OptiMARK™ 0.5 mmol/mL
(Gadoversetamide Injection)

PRESCRIBING INFORMATION

Rx only

Mallinckrodt Inc.

September 2010

OptiMARK™
(gadoversetamide injection)
For Intravenous Injection Only
Mallinckrodt Inc.

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.

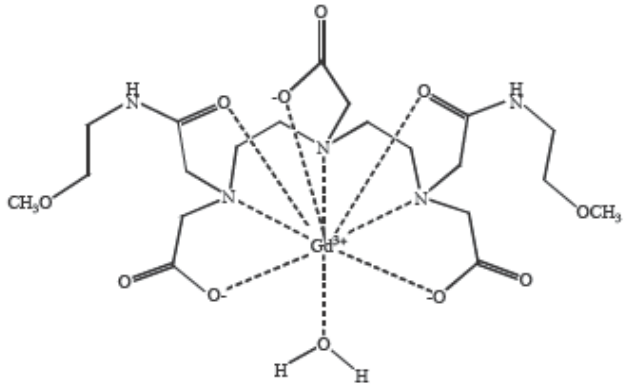
- **Do not administer OptiMARK™ to patients with:**
  - **chronic, severe kidney disease (GFR <30 mL/min/1.73m^2), or**
  - **acute kidney injury (*see* CONTRAINDICATIONS).**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically 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).**

DESCRIPTION

OptiMARK™ (gadoversetamide injection) is a formulation of a nonionic gadolinium chelate of diethylenetriamine pentaacetic acid bismethoxyethylamide (gadoversetamide), for use in magnetic resonance imaging (MRI). OptiMARK™ Injection is to be administered by intravenous injection only.

OptiMARK™ Injection is provided as a sterile, nonpyrogenic, clear, colorless to pale yellow, aqueous solution of gadoversetamide. No preservative is added. Each mL of OptiMARK™ Injection 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.

OptiMARK™ Injection 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™ Injection has a pH of 5.5 to 7.5 and pertinent physiochemical data are provided below:

Table 1: Physiochemical Data	
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™ Injection has an osmolality of approximately 3.9 times that of plasma (285 mOsm/kg water) and is hypertonic under conditions of use.

CLINICAL PHARMACOLOGY

GENERAL

OptiMARK™ Injection contains gadoversetamide, a complex formed between a chelating agent (versetamide) and a paramagnetic ion, gadolinium (III). 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.

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 (*see* PRECAUTIONS, PREGNANCY CATEGORY C and NURSING MOTHERS). The volume of distribution at steady state of gadoversetamide in normal subjects is 162 ± 25 mL/kg, roughly equivalent to that of extracellular water (*see* PRECAUTIONS, PREGNANCY CATEGORY C).

METABOLISM

Biotransformation or decomposition of gadoversetamide was not detected.

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 radioactive [^{153}Gd] MP-1177/10 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 (*see* PRECAUTIONS).

SPECIAL POPULATIONS

Renal Insufficiency: A single intravenous dose of 0.1 mmol/kg of OptiMARK™ Injection was administered to 28 (17 men and 11 women) patients 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 2). The mean cumulative urinary excretion of gadoversetamide at 72 hours was approximately 93.5% for renal impaired patients and 95.8% for subjects with normal renal function (*see* CLINICAL PHARMACOLOGY, ELIMINATION and Hemodialysis).

Hemodialysis: 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 (*see* CLINICAL PHARMACOLOGY, SPECIAL POPULATIONS and ELIMINATION, PRECAUTIONS).

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

GENDER

Gender differences were not statistically significant within the hepatically impaired or renally impaired subgroups (*see* Table 2).

Table 2: 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)

AGE
Pharmacokinetic parameters were retrospectively evaluated in 121 patients with a mean age of 46 years (range 18 to 76 years). In these patients, age related effects on pharmacokinetic parameters were not observed.

RACE
Pharmacokinetic differences due to race after intravenous OptiMARK™ Injection were not studied.

DRUG-DRUG INTERACTIONS
Drug interactions have not been studied.

DIETARY EFFECTS
Dietary effects on the pharmacokinetics of OptiMARK™ Injection have not been studied.

PHARMACODYNAMICS
In magnetic resonance imaging (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).

OptiMARK™ Injection 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 (e.g., cysts, mature post-operative scars, etc.). However, disruption of the blood-brain barrier or abnormal vascularity allows accumulation of OptiMARK™ Injection in the extravascular spaces of lesions such as neoplasms, abscesses, and subacute infarcts. The pharmacokinetic parameters of OptiMARK™ Injection in various lesions are not known.

CLINICAL TRIALS
A total of 790 patients were evaluated in 4 controlled clinical trials (two liver and two central nervous system studies) of OptiMARK™ Injection. Of these 790 patients, 461 received OptiMARK™ Injection. Of the 461 OptiMARK™ patients, there were 252 men and 209 women with a mean age of 49 years (range 12 to 82 years). The racial and ethnic representations were 83% Caucasian, 9% Black, 3% Asian, and 5% other racial or ethnic groups. These trials were designed to evaluate the results of combined non-contrast MRI and OptiMARK™ Injection 0.1 mmol/kg contrast MRIs in comparison to non-contrast MRI alone.

In the two controlled central nervous system (CNS) studies, 395 eligible patients were highly suspect for CNS disorders and had an abnormal entry contrast MRI. After enrollment, patients were randomized to receive repeat MRI evaluations with OptiMARK™ Injection 0.1 mmol/kg or with 0.1 mmol/kg of an approved gadolinium contrast agent. Of these 395 patients, 262 received OptiMARK™ Injection and 133 received the approved gadolinium contrast agent. The studies were not prospectively designed to demonstrate superiority or equivalence of either imaging drug. Approximately 40% and 25% of the patients that were enrolled in Study A and B, respectively, had a history of either surgery, biopsy, and/or radiation, and/or chemotherapy.

Pre-contrast and pre-plus-post-contrast 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 3, 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 3 for these endpoints, when read in combination with the noncontrast images, OptiMARK™ Injection 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 3: Results of MRI Central Nervous System Studies with 0.1 mmol/kg OptiMARK™ Injection

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 Pair [(b)]	 1.8 2.0◊	 3.0 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 controlled liver studies of 395 patients, all eligible patients had a contrast CT that was considered highly suspect for a liver abnormality(ies). Of these 395 patients, 199 received OptiMARK™ Injection 0.1 mmol/kg. 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 4.

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 4 for these endpoints, when read in combination with the noncontrast image, OptiMARK™ Injection provided a statistically significant improvement over noncontrast 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 4: Results of MRI Liver Studies with 0.1 mmol/kg OptiMARK™ Injection

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™ Injection 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.

INDICATIONS AND USAGE

CNS (CENTRAL NERVOUS SYSTEM)

OptiMARK™ Injection 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.

LIVER

OptiMARK™ Injection is indicated for use with MRI 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.

CONTRAINDICATIONS

OptiMARK™ is contraindicated in patients with:

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

WARNINGS

NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (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 a GBCA, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent prior to any re-administration (*see* CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Deoxygenated sickle erythrocytes have been shown in vitro studies to align perpendicular to a magnetic field; this may result in vaso-occlusive complications in vivo. The enhancement of magnetic moment by gadoversetamide may potentiate sickle erythrocyte alignment. OptiMARK™ Injection in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

The potential risk of hemolysis after injection of OptiMARK™ Injection in patients with other hemolytic anemias has not been studied.

Patients with history of allergy, renal insufficiency or drug reaction should be observed for several hours after drug administration (*see* PRECAUTIONS).

PRECAUTIONS

GENERAL

Some paramagnetic contrast agents may impair the visualization of existing lesions, which are seen on the unenhanced, noncontrast MRI. This may be due to effects of the paramagnetic contrast agent, imaging parameters, misregistration, etc. CAUTION SHOULD BE EXERCISED WHEN A CONTRAST ENHANCED INTERPRETATION IS MADE IN THE ABSENCE OF A COMPANION UNENHANCED MRI.

Since gadoversetamide is cleared from the body by glomerular filtration, caution should be exercised in patients with impaired renal function (GFR $\geq$30 and <90 mL/min/1.73m^2). Dose adjustments in renal impairment have not been studied. OptiMARK™ Injection has been shown to be removed from the body by hemodialysis (*see* CLINICAL PHARMACOLOGY, ELIMINATION and SPECIAL POPULATIONS, Renal Insufficiency).

The possibility of a reaction, including serious, life threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered especially in those patients with a known clinical hypersensitivity, a history of asthma, or other respiratory disorders (*see* ADVERSE REACTIONS).

Repeat procedures: The safety of repeated doses has not been studied.

Diagnostic procedures involving the use of MRI contrast agents should be conducted under supervision of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast itself.

INFORMATION FOR PATIENTS

Patients receiving OptiMARK™ Injection should be instructed before injection to:

1. Inform their physician or health care provider if they are pregnant or breast feeding (*see* PRECAUTIONS, PREGNANCY CATEGORY C and NURSING MOTHERS).

2. Inform their physician or health care provider if they have a history of renal and/or liver disease, anemia, hemoglobinopathies, or diseases that affect red blood cells.

3. Inform their physician or health care provider if they have a history of asthma or allergic respiratory disorders, seizures, or heart disease.

4. Inform their physician or health care provider of all medications they may be taking.

5. Inform their physician if they have recently received a GBCA.

GBCAs increase the risk for NSF among 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.

DRUG INTERACTIONS

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

LABORATORY TEST INTERACTIONS

Interference by OptiMARK™ Injection in the measurement of serum iron, copper and zinc has been observed. OptiMARK™ Injection causes interference in the measurement of serum calcium using the ortho-cresophthalin complexone (OCP) colorimetric method. In the presence of OptiMARK™ Injection, OCP produces an erroneous, low value for serum calcium. The magnitude of this artifact is proportional to the concentration of OptiMARK™ Injection in the blood, and accurate values can be obtained approximately 90 minutes following injection. In patients with renal insufficiency, clearance of OptiMARK™ Injection 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™ Injection.

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.

OptiMARK™ Injection 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 0.5 mmol/kg/day (1 times the human dose based on a body surface area).

In a separate 28-day repeat dose study in rats, OptiMARK™ Injection 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, OptiMARK™ Injection 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).

PREGNANCY CATEGORY C

OptiMARK™ Injection 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 a body surface area). Maternal toxicity was not observed at any dose.

OptiMARK™ Injection caused a reduced mean fetal weight, abnormal liver lobation, delayed ossification of sternebrae, and delayed behavioral development (startle reflex and air rights 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.

OptiMARK™ 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.

Adequate and well-controlled studies were not conducted in pregnant women. OptiMARK™ Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

^{153}Gd-labeled OptiMARK™ Injection 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™ Injection administration (*see* CLINICAL PHARMACOLOGY, DISTRIBUTION).

PEDIATRIC USE

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

ADVERSE REACTIONS

A total of 1309 subjects (24 healthy volunteers and 1285 patients) received OptiMARK™ Injection and 46 subjects received placebo (saline). Of the 1309 subjects who received OptiMARK™ Injection, 680 (52%) were men and 629 (48%) were women with a mean age of 50 years (range 12 to 85 years). In this population there were 1102 (84%) white, 116 (9%) black, 33 (3%) Asian, and 58 (4%) subjects and patients of other racial groups.

In the clinical trials there were 8 serious adverse events and 1 death. The one death occurred in a patient with advanced multisystem disease and appeared to be related to the underlying disease. Six of the eight serious events appeared to be related to underlying disease. Two patients had either persistent paresthesia or numbness of unknown etiology that required hospitalization for diagnostic evaluations or treatment.

Of the 1309 subjects, 460 (35%) reported at least one adverse event out of a total of 997 adverse events; and 22 (47.8%) of the 46 subjects who received placebo reported at least one adverse event out of a total of 81 adverse events.

The most commonly noted adverse events were headache (9.4%), vasodilatation (6.4%), taste perversion (6.2%), dizziness (3.7%), nausea (3.2%), and paresthesia (2.2%). All adverse events reported in 1% or greater of all patients are listed in Table 5. Of the subjects and patients who experienced adverse events, 95.8% of the adverse events were of mild or moderate intensity after dosing with OptiMARK™ Injection.

Table 5: Summary Adverse Events Experienced by ≥1% of the Patients

Body System or Event Type	**OptiMARK™ (N = 1309)**
Number of patients with one or more adverse events	460 (35.1%)
Total Number of Adverse Events	997
Patients with any injection associated discomfort	345 (26.4%)
Body as a Whole	193 (14.7%)
Headache	123 (9.4%)
Pain Abdomen	24 (1.8%)
Asthenia	20 (1.5%)
Pain Back	16 (1.2%)
Pain	13 (1.0%)
Cardiovascular	103 (7.9%)
Vasodilatation	84 (6.4%)
Digestive	99 (7.6%)
Nausea	42 (3.2%)
Diarrhea	25 (1.9%)
Dyspepsia	16 (1.2%)
Injection Site	35 (2.7%)

Injection Site Reaction	20 (1.5%)
Musculoskeletal	18 (1.4%)
Nervous System	109 (8.3%)
Dizziness	49 (3.7%)
Paresthesia	29 (2.2%)
Respiratory	46 (3.5%)
Rhinitis	20 (1.5%)
Skin and Appendages	37 (2.8%)
Special Senses	96 (7.3%)
Taste Perversion	81 (6.2%)

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

Body as a Whole: allergic reaction, edema face, fever, flu-like syndrome, malaise, mucous membrane discharge, neck rigidity, neck pain, pelvic pain, increased sweating

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

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

Hemic and Lymphatic: thrombocytopenia

Metabolic and Nutritional: increased creatinine, edema, hypercalcemia, hyperglycemia, hypoglycemia, hyponatremia

Musculoskeletal: arthralgia, leg cramps, myalgia, myasthenia, spasm

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

Respiratory System: asthma, cough, dyspnea, epistaxis, hemoptysis, laryngismus, pharyngitis, sinusitis, voice alteration

Skin and Appendages: application site reaction, edema injection site, erythema multiforme, pruritus, rash macular-papular and vesicullous bullous, skin dry, thrombophlebitis, inflammation injection site, urticaria

Special Senses: amblyopia, conjunctivitis, hyperacusis, parosmia, tinnitus

Urogenital: dysuria, oliguria, urine frequency

Post-marketing surveillance reports have identified cases of seizure.

OVERDOSAGE

Clinical consequences of overdosage with OptiMARK™ Injection have not been reported. Treatment of an overdose is directed toward the support of all vital functions and prompt institution of symptomatic therapy. OptiMARK™ Injection has been shown to be dialyzable (*see* CLINICAL PHARMACOLOGY).

DOSAGE AND ADMINISTRATION

OptiMARK™ Injection should be administered 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 6: Dosage Chart for OptiMARK™ Injection

Body Weight		0.1 mmol/kg
Kilograms (kg)	Pounds (lb)	Volume (mL)
40	88	8.0
50	110	10.0
60	132	12.0
70	154	14.0
80	176	16.0
90	198	18.0
100	220	20.0
110	242	22.0
120	264	24.0
130	286	26.0
140	308	28.0
150	330	30.0

IMAGING

The imaging procedure should be completed within 1 hour of the injection of OptiMARK™ Injection. The safety of repeat doses has not been studied. OptiMARK™ MRI images should be interpreted in comparison to unenhanced MRI (*see* CLINICAL PHARMACOLOGY, PHARMACODYNAMICS and CLINICAL TRIALS).

DRUG HANDLING

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or particulate matter is present.

Concurrent medications or Parenteral Nutrition should not be physically mixed with contrast agents and should not be administered in the same intravenous line because of the potential for chemical incompatibility.

When OptiMARK™ Injection is to be injected using plastic disposable syringes, the

contrast should be drawn into the syringe and used immediately.

This product has not been evaluated for use in magnetic resonance angiography.

OptiMARK™ Injection should be drawn into the syringe and administered using sterile technique. If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents. To ensure complete injection of the contrast medium the injection should be followed by a 5 mL normal saline flush. Unused portions of the drug must be discarded.

HOW SUPPLIED

OptiMARK™ Injection is a clear, colorless to slightly yellow solution containing 330.9 mg/mL, 0.5 mmol/mL of gadoversetamide. OptiMARK™ Injection 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™ Injection 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 0019-1177-10)
15 mL in plastic syringes in cartons of 10 syringes	(NDC Code 0019-1177-15)
20 mL in plastic syringes in cartons of 10 syringes	(NDC Code 0019-1177-20)
30 mL in plastic syringes in cartons of 10 syringes	(NDC Code 0019-1177-30)

STORAGE

OptiMARK™ Injection 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™ Injection 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).

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.

OptiMARK is a trademark of Mallinckrodt Inc.

Manufactured and Distributed by:

Mallinckrodt Inc.
St. Louis, MO 63042 U.S.A.

Printed in U.S.A.

Mallinckrodt Inc.
St. Louis, MO 63042 U.S.A.
www.Mallinckrodt.com

MKR 11770910
Revised 09/10 **Printed in U.S.A.**

OptiMARK™ Pharmacy Bulk Package

OptiMARK™ 0.5 mmol/mL
(Gadoversetamide Injection)

PRESCRIBING INFORMATION

Rx only

Mallinckrodt Inc.

November 2010

OptiMARK™
(gadoversetamide injection)
For Intravenous Injection Only
Mallinckrodt Inc.

PHARMACY BULK PACKAGE – NOT FOR DIRECT INFUSION

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).**
- **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).**

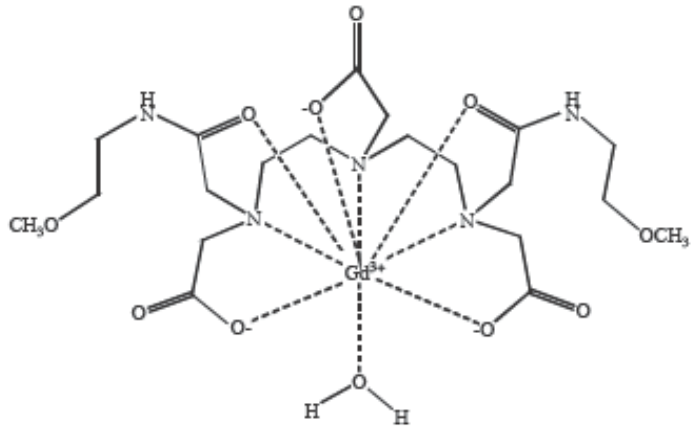
DESCRIPTION

OptiMARK™ (gadoversetamide injection) is a formulation of a nonionic gadolinium chelate of diethylenetriamine pentaacetic acid bismethoxyethylamide (gadoversetamide), for use in magnetic resonance imaging (MRI). OptiMARK™ Injection is to be administered by intravenous injection only.

OptiMARK™ Injection is provided as a sterile, nonpyrogenic, clear, colorless to pale yellow, aqueous solution of gadoversetamide. No preservative is added. Each mL of OptiMARK™

Injection 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.

OptiMARK™ Injection 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™ Injection has a pH of 5.5 to 7.5 and pertinent physiochemical data are provided below:

Table 1: Physiochemical Data	
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™ Injection has an osmolality of approximately 3.9 times that of plasma (285 mOsm/kg water) and is hypertonic under conditions of use.

CLINICAL PHARMACOLOGY

GENERAL

OptiMARK™ Injection contains gadoversetamide, a complex formed between a chelating agent (versetamide) and a paramagnetic ion, gadolinium (III). 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.

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 (*see* PRECAUTIONS, PREGNANCY CATEGORY C and NURSING MOTHERS). The volume of distribution at steady state of gadoversetamide in normal subjects is 162 ± 25 mL/kg, roughly equivalent to that of extracellular water (*see* PRECAUTIONS, PREGNANCY CATEGORY C).

METABOLISM

Biotransformation or decomposition of gadoversetamide was not detected.

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 radioactive [^{153}Gd] MP-1177/10 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 (*see* PRECAUTIONS).

SPECIAL POPULATIONS

Renal Insufficiency: A single intravenous dose of 0.1 mmol/kg of OptiMARK™ Injection was administered to 28 (17 men and 11 women) patients 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 2). The mean cumulative urinary excretion of gadoversetamide at 72 hours was approximately 93.5% for renal impaired patients and 95.8% for subjects with normal renal function (*see* CLINICAL PHARMACOLOGY, ELIMINATION and Hemodialysis).

Hemodialysis: 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 (*see* CLINICAL PHARMACOLOGY, SPECIAL POPULATIONS and ELIMINATION, PRECAUTIONS).

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

GENDER

Gender differences were not statistically significant within the hepatically impaired or renally impaired subgroups (*see* Table 2).

Table 2: 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)

AGE

Pharmacokinetic parameters were retrospectively evaluated in 121 patients with a mean age of 46 years (range 18 to 76 years). In these patients, age related effects on pharmacokinetic parameters were not observed.

RACE

Pharmacokinetic differences due to race after intravenous OptiMARK™ Injection were not studied.

DRUG-DRUG INTERACTIONS

Drug interactions have not been studied.

DIETARY EFFECTS

Dietary effects on the pharmacokinetics of OptiMARK™ Injection have not been studied.

PHARMACODYNAMICS

In magnetic resonance imaging (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).

OptiMARK™ Injection 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 (e.g., cysts, mature post-operative scars, etc.). However, disruption of the blood-brain barrier or abnormal vascularity allows accumulation of OptiMARK™ Injection in the extravascular spaces of lesions such as neoplasms, abscesses, and subacute infarcts. The pharmacokinetic parameters of OptiMARK™ Injection in various lesions are not known.

CLINICAL TRIALS

A total of 790 patients were evaluated in 4 controlled clinical trials (two liver and two central

nervous system studies) of OptiMARK™ Injection. Of these 790 patients, 461 received OptiMARK™ Injection. Of the 461 OptiMARK™ patients, there were 252 men and 209 women with a mean age of 49 years (range 12 to 82 years). The racial and ethnic representations were 83% Caucasian, 9% Black, 3% Asian, and 5% other racial or ethnic groups. These trials were designed to evaluate the results of combined non-contrast MRI and OptiMARK™ Injection 0.1 mmol/kg contrast MRIs in comparison to non-contrast MRI alone.

In the two controlled central nervous system (CNS) studies, 395 eligible patients were highly suspect for CNS disorders and had an abnormal entry contrast MRI. After enrollment, patients were randomized to receive repeat MRI evaluations with OptiMARK™ Injection 0.1 mmol/kg or with 0.1 mmol/kg of an approved gadolinium contrast agent. Of these 395 patients, 262 received OptiMARK™ Injection and 133 received the approved gadolinium contrast agent. The studies were not prospectively designed to demonstrate superiority or equivalence of either imaging drug. Approximately 40% and 25% of the patients that were enrolled in Study A and B, respectively, had a history of either surgery, biopsy, and/or radiation, and/or chemotherapy.

Pre-contrast and pre-plus-post-contrast 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 3, 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 3 for these endpoints, when read in combination with the non-contrast images, OptiMARK™ Injection 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 3: Results of MRI Central Nervous System Studies with 0.1 mmol/kg OptiMARK™ Injection

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 Pair [(b)]	 1.8 2.0◊	 3.0 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 controlled liver studies of 395 patients, all eligible patients had a contrast CT that was considered highly suspect for a liver abnormality(ies). Of these 395 patients, 199 received OptiMARK™ Injection 0.1 mmol/kg. 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 4.

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 4 for these endpoints, when read in combination with the non-contrast image, OptiMARK™ Injection 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 4: Results of MRI Liver Studies with 0.1 mmol/kg OptiMARK™ Injection

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™ Injection 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.

INDICATIONS AND USAGE

CNS (CENTRAL NERVOUS SYSTEM)

OptiMARK™ Injection 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.

LIVER

OptiMARK™ Injection is indicated for use with MRI 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.

CONTRAINDICATIONS

OptiMARK™ is contraindicated in patients with:

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

WARNINGS

NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (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* CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Deoxygenated sickle erythrocytes have been shown in vitro studies to align perpendicular to a magnetic field; this may result in vaso-occlusive complications in vivo. The enhancement of magnetic moment by gadoversetamide may potentiate sickle erythrocyte alignment. OptiMARK™ Injection in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

The potential risk of hemolysis after injection of OptiMARK™ Injection in patients with other hemolytic anemias has not been studied.

Patients with history of allergy, renal insufficiency or drug reaction should be observed for several hours after drug administration (*see* PRECAUTIONS).

PRECAUTIONS

GENERAL

Some paramagnetic contrast agents may impair the visualization of existing lesions, which are seen on the unenhanced, non-contrast MRI. This may be due to effects of the paramagnetic contrast agent, imaging parameters, misregistration, etc. CAUTION SHOULD BE EXERCISED WHEN A CONTRAST ENHANCED INTERPRETATION IS MADE IN THE ABSENCE OF A COMPANION UNENHANCED MRI.

Since gadoversetamide is cleared from the body by glomerular filtration, caution should be exercised in patients with impaired renal function (GFR $\geq$30 and <90 mL/min/1.73m^2). Dose adjustments in renal impairment have not been studied. OptiMARK™ Injection has been shown to be removed from the body by hemodialysis (*see* CLINICAL PHARMACOLOGY, ELIMINATION and SPECIAL POPULATIONS, Renal Insufficiency).

The possibility of a reaction, including serious, life threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered especially in those patients with a known clinical hypersensitivity, a history of asthma, or other respiratory disorders (*see* ADVERSE REACTIONS).

Repeat procedures: The safety of repeated doses has not been studied.

Diagnostic procedures involving the use of MRI contrast agents should be conducted under supervision of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast itself.

INFORMATION FOR PATIENTS

Patients receiving OptiMARK™ Injection should be instructed before injection to:

1. Inform their physician or health care provider if they are pregnant or breast feeding (*see* PRECAUTIONS, PREGNANCY CATEGORY C and NURSING MOTHERS).

2. Inform their physician or health care provider if they have a history of renal and/or liver disease, anemia, hemoglobinopathies, or diseases that affect red blood cells.

3. Inform their physician or health care provider if they have a history of asthma or allergic respiratory disorders, seizures, or heart disease.

4. Inform their physician or health care provider of all medications they may be taking.

5. Inform their physician if they have recently received a GBCA.

GBCAs increase the risk for NSF among 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.

DRUG INTERACTIONS

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

LABORATORY TEST INTERACTIONS

Interference by OptiMARK™ Injection in the measurement of serum iron, copper and zinc has been observed. OptiMARK™ Injection causes interference in the measurement of serum calcium using the ortho-cresophthalin complexone (OCP) colorimetric method. In the presence of OptiMARK™ Injection, OCP produces an erroneous, low value for serum calcium. The magnitude of this artifact is proportional to the concentration of OptiMARK™ Injection in the blood, and accurate values can be obtained approximately 90 minutes following injection. In patients with renal insufficiency, clearance of OptiMARK™ Injection 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™ Injection.

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.

OptiMARK™ Injection 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 0.5 mmol/kg/day (1 times the human dose based on a body surface area).

In a separate 28-day repeat dose study in rats, OptiMARK™ Injection 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, OptiMARK™ Injection 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).

PREGNANCY CATEGORY C

OptiMARK™ Injection 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 a body surface area). Maternal toxicity was not observed at any dose.

OptiMARK™ Injection caused a reduced mean fetal weight, abnormal liver lobation, delayed ossification of sternebrae, and delayed behavioral development (startle reflex and air rights 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.

OptiMARK™ 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.

Adequate and well-controlled studies were not conducted in pregnant women. OptiMARK™ Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

^{153}Gd-labeled OptiMARK™ Injection 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™ Injection administration (*see* CLINICAL PHARMACOLOGY, DISTRIBUTION).

PEDIATRIC USE

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

ADVERSE REACTIONS

A total of 1309 subjects (24 healthy volunteers and 1285 patients) received OptiMARK™ Injection and 46 subjects received placebo (saline). Of the 1309 subjects who received OptiMARK™ Injection, 680 (52%) were men and 629 (48%) were women with a mean age of

50 years (range 12 to 85 years). In this population there were 1102 (84%) white, 116 (9%) black, 33 (3%) Asian, and 58 (4%) subjects and patients of other racial groups.

In the clinical trials there were 8 serious adverse events and 1 death. The one death occurred in a patient with advanced multisystem disease and appeared to be related to the underlying disease. Six of the eight serious events appeared to be related to underlying disease. Two patients had either persistent paresthesia or numbness of unknown etiology that required hospitalization for diagnostic evaluations or treatment.

Of the 1309 subjects, 460 (35%) reported at least one adverse event out of a total of 997 adverse events; and 22 (47.8%) of the 46 subjects who received placebo reported at least one adverse event out of a total of 81 adverse events.

The most commonly noted adverse events were headache (9.4%), vasodilatation (6.4%), taste perversion (6.2%), dizziness (3.7%), nausea (3.2%), and paresthesia (2.2%). All adverse events reported in 1% or greater of all patients are listed in Table 5. Of the subjects and patients who experienced adverse events, 95.8% of the adverse events were of mild or moderate intensity after dosing with OptiMARK™ Injection.

Table 5: Summary Adverse Events Experienced by ≥1% of the Patients

Body System or Event Type	**OptiMARK™ (N = 1309)**
Number of patients with one or more adverse events	460 (35.1%)
Total Number of Adverse Events	997
Patients with any injection associated discomfort	345 (26.4%)
Body as a Whole	193 (14.7%)
Headache	123 (9.4%)
Pain Abdomen	24 (1.8%)
Asthenia	20 (1.5%)
Pain Back	16 (1.2%)
Pain	13 (1.0%)
Cardiovascular	103 (7.9%)
Vasodilatation	84 (6.4%)
Digestive	99 (7.6%)
Nausea	42 (3.2%)
Diarrhea	25 (1.9%)
Dyspepsia	16 (1.2%)
Injection Site	35 (2.7%)
Injection Site Reaction	20 (1.5%)
Musculoskeletal	18 (1.4%)
Nervous System	109 (8.3%)
Dizziness	49 (3.7%)
Paresthesia	29 (2.2%)
Respiratory	46 (3.5%)

Rhinitis	20 (1.5%)
Skin and Appendages	37 (2.8%)
Special Senses	96 (7.3%)
Taste Perversion	81 (6.2%)

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

Body as a Whole: allergic reaction, edema face, fever, flu-like syndrome, malaise, mucous membrane discharge, neck rigidity, neck pain, pelvic pain, increased sweating

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

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

Hemic and Lymphatic: thrombocytopenia

Metabolic and Nutritional: increased creatinine, edema, hypercalcemia, hyperglycemia, hypoglycemia, hyponatremia

Musculoskeletal: arthralgia, leg cramps, myalgia, myasthenia, spasm

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

Respiratory System: asthma, cough, dyspnea, epistaxis, hemoptysis, laryngismus, pharyngitis, sinusitis, voice alteration

Skin and Appendages: application site reaction, edema injection site, erythema multiforme, pruritus, rash macular-papular and vesicullous bullous, skin dry, thrombophlebitis, inflammation injection site, urticaria

Special Senses: amblyopia, conjunctivitis, hyperacusis, parosmia, tinnitus

Urogenital: dysuria, oliguria, urine frequency

Post-marketing surveillance reports have identified cases of seizure.

OVERDOSAGE

Clinical consequences of overdosage with OptiMARK™ Injection have not been reported. Treatment of an overdose is directed toward the support of all vital functions and prompt institution of symptomatic therapy. OptiMARK™ Injection has been shown to be dialyzable (*see* CLINICAL PHARMACOLOGY).

DOSAGE AND ADMINISTRATION

OptiMARK™ Injection should be administered 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 6: Dosage Chart for OptiMARK™ Injection

Body Weight		0.1 mmol/kg
Kilograms (kg)	Pounds (lb)	Volume (mL)
40	88	8.0
50	110	10.0
60	132	12.0
70	154	14.0
80	176	16.0
90	198	18.0
100	220	20.0
110	242	22.0
120	264	24.0
130	286	26.0
140	308	28.0
150	330	30.0

IMAGING

The imaging procedure should be completed within 1 hour of the injection of OptiMARK™ Injection. The safety of repeat doses has not been studied. OptiMARK™ MRI images should be interpreted in comparison to unenhanced MRI (*see* CLINICAL PHARMACOLOGY, PHARMACODYNAMICS and CLINICAL TRIALS).

DRUG HANDLING

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or particulate matter is present.

Concurrent medications or Parenteral Nutrition should not be physically mixed with contrast agents and should not be administered in the same intravenous line because of the potential for chemical incompatibility.

This product has not been evaluated for use in magnetic resonance angiography.

Pharmacy Bulk Package Preparation: 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.

OptiMARK™ Injection should be drawn into the syringe and administered using sterile technique. If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents. To ensure complete injection of the

contrast medium the injection should be followed by a 5 mL normal saline flush. Unused portions of the drug must be discarded.

When OptiMARK™ Injection is to be injected using plastic disposable syringes, the contrast should be drawn into the syringe and used immediately.

a) The transfer of OptiMARK™ Injection from the Pharmacy Bulk Package must be performed in an aseptic work area such as a laminar flow hood using appropriate aseptic technique.
b) Once the Pharmacy Bulk Package is punctured, it should not be removed from the aseptic work area during the entire 24 hour period of use.
c) The contents of the Pharmacy Bulk Package after initial puncture should be used within 24 hours.
d) Any unused OptiMARK™ Injection must be discarded 24 hours after the initial puncture of the bulk package.
e) IV tubing and syringes used to administer OptiMARK™ Injection must be discarded at the conclusion of the radiological examination.

HOW SUPPLIED

OptiMARK™ Injection is a clear, colorless to slightly yellow solution containing 330.9 mg/mL, 0.5 mmol/mL of gadoversetamide. OptiMARK™ Injection is supplied in 50 mL glass bottles containing 50 mL of solution. Each bottle is rubber stoppered with an aluminum seal and the contents are sterile. Bottles are contained in shipping cartons with the following configurations:

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

STORAGE

OptiMARK™ Injection 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™ Injection 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).

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.

OptiMARK is a trademark of Mallinckrodt Inc.

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

Printed in U.S.A.

Mallinckrodt Inc.
St. Louis, MO 63042 U.S.A.
www.Mallinckrodt.com

MKR 11PB1110
Revised 11/10 **Printed in U.S.A.**