HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OPTIMARK safely and effectively. See full prescribing information for OPTIMARK.

OPTIMARK (gadoversetamide) injection, for intravenous use
Initial U.S. approval: 1999

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

See full prescribing information for complete boxed warning.

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs (5.1)

- **Do not administer OptiMARK to patients with:**
  - **chronic, severe kidney disease (GFR <30 mL/min/1.73m^2), or**
  - **acute kidney injury (4)**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.1)**

----------INDICATIONS AND USAGE----------
OptiMARK is a gadolinium-based paramagnetic contrast agent for diagnostic magnetic resonance imaging (MRI) indicated for intravenous use:
- In patients with abnormal blood-brain barrier or abnormal vascularity of the brain, spine and associated tissues (1)
- To provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver in patients who are highly suspect for liver structural abnormalities on computed tomography (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Bolus peripheral intravenous injection at a dose of 0.2 mL/kg (0.1 mmol/kg) (2)
- Follow injection with a 5 mL normal saline flush (2)
- Complete imaging procedure within 1 hour of injection (2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: Each ml of OptiMARK contains 330.9 mg gadoversetamide (3)

----------CONTRAINDICATIONS----------
- Chronic, severe kidney disease (glomerular filtration rate, GFR <30 mL/min/1.73m^2), acute kidney injury (4)
- Prior hypersensitivity reactions to gadolinium, versetamide or any of the inert ingredients (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Nephrogenic Systemic Fibrosis (NSF) has occurred in patients with impaired elimination of Gadolinium Based Contrast Agents (GBCAs). Higher than recommended dosing or repeat dosing appears to increase the risk (5.1)
- Acute Kidney Injury (AKI) has occurred in patients with preexisting renal insufficiency. Use the lowest necessary dose of OptiMARK in these patients (5.2)
- Hypersensitivity reactions including fatal reactions have occurred, particularly in patients with history of allergy, drug reactions, or other hypersensitivity like disorders. Monitor these patients closely during and after administration of OptiMARK (5.3)
- Interference with laboratory measurements of serum iron, copper and zinc and in the measurement of serum calcium using the ortho-cresophthalin complexone (OCP) colorimetric method has occurred (5.4)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence >2%) are: headache, vasodilatation, taste perversion, dizziness, nausea and paresthesia (6)

To report SUSPECTED ADVERSE REACTIONS contact Mallinckrodt Inc. at 1-888-744-1414 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- **Do not administer OptiMARK to patients with:**
  - **chronic, severe kidney disease (GFR <30 mL/min/1.73m^2), or**
  - **acute kidney injury *[see Contraindications (4)]***
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing**
- **Do not exceed the recommended OptiMARK dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration *[see Warnings and Precautions (5.1)]***

1 INDICATIONS AND USAGE

1.1 MRI of Central Nervous System (CNS)

OptiMARK is indicated for use with magnetic resonance imaging (MRI) in patients with abnormal blood-brain barrier or abnormal vascularity of the brain, spine and associated tissues.

1.2 MRI of Liver

OptiMARK is indicated for use with MRI to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver of patients who are highly suspect for liver structural abnormalities on computed tomography.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Guidelines

- Administer OptiMARK as a bolus peripheral intravenous injection at a dose of 0.2 mL/kg (0.1 mmol/kg) and at a rate of 1 to 2 mL/sec delivered by manual or by power injection (Table 1)
- Use sterile technique to withdraw and administer OptiMARK
- Follow injection with a 5 mL normal saline flush to ensure complete administration of the contrast
- Discard unused portions of the drug

Table 1 Dosage Chart for OptiMARK Injection

Body Weight Kilograms (kg)	0.1 mmol/kg Volume (mL)
40	8
50	10
60	12
70	14
80	16
90	18
100	20
110	22
120	24
130	26
140	28
150	30

2.2 Drug Handling

- Visually inspect OptiMARK for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or particulate matter is present
- Do not mix OptiMARK with other medications or parenteral nutrition and do not administer OptiMARK in the same intravenous line as other medications because of the potential for chemical incompatibility

2.3 Imaging

- Complete the imaging procedure within 1 hour of the injection of OptiMARK
- Paramagnetic contrast agents may impair the visualization of lesions seen on non-contrast MRI. Interpret OptiMARK MR images with companion non-contrast MR images *[see Clinical Pharmacology (12.2)]*

3 DOSAGE FORMS AND STRENGTHS

OptiMARK is supplied as a clear, colorless to slightly yellow solution for injection containing 330.9 mg gadoversetamide per mL (equivalent to 0.5 mmol/mL)

4 CONTRAINDICATIONS

OptiMARK is contraindicated in patients with:

- chronic, severe kidney disease (glomerular filtration rate, GFR <30 mL/min/1.73m^2)
- acute kidney injury
- known hypersensitivity reactions to gadolinium, versetamide or any of the inert ingredients

5 WARNINGS AND PRECAUTIONS

5.1 Nephrogenic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR <30 mL/min/1.73m^2) as well as patients with acute kidney injury. Do not administer OptiMARK to these patients. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30 - 59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60 - 89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following OptiMARK administration to Mallinckrodt Inc. (1-800-778-7898) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury, or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronic kidney disease (e.g., age >60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and the degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. When administering OptiMARK, do not exceed the recommended dose and allow a sufficient period of time for elimination of the drug prior to any re-administration *[see Dosage and Administration (2.1)]*.

5.2 Acute Kidney Injury (AKI)

In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging.

5.3 Hypersensitivity Reactions

Severe hypersensitivity reactions including anaphylaxis have been observed with administration of gadolinium products including OptiMARK. Before administering OptiMARK ensure the availability of resuscitation equipment and personnel trained in resuscitation techniques. Patients with a history of allergy, drug reactions or other hypersensitivity-like disorders may be at greater risk and should be closely observed during the procedure and for several hours after drug administration. If a reaction occurs, stop OptiMARK and immediately begin appropriate therapy including resuscitation.

5.4 Interference with Laboratory Testing

Interference by OptiMARK in the measurements of serum iron, copper and zinc has been observed. OptiMARK causes interference in the measurement of serum calcium using the ortho-cresophthalin complexone (OCP) colorimetric method. In the presence of OptiMARK, OCP produces an erroneous, low value for serum calcium. The magnitude of this artifact is proportional to the concentration of OptiMARK in the blood, and accurate values can be obtained approximately 90 minutes following injection. In patients with renal insufficiency, clearance of OptiMARK is slowed and the interference with calcium determination by OCP is prolonged. Neither the arsenazo III dye system nor the inductively coupled plasma mass spectroscopy methods for calcium assay are affected by OptiMARK.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Nephrogenic systemic fibrosis *[see Contraindications (4), Boxed Warning and Warnings and Precautions (5.1)]*
- Hypersensitivity reactions *[see Contraindications (4) and Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The adverse reactions described in this section were observed in a total of 1,309 subjects (24 healthy volunteers and 1,285 patients in clinical trials). Patients ranged in age from 12 to 85 years (mean age of 50 years) and 680 subjects (52%) were men. The ethnic distribution was 84% White, 9% Black, 3% Asian, and 4% other.

Overall, 460 subjects (35%) reported at least one adverse reaction. Most adverse reactions were mild or moderate in severity. The most commonly noted adverse reactions were: injection associated discomfort (26%), headache (9.4%), vasodilatation (6.4%), taste perversion (6.2%), dizziness (3.7%), nausea (3.2%), and paresthesia (2.2%). Table 2 lists adverse reactions reported in 1% or greater of patients.

Table 2 Adverse Reactions Experienced by ≥1% of Patients

Body System or Event	OptiMARK (N = 1309)
Injection associated discomfort	26.4%
Headache	9.4%
Vasodilatation	6.4%
Taste Perversion	6.2%
Dizziness	3.7%
Nausea	3.2%
Paresthesia	2.2%
Diarrhea	1.9%
Pain Abdomen	1.8%
Asthenia	1.5%
Injection Site Reaction	1.5%
Rhinitis	1.5%
Dyspepsia	1.2%
Pain Back	1.2%
Pain	1.0%

The following adverse reactions occurred in less than 1% of the patients:

Body as a Whole:	allergic reaction, facial edema, fever, malaise, neck rigidity, neck pain, pelvic pain, increased sweating
Cardiovascular:	arrhythmia, chest pain, hypertension, hypotension, pallor, palpitation, syncope, tachycardia, vasospasm
Digestive:	anorexia, constipation, dry mouth, dysphagia, eructation, increased salivation, thirst, vomiting
Metabolic and Nutritional:	increased creatinine, edema, hypercalcemia
Musculoskeletal:	arthralgia, leg cramps, myalgia, spasm
Nervous System:	agitation, anxiety, confusion, diplopia, dystonia, hypertonia, hypesthesia, somnolence, tremor, vertigo
Respiratory System:	cough, dyspnea, laryngismus, pharyngitis, sinusitis, voice alteration
Skin and Appendages:	erythema multiforme, pruritus, rash, thrombophlebitis, urticaria
Special Senses:	parosmia, tinnitus
Urogenital:	oliguria

6.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of OptiMARK. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to OptiMARK.

- Nephrogenic Systemic Fibrosis (NSF)
- Hypersensitivity reactions
- Seizures

7 DRUG INTERACTIONS

Drug interactions with other contrast agents and other drugs have not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. OptiMARK should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Gadoversetamide administered to rats reduced neonatal weights from birth through weaning at maternal doses of 0.5 mmol/kg/day (1 times the human dose based on body surface area) for 5 weeks (including gestation) and paternal doses of 0.5 mmol/kg/day for 12 weeks. This effect was not observed at 0.1 mmol/kg (0.2 times the human dose based on body surface area). Maternal toxicity was not observed at any dose.

Gadoversetamide injection caused a reduced mean fetal weight, abnormal liver lobation, delayed ossification of sternebrae, and delayed behavioral development (startle reflex and air righting reflex) in fetuses from female rats dosed with 4.9 mmol/kg/day (10 times the human dose based on body surface area) on days 7 through 17 of gestation. These effects were not observed at 0.7 mmol/kg/day (1 times the human dose based on body surface area). Maternal toxicity was observed at 4.9 mmol/kg/day.

Gadoversetamide injection caused forelimb flexures and cardiovascular changes in fetuses from female rabbits dosed with 0.4 and 1.6 mmol/kg/day (respectively, 1 and 4 times the human dose based on body surface area) on gestation days 6 through 18. The cardiovascular changes were malformed thoracic arteries, a septal defect, and abnormal ventricle. These effects were not observed at 0.1 mmol/kg/day (0.3 times the human dose based on body surface area). Maternal toxicity was not observed at any dose.

8.3 Nursing Mothers

Radiolabeled gadoversetamide (^{153}Gd) was excreted in the milk of lactating rats receiving a single intravenous dose of 0.1 mmol/kg. Women should discontinue nursing and discard breast milk up to 72 hours after OptiMARK administration *[see Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use
The safety and effectiveness of OptiMARK in pediatric patients have not been established. Pediatric patients may be particularly vulnerable to adverse GBCA reactions due to renal immaturity or unrecognized renal insufficiency.

8.5 Geriatric Use
Since gadoversetamide is cleared from the body by glomerular filtration, the risk of adverse reactions may be greater in patients with impaired renal function (GFR ≥30 and <90 mL/min/1.73m^2). Due to the risk for NSF, estimate the GFR through laboratory testing for patients >60 years of age *[see Warning and Precautions (5.1)]*.

8.6 Renal Impairment
A single intravenous dose of 0.1 mmol/kg of OptiMARK was administered to 28 patients (17 men and 11 women) with impaired renal function (mean serum creatinine of 2.4 mg/dL). Sixteen patients had concurrent central nervous system or liver pathology. Renal impairment was shown to delay the elimination of gadoversetamide (*see* Table 3). The mean cumulative urinary excretion of gadoversetamide at 72 hours was approximately 93.5% for renally impaired patients and 95.8% for subjects with normal renal function. Dose adjustments in renal impairment have not been studied. OptiMARK has been shown to be removed from the body by hemodialysis *[see Clinical Pharmacology (12.3)].*

8.7 Hepatic Impairment
A single intravenous dose of 0.1 mmol/kg of OptiMARK was administered to 4 patients (2 men and 2 women) with impaired hepatic function. Hepatically impaired patients with normal renal function had plasma kinetics similar to normal subjects (*see* Table 3).

Table 3 Elimination Profiles of Normal, Renally Impaired and Hepatically Impaired Men and Women (mean ± SD)

Population	**Elimination $t_{1/2}$ (hours)**	
	Men (N = 52)	**Women (N = 48)**
Healthy Volunteers	1.73 ± 0.31 (N = 8)	1.73 ± 0.40 (N = 4)
Normal Patients	1.90 ± 0.50 (N = 25)	1.94 ± 0.57 (N = 31)
Renally Impaired	8.74 ± 5.14 (N = 17)	6.91 ± 2.46 (N = 11)
Hepatically Impaired	2.09 ± 0.03 (N = 2)	2.35 ± 1.09 (N = 2)

10 OVERDOSAGE

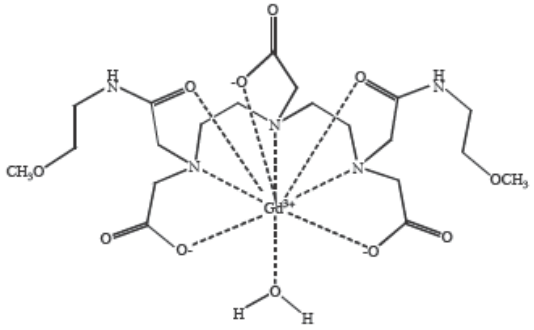
Clinical consequences of overdosage with OptiMARK have not been reported. Treatment of overdose is directed toward supporting vital functions and prompt institution of symptomatic therapy. OptiMARK has been shown to be dialyzable *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

OptiMARK (gadoversetamide) injection is a nonionic gadolinium chelate of diethylenetriamine pentaacetic acid bismethoxyethylamide (gadoversetamide), for intravenous injection.

OptiMARK injection is provided as a sterile, preservative-free, nonpyrogenic, clear, and colorless to pale yellow, aqueous solution of gadoversetamide. Each mL of OptiMARK contains 330.9 mg of gadoversetamide (0.5 millimole), 28.4 mg of calcium versetamide sodium (0.05 millimole), 0.7 mg calcium chloride dihydrate (0.005 millimole), and water for injection. Sodium hydroxide and/or hydrochloric acid may have been added for pH adjustment.

Gadoversetamide is designated chemically as [8, 11-bis(carboxymethyl)-14-[2-[(2-methoxyethyl)amino]-2-oxoethyl]-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(3-)] gadolinium with a formula weight of 661.77 g/mol and empirical formula of $C_{20}H_{34}N_5O_{10}Gd$. The structural formula of gadoversetamide in aqueous solution is:



OptiMARK has a pH of 5.5 to 7.5. Pertinent physiochemical data are provided below (Table 4).

Table 4 Physiochemical Properties of OptiMARK	
Osmolality (mOsmol/kg water) @ 37°C	1110
Viscosity (cP) @ 20°C	3.1
@ 37°C	2.0
Density (g/mL) @ 25°C	1.160

OptiMARK has an osmolality of approximately 3.9 times that of plasma (285 mOsm/kg water) and is hypertonic under conditions of use.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Gadoversetamide is a paramagnetic agent that develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment can enhance the relaxation rates of water protons in its vicinity, leading to an increase in signal intensity (brightness) of tissues.

12.2 Pharmacodynamics
In MRI, visualization of normal and pathological brain, spinal and hepatic tissue depends in part on variations in the radiofrequency signal intensity that occurs with: 1) changes in proton density; 2) alterations of the spin-lattice or longitudinal relaxation time (T1); and 3) variation of the spin-spin or transverse relaxation time (T2). When placed in a magnetic field, gadoversetamide decreases T1 and T2 relaxation times in tissues where it accumulates. At the recommended dose, the effect is primarily on T1 relaxation time, and produces an increase in signal intensity (brightness).

12.3 Pharmacokinetics
The pharmacokinetics of intravenously administered gadoversetamide in normal subjects conforms to a two-compartment open-model with mean distribution and elimination half-lives (reported as mean ± SD) of about 13.3 ± 6.8 and 103.6 ± 19.5 minutes.

Distribution
Gadoversetamide does not undergo protein binding in vitro. In pregnant and lactating rats which received ^{153}Gd-labeled gadoversetamide, radioactivity was detected in the placenta, fetus, and maternal milk. The volume of distribution at steady state of gadoversetamide in normal subjects is 162 ± 25 mL/kg, roughly equivalent to that of extracellular water.

Gadoversetamide does not cross the intact blood-brain barrier, and, therefore, does not accumulate in the normal brain or in lesions that may have a normal blood-brain barrier. However, disruption of the blood-brain barrier or abnormal vascularity allows accumulation of gadoversetamide in the extravascular spaces of lesions. The pharmacokinetic parameters of gadoversetamide in various lesions are not known.

Metabolism
Gadoversetamide is not metabolized.

Elimination

Gadoversetamide (0.1 mmol/kg) is eliminated primarily in the urine with 95.5 ± 17.4% (mean ± SD) of the administered dose eliminated by 24 hours. Animal data demonstrated that insignificant levels of ^{153}Gd-labeled gadoversetamide are eliminated via the feces. In experimentally induced anephria in the rat, hepatobiliary excretion did not significantly compensate for the absence of urinary elimination. The renal and plasma clearance rates of gadoversetamide in normal subjects are similar (69 ± 15.4 and 72 ± 16.3 mL/hr/kg, respectively) indicating that the drug is cleared through the kidneys via glomerular filtration. Within the studied dose range (0.1 to 0.7 mmol/kg), the kinetics of gadoversetamide appear to be linear.

Gadoversetamide is removed from the body by hemodialysis. Approximately 98% of the administered dose (0.1 mmol/kg) was cleared from the circulation over the three dialysis sessions that occurred 2 hours, 48 hours, and 120 hours after injection. After each of three dialysis sessions, respectively, 70%, 93%, and 98% of the administered dose was cleared from the plasma. The mean dialysis clearance of gadoversetamide was 93.2 ± 17.1 mL/min, or 48% of the creatinine clearance (194 ± 18.6 mL/min), using a high flux PMMA membrane.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of gadoversetamide. The results of the following genotoxicity assays were negative: Salmonella/E. Coli reverse mutation (Ames) assay, mouse lymphoma mutagenesis assay, and the in vivo mammalian micronucleus assay. The in vitro CHO chromosome aberration assay without metabolic activation was positive.

Gadoversetamide administered to rats in a fertility study was shown to have irreversible reduction and degeneration of spermatocytes in testes and epididymides, and impaired male fertility following intravenous doses of 2.0 mmol/kg/day (4 times the human dose based on body surface area) for 7 weeks. These effects were not observed at dose of 0.5 mmol/kg/day (1 times the human dose based on body surface area).

In a separate 28-day repeat dose study in rats, gadoversetamide was shown to have irreversible reduction of male reproductive organ weights, degeneration of the germinal epithelium of the testes, presence of germ cells in the epididymides, and reduced sperm count following daily intravenous doses of 3.0 mmol/kg/day (6 times the human dose based on body surface area). These effects were not observed at 0.6 mmol/kg/day (1 times the human dose based on surface area). These effects were not observed in similar studies conducted in dogs.

In a single dose study in rats, gadoversetamide did not produce adverse effects on the male reproductive system 24 hours and 14 days after intravenous administration of 0.5 to 15 mmol/kg (1 to 25 times the human dose based on body surface area

14 CLINICAL STUDIES

OptiMARK was evaluated in 4 controlled clinical trials (two liver and two CNS studies). Out of 461 patients who received OptiMARK, there were 252 men and 209 women with a mean age of 49 years (range 12 to 82 years); 83% were Caucasian, 9% Black, 3% Asian, and 5% other racial or ethnic groups. The trials were designed to compare combined non-contrast and OptiMARK 0.1 mmol/kg contrast MR images to non-contrast MR images, based on pre-specified imaging characteristics (endpoints).

In the two CNS studies, MR images were analyzed from 262 patients who were highly suspect for CNS disorders and received OptiMARK. Pre-contrast and pre-plus-post-contrast (combined) images were independently evaluated by three blinded readers (each reader examined approximately 1/3 of the images). The images were evaluated by the blinded readers for the following endpoints using a scale from 1 to 10: the level of conspicuity of all lesions, the ability to delineate lesion borders from parenchyma/structures, the number of lesions, and the confidence in the number of lesions. As shown in Table 5, the first row of each endpoint group represents the difference in the mean score of the combined pre- and post-contrast MRI from the mean score of the pre-contrast MRI alone. Also, the table shows the number of patients whose paired MRI images were better, worse or the same as the pre-contrast MRI. Results from the contrast image alone were not evaluated. In Table 5 for these endpoints, when read in combination with the non-contrast images, OptiMARK provided a statistically significant improvement over baseline. In addition to these measures, the images were evaluated for the blinded reader's

confidence in the diagnosis. Although improvement over baseline was noted, the diagnosis was not rigorously confirmed.

Table 5 Results of MRI Central Nervous System Studies with 0.1 mmol/kg OptiMARK

Endpoints	Study A OptiMARK N = 132[†]	Study B OptiMARK N = 129
Conspicuity: Difference of Means [(a)]	0.39[*]	0.66[*]
Worse	24 (18%)	24 (19%)
Same	69 (52%)	52 (40%)
Better	39 (30%)	53 (41%)
Border Delineation: Difference of Means	0.70[*]	0.86[*]
Worse	23 (17%)	25 (19%)
Same	55 (42%)	51 (40%)
Better	54 (41%)	53 (41%)
Number of Lesions: Difference of Means		
Pre	1.8	3.0
Pair [(b)]	2.0[◊]	3.3[*]
Worse	9 (7%)	16 (12%)
Same	101 (77%)	86 (67%)
Better	22 (16%)	27 (21%)
Confidence in Number of Lesions: Difference of Means	0.11[*]	0.56[*]
Worse	19 (14%)	18 (14%)
Same	86 (65%)	60 (47%)
Better	27 (20%)	51 (40%)

[(a)] Difference of means = (Side-by-side pre- and post-OptiMARK mean) - (pre-mean)
[(b)] Pair = Side-by-side pre- and post-OptiMARK
[*] Statistically significant for both the median (Wilcoxon test) and mean (paired t test)
[◊] Statistically significant for median (Wilcoxon test)
[†] 1 patient was excluded from this analysis because a non-contrast image was not obtained for that patient

In the two liver studies, MR images were analyzed from 199 patients with a suspected liver abnormality on a contrast CT who received OptiMARK. Patients had both pre-contrast and post-contrast MRI scans covering the entire liver. In each study, the images were read by 3 blinded readers (each reader examined approximately 1/3 of the images). Using a scale of 1 to 10, the images were evaluated by the blinded readers for the level of conspicuity of all lesions, the ability to delineate lesion borders from parenchyma/structures, the number of lesions and confidence in the number of lesions. The results are shown in Table 6. The first row of each endpoint group represents the difference in the mean score of the combined pre- and post-contrast MRI from the mean score of the pre-contrast MRI alone. Also, the table shows the number of patients whose paired MRI images were better, worse or the same as the pre-contrast MRI. Results from the contrast image alone were not evaluated. As shown in Table 6 for these endpoints, when read in combination with the non-contrast image, OptiMARK provided a statistically significant improvement over non-contrast images. In addition to these measures, the images were evaluated for the blinded reader's confidence in the diagnosis. Although improvement over baseline was noted, the trial was not designed to rigorously confirm the diagnosis.

Table 6 Results of MRI Liver Studies with 0.1 mmol/kg OptiMARK

Endpoints	Study C OptiMARK N = 99	Study D OptiMARK N = 100
Conspicuity: Difference of Means [(a)]	0.77*	0.75*
Worse	21 (21%)	14 (14%)
Same	37 (37%)	50 (50%)
Better	41 (41%)	36 (36%)
Border Delineation: Difference of Means	0.77*	0.69*
Worse	21 (21%)	15 (15%)
Same	38 (38%)	45 (45%)
Better	40 (40%)	40 (40%)
Number of Lesions: Difference of Means Pre Pair [(b)]	 2.4 3.0*	 3.5 3.8†
Worse	13 (13%)	16 (16%)
Same	50 (51%)	58 (58%)
Better	36 (36%)	26 (26%)
Confidence in Number of Lesions: Difference of Means	1.6*	1.0*
Worse	39 (39%)	38 (38%)
Same	2 (2%)	8 (8%)
Better	58 (59%)	54 (54%)

(a) Difference of means = (Side-by-side pre- and post-OptiMARK mean) - (pre-mean)
(b) Pair = Side-by-side pre- and post-OptiMARK
* Statistically significant for both the median (Wilcoxon test) and mean (paired t test)
† Borderline statistical significance in paired t test

A subsequent study of 140 normal volunteers evaluated the safety of OptiMARK 0.1 mmol/kg delivered by power injector. Imaging results were not studied. The normal volunteers were randomized to receive OptiMARK injected manually, or OptiMARK or saline injected at 3 different power injector rates. At 2 mL/sec, the adverse event rates were comparable in the OptiMARK and saline controls when delivered manually and by power injector. In these small sample sizes, there was a trend towards increasing adverse events with increasing rates of power injection. Patients with abnormal vascularity were not evaluated. The safety and efficacy of power injector rates higher than 2 mL/sec has not been established.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

OptiMARK is a clear, colorless to slightly yellow solution containing 330.9 mg/mL (equivalent to 0.5 mmol/mL) of gadoversetamide for injection. OptiMARK is supplied in 10 mL vials containing 5 mL or 10 mL of solution and is also provided in 20 mL vials containing 15 mL or 20 mL of solution. Each single dose vial is rubber stoppered with an aluminum seal and the contents are sterile. OptiMARK is supplied in 10 mL, 15 mL, 20 mL or 30 mL syringes containing 10 mL, 15 mL, 20 mL or 30 mL of solution respectively. Each syringe is sealed with rubber closures and the contents are sterile. Vials and syringes are contained in shipping cartons with the following configurations:

5 mL in glass vials in cartons of 10 vials (NDC Code 0019-1177-02)
10 mL in glass vials in cartons of 10 vials (NDC Code 0019-1177-04)

15 mL in glass vials in cartons of 10 vials	(NDC Code 0019-1177-06)
20 mL in glass vials in cartons of 10 vials	(NDC Code 0019-1177-08)
10 mL in plastic syringes in cartons of 10 syringes	(NDC Code 0019-1177-11)
15 mL in plastic syringes in cartons of 10 syringes	(NDC Code 0019-1177-16)
20 mL in plastic syringes in cartons of 10 syringes	(NDC Code 0019-1177-21)
30 mL in plastic syringes in cartons of 10 syringes	(NDC Code 0019-1177-31)

Storage
OptiMARK should be stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] and protected from light and freezing. OptiMARK may be stored at 37°C for up to one month in a contrast media warmer utilizing circulating warm air. For periods longer than one month, store at 20°C to 25°C (68°F to 77°F).

17 PATIENT COUNSELING INFORMATION

Nephrogenic Systemic Fibrosis
Instruct patients to inform their physician if they:
- have a history of kidney disease
- have recently received a GBCA

GBCAs increase the risk for NSF in patients with impaired elimination of the drugs. To counsel patients at risk for NSF:
- describe the clinical manifestations of NSF
- describe procedures to screen for the detection of renal impairment

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following OptiMARK administration, such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness.

Other
Instruct patients to inform their physician if they:
- are pregnant or breast feeding
- have a history of renal disease or heart disease, seizure, asthma or allergic respiratory diseases

This product is covered by U.S. Patent No. 5130120, 5137711, 5508388. The use of this product is covered by U.S. Patent No. 5130120 and 5137711.

Manufactured and Distributed by:
Mallinckrodt Inc.,
St. Louis, MO 63042 U.S.A.

MKR 1177Cb0114

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OPTIMARK PHARMACY BULK PACKAGE safely and effectively. See full prescribing information for OptiMARK.

OPTIMARK (gadoversetamide) injection, for intravenous use, PHARMACY BULK PACKAGE: NOT FOR DIRECT INFUSION
Initial U.S. approval: 1999

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

See full prescribing information for complete boxed warning.

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs (5.1)

- **Do not administer OptiMARK to patients with:**
  - **chronic, severe kidney disease (GFR <30 mL/min/1.73m^2), or**
  - **acute kidney injury (4)**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.1)**

----------INDICATIONS AND USAGE----------
OptiMARK is a gadolinium-based paramagnetic contrast agent for diagnostic magnetic resonance imaging (MRI) indicated for intravenous use:
- In patients with abnormal blood-brain barrier or abnormal vascularity of the brain, spine and associated tissues (1)
- To provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver in patients who are highly suspect for liver structural abnormalities on computed tomography (1)

----------DOSAGE AND ADMINISTRATION----------
- Dispense multiple single doses into separate sterile syringes for intravenous administration (2)
- Recommended dose is 0.2 mL/kg (0.1 mmol/kg) as bolus peripheral intravenous injection (2)
- Follow injection with a 5 mL normal saline flush (2)
- Complete imaging procedure within 1 hour of injection (2)

---------- DOSAGE FORMS AND STRENGTHS----------
- Injection: Each mL of OptiMARK contains 330.9 mg gadoversetamide (3)

---------- CONTRAINDICATIONS ----------
- Chronic, severe kidney disease (glomerular filtration rate, GFR <30 mL/min/1.73m^2), acute kidney injury (4)
- Prior hypersensitivity reactions to gadolinium, versetamide or any of the inert ingredients (4)

---------- WARNINGS AND PRECAUTIONS----------
- Nephrogenic Systemic Fibrosis (NSF) has occurred in patients with impaired elimination of Gadolinium Based Contrast Agents (GBCAs). Higher than recommended dosing or repeat dosing appears to increase the risk (5.1)
- Acute Kidney Injury (AKI) has occurred in patients with preexisting renal insufficiency. Use the lowest necessary dose of OptiMARK in these patients (5.2)
- Hypersensitivity reactions including fatal reactions have occurred, particularly in patients with history of allergy, drug reactions, or other hypersensitivity like disorders. Monitor these patients closely during and after administration of OptiMARK (5.3)
- Interference with laboratory measurements of serum iron, copper and zinc and in the measurement of serum calcium using the ortho-cresophthalin complexone (OCP) colorimetric method has occurred (5.4)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence >2%) are: headache, vasodilatation, taste perversion, dizziness, nausea and paresthesia (6)

To report SUSPECTED ADVERSE REACTIONS contact Mallinckrodt Inc. at 1-888-744-1414 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- **Do not administer OptiMARK to patients with:**
  - **chronic, severe kidney disease (GFR <30 mL/min/1.73m^2), or**
  - **acute kidney injury *[see Contraindications (4)].***
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing**
- **Do not exceed the recommended OptiMARK dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration *[see Warnings and Precautions (5.1)]***

1 INDICATIONS AND USAGE

1.1 MRI of Central Nervous System (CNS)

OptiMARK is indicated for use with magnetic resonance imaging (MRI) in patients with abnormal blood-brain barrier or abnormal vascularity of the brain, spine and associated tissues.

1.2 MRI of Liver

OptiMARK is indicated for use with MRI to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver of patients who are highly suspect for liver structural abnormalities on computed tomography.

2 DOSAGE AND ADMINISTRATION

2.1 Directions for Proper use of Pharmacy Bulk Package

NOT FOR DIRECT INFUSION

The 50 mL Pharmacy Bulk Package is used as a multiple dose container with an appropriate transfer device to fill empty sterile syringes. Use the following procedure when transferring OptiMARK from the pharmacy bulk package to individual syringes:

- Use of this product is restricted to a suitable work area, such as a laminar flow hood, utilizing aseptic technique
- Prior to entering the vial, remove the seal and cleanse the rubber closure with a suitable antiseptic agent
- Once the pharmacy bulk package is punctured, do not remove from the aseptic work area during the entire period of use
- Penetrate the container closure only one time, utilizing a suitable transfer device or dispensing set that allows measured dispensing of the contents
- Withdrawal of container contents should be accomplished without delay. A maximum time of 24 hours from initial closure entry is permitted to complete fluid transfer operations
- Discard any unused OptiMARK 24 hours after the initial puncture of the bulk package

2.2 Dosing Guidelines

- Administer OptiMARK as a bolus peripheral intravenous injection at a dose of 0.2 mL/kg (0.1 mmol/kg) and at a rate of 1 to 2 mL/sec delivered by manual or by power injection (Table 1)
- Follow injection with a 5 mL normal saline flush to ensure complete administration of the contrast
- Discard unused portions of the drug

Table 1 Dosage Chart for OptiMARK Injection	
Body Weight Kilograms (kg)	0.1 mmol/kg Volume (mL)
40	8
50	10
60	12
70	14
80	16
90	18
100	20
110	22
120	24
130	26
140	28
150	30

2.3 Drug Handling

- Visually inspect OptiMARK for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or particulate matter is present
- Do not mix OptiMARK with other medications or parenteral nutrition and do not administer OptiMARK in the same intravenous line as other medications because of the potential for chemical incompatibility

2.4 Imaging

- Complete the imaging procedure within 1 hour of the injection of OptiMARK
- Paramagnetic contrast agents may impair the visualization of lesions seen on non-contrast MRI. Interpret OptiMARK MR images with companion non-contrast MR images *[see Clinical Pharmacology (12.2)]*

3 DOSAGE FORMS AND STRENGTHS

OptiMARK is supplied as a clear, colorless to slightly yellow solution for injection in a 50 mL Pharmacy Bulk Package. Each mL contains 330.9 mg of gadoversetamide (equivalent to 0.5 mmol/mL) for injection

4 CONTRAINDICATIONS

OptiMARK is contraindicated in patients with:

- chronic, severe kidney disease (glomerular filtration rate, GFR <30 mL/min/1.73m^2)
- acute kidney injury
- known hypersensitivity reactions to gadolinium, versetamide or any of the inert ingredients

5 WARNINGS AND PRECAUTIONS

5.1 Nephrogenic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR <30 mL/min/1.73m^2) as well as patients with acute kidney injury. Do not administer OptiMARK to these patients. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30 - 59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR

60 - 89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following OptiMARK administration to Mallinckrodt Inc. (1-800-778-7898) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury, or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronic kidney disease (e.g., age >60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and the degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. When administering Optimark, do not exceed the recommended dose and allow a sufficient period of time for elimination of the drug prior to any re-administration *[see Dosage and Administration (2.1)]*.

5.2 Acute Kidney Injury (AKI)

In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging.

5.3 Hypersensitivity Reactions

Severe hypersensitivity reactions including anaphylaxis have been observed with administration of gadolinium products including OptiMARK. Before administering OptiMARK ensure the availability of resuscitation equipment and personnel trained in resuscitation techniques. Patients with a history of allergy, drug reactions or other hypersensitivity-like disorders may be at greater risk and should be closely observed during the procedure and for several hours after drug administration. If a reaction occurs, stop OptiMARK and immediately begin appropriate therapy including resuscitation.

5.4 Interference with Laboratory Testing

Interference by OptiMARK in the measurement of serum iron, copper and zinc has been observed. OptiMARK causes interference in the measurement of serum calcium using the ortho-cresophthalin complexone (OCP) colorimetric method. In the presence of OptiMARK, OCP produces an erroneous, low value for serum calcium. The magnitude of this artifact is proportional to the concentration of OptiMARK in the blood, and accurate values can be obtained approximately 90 minutes following injection. In patients with renal insufficiency, clearance of OptiMARK is slowed and the interference with calcium determination by OCP is prolonged. Neither the arsenazo III dye system nor the inductively coupled plasma mass spectroscopy methods for calcium assay are affected by OptiMARK.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Nephrogenic systemic fibrosis *[see Contraindications (4), Boxed Warning and Warnings and Precautions (5.1)]*
- Hypersensitivity reactions *[see Contraindications (4) and Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The adverse reactions described in this section were observed in a total of 1,309 subjects (24 healthy volunteers and 1,285 patients in clinical trials). Patients ranged in age from 12 to 85 years (mean age of 50 years) and 680 subjects (52%) were men. The ethnic distribution was 84% White, 9% Black, 3% Asian, and 4% other.

Overall, 460 subjects (35%) reported at least one adverse reaction. Most adverse reactions were mild or moderate in severity. The most commonly noted adverse reactions were: injection associated discomfort (26%), headache (9.4%), vasodilatation (6.4%), taste perversion (6.2%), dizziness (3.7%), nausea (3.2%), and paresthesia (2.2%). Table 2 lists adverse reactions reported in 1% or greater of patients.

Table 2 Adverse Reactions Experienced by ≥1% of Patients

Body System or Event	OptiMARK (N = 1309)
Injection associated discomfort	26.4%
Headache	9.4%
Vasodilatation	6.4%
Taste Perversion	6.2%
Dizziness	3.7%
Nausea	3.2%
Paresthesia	2.2%
Diarrhea	1.9%
Pain Abdomen	1.8%
Asthenia	1.5%
Injection Site Reaction	1.5%
Rhinitis	1.5%
Dyspepsia	1.2%
Pain Back	1.2%
Pain	1.0%

The following adverse reactions occurred in less than 1% of the patients:

Body as a Whole: allergic reaction, edema face, fever, malaise, neck rigidity, neck pain, pelvic pain, increased sweating

Cardiovascular: arrhythmia, chest pain, hypertension, hypotension, pallor, palpitation, syncope, tachycardia, vasospasm

Digestive: anorexia, constipation, dry mouth, dysphagia, eructation, increased salivation, thirst, vomiting

Metabolic and Nutritional: increased creatinine, edema, hypercalcemia

Musculoskeletal: arthralgia, leg cramps, myalgia, spasm

Nervous System: agitation, anxiety, confusion, diplopia, dystonia, hypertonia, hypesthesia, somnolence, tremor, vertigo

Respiratory System: cough, dyspnea, laryngismus, pharyngitis, sinusitis, voice alteration

Skin and Appendages: erythema multiforme, pruritus, rash, thrombophlebitis, urticaria

Special Senses: parosmia, tinnitus

Urogenital: oliguria

6.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of OptiMARK. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to OptiMARK.

- Nephrogenic Systemic Fibrosis (NSF)
- Hypersensitivity reactions
- Seizures

7 DRUG INTERACTIONS

Drug interactions with other contrast agents and other drugs have not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. OptiMARK should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Gadoversetamide administered to rats reduced neonatal weights from birth through weaning at maternal doses of 0.5 mmol/kg/day (1 times the human dose based on body surface area) for 5 weeks (including gestation) and paternal doses of 0.5 mmol/kg/day for 12 weeks. This effect was not observed at 0.1 mmol/kg (0.2 times the human dose based on body surface area). Maternal toxicity was not observed at any dose.

Gadoversetamide injection caused a reduced mean fetal weight, abnormal liver lobation, delayed ossification of sternebrae, and delayed behavioral development (startle reflex and air righting reflex) in fetuses from female rats dosed with 4.9 mmol/kg/day (10 times the human dose based on body surface area) on days 7 through 17 of gestation. These effects were not observed at 0.7 mmol/kg/day (1 times the human dose based on body surface area). Maternal toxicity was observed at 4.9 mmol/kg/day.

Gadoversetamide injection caused forelimb flexures and cardiovascular changes in fetuses from female rabbits dosed with 0.4 and 1.6 mmol/kg/day (respectively, 1 and 4 times the human dose based on body surface area) on gestation days 6 through 18. The cardiovascular changes were malformed thoracic arteries, a septal defect, and abnormal ventricle. These effects were not observed at 0.1 mmol/kg/day (0.3 times the human dose based on body surface area). Maternal toxicity was not observed at any dose.

8.3 Nursing Mothers

Radiolabeled gadoversetamide (^{153}Gd) was excreted in the milk of lactating rats receiving a single intravenous dose of 0.1 mmol/kg. Women should discontinue nursing and discard breast milk up to 72 hours after OptiMARK administration *[see Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use

The safety and effectiveness of OptiMARK in pediatric patients have not been established. Pediatric patients may be particularly vulnerable to adverse GBCA reactions due to renal immaturity or unrecognized renal insufficiency.

8.5 Geriatric Use

Since gadoversetamide is cleared from the body by glomerular filtration, the risk of adverse reactions may be greater in patients with impaired renal function (GFR ≥30 and <90 mL/min/1.73m^2). Due to the risk for NSF, estimate the GFR through laboratory testing for patients >60 years of age *[see Warning and Precautions (5.1)]*.

8.6 Renal Impairment

A single intravenous dose of 0.1 mmol/kg of OptiMARK was administered to 28 patients (17 men and 11 women) with impaired renal function (mean serum creatinine of 2.4 mg/dL). Sixteen patients had concurrent central nervous system or liver pathology. Renal impairment was shown to delay the elimination of gadoversetamide (*see* Table 3). The mean cumulative urinary excretion of gadoversetamide at 72 hours was approximately 93.5% for renally impaired patients and 95.8% for subjects with normal renal function. Dose adjustments in renal impairment have not been studied. OptiMARK has been shown to be removed from the body by hemodialysis *[see Clinical Pharmacology (12.3)].*

8.7 Hepatic Impairment

A single intravenous dose of 0.1 mmol/kg of OptiMARK was administered to 4 patients (2 men and 2 women) with impaired hepatic function. Hepatically impaired patients with normal renal function had plasma kinetics similar to normal subjects (*see* Table 3).

Table 3 Elimination Profiles of Normal, Renally Impaired and Hepatically Impaired Men and Women (mean ± SD)		
Population	**Elimination $t_{1/2}$ (hours)**	
	Men (N = 52)	**Women (N = 48)**
Healthy Volunteers	1.73 ± 0.31 (N = 8)	1.73 ± 0.40 (N = 4)
Normal Patients	1.90 ± 0.50 (N = 25)	1.94 ± 0.57 (N = 31)
Renally Impaired	8.74 ± 5.14 (N = 17)	6.91 ± 2.46 (N = 11)
Hepatically Impaired	2.09 ± 0.03 (N = 2)	2.35 ± 1.09 (N = 2)

10 OVERDOSAGE

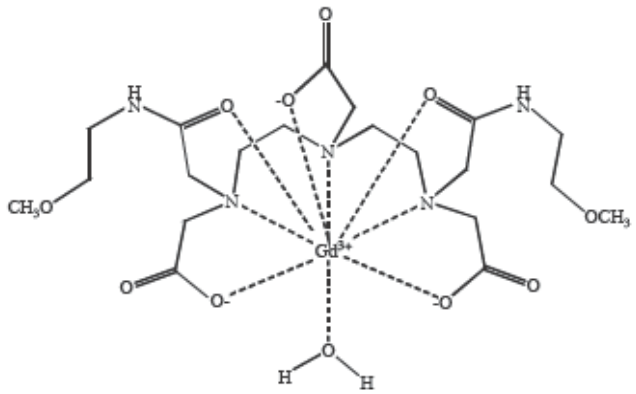
Clinical consequences of overdosage with OptiMARK have not been reported. Treatment of overdose is directed toward supporting vital functions and prompt institution of symptomatic therapy. OptiMARK has been shown to be dialyzable *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

OptiMARK (gadoversetamide) injection is a nonionic gadolinium chelate of diethylenetriamine pentaacetic acid bismethoxyethylamide (gadoversetamide), for intravenous injection.

OptiMARK injection is provided as a sterile, preservative-free, nonpyrogenic, clear, and colorless to pale yellow, aqueous solution of gadoversetamide. Each mL of OptiMARK contains 330.9 mg of gadoversetamide (0.5 millimole), 28.4 mg of calcium versetamide sodium (0.05 millimole), 0.7 mg calcium chloride dihydrate (0.005 millimole), and water for injection. Sodium hydroxide and/or hydrochloric acid may have been added for pH adjustment.

Gadoversetamide is designated chemically as [8, 11-bis(carboxymethyl)-14-[2-[(2-methoxyethyl)amino]-2-oxoethyl]-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(3-)] gadolinium with a formula weight of 661.77 g/mol and empirical formula of $C_{20}H_{34}N_5O_{10}Gd$. The structural formula of gadoversetamide in aqueous solution is:



OptiMARK has a pH of 5.5 to 7.5. Pertinent physiochemical data are provided below (Table 4).

Table 4 Physiochemical Properties of OptiMark	
Osmolality (mOsmol/kg water) @ 37°C	1110
Viscosity (cP) @ 20°C	3.1
@ 37°C	2.0
Density (g/mL) @ 25°C	1.160

OptiMARK has an osmolality of approximately 3.9 times that of plasma (285 mOsm/kg water) and is hypertonic under conditions of use.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gadoversetamide is a paramagnetic agent that develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment can enhance the relaxation rates of water protons in its vicinity, leading to an increase in signal intensity (brightness) of tissues.

12.2 Pharmacodynamics

In MRI, visualization of normal and pathological brain, spinal and hepatic tissue depends in part on variations in the radiofrequency signal intensity that occurs with: 1) changes in proton density; 2) alterations of the spin-lattice or longitudinal relaxation time (T1); and 3) variation of the spin-spin or transverse relaxation time (T2). When placed in a magnetic field, gadoversetamide decreases T1 and T2 relaxation times in tissues where it accumulates. At the recommended dose, the effect is primarily on T1 relaxation time, and produces an increase in signal intensity (brightness).

12.3 Pharmacokinetics

The pharmacokinetics of intravenously administered gadoversetamide in normal subjects conforms to a two-compartment open-model with mean distribution and elimination half-lives (reported as mean ± SD) of about 13.3 ± 6.8 and 103.6 ± 19.5 minutes.

Distribution

Gadoversetamide does not undergo protein binding in vitro. In pregnant and lactating rats which received ^{153}Gd-labeled gadoversetamide, radioactivity was detected in the placenta, fetus, and maternal milk. The volume of distribution at steady state of gadoversetamide in normal subjects is 162 ± 25 mL/kg, roughly equivalent to that of extracellular water.

Gadoversetamide does not cross the intact blood-brain barrier, and, therefore, does not accumulate in the normal brain or in lesions that may have a normal blood-brain barrier. However, disruption of the blood-brain barrier or abnormal vascularity allows accumulation of gadoversetamide in the extravascular spaces of lesions. The pharmacokinetic parameters of gadoversetamide in various lesions are not known.

Metabolism

Gadoversetamide is not metabolized.

Elimination

Gadoversetamide (0.1 mmol/kg) is eliminated primarily in the urine with 95.5 ± 17.4% (mean ± SD) of the administered dose eliminated by 24 hours. Animal data demonstrated that insignificant levels of ^{153}Gd-labeled gadoversetamide are eliminated via the feces. In experimentally induced anephria in the rat, hepatobiliary excretion did not significantly compensate for the absence of urinary elimination. The renal and plasma clearance rates of gadoversetamide in normal subjects are essentially identical (69 ± 15.4 and 72 ± 16.3 mL/hr/kg, respectively) indicating that the drug is essentially cleared through the kidneys via glomerular filtration. Within the studied dose range (0.1 to 0.7 mmol/kg), the kinetics of gadoversetamide appear to be linear.

Gadoversetamide is removed from the body by hemodialysis. Approximately 98% of the administered dose (0.1 mmol/kg) was cleared from the circulation over the three dialysis sessions that occurred 2 hours, 48 hours, and 120 hours after injection. After each of three dialysis sessions, respectively, 70%, 93%, and 98% of the administered dose was cleared from the plasma. The mean dialysis clearance of gadoversetamide was 93.2 ± 17.1 mL/min, or 48% of the creatinine clearance (194 ± 18.6 mL/min), using a high flux PMMA membrane.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of gadoversetamide. The results of the following genotoxicity assays were negative: Salmonella/E. Coli reverse mutation (Ames) assay, mouse lymphoma mutagenesis assay, and the in vivo mammalian micronucleus assay. The in vitro CHO chromosome aberration assay without metabolic activation was positive.

Gadoversetamide administered to rats in a fertility study was shown to have irreversible reduction and degeneration of spermatocytes in testes and epididymides, and impaired male fertility following intravenous doses of 2.0 mmol/kg/day (4 times the human dose based on body surface area) for 7 weeks. These effects were not observed at dose of 0.5 mmol/kg/day (1 times the human dose based on body surface area).

In a separate 28-day repeat dose study in rats, gadoversetamide was shown to have irreversible reduction of male reproductive organ weights, degeneration of the germinal epithelium of the testes, presence of germ cells in the epididymides, and reduced sperm count following daily intravenous doses of 3.0 mmol/kg/day (6 times the human dose based on body surface area). These effects were not observed at 0.6 mmol/kg/day (1 times the human dose based on surface area). These effects were not observed in similar studies conducted in dogs.

In a single dose study in rats, gadoversetamide did not produce adverse effects on the male reproductive system 24 hours and 14 days after intravenous administration of 0.5 to 15 mmol/kg (1 to 25 times the human dose based on body surface area).

14 CLINICAL STUDIES

OptiMARK was evaluated in 4 controlled clinical trials (two liver and two CNS studies). Out of 461 patients who received OptiMARK, there were 252 men and 209 women with a mean age of 49 years (range 12 to 82 years); 83% were Caucasian, 9% Black, 3% Asian, and 5% other racial or ethnic groups. The trials were designed to compare combined non-contrast and OptiMARK 0.1 mmol/kg contrast MR images to non-contrast MR images, based on pre-specified imaging characteristics (endpoints).

In the two CNS studies, MR images were analyzed from 262 patients who were highly suspect for CNS disorders and received OptiMARK. Pre-contrast and pre-plus-post-contrast (combined) images were independently evaluated by three blinded readers (each reader examined approximately 1/3 of the images). The images were evaluated by the blinded readers for the following endpoints using a scale from 1 to 10: the level of conspicuity of all lesions, the ability to delineate lesion borders from parenchyma/structures, the number of lesions, and the confidence in the number of lesions. As shown in Table 5, the first row of each endpoint group represents the difference in the mean score of the combined pre- and post-contrast MRI from the mean score of the pre-contrast MRI alone. Also, the table shows the number of patients whose paired MRI images were better, worse or the same as the pre-contrast MRI. Results from the contrast image alone were not evaluated. In Table 5 for these endpoints, when read in combination with the non-contrast images, OptiMARK provided a statistically significant improvement over baseline. In addition to these measures, the images were evaluated for the blinded reader's confidence in the diagnosis. Although improvement over baseline was noted, the diagnosis was not rigorously confirmed.

Table 5 Results of MRI Central Nervous System Studies with 0.1 mmol/kg OptiMARK

Endpoints	Study A OptiMARK N = 132†	Study B OptiMARK N = 129
Conspicuity: Difference of Means [(a)]	0.39*	0.66*
Worse	24 (18%)	24 (19%)
Same	69 (52%)	52 (40%)
Better	39 (30%)	53 (41%)
Border Delineation: Difference of Means	0.70*	0.86*
Worse	23 (17%)	25 (19%)
Same	55 (42%)	51 (40%)
Better	54 (41%)	53 (41%)
Number of Lesions: Difference of Means		
Pre	1.8	3.0
Pair [(b)]	2.0◊	3.3*
Worse	9 (7%)	16 (12%)
Same	101 (77%)	86 (67%)
Better	22 (16%)	27 (21%)
Confidence in Number of Lesions: Difference of Means	0.11*	0.56*
Worse	19 (14%)	18 (14%)
Same	86 (65%)	60 (47%)
Better	27 (20%)	51 (40%)

[(a)] Difference of means = (Side-by-side pre- and post-OptiMARK mean) - (pre-mean)
[(b)] Pair = Side-by-side pre- and post-OptiMARK
* Statistically significant for both the median (Wilcoxon test) and mean (paired t test)
◊ Statistically significant for median (Wilcoxon test)
† 1 patient was excluded from this analysis because a non-contrast image was not obtained for that patient

In the two liver studies, MR images were analyzed from 199 patients with a suspected liver abnormality on a contrast CT who received OptiMARK. Patients had both pre-contrast and post-contrast MRI scans covering the entire liver. In each study, the images were read by 3 blinded readers (each reader examined approximately 1/3 of the images). Using a scale of 1 to 10, the images were evaluated by the blinded readers for the level of conspicuity of all lesions, the ability to delineate lesion borders from parenchyma/structures, the number of lesions and confidence in the number of lesions. The results are shown in Table 6. The first row of each endpoint group represents the difference in the mean score of the combined pre- and post-contrast MRI from the mean score of the pre-contrast MRI alone. Also, the table shows the number of patients whose paired MRI images were better, worse or the same as the pre-contrast MRI. Results from the contrast image alone were not evaluated. As shown in Table 6 for these endpoints, when read in combination with the non-contrast image, OptiMARK provided a statistically significant improvement over non-contrast images. In addition to these measures, the images were evaluated for the blinded reader's confidence in the diagnosis. Although improvement over baseline was noted, the trial was not designed to rigorously confirm the diagnosis.

Table 6 Results of MRI Liver Studies with 0.1 mmol/kg OptiMARK

Endpoints	Study C OptiMARK N = 99	Study D OptiMARK N = 100
Conspicuity: Difference of Means [(a)]	0.77*	0.75*
Worse	21 (21%)	14 (14%)
Same	37 (37%)	50 (50%)
Better	41 (41%)	36 (36%)
Border Delineation: Difference of Means	0.77*	0.69*
Worse	21 (21%)	15 (15%)
Same	38 (38%)	45 (45%)
Better	40 (40%)	40 (40%)
Number of Lesions: Difference of Means Pre Pair [(b)]	 2.4 3.0*	 3.5 3.8†
Worse	13 (13%)	16 (16%)
Same	50 (51%)	58 (58%)
Better	36 (36%)	26 (26%)
Confidence in Number of Lesions: Difference of Means	1.6*	1.0*
Worse	39 (39%)	38 (38%)
Same	2 (2%)	8 (8%)
Better	58 (59%)	54 (54%)

(a) Difference of means = (Side-by-side pre- and post-OptiMARK mean) - (pre-mean)
(b) Pair = Side-by-side pre- and post-OptiMARK
* Statistically significant for both the median (Wilcoxon test) and mean (paired t test)
† Borderline statistical significance in paired t test

A subsequent study of 140 normal volunteers evaluated the safety of OptiMARK 0.1 mmol/kg delivered by power injector. Imaging results were not studied. The normal volunteers were randomized to receive OptiMARK injected manually, or OptiMARK or saline injected at 3 different power injector rates. At 2 mL/sec, the adverse event rates were comparable in the OptiMARK and saline controls when delivered manually and by power injector. In these small sample sizes, there was a trend towards increasing adverse events with increasing rates of power injection. Patients with abnormal vascularity were not evaluated. The safety and efficacy of power injector rates higher than 2 mL/sec has not been established.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

OptiMARK is a clear, colorless to slightly yellow solution containing 330.9 mg/mL, (equivalent to 0.5 mmol/mL) of gadoversetamide for injection. OptiMARK is supplied in 50 mL Pharmacy Bulk Packages containing 50 mL of solution. Each glass bottle is rubber stoppered with an aluminum seal and the contents are sterile. Bottles are contained in shipping cartons with the following configuration:

50 mL in glass bottles in cartons of 5 bottles (NDC Code 0019-1177-50)

Storage
OptiMARK should be stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] and protected from light and freezing. OptiMARK may be stored at 37°C for up to one month in a contrast media warmer utilizing circulating warm air. For periods longer than one month, store at 20°C to 25°C (68°F to 77°F).

17 PATIENT COUNSELING INFORMATION

Nephrogenic Systemic Fibrosis
Instruct patients to inform their physician if they:
- have a history of kidney disease
- have recently received a GBCA

GBCAs increase the risk for NSF in patients with impaired elimination of the drugs. To counsel patients at risk for NSF:
- describe the clinical manifestations of NSF
- describe procedures to screen for the detection of renal impairment

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following OptiMARK administration, such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness.

Other
Instruct patients to inform their physician if they:
- are pregnant or breast feeding
- have a history of renal disease or heart disease, seizure, asthma or allergic respiratory diseases

This product is covered by U.S. Patent No. 5130120, 5137711, 5508388. The use of this product is covered by U.S. Patent No. 5130120 and 5137711.

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