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APPLICATION NUMBER: NDA 20937

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-937

TITLE: OptiMARK (Gadoversetamide injection).

REVIEWER: Alfredo R. Sancho, Ph.D.

REF: Labeling

RESUBMISSION DATE: 16 July 1999

REVIEW DATE: 30 August 1999

INDICATION: Intravenous Magnetic Resonance Imaging (MRI) agent for diagnostic purpose of 1) intracranial lesions with abnormal vascularity or those thought to cause abnormalities in the blood-brain-barrier (BBB) (e.g. brain tumors); 2) to provide contrast enhancement and facilitate visualization of spine lesions, associated tissues and liver lesions.

SPONSOR: Mallinckrodt, Inc.

ADDRESS: 675 McDonnell Blvd., P. O. Box 5840, St. Louis, MO 63134

SYNOPSIS

The sponsor originally submitted the original NDA 20-937 application for review on February 02, 1998. Subsequently on December 23, 1998, a letter of not approvable was issued by the Agency to the sponsor. To which on June 7, 1999 the sponsor submitted their response as a Class I resubmission.

The present document relates to the review of the proposed *Package Insert* and *Container Labels*. Changes (underlined for inclusions and ~~strikethrough~~ for deletions) to the proposed labeling are as follow:

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacological Evaluation II has reviewed the NDA 20-937 labeling information submitted July 16, 1999. The changes to the proposed *Package Insert* and *Container Labels* should be forwarded to the sponsor.

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06 Oct 99
/S/

Alfredo R. Sancho, Ph.D.
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Radiopharmaceutics and Medical Imaging Division
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Concurrence:

IS/ *10/20/99*

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Cc: HFD-160 NDA 20-937 (1x); DIV FILE (1x); MOORE (1X); SANCHO (1X); LEE (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG, LESKO
CDR Attn.: Barbara Murphy

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-937

TITLE: OptiMARK (Gadoversetamide injection).

REVIEWER: Alfredo R. Sancho, Ph.D.

REF: Class 1 Resubmission

RESUBMISSION DATE: 07 June 1999

REVIEW DATE: 15 July 1999

INDICATION: Intravenous Magnetic Resonance Imaging (MRI) agent for diagnostic purpose of 1) intracranial lesions with abnormal vascularity or those thought to cause abnormalities in the blood-brain-barrier (BBB) (e.g. brain tumors); 2) to provide contrast enhancement and facilitate visualization of spine lesions, associated tissues and liver lesions.

SPONSOR: Mallinckrodt, Inc.

ADDRESS: 675 McDonnell Blvd., P. O. Box 5840, St. Louis, MO 63134

SYNOPSIS

The sponsor originally submitted the original NDA 20-937 application for review on February 02, 1998. Subsequently on December 23, 1998, a letter of not approvable was issued by the Agency to the sponsor. To which on June 7, 1999 the sponsor submitted their response as a Class 1 resubmission.

The present review will focus solely on the issues forwarded to the sponsor in the not approvable letter above mentioned; any other issues were covered in the original review dated November 03, 1998 written by Young Moon-Choi, Ph.D. Specifically, in the not approvable letter sent to the sponsor on December 23, 1998 under the Clinical Pharmacology and Biopharmaceutics section the following comment was included:

FDA is aware that the applicant performed non-compartmental analysis, and it is the opinion of the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) that this non-compartmental analysis was appropriate. However, the renal clearance values appeared to be larger than the total clearance values in Study 433. In theory, the renal clearance should not be larger than total clearance.

Please calculate renal clearance values using the most appropriate method for the Studies 433, 489, and 538. Please compare the renal clearance values to the total clearance values. If there are significant differences between these values please explain. Also, if there are significant differences in these two parameters between studies please explain.

The sponsor has complied with the request to address and clarify the observed discrepancies between the renal clearance (Cl_R) and total clearance (Cl_T) in the three study groups by recalculating these parameters. The resubmitted data and calculations now demonstrate that Cl_R is not larger than Cl_T , as it would be expected. Further source of variability is derived from the differences in demographics between each of the study groups, i.e. gender ratios and group mean-age differences.

This NDA application, after the total clearance and renal clearance data was recalculated is found to have no pending issues by this reviewer.

RESULTS

The renal clearance (Cl_R) and total clearance (Cl_T) data was recalculated and presented in Table 1 of Appendix 2 of the resubmission package dated June 7, 1999. In the original OptiMARK NDA submission, total clearance was calculated in the three primary pharmacokinetic studies (Studies 433, 489, and 538). Renal clearance was estimated in studies 433 and 538, but not in study 489. This latter study was a large scale, placebo-controlled safety study, not a traditional pharmacokinetic study, thus the protocol did not specify either balance or estimation of clearance as objectives. In fact, the applicant states that the smaller study 538 was intended as and carried out as a complementary pharmacokinetic study in the same patient population. Nevertheless, the applicant provided renal and total clearance values for study 489 in their communication of June 7, 1999.

The clearance for all three studies were calculated with the following formulas:

$$\text{Total Clearance or } Cl_T = [\text{Dose}]/\text{AUC}$$

$$\text{Renal Clearance or } Cl_R = [Xu]/\text{AUC}$$

Where [Dose] was expressed as the total μg of Gd (studies 433 and 489) or gadoversetamide complex (study 538) administered, while [Xu] is the total μg recovered in excreted urine, on the same molecular weight basis, for the entire urine collection period in each subject. The collection period was 72 hours for each study. The clearances were normalized to 1.73 m^2 body surface area (BSA) to allow comparison among individuals of different body size.

Both study 489 and study 538 enrolled a substantial number of patients with moderate to severe renal impairment. The applicant, as per the Agency's suggestion, did not attempt to stratify these patients by degree of impairment.

In study 433, the mean total clearance and mean renal clearance were 108.7 ± 13 and 96.6 ± 13.7 ml/min/ 1.73 m^2 , respectively. These clearance data were calculated from serum Gd data for the lowest (0.1 mmol/kg) and highest (0.7 mmol/kg) dose groups. The subject population of this study consisted of healthy males with a mean age of 31.0 ± 9.3 years.

For study 489, the estimates of mean total and renal clearance were 92.5 ± 17.6 and 83.3 ± 18.5 ml/min/ 1.73 m^2 , respectively. This study consisted of 42 males and 38 females, with a mean age of 44.5 ± 12.1 years.

Study 538, was supportive to study 489, in the same patient populations, with the additional enrollment of age and sex matched groups of normal subjects and patients whose only disease state was renal impairment. The total clearance and renal clearance, as measured by intact plasma gadoversetamide complex, were 82.8 ± 20.7 and 78.7 ± 24.9 ml/min/ 1.73 m^2 , respectively.

In all three studies, the mean renal clearance of this drug product is slightly less than the mean total clearance, representing 89-95% of total clearance. The mean clearance values for study 433 (Phase 1 healthy male volunteers) are on an average 25% higher than their respective estimates in studies 489 and 538. The demographics of those enrolled in these studies must be considered to understand the observed differences. That is, in study 433 the average age of the healthy male volunteers was 31, while in studies 489 and 538, patients of both genders (approximately 50:50 ratio between males and females) had an average age of approximately 45 years. Additionally, in studies 489 and 538, with the exception of 8 healthy volunteers, the remaining subjects had pre-existing disease states (either liver or

CNS disease). The expected difference of clearance between young, healthy male volunteers and older mixed-gender patients with some form and level of disease state was observed in the differences of renal and total clearance between the three studies submitted.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacological Evaluation II has reviewed the NDA 20-937 information and data submitted June 07, 1999 in response to the not approvable letter issued to the applicant on December 23, 1998. At this time, it is recommended that this NDA submission be considered approvable.

/S/

15 July 1999

Alfredo R. Sancho, Ph.D.
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Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

/S/

7/19/99

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Cc: HFD-160 NDA 20-937 (1x); DIV.FILE (1x); MOORE (1X); SANCHO (1X); LEE (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG, LESKO
CDR Attn.: Barbara Murphy

DF

Memorandum
Clinical Pharmacology and Biopharmaceutics Review

JUL 14 1999

NDA: 20-937

Drug Name: OptiMARK (gadoversetamide injection)

Type of Submission: Class 1 Resubmission

Submission Date: June 7, 1999

Reviewer: Alfredo R. Sancho, Ph.D.

Sponsor: Mallinckrodt, Inc.

Sponsor's Address: 675 McDonnell Blvd., P.O. Box 5840, St. Louis, MO 63134

The sponsor originally submitted the NDA 20-937 for review and approval on February 02, 1998. Subsequently on December 23, 1998, a letter of not approvable was issued by the Agency to the sponsor. To which on June 7, 1999 the sponsor submitted their response.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacological Evaluation II has reviewed the information and data submitted June 7th, 1999 related to NDA 20-937 in response to the not approvable letter dated December 23, 1998. Based upon an evaluation of the provided information and data it is concluded that this application can be filed for review.

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July 14, 1999

Alfredo R. Sancho, Ph.D.
Clinical Pharmacology and Biopharmaceutics Reviewer
Radiopharmaceutical and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

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Cc: HFD-160 NDA 20-937 (1x); DIV FILE (1x); MOORE (1X); SANCHO (1X); LEE (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG
CDR Attn.: Barbara Murphy

160/HFD New file

NOV - 3 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA Number:	NDA 20-937
Drug:	OptiMark (Gadoversetamide)
Sponsor:	Malinckrodt Inc.
Submission Date:	2/28/98
Type of Submission:	Original NDA (NME)
Code:	1 S
Reviewer:	Young Moon Choi, Ph.D.

1. SYNOPSIS

Malinckrodt, Inc. has submitted NDA 20-937 on 2/28/98 for the approval of OptiMARK™ (gadoversetamide), an intravenous magnetic resonance imaging (MRI) agent for diagnostic purpose. This product was developed under IND

Proposed Indication

OptiMARK Injection is indicated for use with magnetic resonance imaging (MRI) in adults to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause an abnormalities in the blood-brain barrier. OptiMARK injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.

OptiMARK Injection is also indicated for use MRI in adults to provide contrast enhancement and facilitate visualization of lesions of the spine and associated tissues.

OptiMARK Injection is also indicated for use with MRI in adults to provide contrast enhancement and facilitate visualization of lesions in the liver.

In MRI, visualization of normal and pathological brain, spinal and hepatic tissues depends in part on variations in the radio frequency signal intensity that occurs with:

- (1) changes in proton density;
- (2) alterations of the spin-lattice of longitudinal relaxation time (T1); and
- (3) variation of the spin-spin of transverse relaxation time (T2).

When placed in a magnetic field, OptiMARK decreases T1 and T2 relaxation times in tissues where it accumulates. At usual doses the effect is primarily in T1 relaxation time, and produces an increase in signal intensity (brightness).

OptiMARK (gadoversetamide injection) formulation is a nonionic gadolinium chelate of diethylenetriamine pentaacetic acid bismethoxyethylamide (gadoversetamide), and is to be administered by intravenous bolus injection. It is a sterile, nonpyrogenic, clear, colorless to pale yellow, aqueous solution of gadoversetamide. No preservative is added. Each ml of OptiMARK contains 330.9 mg of gadoversetamide, 25.4 mg of versetamide, 3.7 mg calcium hydroxide, 0.74 mg calcium chloride dihydrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added for pH adjustment.

There were two formulations used in pharmacokinetic studies, MP-1177/10, a clinical formulation, and the "to-be-marketed" OptiMARK formulation. However, two formulations contain identical ingredients. Therefore, these formulations should be considered as one formulation.

Dosage and Administration

The recommended dose of OptiMARK is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid bolus (1.0 mL/min/kg). To ensure complete injection of OptiMARK, the injection should be followed by a normal saline flush (approximately 5 mL).

The applicant submitted 5 pharmacokinetic studies in the Item 6, the Human Pharmacokinetics and Bioavailability. Table I presents the basic study design for each study. The protocol 1177/01, which is conducted in Japan, is submitted as a supportive data. All other studies are equally significant for the evaluation of safety and pharmacokinetics.

Table I. Human pharmacokinetic studies of OptiMARK.

Protocol No.	Country No. Of Sites [Start Date - End Date]	Formulation [Concentration]	Study Design	Dose(s) (mmol/kg) per Dose	No. Of Subjects Total & [M/F]	Age (yr) Mean [Range] by Dose
433	US 1 Site [03/01/93 - 04/30/93]	MP-1177/10 Injection [0.5 mmol/mL]	Randomized, double-blind, ascending-dose, safety, tolerance & PK; in healthy male subjects; analysis of Gd in serum & urine; analysis of selected samples for complex by HPLC.	Placebo Drug 0.1 0.3 0.5 0.7	4 [4/0] 16 [16/0] 4 [4/0] 4 [4/0] 4 [4/0] 4 [4/0]	Placebo 30.3 [21 - 39] 0.1 35.8 [23 - 43] 0.3 33.0 [29 - 37] 0.5 22.5 [19 - 30] 0.7 26.3 [20 - 37]
1177-01	Japan 1 Site [05/23/94 - 06/30/94]	MP-1177/10 Injection [0.5 mmol/mL]	Randomized, double-blind, ascending-dose, safety, tolerance & PK; in healthy male subjects; analysis of Gd in serum & urine; analysis of selected samples for complex by HPLC; in vivo serum protein binding.	Placebo Drug 0.05 0.1 0.3 0.5	4 [4/0] 16 [16/0] 4 [4/0] 4 [4/0] 4 [4/0] 4 [4/0]	Placebo 23.8 [21 - 29] 0.05 23.3 [21 - 26] 0.1 23.8 [21 - 27] 0.3 23.8 [22 - 28] 0.5 23.8 [21 - 29]
489	US 10 Sites [06/04/96 - 08/12/97]	OptiMARK Injection [0.5 mmol/mL]	Multicenter, randomized, double-blind, safety and PK; in male and female CNS & liver patients, with or without renal impairment; analysis of Gd in serum & urine.	Placebo Drug 0.1 0.3 0.5	42 [21/21] 121 [63/58] 40 [19/21] 42 [23/19] 39 [21/18]	Placebo 45.8 [23 - 73] 0.1 43.7 [20 - 76] 0.3 45.6 [18 - 71] 0.5 48.0 [19 - 73]
538	US 6 Sites [06/02/97 -	OptiMARK Injection [0.5 mmol/mL]	Multicenter, PK and safety; in male and female CNS & liver patients and normal	Drug Non-Renal (incl. Normal Subj.)	54 [27/27]	Drug (0.1) 48.5 [26 - 78]

Protocol No.	Country No. Of Sites [Start Date - End Date]	Formulation [Concentration]	Study Design	Dose(s) (mmol/kg) per Dose	No. Of Subjects Total & [M/F]	Age (yr) Mean [Range] by Dose
	11/15/97]		volunteers, with or without renal impairment; analysis of Gd and intact gadoversetamide complex in plasma & urine.	0.1 <u>Renal</u> 0.1	32 [15/17] 22 [12/10]	
543	US 1 Site [10/20/97 - 11/25/97]	OptiMARK Injection [0.5 mmol/mL]	Safety and PK; in stable hemodialysis patients; analysis of Gd in plasma & dialysate.	0.1	8 [7/1]	<u>Drug (0.1)</u> 50 [32 - 68]

The sample analyses were conducted with two methods:

- (1) an inductively coupled plasma-atomic emission spectrometry (ICP/AES) for total gadolinium assay and
- (2) assay for the intact gadoversetamide complex.

It appears that both methods seem appropriate. The analysis results indicated that the total gadolinium in biological samples appeared to represent the gadoversetamide, indicating that the gadolinium is not dissociated from the gadoversetamide.

From the five pharmacokinetic studies the following information was obtained:

- (1) OptiMARK was observed to distribute rapidly into the extracellular fluid volume following an intravenous bolus dose;
- (2) The plasma protein binding of OptiMARK appeared to be negligible;
- (3) The pharmacokinetics and elimination of OptiMARK are not affected by gender, age or disease state (CNS or liver); this evaluation included a limited number of patients who were judged to be hepatically impaired;
- (4) OptiMARK is completely eliminated into the urine as the intact complex and not metabolized in humans;
- (5) The mean terminal elimination half-life in normal subjects was 1.73 hr;
- (6) The pharmacokinetics of OptiMARK appear to be linear within the dose range (0.1 - 0.7 mmol/kg) studied;
- (7) Renal impairment decreases the rate of OptiMARK excretion, however, almost all the injected dose was excreted eventually through renal route; and
- (8) OptiMARK can be efficiently removed from the circulation by extracorporeal hemodialysis.

TABLE OF CONTENTS

1. Synopsis
2. Recommendation
3. Background Information
 - 3-1. Chemistry
 - 3-2. Formulation
 - 3-3. Indications and usage
 - 3-4. Dosage Administration
4. Pharmacokinetics
 - 4-1. Compilation of the pharmacokinetic data
 - 4-2. Distribution
 - 4-3. Elimination
 - 4-3-1. Metabolism
 - 4-3-2. Urinary excretion
 - 4-4. Special Populations
 - 4-4-1. Gender and Age effect
 - 4-4-2. Hepatic and CNS disease (Target populations)
 - 4-4-3. Renal Impairment
 - 4-4-4. Hemodialysis
 - 4-5. Protein binding
5. Overall comments
6. Labeling comments

Appendix

Appendix-1. Summary of Individual Studies

- Appendix 1-1. Study No.433
- Appendix 1-2. Study No: MP1177/01 (Japan)
- Appendix 1-3. Study No. 489
- Appendix 1-4. Study No. 538
- Appendix 1-5. Study No. 543

Appendix -2. Applicant Labeling

3. BACKGROUND INFORMATION

Magnetic resonance imaging (MRI) has been proved to be a valuable diagnostic imaging modality. MRI has provided several benefits over previously existing diagnostic imaging modalities. These advantages includes:

- (1) multiplanar capabilities (axial, coronal, sagittal, and oblique sections),
- (2) no exposure to ionizing radiation, and
- (3) several intrinsic tissue characteristics (T1, T2, and proton density) that provide tissue contrast resolution between various tissues.

Even though MRI inherently provides for tissue contrast, exogenous MRI contrast agents demonstrated the ability to improve the diagnostic accuracy of magnetic resonance imaging.

Mallinckrodt Medical, Inc. has developed OptiMARK (gadoversetamide injection), a nonionic (neutral), extracellular, linear gadolinium chelate for use as an intravenous MRI contrast agent.

The ability to distinguish normal and abnormal tissue in MRI depends on the signal intensity differences between tissues, which are, in part, a function of T1 and T2 relaxation time. OptiMARK enhances the rate of relaxation (return to magnetic equilibrium) in hydrogen nuclei (protons) that are in its vicinity. This decreases T1 (spin lattice relaxation time) and T2 (spin-spin relaxation time) of tissues in which it is present. Due to such an effect of OptiMARK on relaxation time, the ability to distinguish pathologic tissue from normal tissue may be improved.

3-1. CHEMISTRY

Commercial Name: OptiMARK™

Drug Product Name: gadoversetamide injection

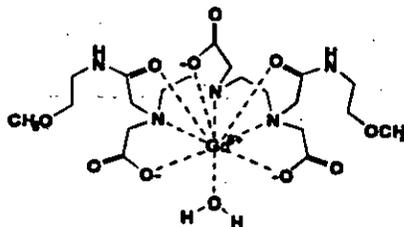
Code Name: MP-1177/10

Chemical Name: [8,11-bis(carboxymethyl)-14-[2-[(2-methoxyethyl)amino]-2-oxoethyl]-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(3-)] gadolinium

Molecular Formula: $C_{20}GdH_{34}N_5O_{10}$

Formula Weight: 661.77 g/mol

Structure:



3-2. FORMULATION

OptiMARK (gadoversetamide injection) formulation is a nonionic gadolinium chelate of diethylenetriamine pentaacetic acid bismethoxyethylamide (gadoversetamide), and is to be administered by intravenous injection.

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 contains:

- (1) 330.9 mg of gadoversetamide,
- (2) 25.4 mg of versetamide,
- (3) 3.7 mg calcium hydroxide,
- (4) 0.74 mg calcium chloride dihydrate, and water for injection.
- (5) Sodium hydroxide and hydrochloric acid may be added for pH 5.5-7.5.

3-3. INDICATIONS AND USAGE

- OptiMARK Injection is indicated for use with magnetic resonance imaging (MRI) in adults to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause abnormalities in the blood-brain barrier. OptiMARK injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.
- OptiMARK Injection is also indicated for use MRI in adults to provide contrast enhancement and facilitate visualization of lesions of the spine and associated tissues.
- OptiMARK Injection is also indicated for use with MRI in adults to provide contrast enhancement and facilitate visualization of lesions in the liver.

3-4. DOSAGE ADMINISTRATION

The recommended dose of OptiMARK is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous bolus injection. To ensure complete injection of OptiMARK, the injection should be followed by a normal saline flush (approximately 5 mL).

4. PHARMACOKINETICS

4-1. Compilation of the pharmacokinetic data

The pharmacokinetic parameters for five studies are compiled in Table II.

In Studies 433 and 1177-01, the applicant estimated the pharmacokinetic parameters (except AUC) from non-linear regression fits to an open two-compartment pharmacokinetic model. When the graphical output from this procedure was examined (see Study 433) it was apparent that in most subjects the last point was being consistently above the regression line. This led to underestimation of the apparent terminal elimination half-life in these studies, relative to the non-compartment estimates derived in Studies 489 and 538. Therefore, the applicant re-estimated the pharmacokinetic parameters from studies 433 and 1177-01 using the non-compartment approach, which had been used for the other human pharmacokinetics studies.

The noncompartmental parameter estimates for these studies are presented in Tables III and IV.

It appears, when comparing these estimates with those in Table II that the compartmental model does modestly underestimate half-life and overestimate clearance. In order to combine pharmacokinetic estimates across studies, it is important that they be estimated in a similar manner. Thus, even though these differences are not large, the recalculated values (Tables III and IV) should be for the compilation of the pharmacokinetic data.

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Table II. Pharmacokinetic Parameters (Mean ± SD)									
Study No.	Route & Dosage Form	Dose (mmol/kg)	T _{1/2} (hr)	AUC μg Gd hr/mL	V _{0.5s} (mL/kg)	CL _T (mL/hr/kg)	CL _R (mL/hr/kg)	Urinary Excretion (% Dose)	Comments
489	IV Bolus OptiMARK (0.5 mmol/mL)	Normal Renal Function							
		0.1 (N=32)	1.74 ± 0.40	207 ± 55	163 ± 33	81 ± 17	65 ± 21	79.5 ± 16.5	CNS or Liver patients with normal renal function.
		0.3 (N=38)	1.94 ± 0.44	613 ± 156	176 ± 31	79 ± 16	64 ± 19	82.6 ± 18.1	Based on Gd only
		0.5 (N=33)	2.09 ± 0.62	1069 ± 300	189 ± 42	78 ± 17	66 ± 20	85.3 ± 16.1	
		Renally Impaired							
		0.1 (N=6)	8.89 ± 4.1	777 ± 328	240 ± 78	24 ± 11	19 ± 8.3	78 ± 11	CL _R values were estimated using cumulated amount of drug excreted 0-72 hour urine
		0.3 (N=4)	5.45 ± 3.4	1935 ± 839	171 ± 44	28 ± 12	24 ± 11	85 ± 11	
		0.5 (N=4)	6.44 ± 3.5	3392 ± 1722	213 ± 19	27 ± 10	23 ± 8	84 ± 5.5	
538	IV Bolus OptiMARK (0.5 mmol/mL)	Normal Renal Function							
		0.1 (N=32)	2.11 ± 0.62	1062 ± 378 (g GV hr/mL)	159 ± 29	69 ± 19 (n=32) 72 ± 16 (n=8)	65 ± 20 (n=32) 69 ± 15.4 (n=8)	95.8 ± 21.0	-CNS or Liver patients with normal control group (n=32) -Normal subjects N=8 - Data were based on gadoversetamide, intact complex.
		Renally Impaired							
		0.1 (N=22)	7.76 ± 4.5	3659 ± 1677 (g GV hr/mL)	183 ± 41	22 ± 9	20 ± 10	93.5 ± 11.9	

Table II. Pharmacokinetic Parameters (Mean ± SD)									
Study No.	Route & Dosage Form	Dose (mmol/kg)	T _{1/2} (hr)	AUC µg Gd hr/mL	V _{DSS} (mL/kg)	CL _T (mL/hr/kg)	CL _R (mL/hr/kg)	Urinary Excretion (% Dose)	Comments
543	IV Bolus OptiMARK (0.5 mmol/mL)	0.1 (N=8)	1.74 ± 0.37	N/A	N/A	N/A	93 ± 17 (mL/min) [CL ₀]	N/A	Hemodialysis patients Dialysis parameters
433	IV Bolus OptiMARK (0.5 mmol/mL)	0.1 (N=4)	1.38 ± 0.33	Please refer to Table IV	16.7 ± 3.6 (V _z) [L]	135 ± 24 (mL/min)	138 ± 24 (mL/min)	89.9 ± 4.2	Normal volunteers Based on Gd only
		0.7 (N=4)	1.26 ± 0.38	Please refer to Table IV	15.0 ± 1.9 (V _z) [L]	125 ± 26 (mL/min)	120 ± 23 (mL/min)	88.0 ± 11.3	% Dose thru 48 hr
1177-01 (Japan)	IV Bolus OptiMARK (0.5 mmol/mL)	0.05 (N=4)	1.28 ± 0.13	70.8 ± 7.0	197 ± 11	117 ± 11	110 ± 9 (mL/hr/kg)	96.3 ± 2.7	Normal volunteers Based on Gd only
		0.1 (N=4)	1.38 ± 0.14	141 ± 13	209 ± 14	116 ± 11	115 ± 12 (mL/hr/kg)	100.2 ± 2.4	% Dose thru 48 hr
		0.3 (N=4)	1.43 ± 0.13	454 ± 30	206 ± 27	108 ± 7	105 ± 10 (mL/hr/kg)	99.1 ± 1.0	
		0.5 (N=4)	1.53 ± 0.06	1071 ± 142	155 ± 23	77 ± 10	69 ± 4 (mL/hr/kg)	91.2 ± 10.5	

Table III. Recalculated Non-Compartmental PK Parameters - Study 1177-01 (Japan)						
Subject	Dose (mmol/kg)	k_{el} (1/hr)	$T_{1/2}$ (hr)	AUC (g Gd hr/mL)	CL_T (mL/hr/kg)	V_{dss} (mL/kg)
A	0.05	0.575	1.20	63.4	123.9	193.6
B	0.05	0.470	1.47	79.8	98.6	182.2
D	0.05	0.500	1.26	68.9	114.1	177.9
E	0.05	0.544	1.27	70.8	111.0	174.5
Mean	0.05	0.522	1.30	70.7	111.9	182.1
SD		0.046	0.12	6.8	10.4	8.3
A	0.1	0.437	1.59	162.0	97.0	183.7
C	0.1	0.551	1.26	132.0	119.1	182.4
D	0.1	0.455	1.52	136.1	115.5	208.2
E	0.1	0.468	1.48	137.4	114.4	210.0
Mean	0.1	0.478	1.46	141.9	111.5	196.1
SD		0.050	0.14	13.6	9.9	15.1
A	0.3	0.430	1.61	483.2	97.6	195.8
B	0.3	0.521	1.33	443.9	106.3	172.4
C	0.3	0.433	1.60	420.7	112.1	226.4
E	0.3	0.460	1.51	476.7	98.7	177.8
Mean	0.3	0.461	1.51	456	103.7	193.1
SD		0.042	0.13	29.2	6.8	24.3
B	0.5	0.429	1.62	1079	72.9	147.7
C	0.5	0.445	1.56	902.7	87.1	170.0
D	0.5	0.475	1.46	1051	74.8	139.1
E	0.5	0.451	1.54	1217	63.0	118.6
Mean	0.5	0.450	1.55	1062	74.5	143.9
SD		0.019	0.07	129	10	21.3

Table IV. Recalculated Non-compartmental PK Parameters - Study 433 (US)						
Subject	Dose (mmol/kg)	k_{el} (1/hr)	$T_{1/2}$ (hr)	AUC (g Gd hr/mL)	CL_T (mL/hr/kg)	V_{DSS} (mL/kg)
104	0.1	0.430	1.61	166.7	94.2	184.4
106	0.1	0.604	1.15	156.6	100.0	173.2
107	0.1	0.481	1.44	151.0	104.1	205.2
108	0.1	0.402	1.72	186.1	84.5	178.1
Mean	0.1	0.479	1.48	165	95.7	185.2
SD		0.089	0.25	15.4	8.5	14.1
122	0.7	0.426	1.63	1177	93.5	213.7
123	0.7	0.519	1.34	1108	99.3	184.5
125	0.7	0.478	1.45	934	117.8	215.2
126	0.7	0.438	1.58	1174	93.7	182.6
Mean	0.7	0.465	1.5	1098	101.1	199.0
SD		0.042	0.13	114	11	17.9

4-2. Distribution

The serum (or plasma) gadolinium vs. time profile following bolus administration of gadoversetamide appears to be qualitatively the same in all of the studies reported. A brief distribution phase appears to be complete in almost all subjects by 1 hour post-dose. (Please refer to the plasma concentration-time profile in the individual study review in the Appendix.)

The mean distribution half-life in normal subjects, calculated by the method of residuals in the twelve normal volunteers in Studies 489 and 538, is 0.22 ± 0.11 hr (13.3 ± 6.8 min). In the same twelve subjects, the mean volume of distribution (V_{DSS}) is 162 ± 25 mL/kg. The distribution half-life was not re-estimated in the non-compartmental re-analysis of the two earlier studies in normal subjects; the existing estimates in those studies are slightly shorter (<12 min), likely due to the different mode of calculation. No large difference in distribution rate, ascribable to disease states (or renal status) is noted in the patients.

Mean estimates of the volume of distribution at steady state (V_{DSS}) in normal renal function groups across all studies range from about 150 to 210 mL/kg. Dose level has no consistent effect on V_{DSS} in any of the studies. The effect of renal impairment on this parameter appears to be to increase the volume slightly, by about 20-60 mL/kg. This increase may be due to a higher body water content of renally-impaired patients, due to edema. This distribution volume (10-15 liters for a 70 kg person) is within the range of that reported (10-20 liters) for extracellular fluid.

Area under the serum concentration vs. time curve ($AUC_{0-\infty}$) appeared to increase with dose in all of the studies where multiple dose levels were examined. The Japanese Phase I study (1177-01), though not formally analyzed for proportionality, appears to be in fundamental agreement with this result based on $AUC_{0-\infty}$. In Study 433, the $AUC_{0-\infty}$ (based on the noncompartmental analysis) appears to be increased 6.65 times by a 7-fold increase of dose. The $AUC_{0-\infty}$ determined in Study 538 for gadoversetamide at the 0.1 mmol/kg dose (1062 ± 378) in the non-impaired group, is comparable with those based on total gadolinium. Using the molecular weight ratio (0.2376) to convert this $AUC_{0-\infty}$ to gadolinium equivalents (252 ± 90 μ g Gd hr/kg), agreement is observed with $AUC_{0-\infty}$ based on gadolinium at the same dose in Study 489 (207 ± 55 μ g Gd hr/kg).

In Study 489, a statistical analysis of $AUC_{0-\infty}$ demonstrated this parameter to be dose proportional in patients (with or without renal impairment) within the OptiMARK dose range of 0.1-0.5 mmol/kg. From the above observation, OptiMark kinetics seems to be linear over the dose range of 0.1 to 0.7 mmol/kg.

4-3. Elimination

The estimates of apparent terminal elimination half-life in normal subjects and renally-normal patients range from 1.48 ± 0.25 hr in the 0.1 mmol/kg dose group in Study 433 (and a similar range in Study 1177-01) to 2.09 ± 0.62 hr at the 0.5 mmol/kg dose in Study 489. In this latter study, there was a statistically significant dose effect on k_{el} (and therefore $t_{1/2}$) in the normal group only. The half-life of gadoversetamide (0.1 mmol/kg) in the non-renally impaired patients (including the normal subjects) in Study 538 was 2.11 ± 0.62 hr.

In order to arrive at the best estimates of elimination half-life for each of the different patient groups studied, estimates were derived from data pooled across studies. Table V presents a comparison of the population mean half-life estimates, which are calculated from 0.1 mmol/kg dose data (due to the small but statistically significant dose effect and the fact that this is the intended clinical dose). Data from Studies 433, 489 and 538, but not Study 1177-01 (considered supportive data only), was used in constructing these estimates.

Population	Elimination t (hours)	
	Men	Women
Normal Subjects	1.73 ± 0.31^a	1.73 ± 0.40^b
CNS/Liver Patients with normal renal function	1.90 ± 0.50^c	1.94 ± 0.57^d
Renally Impaired	8.74 ± 5.14^e	6.91 ± 2.46^f
Hepatically Impaired	2.09 ± 0.03^g	2.35 ± 1.09^h

^a N = 8 (4 from Study 433 and 4 Normal Subjects from Study 538)
^b N = 4 (4 Normal Subjects from Study 538)
^c N = 25 (15 CNS/Liver Patients from Study 489, 10 from Study 538; No Renal Impairment)
^d N = 31 (17 CNS/Liver Patients from Study 489, 14 from Study 538; No Renal Impairment)
^e N = 17 (17 Renal Impairment / With or Without Pathology from Studies 489 & 538)
^f N = 11 (11 Renal Impairment / With or Without Pathology from Studies 489 & 538)
^g N = 2 (489-F-011 and 538-E-001; No Renal Impairment)
^h N = 2 (489-F-019 and 538-E-005; No Renal Impairment)

Pooling the male and female half-life estimates for normal subjects from Studies 489 and 538 (twelve subjects) gives an overall terminal elimination half-life estimate of 1.73 ± 0.32 hr (103.6 \pm 19.5 min).

The data compiled in Table V demonstrate the lack of gender difference in gadoversetamide elimination in each of the patient/subject groups. The half-life is slightly longer in the Normal

Patients (which is comprised of an older group of individuals with an existing disease state, either CNS or liver) than the Normal Subjects. The effect of renal impairment is also evident, with the 3- to 4-fold increase in the half-life. Five patients were identified from Studies 489 and 538 who were Hepatically Impaired (489-F-011, 489-F-019, 538-E-001, 538-E-005 and 538-E-009). These five patients are a subset of the groups above, with the first four being Normal Patients, while 538-E-009 was Renally-Impaired also (and for this reason was excluded from the Hepatically-Impaired means). Hepatic impairment appears to have no effect on the disposition of gadoversetamide.

Total serum clearance of gadolinium was not dose related in study 489 in either the renally impaired patients or the normal group. Therefore, it seems that the pharmacokinetics of gadoversetamide are linear from doses of 0.1 to 0.7 mmol/kg. The estimates of serum/plasma clearance in normal subjects and in the CNS or liver patients with normal renal function were generally between 80 and 100 mL/hr/kg.

4-3-1. Metabolism

Following information and results supports no significant metabolism of OptiMARK:

- From preclinical data: The ^{153}Gd -labelled complex and ^{153}Gd methods were used to profile urine and serum samples for metabolites in preclinical studies. No detectable metabolites were observed.
- From the two Phase 1 studies (Studies 433 and 1177-01) : The selected serum and urine samples were analyzed using an ^{153}Gd method for intact gadoversetamide, as well as the ICP-AES method for total gadolinium. The results indicated that there were agreements between the concentrations of these two chemical species.
- From Study 538: Each plasma and urine sample collected in the definitive pharmacokinetic study (Study 538) was analyzed twice, with an ICP-AES method for total gadolinium and a ^{153}Gd method for the intact complex (gadoversetamide). Since a large number of samples were analyzed, a high level of confidence was obtained in the comparison of these two values.

If, in conjunction with a high recovery of the administered dose in urine as the intact complex, these two analytical values closely matched in a given sample, this would be considered that no significant metabolism of gadoversetamide had occurred. Indeed, in Study 538, the high recovery of the administered dose as intact complex (95.8%) in urine is described. The individual concentration values for the two methods in plasma and urine were in excellent agreement. The ratio of complex / total gadolinium data is shown in Table VI. The complex, within the error limits of the assays, accounts for all of the gadolinium. It is concluded from this data that no significant metabolism of gadoversetamide occurs in humans.

Table VI. Comparison of Mean Complex /Total Gd (MS/ICP) Ratio of Unknown Samples with that of Quality Control Samples

Matrix	Mean \pm SD: MS/ICP Ratio	
	QC	Study Samples
Plasma	1.07 \pm 0.12 (N = 203)	1.13 \pm 0.12 (N = 652)
Urine	1.05 \pm 0.14 (N = 154)	1.07 \pm 0.20 (N = 328)

4-3-2. Urinary Excretion

The preclinical studies conducted with OptiMARK suggested that it should be excreted entirely in the urine. Other gadolinium chelates, similar to gadoversetamide, are eliminated completely in urine and essentially at the glomerular filtration rate in man.

For this reason, the applicant collected only urine in these clinical studies to examine gadoversetamide excretion. The recovery of the administered doses varies from study to study. The Japanese Phase 1 study (Study 1177-01) provided a quantitative recovery of the dose within 48 hours. Study 489 fails to account for about 20 % of the dose overall; the applicant stated that this is believed to be due to a lack of emphasis on strict adherence to urine collection, since this was not primarily a pharmacokinetic study. The other data from Study 538, and Study MP1177-01 showed almost complete excretion of the injected dose through renal route.

The best available recovery data in humans is regarded as that obtained in Study 538, where the overall (0-72 hr) urinary recovery of the dose (measured as intact complex) was 95.8 ± 21.0 % in the normal renal function patients / subjects and 93.5 ± 11.9 % in the renally-impaired patients. The overall mean total recovery of gadoversetamide in normal male and female subjects is calculated to be 95.5 ± 17.4 % of dose (N = 12, Studies 489 and 538).

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

For the eight normal subjects in Study 538, the mean renal and total (plasma) clearances were 69 ± 15.4 and 72 ± 16.3 mL/hr/kg, respectively. It is important to note that preclinical studies with inorganic gadolinium have demonstrated that it has a very low clearance and is highly retained in tissues. For example, in mice at a dose of 0.1 mmol/kg of $^{153}\text{GdCl}_3$, about 60% of the dose remained in the body at 21 days. Thus, the high recoveries in urine again support the non-significant dechelation of gadolinium from gadoversetamide.

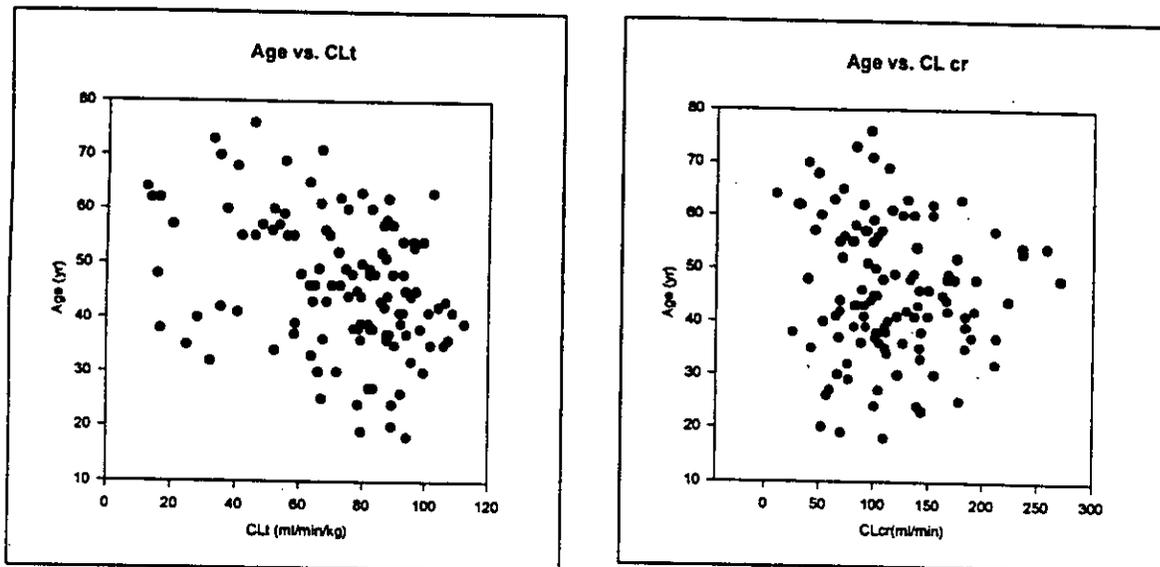
4-4. Special Population

4-4-1. Gender and Age Effect

The effects of gender and age on pharmacokinetic parameters and urinary recovery were obtained in Study 489. The results indicated that neither was determined to affect pharmacokinetics or recovery.

In Study 538 the number of patients in each pathology/renal status group were too small to analyze, so the effect of gender and age were not re-examined. The statistical analysis instead focused on pathology and renal status.

The following figures show that there is no age effect on the clearance of OptiMARK.



4-4-2. Hepatic and CNS Disease (Target Populations)

In the Study No. 489 and 538, the pharmacokinetic parameters and the urinary recovery data were examined for differences related to disease category. No significant effects of hepatic and CNS disease on the pharmacokinetics were noted in either study. Since neither of these disease states significantly affect glomerular filtration, it is expected that the above disease does not affect the elimination of OptiMARK.

4-4-3. Renal Impairment

The level of renal impairment of the patients enrolled in Studies 489 and 538 had a statistically significant impact on exposure, as measured by $AUC_{0-\infty}$. At each dose level examined, $AUC_{0-\infty}$ was increased 3- to 4-fold in the impaired group vs. the normal renal function comparators. In both studies impaired patients were rated as "moderate to severe", on the basis of pre-dose serum creatinine concentrations $> 1.5 \times$ upper limit of normal. Systemic drug clearance was reduced in most impaired patients in both studies to 20-30 mL/hr/kg. The apparent elimination half-lives ranged from means of 5.5 to 8.9 hours, in the renally-impaired groups in the two studies. These 3- to 4-fold changes in clearance and half-life are consistent with the differences in $AUC_{0-\infty}$. In Study 538, a good correlation was observed between total and renal clearance of gadoversetamide. The excretion rates of gadoversetamide are related to the degree of renal impairment. However, by 72 hours post-dose the overall recovery of gadoversetamide (or gadolinium) does not differ by renal status. Thus, renal impairment affects the rate of gadoversetamide excretion, but not the extent. It seems that the injected OptiMARK seems to be eliminated through the renal route even in the renally impaired patients.

4-4-4. Hemodialysis

The safety and dialysis clearance of OptiMARK was studied in eight stable patients maintained on extracorporeal hemodialysis in Study 543. The mean dialysis clearance of gadoversetamide, estimated from the recovery rate in dialysate, was 93.2 ± 17.1 mL/min, or 48% of the creatinine clearance (194 ± 18.6 mL/min). At the end of the 5-day period (encompassing three dialysis sessions) approximately 98% of the drug had been cleared from the circulation based on plasma concentrations, with about 70% recovered in the dialysis fluid. The difference between these numbers is attributed to a small residual renal clearance in the patients, which could be observed as a decline in plasma concentrations during the inter-dialytic periods. No effect of blood flow in the range of 400-600 mL/min on clearance was noted. The mean dialysis half-life of gadoversetamide was 1.74 ± 0.37 hours.

4-5. PROTEIN BINDING

The plasma protein binding of OptiMARK was studied in human, dog, and rat plasma *in vitro*. The concentration was 0.33 and 3.33 mM. It should be noted that these concentration range includes the clinically related concentrations (Please refer to the plasma concentration vs time graphs in the individual study review).

Plasma obtained in three species was incubated with OptiMark radiolabeled with Gd -153 for 30 minutes. Subsequently, an ultrafiltration technique was used to separate the bound and unbound fractions. The percent bound was calculated as the ratio of the radioactive counts in the ultrafiltrate (unbound) to the total amount of radioactive present in the sample.

The result showed that OptiMARK does not bind to plasma proteins in either human, dog or rat at concentration of 0.33 and 3.33 mM. The result in human plasma was $0.34 \% \pm 2.55 \%$ (n=2).

In addition to the *in vivo* serum protein binding data from the Japanese study, Study No. MP 1177/01, indicates no protein binding (approximately +/- 2 %) in the serum samples at 15 min and 2 hour post injection.

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5. OVERALL COMMENTS

The applicant submitted the appropriate information and supportive results to adequately describe the pharmacokinetics and disposition of OptiMARK (Gadoversetamide Injection) in normal human subjects, in patients with CNS or liver pathology, and also in selected special populations.

In all groups, OptiMARK was observed to distribute rapidly into the extracellular fluid volume following an intravenous bolus dose. The pharmacokinetics and elimination of OptiMARK are not affected by gender, age or disease state (CNS or liver); this evaluation included a limited number of patients who were judged to be hepatically impaired.

OptiMARK is completely eliminated into the urine as the intact complex and not metabolized in humans. The mean terminal elimination half-life in normal subjects was 1.73 hr. The pharmacokinetics of OptiMARK appear to be linear within the dose range (0.1 - 0.7 mmol/kg) studied. Renal impairment decreases the rate, but not the extent, of OptiMARK excretion. OptiMARK can be efficiently removed from the circulation by extracorporeal hemodialysis.

6. LABELING COMMENTS

The labeling Comments will be covered under a separate review.

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APPENDIX

APPENDIX 1. Summary of Individual Studies

Appendix 1-1. Study No. 433

The Applicant's Summary:

Title: Double-Blind Study to Assess the Dose-Related Safety, Tolerance and Pharmacokinetics of MP-1177/10 Injection in Normal Healthy Male Volunteers
OBJECTIVES: To assess the dose-related safety, tolerance and pharmacokinetics of MP-1177/10 injection in normal healthy male volunteers.
METHODOLOGY: This was a single center, multidose, double-blind, placebo-controlled study of four ascending dose levels of OptiMARK (MP1177/10 Injection) in 20 normal, healthy adult male volunteers. The volunteers were evenly divided into five dosing groups: OptiMARK; 0.1 mmol/kg, 0.3 mmol/k, 0.5 mmol/kg, 0.7 mmol/kg; or placebo (normal saline). Each volunteer received a single dose of OptiMARK or placebo. All volunteers were confined to the research facility from 36 hours prior to the study drug injection to 72 hours following administration. Volunteers returned at 7 days (\pm 24 hours) for further assessment.
NUMBER OF PATIENTS: 20 enrolled, 20 received study drug
DIAGNOSIS/INCLUSION CRITERIA: Healthy adult male volunteers, between the ages of 18 and 45 years of age (inclusive) were eligible for enrollment in this study. Each subject's weight was to be within 15% of his ideal body weight. Volunteers were to be in good health based upon results of medical history, physical examination, clinical laboratory results (including chemistry, hematology, urinalysis, hepatitis B, HIV, urine drug screen and spermatozoa counts) and electrocardiogram (ECG) performed within two weeks prior to dosing. Volunteers must have been willing to be confined to the research facility from 36 hours prior to the study drug injection to 72 hours following administration and to return to the facility at 7 days (\pm 24 hours) for further assessment.
DOSE/ROUTE: A single intravenous dose of OptiMARK; 0.1 mmol/kg, 0.3 mmol/k, 0.5 mmol/kg, 0.7 mmol/kg; or placebo (normal saline) was injected at a rate of 1.0 ml/kg/min.
DURATION OF TREATMENT: Each patient received a single dose of OptiMARK and was monitored for 7 days.
CRITERIA FOR EVALUATION: Safety: Safety was monitored in terms of pre- and post- dose vital signs, physical examination, ECG, and clinical laboratory measurements. Tolerance was assessed through the grading of heat, cold and pain at the injection site. Volunteers were closely observed for adverse events for 72 hours following dosing and adverse event information was for 7 days. Pharmacokinetics: Pharmacokinetic and elimination parameters for volunteers receiving 0.1 mmol/kg and 0.7 mmol/kg doses of OptiMARK were assessed through analysis of serum and urine samples for gadolinium content. Analysis of serum and urine samples for potential metabolites was also performed.
STATISTICAL METHODS: Descriptive methods were used to evaluate data due to the sample size of each group. Quantitative data were summarized using sample number, mean, standard deviation, minimum, median and maximum values. Categorical variables were summarized using sample number and percent. Change from baseline was analyzed descriptively for apparent differences between treatment groups. Descriptive comparisons of frequencies of clinically significant changes from baseline, and drug relationship were performed by treatment group.

Title: Double-Blind Study to Assess the Dose-Related Safety, Tolerance and Pharmacokinetics of MP-1177/10 Injection in Normal Healthy Male Volunteers

SUMMARY - CONCLUSIONS:

Safety Results:

Four groups of 4 patients received single doses of OptiMARK (0.1, 0.3, 0.5 or 0.7 mmol/kg) and one group of 4 patients received placebo. Results of the study showed no clinically significant changes in physical examination, ECG, vital signs, standard hematological, serum chemistry, urinalysis, special kidney function or male reproductive system function.

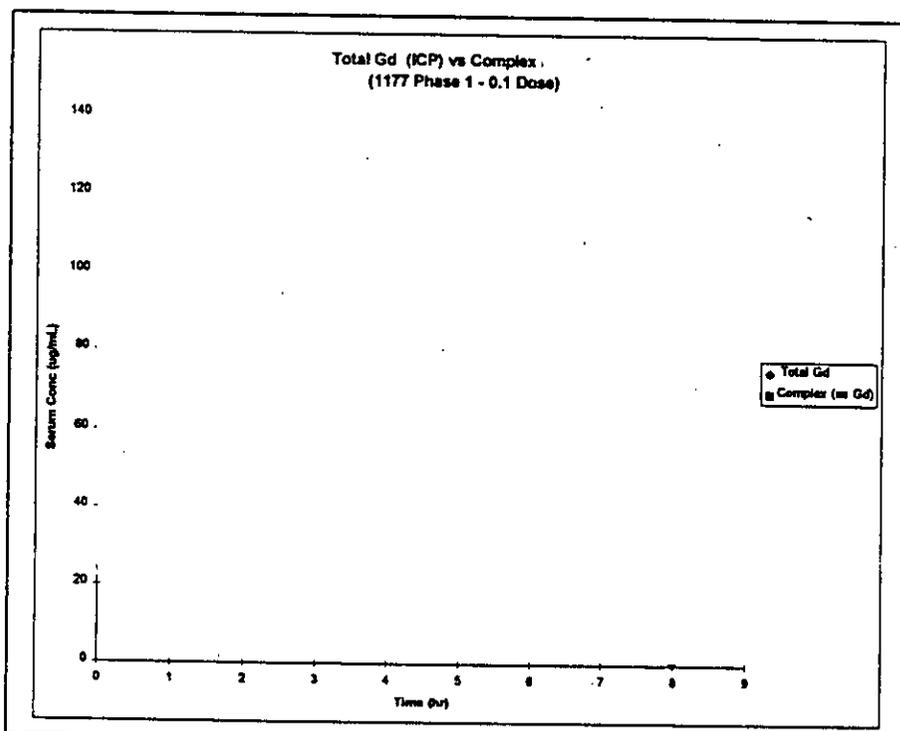
Five subjects (4 OptiMARK and 1 placebo) reported vasodilatation after injection. The incidence of vasodilatation appeared to be dose dependent, as it was reported by 3 of 4 subjects at the 0.7 mmol/kg dose level. Instances of vasodilatation, taste perversion, parosmia, paresthesia, headache and dizziness were considered related to treatment administration. No serious adverse events or severe adverse events were reported. A small number of subjects experienced mild or moderate heat, cold and pain during injection. There were no reports of severe heat, cold and pain during injection. Serum iron results appeared to increase in dose-dependent fashion within 4 to 8 hours after injection at the 0.3 mmol/kg dose level and higher, however, the increases may have been superimposed upon a diurnal effect of low and inconclusive magnitude.

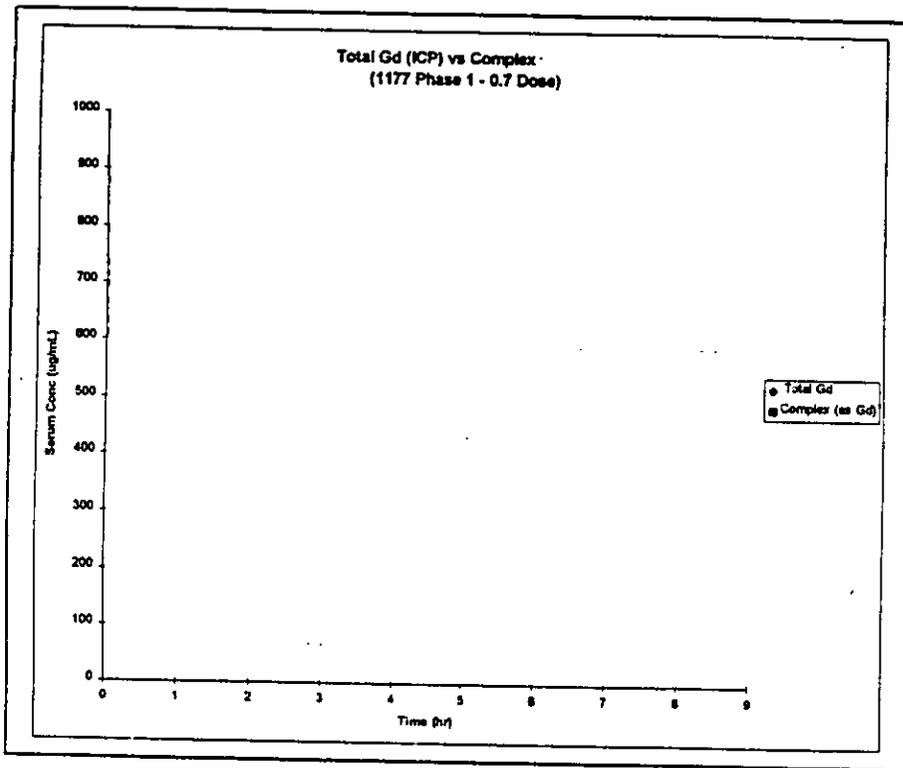
Pharmacokinetic Results:

Elimination half-life (80 minutes) and volume of distribution (21% of body weight) results for 0.1 and 0.7 mmol/kg dose levels were consistent with the pharmacokinetic profile of an extracellular contrast agent, which is eliminated by glomerular filtration into urine. Seventy-five percent and 90% of the injected dose was recovered in the urine at 4 and 24 hours post-injection, respectively. Renal and total serum clearance results indicated that the route of elimination was via the kidneys. There did not appear to be any dose-related alteration in biologic handling of the drug. Chromatographs of serum and urine demonstrated that essentially all of the gadolinium was present in the form of the parent drug.

Conclusion:

OptiMARK appeared to be safe and well tolerated by healthy adult males at single intravenous dose levels of 0.1, 0.3, 0.5 and 0.7 mmol/kg dose levels.





Reviewer's Comment:

Study 433 was a placebo controlled, double-blind, ascending-dose Phase 1 study in 20 healthy male volunteers. The subjects were divided into four dose groups, each consisting of five individuals, with four subjects receiving OptiMARK (Gadoversetamide Injection) and one subject receiving placebo. Each of the four dose groups received one dose level of OptiMARK in ascending order as an IV bolus dose. The dose levels of OptiMARK were 0.1, 0.3, 0.5 and 0.7 mmol/kg.

Serum samples for pharmacokinetics were collected pre-injection, at 3, 5, 10, 15 and 30 minutes, and 1, 1.5, 2, 4, 8, 24 and 48 hours following injection. Complete urine collection as serial pools continued throughout the 72-hour study period. Urine was pooled within collection intervals ending at 0, 1, 2, 4, 8, 12, 24, 36, 48, 60 and 72 hours post-dose. The samples were analyzed using validated ICP-AES methods to determine total gadolinium in each fluid. The resulting serum concentrations were used to estimate pharmacokinetic parameters for gadolinium. The urine concentrations, together with the total collection period volumes were used to estimate total recovery (%) of the gadolinium dose. These estimates are presented only for the lowest (0.1 mmol/kg) and highest (0.7 mmol/kg) doses. Selected serum (5 and 30 minutes and 1, 2, 4, 8, and 24 hours) and urine samples (all pools from 0 to 24 hours) were also analyzed for intact gadoversetamide complex using a

validated method. This intact complex data are presented for comparison with corresponding gadolinium concentrations.

The serum gadolinium data were fit to an open two-compartment model for six of the eight subjects, with the remaining two subjects (one at the low dose and one at the high dose) more closely fitting a one-compartment model. The mean apparent terminal elimination half-lives were 1.38 ± 0.33 hr and 1.26 ± 0.38 hr at the 0.1 and 0.7 mmol/kg doses, respectively, while the corresponding mean total clearances were 135 ± 24 and 125 ± 26 mL/min. These clearances do not differ from the mean renal clearances for subjects in the same groups (138 ± 24 and 120 ± 33 mL/min, respectively). The mean overall (0-72 hr) urinary recovery as percent of dose was 89.9 ± 4.2 % and 88.0 ± 11.3 % in the two dose groups, respectively.

The mean $AUC_{0-\infty}$ increased from 165 ± 15.4 μ g Gd hr/mL at the 0.1 mmol/kg dose to 1098 ± 114 μ g Gd hr/mL at the 0.7 mmol/kg dose, or an increase of 6.65-fold for a 7-fold increase in dose (based on noncompartmental parameters, Table IV).

A comparison of gadolinium and gadoversetamide complex concentrations in both urine and serum presents considerable scatter in the values, however, most subjects show considerable agreement in the concentrations of gadolinium and gadoversetamide.

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Appendix 1-2. Study No. MP1177/01 (Japan)

The Applicant's Summary:

TITLE: A Double-Blind Study to Assess the Dose-Related Safety, Tolerance and Pharmacokinetics of MP-1177/10 Injection in Normal Healthy Male Volunteers
OBJECTIVES: To assess the dose-related safety, tolerance and pharmacokinetics of MP1177/10 injection in healthy male volunteers.
METHODOLOGY: This was a single center, multidose, double-blind, placebo-controlled study of four ascending dose levels of OptiMARK (MP1177/10 Injection) in 20 normal, healthy adult male volunteers. The volunteers were evenly divided into four dosing groups: OptiMARK; 0.05 mmol/kg, 0.1 mmol/kg, 0.3 mmol/k and 0.5 mmol/kg. One volunteer in each dosing group received placebo (normal saline). Each volunteer received a single dose of OptiMARK or placebo. Volunteers were followed for 7 days.
NUMBER OF PATIENTS: 20 enrolled, 20 received study drug
DIAGNOSIS/INCLUSION CRITERIA: Healthy adult male volunteers, between the ages of 20 and 40 years of age were eligible for enrollment in this study. Volunteers were to be in good health based upon results of medical history, physical examination, clinical laboratory results, chest x-ray and electrocardiogram (ECG).
DOSE/ROUTE/REGIMEN/LOT NUMBER: A single intravenous dose of OptiMARK; 0.05 mmol/kg, 0.1 mmol/kg, 0.3 mmol/kg, 0.5 mmol/kg; or placebo (normal saline) was injected at a rate of 20 ml/min. OptiMARK, Lot Number J9307PRE, was used for this study.
DURATION OF TREATMENT: Each patient received a single dose of OptiMARK or placebo and was monitored for 7 days.
CRITERIA FOR EVALUATION: Safety: Safety was monitored in terms of pre- and post- dose vital signs, physical examination, ECG, and clinical laboratory measurements. Tolerance was assessed through the grading of heat, cold and pain at the injection site. Volunteers were closely observed for adverse events the day of dosing and physical exam, vital signs, ECG and clinical labs were evaluated at 24 and 48 hours following dosing. Vital signs and clinical laboratory values were also evaluated at 7 days post dosing. Pharmacokinetics: Pharmacokinetic and elimination parameters for volunteers were assessed through analysis of serum and urine samples for gadolinium content. Analysis of serum and urine samples for potential metabolites was also performed.
STATISTICAL METHODS: Vital signs and clinical test values were analyzed using ANOVA. Quantitative data were summarized using sample number, mean and standard deviation. Categorical variables were summarized using N and percent. Change from baseline was analyzed for differences between treatment groups.
SUMMARY - CONCLUSIONS: Safety Results: Four groups of 4 volunteers received single doses of OptiMARK (0.05, 0.1, 0.3, or 0.5 mmol/kg) and one volunteer in each group received placebo. Results of the study showed no clinically significant changes in physical examination, standard hematological, serum chemistry or urinalysis values. For the 0.5 mmol/kg dose, diastolic blood pressure was statistically

TITLE: A Double-Blind Study to Assess the Dose-Related Safety, Tolerance and Pharmacokinetics of MP-1177/10 Injection in Normal Healthy Male Volunteers

significantly higher at 24 hours post-dosing than the value with placebo. However, the difference was 11.8 mmHg so the statistical difference was thought to likely represent a random chance difference. There were no other conclusive or clinically significant effects for any other vital sign measurements at any dose level. Sinus bradycardia was sometimes observed in 11 of 20 volunteers. However, since all volunteers were young and healthy, this was not considered to be an abnormal finding.

No adverse events were reported. No tolerance symptoms were reported.

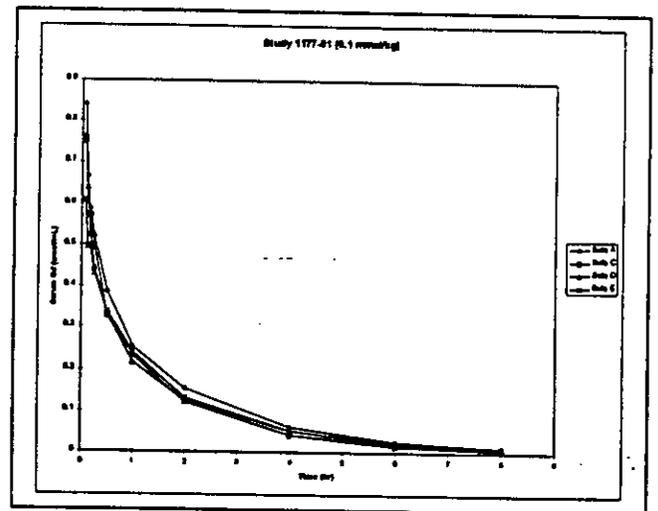
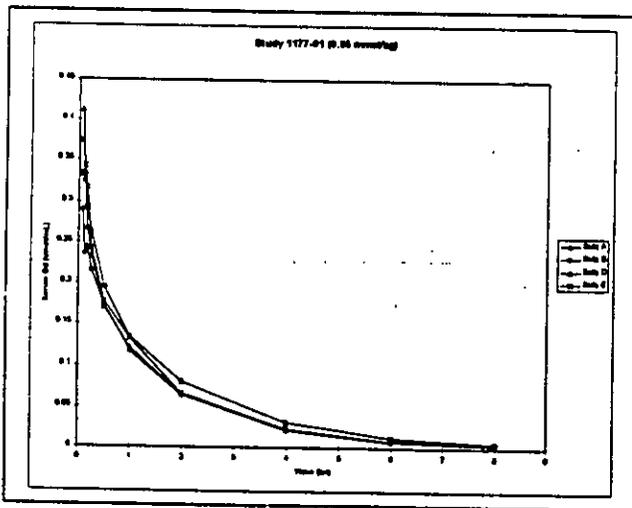
Pharmacokinetic Results:

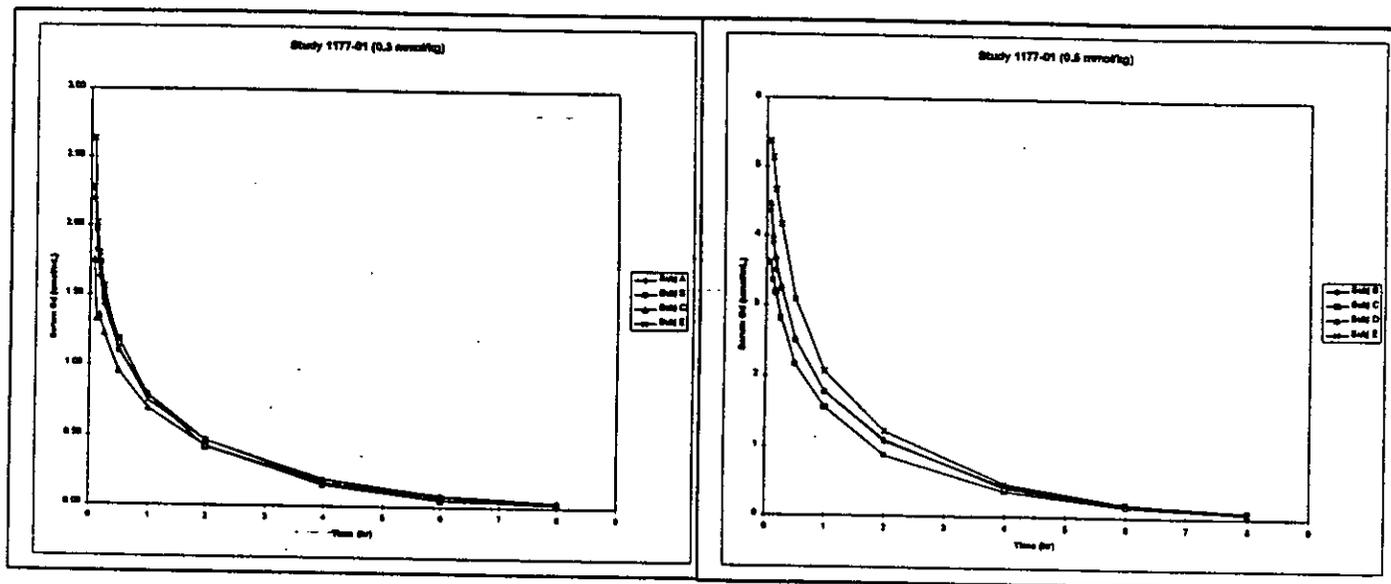
Elimination half-life (77 to 92 minutes) and volume of distribution (16 to 21% of body weight) results for all dose levels were consistent with the pharmacokinetic profile of an extracellular contrast agent, which is eliminated by glomerular filtration into urine. Seventy-eight percent and 91 to 100% of the injected dose was recovered in the urine at 4 and 24 hours post-injection, respectively. Renal and total serum clearance results indicated that the route of elimination was via the kidneys. There did not appear to be any dose-related alteration in biologic handling of the drug. Chromatographs of serum and urine demonstrated that essentially all of the gadolinium was present in the form of the parent drug.

Conclusion:

OptiMARK appeared to be safe and well tolerated by healthy adult males at single intravenous dose levels of 0.05, 0.1, 0.3, 0.5 mmol/kg.

Reviewer's Comment:





Study MP 1177-01 was a placebo controlled, double-blind, ascending dose Phase 1 study in 20 healthy male volunteers, conducted in Japan according to a design very similar to Study No. 433. The subjects were divided into four dose groups, each consisting of five individuals, with four subjects receiving OptiMARK (Gadoversetamide Injection) and one subject receiving placebo. Each of the four dose groups received one dose level of OptiMARK in ascending order as an IV bolus dose. The dose levels of OptiMARK were 0.05, 0.1, 0.3 and 0.5 mmol/kg.

Serum samples for pharmacokinetics were collected pre-injection, at 4, 7, 10, 15 and 30 minutes, and 1, 2, 4, 6, 8 and 24 hours following injection. Serial urine samples were pooled within intervals from pre-dose through 48 hours. The intervals ended at 0, 2, 4, 8, 12, 24, and 48 hours post-dose. The samples were analyzed using validated methods to determine total gadolinium in each fluid. The resulting serum concentrations were used to estimate pharmacokinetic parameters for gadolinium. The urine concentrations, together with the total collection period volumes, were used to estimate total recovery (%) of the dose. Selected serum (0, 10 and 30 min and 2, 4, 8, and 24 hours) and urine samples (all pools from 0 to 24 hours) were also analyzed for intact gadoversetamide complex using a validated HPLC method. The intact complex data are presented for comparison with corresponding gadolinium concentrations. The concentration of gadolinium in serum samples taken at selected times (15 min and 2 hr), were compared before and after ultrafiltration, to assess the fraction bound to serum proteins. The serum gadolinium data were fit to an open two-compartment model for all 16 subjects. The mean distribution half-lives at the four dose levels did not display any obvious dose-related differences, and ranged from 6.4 min at 0.3 mmol/kg to 12.3 min at 0.5 mmol/kg. The mean apparent terminal elimination half-life of gadolinium increased slightly at each higher dose, from 1.28 ± 0.13 hr at 0.05 mmol/kg to 1.53 ± 0.06 hr at 0.5 mmol/kg. The corresponding total clearances decreased from 117 ± 11 mL/hr/kg to 77 ± 10 mL/hr/kg over the same dose range. The total and renal clearances of gadolinium were not significantly different in any dose group. The mean volume of distribution at steady-state did not vary with dose, and ranged from 155 to 209 mL/kg in these subjects. The mean overall (0-48 hr) urinary recovery of gadolinium as a percent of dose in the 15 evaluable subjects (complete collection was not achieved in one subject at 0.3 mmol/kg) was 96.5 ± 6.3 %. Recovery did not differ as a function of dose level. Over 78 % of the

injected dose was recovered in the urine by 4 hours after injection in these normal subjects, and 77 - 103 % of the injected dose was recovered by 24 hours post-dose.

The mean concentrations of gadolinium and gadoversetamide in serum are virtually identical, with gadoversetamide accounting for 95.5%, 99.9% and 95.4% of the total gadolinium at the first three time points examined (10 min, 30 min and 2 hr) at all doses, suggesting that almost all of the gadolinium is present in the form of gadoversetamide. The serum protein binding of gadoversetamide (quantitated as gadolinium) was measured at 15 min and 2 hours post-dose. No binding of gadoversetamide to serum proteins was detected in vivo.

Transient decreases in endogenous serum zinc concentrations (but not iron and copper) were seen 2 and 8 hours post-dose, which returned to normal by 24 hours. Also, a significantly increased urinary excretion of all three metals was observed in the 0-24 hour urine, at all doses for zinc and only at the highest two doses for iron and copper. This suggests the affinity of the free ligand in the formulation is highest for zinc.

**APPEARS THIS WAY
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Appendix 1-3. Study No. 489

Title: A Study to Evaluate the Pharmacology of OptiMARK (Gadoversetamide Injection) in Patients with Central Nervous System or Liver Pathology
OBJECTIVES: To evaluate the dose-related effects of intravenously administered OptiMARK as an MRI contrast agent in patients with existing CNS or liver pathology, utilizing doses of 0.1 mmol/kg, 0.3 mmol/kg, or 0.5 mmol/kg. The primary objective is to evaluate the pharmacological dose-related effects on vital signs, electrocardiograms, and clinical laboratory measurements. Secondary objectives include determination of the safety and tolerability profiles of OptiMARK.
METHODOLOGY: This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, study designed to evaluate the dose related effects of OptiMARK in patients with existing CNS or liver pathology with or without renal insufficiency. A total of 201 potential subjects were enrolled at 10 study centers. Of these patients, 171 were randomized using two stratifications, the presence or absence of renal insufficiency and for renally sufficient patients, pathology (CNS or liver). Of the patients who were randomized, 163 subjects received one of the following doses: 0.1 mmol/kg, 0.3 mmol/k, 0.5 mmol/kg or placebo. Pharmacodynamic dose-related effects, safety, and tolerability were assessed pre- and post-dose, and for up to 7 days following administration of OptiMARK or placebo.
NUMBER OF PATIENTS: 201 enrolled; 163 evaluable
DIAGNOSIS/INCLUSION CRITERIA: Males or females at least 2 years of age who had central nervous system or liver pathology, with or without renal insufficiency, for which a contrast-enhanced MRI was indicated. Patients were willing to be housed within the Investigational facility for a minimum of 48 hours after dosing.
DOSE/ROUTE: A single intravenous dose of 0.1 mmol/kg OptiMARK, 0.3 mmol/kg OptiMARK, or 0.5 mmol/kg OptiMARK, or placebo (normal saline) was administered at a rate of 1 - 2 mL per second, followed by a saline flush.
DURATION OF TREATMENT: Each patient was monitored for 7 days after study drug administration.
CRITERIA FOR EVALUATION: Pharmacodynamic: Dose-related effects on vital signs, electrocardiograms, and clinical laboratory measurements were evaluated. Pharmacokinetic: The pharmacokinetics and urinary excretion of OptiMARK were characterized in these patients through analysis of serum and urine samples for total gadolinium (ICP-AES). Safety: Safety was monitored in terms of pre- and post-dose vital signs, physical examinations, electrocardiograms, and clinical laboratory measurements. Tolerance was assessed through the patient's grading of heat, cold, and/or occurrence of pain at the injection site. Adverse events were recorded throughout the study.
STATISTICAL METHODS: Continuous variables were summarized using sample number, mean, standard deviation, minimum, and maximum. Categorical variables were summarized using N and percent. Change from baseline was analyzed using the t-test, and incidence parameters by the chi-square statistic.
SUMMARY: One hundred sixty-three patients received a study treatment: 121 patients received OptiMARK (0.1, 0.3 or 0.5 mmol/kg) and 42 patients received placebo. OptiMARK was well tolerated at

Title: A Study to Evaluate the Pharmacology of OptiMARK (Gadoversetamide Injection) in Patients with Central Nervous System or Liver Pathology

the doses studied within this study with no deaths or patients discontinued study participation due to an adverse event. One serious adverse event (meningitis) was reported in the 0.3 mmol/kg OptiMARK dose group and was considered by the investigator not to be related to study drug but due to concurrent viral syndrome.

One hundred nine of the 163 patients (66.9%) who received either OptiMARK (any dose) or placebo reported a total of 330 adverse events. Eighty-eight of the 121 patients (72.7%) who received OptiMARK experienced 250 events; 26 patients in the 0.1 mmol/kg group reported 74 events, 29 patients in the 0.3 mmol/kg group reported 81 events and 33 patients in the 0.5 mmol/kg group reported 95 events. Twenty-one placebo patients (50%) reported a total of 80 adverse events. The majority of adverse events in the OptiMARK groups were mild in intensity and similar in profile to adverse events reported for the placebo group. The most frequently reported adverse events were headache, vasodilation, dizziness, taste perversion, nausea, asthenia, and dyspepsia.

A dose-related increase in the frequency of adverse events was demonstrated in patients receiving OptiMARK. There were no statistically significant differences between treatment groups with respect to adverse event intensity or demographic characteristics. There were no unexpected changes in laboratory parameters, vital signs, ECGs, physical examinations, or tolerance measurements. In both OptiMARK and placebo treatment groups, transitory asymptomatic changes in phosphorus, TIBC, total protein, and zinc were observed. No clear dose- or time-related trend was observed.

The pharmacokinetic determinations in this study demonstrate that for gadoversetamide administered to subjects with normal or impaired renal function, the $AUC_{0-\infty}$ is dose proportional, and the $t_{1/2}$, CL_T , and V_{DSS} are dose independent. In patients with normal renal function who also have CNS or liver disease, neither sex, age nor differing pathology had an effect on the kinetics or elimination of gadoversetamide (measured as gadolinium). The pharmacokinetics of gadoversetamide (measured as gadolinium) in subjects with renal impairment are dependent on the degree of impairment; with increasing severity resulting in an increase in the $AUC_{0-\infty}$, a prolongation in the $t_{1/2}$, a decrease in the CL_T , and a slight increase in the V_{DSS} . The data were insufficient to estimate renal clearance of gadolinium, but total serum clearance of gadolinium and baseline creatinine clearance were demonstrated to be linearly related for the renally impaired patients. The exposure of the patients with moderate to severe renal impairment in this study was increased about 2-4 fold (based on $AUC_{0-\infty}$) compared with liver or CNS patients without renal disease.

Conclusion:

Administration of OptiMARK in single doses of 0.1, 0.3, and 0.5 mmol/kg to patients with CNS or liver pathology, with or without renal insufficiency did not result in clinically significant or unexpected changes from baseline in laboratory values, physical exams or ECGs. Additionally, consistent dose-related changes in vital signs were not observed. In patients with CNS or liver pathology, combined with renal insufficiency, the elimination half life OptiMARK is prolonged and the exposure time is increased.

OptiMARK is safe and well tolerated. The degree of renal impairment prolongs the elimination half life of OptiMARK resulting in increased exposure to the drug.

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, study designed to evaluate the dose related effects of OptiMARK (Gadoversetamide Injection) in patients with existing CNS or liver pathology, with or without renal insufficiency. The 163 patients

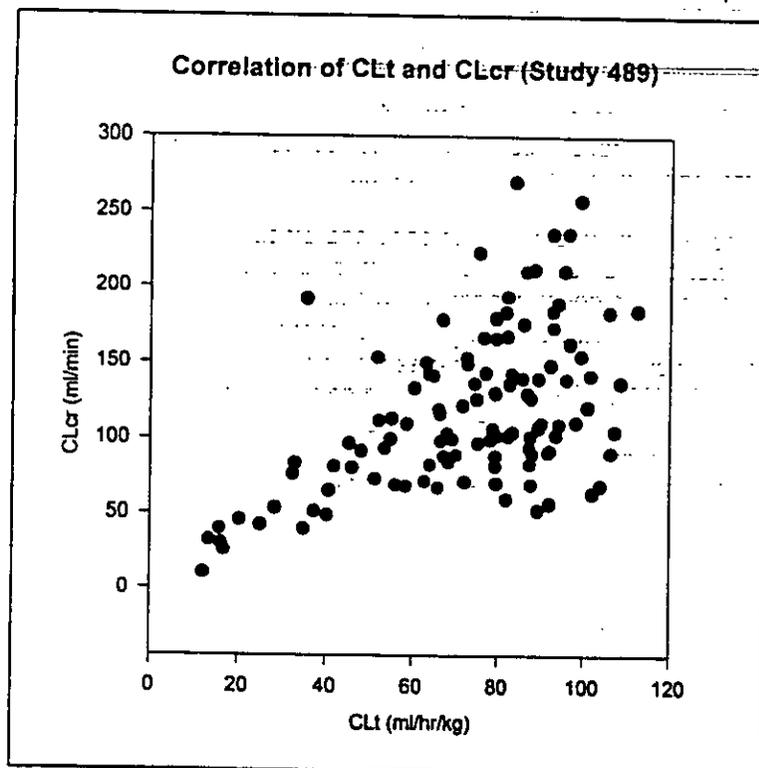
enrolled were randomized to receive one of the following doses: 0.1 mmol/kg (N = 40), 0.3 mmol/kg (N = 42), 0.5 mmol/kg (N = 39) or placebo (N = 42). Pharmacodynamic dose-related effects, safety, and tolerability were assessed pre- and post-dose, and for up to 7 days following administration of OptiMARK. Males or females at least 2 years of age who had central nervous system or liver pathology, with or without renal insufficiency, for which a contrast-enhanced MRI was indicated, were eligible. Patients must have been willing to be housed within the investigational facility for a minimum of 48 hours following dosing.

A single intravenous dose of OptiMARK or placebo at one of the dose levels was administered at a rate of 1 - 2 mL per second, followed by a saline flush. Serum samples for pharmacokinetics were collected pre-injection and at 1, 4, 8, 16, 24, 48, 72 and 168 hours following injection. It should be noted that the expected serum distribution phase of gadolinium (ending at about 1 hr) is not captured by this sampling schedule. Serial urine samples were pooled within intervals from pre-dose through 72 hours. The intervals ended at 0, 1, 4, 8, 16, 24, 48 and 72 hours post-dose. Serum and urine concentrations of gadolinium were determined using validated inductively-coupled plasma - mass spectrometry (ICP-MS) assays. Non-compartmental pharmacokinetic parameters were calculated from this data.

The $AUC_{0-\infty}$ was found to be proportional to dose, regardless of the level of renal function. There was no effect of dose on total clearance, but a statistically significant increase in $t_{1/2}$ was seen as dose increased, but this magnitude of increase (from a mean of 1.74 at 0.1 mmol/kg to a mean 2.09 hours at 0.5 mmol/kg) is of no pharmacokinetic significance. The effect of dose on volume of distribution was likewise statistically significant in the non-impaired group only.

The mean recovery of the dose was slightly more than 80% in all dose groups, with an individual range from 32 to 132 %. The lack of strict accountability for the dose in urine is ascribed to incomplete urine collection. The cumulative percentage of gadolinium excreted by 24 hours and 72 hours post-dose was independent of the dose and was not affected by either the renal status or the pathology type of the subjects

The total serum clearance of gadolinium and baseline creatinine clearance were demonstrated to be linearly related for the renally impaired patients. (Please refer to the following graph). The exposure of the patients with moderate to severe renal impairment in this study was increased about 2-4 fold (based on $AUC_{0-\infty}$) compared with CNS or liver patients without renal disease.



The pharmacokinetic determinations in this study demonstrate that for gadoversetamide administered to subjects / patients with normal or impaired renal function, the $AUC_{0-\infty}$ is dose proportional, and the $t_{1/2}$, CL_T , and V_{DSS} are dose independent. In patients with normal renal function who also have CNS or liver disease, neither sex, age nor differing pathology had an effect on the kinetics or elimination of gadoversetamide. The pharmacokinetics of gadoversetamide in subjects with renal impairment are dependent on the degree of impair with increasing severity resulting in an increase in the $AUC_{0-\infty}$, a prolongation in the $t_{1/2}$, a decrease in the CL_T , and a slight increase in the V_{DSS} .

The removal of iron and zinc from the body was examined by analysis of the serial urine collections for both metals by atomic spectroscopy. The amount of iron removed (<0.3 mg more than placebo at the 0.5 mmol/kg dose) is physiologically inconsequential, and represents chelation of only a very small fraction of the administered versetamide salt. Though much more zinc than iron is removed by chelation (8 mg at 0.1 mmol/kg, 17 mg at 0.5 mmol/kg) in the first 24 hours post-dose, the excess (i.e. over placebo) amount removed is still small in comparison to the amount of zinc in the body (1.4 to 2.3 g.). The increase in both iron and zinc excretion occurs almost entirely in the 24-hour period following the administration of OptiMARK. It should also be noted that the increase in excreted excess zinc is not proportional to dose, suggesting a relatively low limit to the amount of zinc capable of being removed by versetamide.

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Appendix 1-1. Study No. 538

Title:	A Study Comparing the Pharmacokinetics of OptiMARK™ (Gadoversetamide Injection) in Normal Subjects, Patients with Central Nervous System or Liver Pathology Who May Have Renal Insufficiency and Patients Who Have Renal Insufficiency and No Pathology
OBJECTIVES:	The objective of this study was to evaluate the pharmacokinetic profile of OptiMARK at the standard clinical dose of 0.1 mmol/kg in patients diagnosed with central nervous system (CNS) or liver pathology, patients with CNS or liver pathology who also demonstrate renal insufficiency, and patients without pathology who demonstrate renal insufficiency. These results were compared with those obtained in healthy subjects.
METHODOLOGY:	This was a Phase 1, open-label, single-dose, multi-center study. Approximately 42 patients and subjects were to be enrolled: 12 with liver pathology, 4 to 6 of whom demonstrated renal insufficiency; 12 with central nervous system pathology, 4 to 6 of whom demonstrated renal insufficiency; 12 renally impaired patients without pathology; and 6 healthy subjects.
NUMBER OF PATIENTS:	58 enrolled, 54 received study drug
DIAGNOSIS/INCLUSION CRITERIA:	Males or females 18 years of age or older who have CNS (brain and/or spine) or liver pathology, with or without renal insufficiency, with or without pathology, for which a contrast-enhanced MRI would be indicated. Patients and subjects must have been willing to be housed within the investigational facility for a minimum of 48 hours.
DOSE/ROUTE:	A single intravenous dose of 0.1 mmol/kg OptiMARK, was administered at a rate of 1 - 2 mL per second, followed by a saline flush.
DURATION OF TREATMENT:	Each patient and subjects was to receive a single dose of OptiMARK, and be monitored for 7 days.
CRITERIA FOR EVALUATION:	<p>Safety: Safety was monitored in terms of pre- and post-contrast vital signs, physical examinations, electrocardiograms, and clinical laboratory measurements. Tolerance was assessed through the grading of heat, cold, and/or occurrence of pain at the injection site. Adverse events were collected throughout the study.</p> <p>Pharmacokinetics: The pharmacokinetics and elimination of OptiMARK in six groups of patients and subjects was characterized through analysis of plasma and urine samples for total gadolinium (ICP-AES) and gadoversetamide</p>
STATISTICAL METHODS:	Continuous variables were summarized using sample number, mean, standard deviation, minimum, and maximum. Categorical variables were summarized using sample number and percent. Change from baseline was analyzed using analysis of variance.
SUMMARY:	<p>Nineteen patients had CNS pathology and 14 patients had liver pathology. Within each patient population, 2 to 7 patients had consistent renal insufficiency defined as a serum creatinine of 1.5 mg/dL. Twenty-one patients were renally insufficient without pathology. Appropriate screening of serum creatinine values was performed at each site prior to obtaining baseline measurements to ensure that renally insufficient patients met enrollment criteria. Additionally, 8 normal subjects free from disease were evaluated.</p> <p>Thirty-two of the 54 patients (59.3%) who received OptiMARK reported experiencing at least</p>

Title: A Study Comparing the Pharmacokinetics of OptiMARK™ (Gadoversetamide Injection) in Normal Subjects, Patients with Central Nervous System or Liver Pathology Who May Have Renal Insufficiency and Patients Who Have Renal Insufficiency and No Pathology

one adverse event; a total of 85 adverse events were reported. Two patients experienced serious adverse events: Patient 538-C-010 was hospitalized for dilutional hyponatremia and Patient was hospitalized for facial numbness and tingling. Both of these events were considered by the investigator to be coincidental to OptiMARK administration. There was no statistically significant difference between treatment subgroups with respect to the frequency of adverse events. Across treatment groups, the three most common body systems in which adverse events were recorded were the body as a whole (24 patients, 44.4%), digestive system (8 patients, 14.8%), nervous system (7 patients, 13.0%), and cardiovascular and respiratory system (6 patients in each category, 11.1%). The distribution of adverse events by body system were similarly distributed between subgroups with no apparent overall trend.

For all patients dosed in all subgroups, the most frequently reported adverse events were headache (20/54, 37.0%), nausea (4/54, 7.4%), and dizziness (4/54, 7.4%). All other types of adverse events were reported by less than 6% of the patients. There was no apparent adverse event clustering or trend to suggest a predilection that one subgroup was at a higher risk for a specific event type. Comparison of adverse event rates by subgroup revealed no statistically significant differences.

The majority of the 85 reported adverse events were considered by the investigator to be of mild or moderate intensity (84/85, 98.8%). Only one of the 85 events was considered as severe (1/85, 1.2%). The severe adverse event was one report of dilutional hyponatremia which occurred in the renally impaired subgroup. Comparison of adverse event intensity by subgroups revealed no statistically significant differences. There were no statistically significant differences between treatment subgroups with respect to adverse event frequency, intensity or demographics (gender and race) with the exception of race for patients with CNS pathology with renal impairment. All 5 white patients within this subgroup experienced an adverse event whereas the 2 non-white patients did not.

Seventeen (20%) of the 85 adverse events were considered to be likely related to OptiMARK administration. The events considered by the investigator to be likely related to the contrast agent were 7 reports of headache; 2 reports each of parosmia, taste perversion and paresthesia and one report each of chills, chest pain, paresthesia, and diarrhea. There was no specific adverse event type or group of events that occurred solely in one treatment subgroup.

There were no clinically meaningful changes in clinical chemistry, hematology, urinalysis, vital sign, ECG, physical examination, or injection tolerance parameters.

Pharmacokinetic Results:

The differences in the pharmacokinetic parameters among the six pathology groups were examined statistically and only renal impairment emerged as a significant factor. When correction is applied for diurnal variability, there is no significant effect of OptiMARK on serum iron or related parameters.

The mean apparent elimination half-life in the renally impaired patients was 7.8 ± 4.5 hr, while that for the normal group (including CNS and liver patients without renal deficit) was 2.1 ± 0.62 hr. This same 3- 4-fold difference was manifested in the $AUC_{0-\infty}$ and clearance (CL_T). There was only a small difference in apparent volume of distribution (V_{DSS}), which presented a mean value of 159 mL/kg in the non-impaired patients, implying distribution of the drug in the extracellular fluid volume.

The renal clearance in all patients and subjects in the study represented a mean of

Title: A Study Comparing the Pharmacokinetics of OptiMARK™ (Gadoversetamide Injection) in Normal Subjects, Patients with Central Nervous System or Liver Pathology Who May Have Renal Insufficiency and Patients Who Have Renal Insufficiency and No Pathology

approximately 95% of total plasma clearance. The mean total (72-hour) recovery of the administered dose, as intact gadoversetamide, was 95.8% in renally-normal patients and 93.5% in renally-impaired, and was not significantly different in the two groups. Renal impairment thus affects only the rate of gadoversetamide excretion and not the extent. Agreement between plasma and urine concentrations of intact gadoversetamide complex and total Gd was excellent, with the complex accounting for all of the Gd. This, combined with the recovery data, demonstrates that OptiMARK is not significantly metabolized.

Conclusion:

OptiMARK was safe at the dose of 0.1 mmol/kg in this study of 54 males and females 18 years or older with suspected central nervous system or liver pathology, with or without renal insufficiency, with or without pathology who were referred for contrast-enhanced MRI examinations.

Study No. 538 was a Phase 1, open-label, single-dose, multicenter study. The pharmacokinetics and elimination of OptiMARK in six groups of patients with different combinations of CNS, liver or renal disease were characterized through analysis of plasma and urine samples for total gadolinium (ICP-AES) and gadoversetamide

A total of 54 patients were dosed: 14 with liver pathology, 2 of whom demonstrated renal insufficiency; 19 with central nervous system pathology, 7 of whom demonstrated renal insufficiency; 13 renally impaired patients without pathology, and 8 normal healthy subjects.

Patients with CNS or liver pathology included: tumor, inflammation (infectious and non-infectious), congenital anomaly, metabolic, trauma/iatrogenic, and vascular. Males or females 18 years of age or older with CNS (brain and/or spine) or liver pathology with or without renal insufficiency, or with renal insufficiency with or without pathology were eligible (in addition to the normal subjects). The numbers of males and females who were enrolled were balanced overall, and within groups to the extent possible, such that 27 of each gender were entered. Patients must have been willing to be housed within the investigational facility for a minimum of 48 hours. A single intravenous dose of 0.1 mmol/kg OptiMARK was administered at a rate of 1 - 2 mL per second, followed by a saline flush.

Safety was monitored in terms of pre- and post-contrast administration vital signs, physical examinations, electrocardiograms, and clinical laboratory measurements. Tolerance was assessed through the grading of heat, cold, and/or occurrence of pain at the injection site. Adverse events were collected throughout the study.

In this study, the pharmacokinetics of OptiMARK at a dose of 0.1 mmol/kg were examined in both normal patients (i.e., no active disease process) and patients with CNS or liver disease, all with either the presence or absence of renal impairment. Pharmacokinetic parameters were calculated from gadoversetamide plasma and urine concentrations. The mean apparent elimination half-life in the renally impaired patients was 7.8 ± 4.5 hr, while that for the normal group (including CNS and liver patients without renal deficit and normal subjects) was 2.1 ± 0.62 hr. The same 3-4 fold difference was manifested in the $AUC_{0-\infty}$ and clearance (CL_T). There was only a small difference in apparent volume of distribution (V_{DSS}), which presented a mean value of 159 mL/kg in the non-impaired patients, implying distribution of the drug in the extracellular fluid volume.

The mean pharmacokinetic parameters in the two pooled groups, based on the presence or absence of renal impairment, are presented in Table VII. These parameters were calculated from intact gadoversetamide plasma concentrations.

Table VII Pharmacokinetic Parameters for All Subjects and by Renal Status					
Renal Status	AUC ₀ μg·hr/mL)	k _{el} (hr ⁻¹)	Vd _{ss} (mL/kg)	Cl _T (mL/hr/kg)	k _{el} * (hr ⁻¹)
All subjects (N=54)	2121 ± 1690	0.255 ± 0.138	168.5 ± 36.2	49.5 ± 28.0	3.08 ± 1.56
Normal (N=32)	1063 ± 378	0.351 ± 0.086	158.7 ± 29.0	68.6 ± 18.9	2.72 ± 1.22
Impaired (N=22)	3660 ± 1677	0.116 ± 0.056	182.9 ± 41.3	21.6 ± 9.0	3.72 ± 1.92

* For calculation of distribution rate constant (k_{el}) N=42, with 27 normals, 15 impaired and 12 not calculable.

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The data in the table above shows the approximately 3- to 4-fold difference in exposure as measured by k_{el} , AUC_0 and Cl_T , which results from the level of renal impairment of the patients enrolled in this study. The mean apparent elimination half-life in the renally impaired group was 7.8 ± 4.5 hr, and that for the normal group was 2.1 ± 0.62 hr. The differences in kinetic parameters based on renal status are physiologically significant. The approximately 25 mL/kg difference in V_{DSS} is likely based on the larger extracellular water volume expected in renally insufficient patients (due to edema).

An examination of the apparent distribution-phase rate constant (k_{d1}) based on the means by group suggests that the differences in distribution rates are small, with the various group mean distribution half-lives ranging from approximately 12 to 22 minutes. When examined by renal status, the mean distribution half-lives are 14 minutes for the renally-impaired and 20 minutes for the renally-normal groups.

The renal clearance of gadoversetamide in all patients in the study was approximately 95% of total plasma clearance. A relationship was demonstrated between total gadoversetamide clearance and baseline creatinine clearance, suggesting that the degree of renal impairment alone will determine the magnitude of increased exposure to gadoversetamide.

The excretion of gadoversetamide as the intact complex was measured over time in urine. Table VIII presents this recovery data at three times following dosing: 8, 24 and 72 hours.

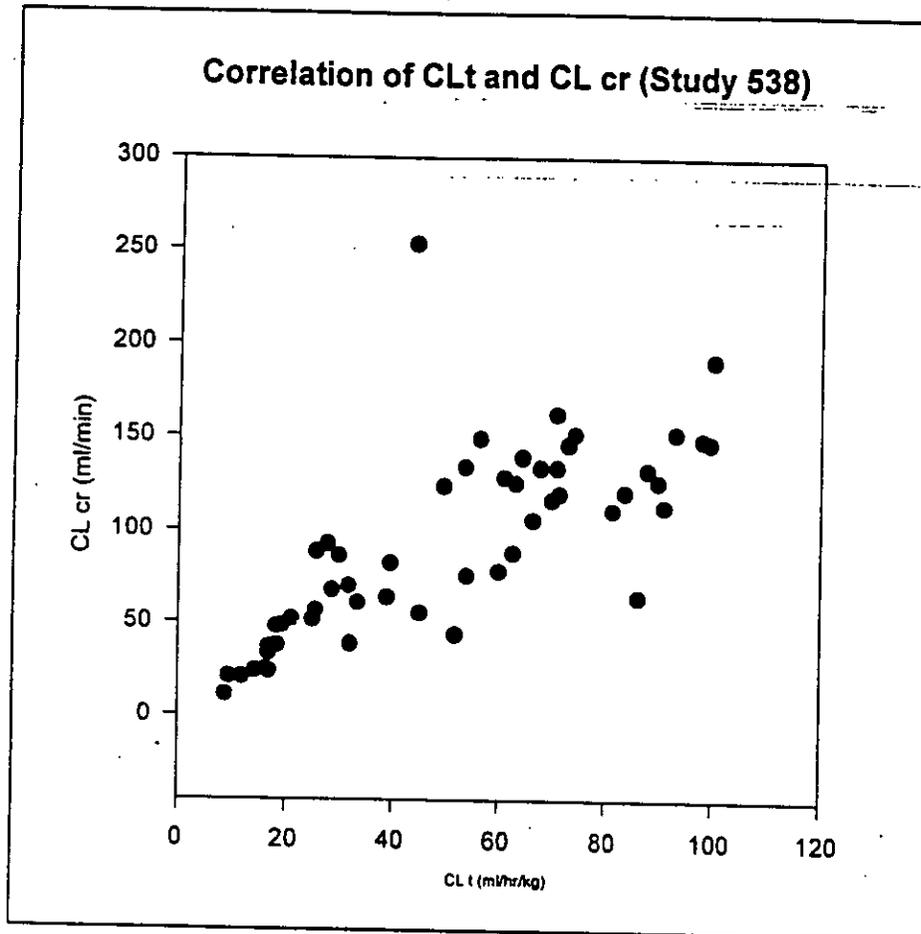
Table VIII. Cumulative Urinary Excretion of Gadoversetamide at 8, 24 and 72 Hours Post-Dose			
Renal Status	Percent of Administered Gadoversetamide Excreted by Time Period		
	8 Hours	24 Hours	72 Hours
Normal (N=32)	89.6 ± 20.4	95.4 ± 20.9	95.8 ± 21.0
Impaired (N= 21)	$56.6 \pm 20.9^*$	$84.3 \pm 15.9^{**}$	93.5 ± 11.9
* $p < 0.0001$ ** $p < 0.05$ (for difference in means between normal and renally-impaired patients)			

These data demonstrate that renal impairment affects the rate but not the extent of urinary excretion of gadoversetamide. Also, based on the virtually quantitative recovery of gadoversetamide in the urine as intact complex, it appears that no significant metabolism occurs.

For each sample of plasma and urine for which both mass spectrometric (MS) and ICP-AES (ICP) concentrations were available, the MS/ICP (i.e. complex to total gadolinium) ratio was calculated. The mean (\pm SD) ratio, irrespective of concentration magnitude, for all evaluable plasma samples was 1.13 ± 0.12 , while that for urine was 1.07 ± 0.20 . These mean ratios are > 1.00 , which is not chemically possible. However, these ratios must be viewed in light of what is observed for the same ratio in the QC samples, which have an assumed true MS/ICP ratio of 1.00. The same ratio was thus determined for all of the assay QC samples, irrespective of concentration, which were analyzed in the plasma and urine sets. The ratio of the two assays for QC samples is expected to be the same as the ratio for the unknown samples. Table VI presents this comparison (with the number of observations noted for each mean value).

This data combined with the parallelism of the plasma curves, the high (>95%) recovery of the administered dose as intact gadoversetamide complex, and the unique specificity of the assays demonstrate that there is no significant metabolic transformation of gadoversetamide.

The total serum clearance of gadolinium and baseline creatinine clearance were linearly related. (Please refer to the following graph.)



Appendix 1-5. Study 543

Title: An Open-Label, Phase 1 Study to Determine the Safety and Dialysis Clearance-Rate of OptiMARK (Gadoversetamide Injection) in Patients with End-Stage Renal Disease Undergoing Hemodialysis
OBJECTIVES: To determine the pharmacokinetic and safety profile and dialysis clearance rate of OptiMARK in patients with end-stage renal disease currently maintained on hemodialysis.
METHODOLOGY: This was a single center study in which renally compromised patients requiring hemodialysis were administered a single 0.1 mmol/kg dose of OptiMARK. Dosing and the first of three dialysis sessions were performed on a regular midweek dialysis day for the patient. Systemic venous blood was drawn immediately prior to and 30 and 60 minutes following OptiMARK administration. In addition, another systemic venous blood sample was drawn immediately prior to the start of hemodialysis (approximately 2 hours following OptiMARK administration). Two hours after OptiMARK administration, hemodialysis began with blood (arterial and venous) and dialysate samples (from complete collection) obtained throughout the hemodialysis session. Complete collections of dialysate were obtained from each dialysis session. Patients were discharged from the clinical research unit after completion of the second dialysis period and returned for the third dialysis session and final safety assessments.
NUMBER OF PATIENTS: 10 enrolled, 8 dosed
DIAGNOSIS/INCLUSION CRITERIA: Males or females at least 18 years of age who were renally impaired with at least a 6-month history of hemodialysis and were within 40% of their ideal body weight. Patients must have been willing to be housed in the investigational facility for approximately 72 to 80 hours.
DOSE/ROUTE: A single intravenous dose of 0.1 mmol/kg OptiMARK
DURATION OF TREATMENT: Each patient received a single dose of OptiMARK 0.1 mmol/kg.
CRITERIA FOR EVALUATION: Safety: Safety was monitored through the recording of adverse events, vital signs, ECG, physical examinations, and clinical laboratory evaluations throughout the study. Pharmacokinetics: The following pharmacokinetic parameters were determined for each patient: dialysis clearance (dialysance), total dialysis recovery and recovery clearance, and dialysis elimination half-life.
STATISTICAL METHODS: Continuous data were summarized using descriptive statistics. Categorical variables were summarized using counts and percents.
SUMMARY - CONCLUSIONS: Safety Results: There were no deaths or patients discontinued due to an adverse event. Overall, all of the changes in safety observations which occurred in this study, i.e., adverse events, vital signs, laboratory parameters, ECGs, etc. were consistent with the uremic disease process in patients with reduced renal function maintained on chronic hemodialysis. Seven of the eight patients (87.5%) who received OptiMARK reported a total of 30 adverse events. Dizziness was the most common adverse event occurring in 3 (37.5%) of the eight OptiMARK patients and all other events were reported by 2 patients. None of the adverse events was attributed to OptiMARK administration and 28 of the 30 events were considered to be coincidental (93.3%) and 2 events were procedure related (6.7%). Onset for a majority of the

Title: An Open-Label, Phase 1 Study to Determine the Safety and Dialysis Clearance Rate of OptiMARK (Gadoversetamide Injection) in Patients with End-Stage Renal Disease Undergoing Hemodialysis
adverse events coincided with the initiation of the second dialysis session.
All but one of the adverse events was considered of mild or moderate intensity (29/30, 96.7%) and only one event of dyspnea was of severe intensity. This event was also reported as a serious adverse event. Comparison of adverse event rates by gender and race revealed no statistically significant differences. There were no clinically meaningful trends observed in laboratory parameters, ECG, physical exams or vital signs after OptiMARK dosing.
Pharmacokinetic Results: The mean dialysis clearance of gadoversetamide, estimated from the recovery rate in dialysate was 93.2 ± 17.1 mL/min, or 48% of the creatinine clearance (194 ± 18.6 mL/min). At the end of the 5-day period (encompassing three dialysis sessions) about 98% of the drug had been cleared based on plasma concentrations, with about 70% recovered in the dialysis fluid of most patients. The difference between these numbers is attributed to a small residual renal clearance in the patients, which could be observed as a decline in plasma concentrations during the inter-dialytic periods. Within the blood flow range of 400-600 mL/min, no significant effect of this parameter on clearance was noted. The mean dialysis half-life of gadoversetamide was 1.74 ± 0.37 hr.
Conclusion: The administration of 0.1 mmol/kg OptiMARK to patients with end-stage renal disease undergoing extracorporeal hemodialysis is safe, and the administered dose is cleared over several routine dialysis sessions using a high-flux membrane.

Study No. 543 was a single center study in which eight (7 men/1 woman) renally compromised patients requiring hemodialysis were administered a single 0.1 mmol/kg dose of OptiMARK (Gadoversetamide Injection). Dosing and the first of three dialysis sessions were performed on a regular midweek dialysis day for the patient. Systemic venous blood was drawn immediately prior to and 30 and 60 minutes following OptiMARK administration. In addition, another systemic venous blood sample was drawn immediately prior to the start of hemodialysis (approximately 2 hours following OptiMARK administration). Two hours after OptiMARK administration, hemodialysis began with blood (arterial and venous) and dialysate samples (from complete collection) obtained throughout the hemodialysis session. The dialyses were conducted using a high-flux PMMA membrane at blood flow rates of 400-600 mL/min. At the time of the patient's second and third sequential dialysis session(s) pre-, mid- and post-dialysis blood (arterial and venous samples) and dialysate samples were obtained. Patients were discharged from the clinical research unit after completion of the second dialysis session and returned for the third dialysis session and final safety assessments. Males or females at least 18 years of age who were renally impaired with at least a 6-month history of hemodialysis and were within 40% of their ideal body weight were eligible for enrollment. Patients must have been willing to be housed in the investigational facility for approximately 72 to 80 hours following dosing.

Safety was monitored through the recording of adverse events, vital signs, ECG, physical examinations, and clinical laboratory evaluations throughout the study. The following pharmacokinetic parameters were determined for each patient: dialysis clearance (dialysance), total dialysis recovery and recovery clearance, and dialysis elimination half-life. There were no deaths or patients discontinued due to an adverse event. Overall, the changes in safety observations which occurred in this study, i.e., adverse events, vital signs, laboratory parameters, ECGs, etc. were consistent with the uremic disease process in patients with renal failure maintained on chronic hemodialysis. There were no clinically meaningful trends observed in laboratory parameters, ECG, physical exams or vital signs after OptiMARK dosing.

Concentrations of gadoversetamide (analyzed as gadolinium) were determined in this study using a validated method for plasma and a similar validated method for dialysate. The methods each involved determination of total gadolinium concentration using an inductively-coupled plasma atomic emission spectroscopy (ICP-AES) assay. Plasma and dialysate creatinine concentrations were determined using standard clinical laboratory methods. The dialysis clearance was calculated from AUC (area under the arterial plasma concentration vs. time curve) during a given dialysis session and the amount of drug (or creatinine) removed into the dialysate.

The mean dialysis clearance of gadoversetamide, estimated from the recovery rate in dialysate was 93.2 ± 17.1 mL/min, or 48% of the creatinine clearance (194 ± 18.6 mL/min). At the end of the 5-day period (encompassing three dialysis sessions) about 98% of the drug had been cleared from the circulation based on plasma concentrations.

No significant effect of blood flow, within the range of 400-600 mL/min, on dialysis clearance was noted. The mean dialysis half-life of gadoversetamide was 1.74 ± 0.37 hours.

Gadoversetamide can be efficiently removed by extracorporeal hemodialysis.

**APPEARS THIS WAY
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Appendix-2. Applicant Labeling

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confidential

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information

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-937
 DRUG(S): OptiMARK™ (gadoversetamide) injection
 Sponsor: Malinckrodt, Inc.
 Subject: 45-Day Filing Meeting for Optimark™ (1-S)

REVIEWER: Young-Moon Choi, Ph.D.
 SUBMIT: 2/28/98
 STAMPED: 3/5/98
 REVIEWED: 4/2/98

SYNOPSIS

Malinckrodt, Inc. has submitted NDA 20-937 on 2/26/98 for the approval of OptiMARK™ (gadoversetamide), an intravenous magnetic resonance imaging (MRI) agent for diagnostic purpose.

This product was developed under IND

OptiMARK is indicated for use with MRI:

- (1) in adults to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause abnormalities in the blood-brain barrier. OptiMARK has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.
- (2) in adults to provide contrast enhancement and facilitate visualization of lesions of the spine and associated tissues.
- (3) in adults to provide contrast enhancement and facilitate visualization of lesions of the liver.

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

This NDA contains 5 pharmacokinetic studies and the study reports are submitted in the Item 6, the Human Pharmacokinetics and Bioavailability. Table I presents the basic study design for each study. The protocol 1177/10, which is conducted in Japan, is submitted as a supportive data. All other 4 studies are equally significant for the evaluation of safety and pharmacokinetics.

Table I. Human Pharmacokinetic Studies of OptiMARK™.

Protocol No.	Formulation (Concentration)	Study Design	Dose (mmol/kg) n= No. of subjects (M/F)	NDA vol
433	MP-1177/10 (0.5 mmol/ml)	Randomized, double-blind, ascending dose, safety and tolerance & PK: in healthy male subject; analysis of Gd in serum & urine: analysis of selected samples of complex by	Placebo (n=4: 4/0) 0.1 (n=4: 4/0) 0.3 (n=4: 4/0) 0.5 (n=4: 4/0) 0.7 (n=4: 4/0)	Vol. 2-6
1177-01	MP-1177/10 (0.5 mmol/ml)	Randomized, double-blind, ascending dose, safety and tolerance & PK: in healthy male subject; analysis of Gd in serum & urine: analysis of selected samples of complex by in vivo serum protein binding.	Placebo (n=4: 4/0) 0.05 (n=4: 4/0) 0.1 (n=4: 4/0) 0.3 (n=4: 4/0) 0.5 (n=4: 4/0)	Vol 2-10

	OptiMARK™ (0.5 mmol/ml)	Multi center (10 sites), randomized, double blind, PK and safety; in men and women CNS & liver patients and normal volunteers, with or without renal impairment; analysis of Gd serum and urine.	Placebo (n=42: 21/21) 0.1 (n=40:19/21) 0.3 (n=42: 23/19) 0.5 (n=39: 21/18)	Vol. 1-7
538	OptiMARK™ (0.5 mmol/ml)	Multi center (6 sites), PK and safety; in men and women CNS & liver patients and normal volunteers, with or without renal impairment; analysis of Gd and intact gadoversetamide complex in plasma & urine.	Non-Renal (Including Normal Subjects): 0.1 (n=32: 15/17) Renal 0.1 (n=22: 12/10)	Vol. 2-8
543	OptiMARK™ (0.5 mmol/ml)	Safety and PK; in stable hemodialysis patients; analysis of Gd in plasma & dialysate.	0.1 (n=8: 7/1)	Vol 2-9

The to-be-marketed formulation was used in the pharmacokinetic studies:

OptiMARK (gadoversetamide injection) is the formulation of a nonionic gadolinium chelate of diethylenetriamine pentaacetic acid bismethoxyethyamide (gadoversetamide), and is to be administered by intravenous injection.

OptiMARK injection is a sterile, nonpyrogenic, clear, colorless to pale yellow, aqueous solution of gadoversetamide. No preservative is added. Each ml of OptiMARK contains 330.9 mg of gadoversetamide, 25.4 mg of versetamide, 3.7 mg calcium hydroxide, 0.74 mg calcium chloride dihydrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added for pH adjustment.

The studies all used essentially the same 0.5 mmol/ml formulation of OptiMARK™ referred to as "MP-1177/10". The formulation is identical to the "to-be-marketed formulation."

Recommended dose of OptiMARK and dose range studied

The pharmacokinetic studies include the recommended dosage (0.1 mmol/kg; 0.2 ml/kg of 0.5 mmol/ml formulation).

Organization of the NDA submission:

All 5 study reports are submitted in five volumes (total 35 binders) as indicated in Table I.

Assay validation data:

Assay validation data have not been submitted yet. To this reviewer's inquiry on 3/31/98 regarding the lack of the assay data in the NDA submission, the sponsor responded on 4/1/98 that the data has been prepared and would be submitted on 4/3/98 or 4/5/98.

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RECOMMENDATION

NDA 20-937 package, Item 6, Human Pharmacokinetics and Bioavailability section, for OptiMARK TM, submitted by the applicant on February 28, 1998, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. Based on the information provided by the applicant, the NDA is considered filable.

/S/

Young-Moon Choi, Ph.D.
Pharmacokineticist
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

/S/

4/3/98

David J. Lee, Ph.D.
Team Leader
Pharmacokineticist
Radiopharmaceuticals and Imaging Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: HFD-160 NDA 20-937...
HFD-160 DIV FILE
HFD-160 /CSO/KCOLANGELO (1X)
HFD-870 /OCPB/JHUNT (1x)
HFD-160 /OCPB/DLEE (1x)
HFD-160 /OCPB/YCHOI (1x)
HFD-870 /OCPB/MLCHEN (1X)
CDR ATTN: BARBARA MURPHY

NDA 20-937