracking label on the pre-filled syringes should be stuck onto the patients 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.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Optimark 500 micromol/ml solution for injection in vial
Gadoversetamide

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are being given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Optimark is and what it is used for

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Optimark is for diagnostic use, only. It is used in adult patients and children of two years and older, who are undergoing magnetic resonance imaging (MRI), a type of scan where images of the internal organs are taken. Optimark is used to obtain a clearer scan in patients who have or are thought to have abnormalities in the brain, spine or liver.

2. What you need to know before you are given Optimark

Do not use Optimark
if you are allergic
- to the active substance gadoversetamide or
- to any of the other ingredients of Optimark (see section 6), or
- to other gadolinium contrast agents

You must not be given Optimark if
- you suffer from severe and/or acute kidney impairment, or
- if you are a patient who is about to have or has had a liver transplant as use of Optimark in patients with these conditions has been associated with a disease called nephrogenic systemic fibrosis (NSF). NSF is a disease involving thickening of the skin and connective tissues. NSF may result in debilitating joint immobility, muscle weakness or may affect the normal working of internal organs which may potentially be life-threatening.
- Optimark must not be used in newborn babies up to the age of 4 weeks.

Before you receive Optimark, you will need to have a blood test to check how well your kidneys are working.

Warnings and precautions
Talk to your doctor before Optimark is used, if:

- you suffer from allergies (e.g. medicinal products, seafood, hay fever, hives) or asthma
- you had any reactions to previous injections of a contrast agent, including a previous history of reaction to iodine-based contrast agents
- your kidneys do not work properly
- you have recently had, or soon expect to have, a liver transplant
- you are feeling thirsty and/or if you have only had small quantities or nothing to drink before the examination
- you are taking a special kind of antihypertensive medicine, i.e. a beta-blocker
- you have heart disease
- you suffer from epilepsy or brain lesions
- you are on a controlled sodium diet

If any of these apply to you, your doctor will decide whether the intended examination is possible or not.

Children and adolescents
Optimark is not recommended in children who are below the age of two years.

Other medicines and Optimark
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Optimark should not be used during pregnancy unless strictly necessary.
Breast-feeding should be discontinued for at least 24 hours after you receive Optimark.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines
If you are an ambulant patient and plan to drive or use tools or machines, take into account that dizziness may incidentally occur after you undergo a procedure involving the injection of Optimark. Up to 1 in 100 people may be affected.

Optimark contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose of up to 17 ml, i.e. it is essentially ‘sodium-free’.
10 ml vials and 15 ml vials contain less than 1mmol sodium; i.e. they are essentially sodium free.
Higher doses contain 1 mmol of sodium or more, which should be taken into consideration for patients on a controlled sodium diet.
20 ml of the solution contain 28.75 mg of sodium.

3. How Optimark is given

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.

The usual dose
The usual dose of 0.2 ml/kg body weight is the same in adults and children of 2 years and older.
It would account for 14 ml for a 70 kg individual, and this volume would be injected over about 7 -14 seconds into a vein, usually a vein in an arm. The injection is then flushed through with a saline injection to make sure none is left in the needle or tube used for the injection.

In adults, a second dose may be given within 30 minutes of the first injection. When looking at certain abnormalities in the brain, Optimark may need to be used at three times the usual dose in one injection in adults. The doctor will decide how much Optimark is needed for your examination. You must tell

the doctor or nurse/technologist immediately if you feel pain around the area where the needle is placed.

Dosage in special patient groups
In patients with moderate kidney problems, more than one dose of Optimark should not be used during a scan. Optimark injections should not be repeated unless the interval between injections is at least 7 days.

It is not necessary to adjust your dose if you are 65 years of age or older but you will have a blood test to check how well your kidneys are working.

If you are given more Optimark than you should have been
If too much Optimark was injected it is unlikely that it will do you much harm, as much higher doses did not lead to any problems when some people received them. If your kidneys are working normally it is unlikely you will have any problems. Optimark can be removed using dialysis. If you think you have been injected with too much Optimark, tell the doctor or nurse/technologist immediately.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You must report any of the following symptoms immediately to the doctor or nurse/technologist, and get immediate treatment as they can be or can become very serious:
side effects affecting the heart (fainting, extra heart beats, chest pain) or the respiratory system (shortness of breath, tightening of the airways, swollen or tight throat, itchy or runny nose, sneezing).

Most of the side effects observed after the use of Optimark were of mild to moderate intensity and transient in nature. The most common side effects were a strange taste in the mouth, feeling hot, headache and dizziness.
Possible side effects are described in greater detail below.

The frequencies below and the following symptoms are based on clinical trials, and on the experience in using Optimark after it was on the market:

Frequency	**Possible side effects**
Common (may affect up to 1 in 10 people)	headache, strange taste in the mouth, feeling hot
Uncommon (may affect up to 1 in 100 people)	allergic/hypersensitivity reaction, dizziness, tingling sensation, numbness, reduced sense of smell, skin red and warm, nasal congestion, sore throat, nausea, diarrhoea, itching, rash, chest discomfort, chest pain, feeling cold including cold feeling in extremities, administration site reactions, changes in blood calcium levels

Frequency	Possible side effects
Rare (may affect up to 1 in 1000 people)	decreased appetite, feeling anxious, sleep disorder, drowsy feeling, burning sensation, a sensation of movement or spinning, ringing in the ears, eyelid redness, eye pain, vision blurred, bloodshot eyes, awareness of the heartbeat, irregular heartbeats, extra heartbeats, low blood pressure, shortness of breath, hoarseness, runny nose, throat constriction, mouth watering, abdominal pain, constipation, dry mouth, hives, cold sweat, redness, higher blood level of a substance (creatinine) usually eliminated by the kidneys, blood in urine, face swollen, weakness and similar symptoms like fatigue and general feeling of being unwell, fever, swelling in limbs, chill, pain, cold feeling in extremities, liver enzyme increased, urine analysis abnormal, mineral values in urine increased, protein in urine, heart and muscle enzyme increased, decreased haemoglobin, feeling confused and disoriented, shaking, convulsion, pink eye, fast heart beat, high blood pressure, tightening of the airways, swollen throat or voice box, raw throat, cough, itchy nose, sneezing, sweating
Very rare (may affect up to 1 in 10,000 people)	swelling around the eyes, abnormal ECG heart tracing, fainting, vomiting
Not known (frequency cannot be estimated from the available data)	hardening of the skin which may affect also soft tissue and internal organs (nephrogenic systemic fibrosis), feeling unwell

There have been reports of nephrogenic systemic fibrosis (which causes hardening of the skin and may affect also soft tissue and internal organs).

When Optimark was used in children aged 2 or older they had similar side effects as in adults.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Optimark

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and on the vial label after EXP.
Keep the vial in the outer carton in order to protect from light.

Do not refrigerate or freeze.

The medicine should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Do not use the solution if it is discoloured or particulate matter is present.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Optimark contains

- The active substance is gadoversetamide.
  1 ml contains 330.9 mg gadoversetamide, equivalent to 500 micromol.
  Each 10 ml vial contains 3309 mg gadoversetamide.
  Each 15 ml vial contains 4963.5 mg gadoversetamide.
  Each 20 ml vial contains 6618 mg gadoversetamide.
- The other ingredients are: versetamide, calcium hydroxide, calcium chloride dihydrate, sodium hydroxide and/or hydrochloric acid, water for injections.

What Optimark looks like and contents of the pack
Optimark vials contain a clear, colourless to pale yellow solution.
Optimark is supplied in vials, fitted with bromobutyl rubber closures and aluminium cap seals.

Optimark vials are supplied in the following package sizes:
1 x 10 ml 10 x 10 ml
1 x 15 ml 10 x 15 ml
1 x 20 ml 10 x 20 ml
Not all package sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Mallinckrodt Deutschland GmbH
Josef-Dietzgen-Str.1
53773 Hennef
Germany
For any information about this medicine, please contact the Marketing Authorisation Holder.

Manufacturer
Mallinckrodt Medical Imaging Ireland
Damastown
Mulhuddart, Dublin 15
Ireland

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency (EMA) web site http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Therapeutic indications
Optimark is indicated for use with magnetic resonance imaging (MRI) of the central nervous system (CNS) and liver. It provides contrast enhancement and facilitates visualization and helps with characterization of focal lesions and abnormal structures in the CNS and liver in adult patients and in children of two years and older with known or highly suspected pathology.

Contraindications

- Hypersensitivity to gadoversetamide or to other gadolinium containing products or to any of the excipients.
- Optimark is contraindicated in patients with severe renal impairment (GFR <30ml/min/1.73m²) and/or acute kidney injury, in
- patients who have had liver transplantation or in
- patients in the perioperative liver transplantation period and in

- neonates up to 4 weeks of age.

Special warnings and precautions for use
As with any paramagnetic contrast agent, enhancement of MRI with Optimark may impair the visualization of existing lesions. Some of these lesions may be seen on unenhanced, non-contrast MRI. Therefore, caution should be exercised when contrast enhanced scan interpretation is made in the absence of a companion unenhanced MRI.
Before the examination, care must be taken that patients are sufficiently hydrated.

Hypersensitivity
Allergoid and other idiosyncratic reactions also may occur with gadoversetamide, which could become manifest in form of cardiovascular, respiratory and skin reactions. Most of these reactions occur within half an hour after administering the contrast medium. As with all other contrast media of the same class, late reactions may occur (after hours or days) in rare cases; however, none were reported in the completed clinical trials.
If hypersensitivity reactions occur, the administration of the contrast medium must be discontinued immediately and intravenous treatment initiated, if necessary.
During the examination, supervision by a physician is necessary and insertion of a flexible in-dwelling catheter is recommended. To enable immediate action in emergencies, the necessary medicinal products (e.g. epinephrine/adrenaline, theophylline, antihistamines, corticosteroids and atropines), endotracheal tube and ventilator 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 it is especially the risk of bronchospasm which is increased
- patients with a history of reactions to contrast agents, including a previous history of reaction to iodine-based contrast agents

Before the injection of contrast media, patients should be asked whether they have any allergies (e.g. allergies to seafood or medicinal products, hay fever, urticaria), whether they are hypersensitive to contrast media and whether they have bronchial asthma. Premedication with antihistamines and/or glucocorticoids may be considered.

Patients taking beta-blockers
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 reactions may be severe. Especially in patients with serious heart diseases (e.g. severe heart failure, coronary artery disease) cardiovascular reactions may deteriorate. However, these were not evident from clinical trials with Optimark.

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.

Patients with impaired renal function
Prior to administration of Optimark, 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 Optimark and some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR <30ml/min/1.73m²) and/or acute kidney injury. Optimark is contraindicated in these patients (see section 4.3). Patients who have had or are undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. Therefore, Optimark must not be used in patients who have had or are undergoing liver transplantation and in neonates. The risk for development of NSF in patients with moderate renal impairment (GFR 30–59 ml/min/1.73 m^2) is

unknown; therefore, Optimark should only be used after careful risk-benefit evaluation in patients with moderate renal impairment. Gadoversetamide is dialysable. Haemodialysis shortly after Optimark administration may be useful at removing Optimark 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.

Children and adolescents
Optimark must not be administered with an autoinjector. The required dose should be administered by hand to children of 2 to 11 years to avoid overdosage by mistake.

Neonates and infants
Optimark should not be used in children below the age of two years. Safety and efficacy have not been studied in this age group.

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

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose of up to 17 ml, i.e. it is essentially 'sodium-free'.
10 ml vials and 15 ml vials contain less than 1mmol sodium; i.e. they are essentially sodium free. Higher doses contain 1 mmol of sodium or more, which should be taken into consideration for patients on a controlled sodium diet.
20 ml of the solution contain 28.75 mg of sodium.

Serum iron and zinc
Caution should be exercised because transient decreases in serum iron and zinc parameters have been observed in clinical trials. The clinical significance of this is unknown.

Fertility, pregnancy and lactation
Pregnancy
There are no data from the use of gadoversetamide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Optimark should not be used during pregnancy unless the clinical condition of the woman requires use of gadoversetamide.

Breast-feeding
It is unknown whether gadoversetamide is excreted in human milk. There is insufficient information on the excretion of gadoversetamide in animal milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued for at least 24 hours after the administration of Optimark.

Fertility
Nonclinical data did not reveal special hazards for humans based on conventional studies of reproductive toxicity. Clinical studies on fertility have not been performed.

Posology and method of administration
Optimark should only be administered by physicians experienced in clinical MRI practice.
To enable immediate action in emergencies, the necessary medicinal products (e.g. epinephrine/ adrenaline, theophylline, antihistamines, corticosteroids and atropines), endotracheal tube and ventilator must be immediately available.

Posology
The agent should be administered as a bolus peripheral intravenous injection at a dose of 0.2 ml/kg (100 micromol/kg) body weight. To ensure complete injection of the contrast medium, the injection should be followed by a 5 ml flush of sodium chloride 9 mg/ml (0.9 %) solution for injection. The imaging procedure should be completed within 1 hour of administration of the contrast medium.

Repeat dose
In cranial MRI, if a strong clinical suspicion of a lesion persists despite a single dose contrast-enhanced MRI or when more accurate information on the number, size or extent of lesions might influence management or therapy of the patient, in subjects with normal renal function, a second bolus injection of 0.2ml/kg (100 micromol/kg) may be administered within 30 minutes of the first injection as it may increase the diagnostic yield of the examination.
The safety of repeat doses has not been established in children and adolescents(2 years and older), in patients with renal impairment, or the elderly. The repeat dose is not recommended in these populations.

Limited data with other gadolinium contrast agents suggests that for the exclusion of additional cranial metastases in a patient with a known solitary resectable metastasis, an MR exam with the injection of 300 micromol/kg body weight of Optimark may lead to higher diagnostic confidence.

Paediatric population
No dose adjustment is considered necessary in children more than 2 years of age.
Optimark is contraindicated in neonates up to 4 weeks of age. Use of Optimark is not recommended in children less than 2 years of age because the safety, efficacy, and impact of immature kidney function have not been studied in this age group.

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

Renal and hepatic impairment
Optimark is contraindicated in patients with severe renal impairment (GFR < 30 ml/min/1.73m²) and/or acute renal injury and in patients who have had liver transplantation or in patients in the perioperative liver transplantation period. Optimark 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 100 micromol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Optimark injections should not be repeated unless the interval between injections is at least 7 days.

Method of administration
The agent should be administered as a bolus peripheral intravenous injection. To ensure complete injection of the contrast medium, the injection should be followed by a 5 ml flush of sodium chloride 9 mg/ml (0.9 %) solution for injection. Insertion of a flexible in-dwelling venous catheter is recommended.
Optimark must not be administered with an autoinjector to children of 2 to 11 years.

Precautions to be taken before handling or administering the medicinal product
The container and the solution should be inspected prior to use.

Interaction with other medicinal products and other forms of interaction
No formal interaction studies have been performed.
Gadoversetamide has been shown to cause interference in the measurement of serum calcium using the ortho-cresolphthalein complexone (OCP) colorimetric method. However, the administration of gadoversetamide does not cause a true decrease in serum calcium. In the presence of gadoversetamide, the OCP technique produces an erroneous, low value for plasma calcium. The magnitude of this measurement artefact is proportional to the concentration of gadoversetamide in the blood, and in patients with normal renal clearance accurate values can be obtained approximately 90 minutes following injection. In patients with compromised renal function, clearance of gadoversetamide will be slowed and the interference with calcium determination by OCP prolonged. Gadoversetamide does not affect other methods of measuring serum calcium, such as the arsenazo III colorimetric method, atomic absorption spectroscopy, and inductively coupled plasma mass spectroscopy.

Special precautions for disposal and other handling
Optimark is intended for single use only; any unused portions should be discarded.

Optimark should be drawn into the syringe and used immediately.
Do not use the solution if it is discoloured or particulate matter is present. If non-disposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

The product must be examined before use to confirm that all solids are dissolved and that the container and closure are un-damaged. If solids remain, the vial must be discarded.

Discard syringe and unused portion of the solution after use.
Any unused product or waste material should be disposed of in accordance with local requirements.
The peel-off tracking label on the vials should be stuck onto the patients 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.